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I. Introduction

The penetration of animal viruses into cells is the result of an active process of specific interactions with cell surface macromolecules. Differentiated organisms do not express identical sets of surface macromolecules on different cell types, tissues, and organs. This basic feature of organisms results in a compartmentalization of susceptibilities to infection by viruses. As observed repeatedly in nature, different viruses infect distinct target cells in one or a group of host species. This
is the expected evolutionary outcome of a population equilibrium between organisms and their parasites that must have been favored by mutual long-term interactions. Although permissivity of virus entry into cells is by no means the only determinant of host cell tropism, it is certainly an important element with implications in viral pathogenesis. Changes in the specificity of virus entry into cells may be of consequence also for viral disease emergence and disease prevention and control.

Early reports (reviewed in McLaren et al., 1959) suggested the presence of receptors for bacteriophage in *Escherichia coli* cells and for influenza virus, Newcastle disease virus, and enteroviruses in some animal cells. The studies of McLaren, Holland, and their colleagues with poliovirus (Holland, 1961; Holland and McLaren, 1959; McLaren et al., 1959) indicated that the productive adsorption of poliovirus was associated with specific antigenic structures possessed only by susceptible primate cells (or subcellular cell debris). We term viral receptor any cell surface macromolecule involved in the recognition of the cell by a virus or in the penetration of a virus into the cell. For simplification, we do not establish a difference between receptor and coreceptor (Young, 2001) because such a distinction is at times ambiguous, and it is not essential to the main aims of the present review. However, we maintain the term coreceptor when referring to some of the molecules that participate in retrovirus entry, as in this case the term is amply employed in the literature. The problems addressed in this review are in the interphase between virus evolution and cell recognition by viruses. Topics include changes in receptor usage, shared use of the same receptors by different viruses, and coevolution of antigenicity and host cell tropism. We then review briefly some of the implications of flexibility in receptor usage for the host range of viruses, for the emergence of viral diseases, and consequences for the use of viruses as vectors for gene delivery. In this regard, we discuss the possible involvement of viruses as agents of lateral gene transfer during the evolution of cellular life on earth as a means to accelerate functional diversification of cells and cell collectivities. In none of these topics can we (or intend to) be exhaustive. Selected examples are used to unveil the implications of the highly dynamic nature of viral genomes for modifications of receptor specificity, particularly for those viruses with RNA as genetic material. Recent introductions to the mechanisms of virus entry into cells can be found in general virology textbooks (Cann, 2001; Flint et al., 2000). Among excellent reviews on viral receptors are those published by Wimmer (1994), Weiss and Tailor (1995), Miller (1996), Hunter (1997), Evans and Almond (1998), Sommerfelt (1999), Berger et al. (1999), Nemerow (2000), Schneider-Schaulies (2000),
II. Basic Concepts of Virus Evolution

A. Types of Interactions between Viruses and Cells

Viruses are highly diverse molecular parasites of cells that have an intracellular phase of replication and an extracellular stage in the form of discrete particles. Despite their remarkable diversity in size, shape, and biological properties, a few definitive features are common to all viruses: (i) they have DNA or RNA (but not both) as genetic material; (ii) their genome encodes a distinctive genetic program, and (iii) the expression of this program, which results in virus replication, is totally dependent on cell structures and cell metabolism.

In their dependence on cells, viruses can produce a wide range of perturbations, such as modifications of specialized (luxury) functions, without an immediate effect on cell survival, or they may cause cell death by apoptosis or necrosis. Viral infections may be inapparent or they may cause acute or chronic disease either directly by affecting cell subpopulations or indirectly by triggering immunopathological responses (Mims et al., 2001; Nathanson et al., 1997). These disparate effects on cells have not been correlated with genome type, virion structure, or receptor usage, presumably because many host functions, as much as viral functions, influence the outcome of an infection.

The genetic complexity of viruses, as reflected in the size of their genome, varies from a few thousand nucleotides in the case of RNA viruses (the genome of bacteriophage MS2 is 3569 nucleotides long, and that of the largest coronaviruses comprises about 32,000 nucleotides) to a broader range in the case of DNA viruses (the double-stranded DNA of hepatitis B virus has about 3200 bp, whereas the large poxviruses, iridoviruses, and herpesviruses have DNA of 130,000 up to 370,000 bp). Genome complexity appears to influence the strategies
of the interactions between viruses and cells. Hosts must have evolved defense mechanisms to limit virus replication at the expense of their cells, and in turn, viruses must have evolved mechanisms to counteract cell responses (at least to survive to be an object of interest for a review article). The most complex DNA viruses encode a number of proteins that may or may not have a cellular homologue and that may modulate host defense responses. Classical examples are the glycoprotein C of herpes simplex virus, which blocks complement activation, or proteins E3/19K and E1a of adenovirus, which suppress major histocompatibility complex (MHC) class I and class II molecules that are required for the T-cell recognition of infected cells. Other viral proteins are homologues of cytokines, chemokines, or their receptors or may induce or inhibit apoptosis. An increasing number of viral-coded, immunomodulating proteins is being discovered, some with seemingly redundant functions, and others with multiple effects on cells, playing active roles as determinants of virus survival and pathogenesis (reviews in Alcamí and Koszinowski, 2000; Alcamí, 2003; Seet et al., 2003; Xu et al., 2001). Host-interfering proteins may also be expressed by RNA viruses (HIV-1 nef, RNA silencing suppressor B2 in flock house virus, several interferon antagonists such as NS1 of human influenza virus A, etc.), albeit their number appears to be more limited than for complex DNA viruses. This probably reflects two fundamentally different viral strategies to cope with host defenses: interaction versus evasion.

In contrast to the complex DNA viruses, RNA viruses have condensed essential genetic information for replication in a minimal number of nucleotides. Compressing mechanisms include the presence of overlapping reading frames; ambisense RNA; common leader RNA sequences for the synthesis of subgenomic messenger RNAs; untranslated regions, which include signals for RNA replication and protein synthesis; cis-acting regulatory elements within open reading frames; RNA editing; partial read-through of termination codons, leading to two forms of a protein that differ in a carboxy-terminal extension; leaky ribosome scanning with initiation of protein synthesis occurring at two in-frame AUGs, leading to two forms of a protein that differ by an amino-terminal extension; ribosome hopping, shunting, and bypassing; ribosome frameshifting, resulting in a change of the order of triplet reading to yield a single fused polypeptide from two overlapping open reading frames; and synthesis of a polyprotein, which is then cleaved to produce functional intermediates and fully processed proteins, with processing intermediates and processed proteins having distinct functional roles in interaction with viral RNA, viral proteins, or cellular proteins. In addition, many viral proteins appear to be
multifunctional, thereby expanding the role of a single nucleotide stretch in the completion of a virus replication cycle (reviews in Flint et al., 2000; Knipe and Howley, 2001; Semler and Wimmer, 2002).

Genome compactness imposes a conflict between the requirement of genetic variation to permit adaptation to changing environments and the need to maintain infectivity in genomes in which virtually every single nucleotide appears to be involved in some structural or functional role. Genetic variation to escape from selective constraints is generally reflected in the survival of subpopulations of genomes that may show little alteration in replication capacity (fitness) or, despite a reduction of fitness, may still replicate to generate new mutant distributions of higher fitness.

B. Genetic Variation and the Dynamics of Viral Populations

The tolerance of viral genomes (or other replicons) to accept mutations decreases with genome complexity (Domingo et al., 2001; Eigen and Biebricher, 1988). RNA viruses display mutation rates and frequencies in the range of $10^{-3}$ to $10^{-5}$ errors per nucleotide copied (Batschelet et al., 1976; Drake and Holland, 1999), values that imply the continuous generation of dynamic mutant distributions in a replicating RNA virus population. These high mutation rates in RNA genomes would be incompatible with maintenance of the genetic information contained in large viral or cellular DNA genomes (Eigen and Biebricher, 1988). This evolutionary adaptation of mutation rates is mirrored in the biochemical activities of the relevant DNA and RNA polymerases. Cellular DNA polymerases involved in DNA replication generally contain a 3′ → 5′ exonuclease proofreading–repair activity capable of excising misincorporated nucleotides to allow incorporation of the correct complementary nucleotide prior to further elongation of the nascent DNA chain. Such a proofreading–repair activity is absent in viral RNA replicases and reverse transcriptases, as evidenced by both structural and biochemical studies (Menéndez-Arias, 2002; Steinhauser et al., 1992). Furthermore, a number of postreplicative repair pathways are active on double-stranded DNA but cannot act on RNA, therefore contributing to a final 10^5- to 10^6-fold higher average copying fidelity during cellular DNA replication than during RNA genome replication (Domingo et al., 2001; Drake and Holland, 1999; Friedberg et al., 1995; Goodman and Fygenson, 1998).

Viruses exploit the same mechanisms of genetic variation as cells: mutation, homologous and nonhomologous recombination, and genome segment reassortment in the case of viruses with segmented
genomes. Different virus families vary in the extent of utilization of these different variation mechanisms. For example, homologous recombination is very active in positive-strand RNA viruses and retroviruses, but appears to be rare in negative-strand RNA viruses. Because of general high mutation rates, RNA virus populations consist of complex mutant distributions termed viral quasispecies (Domingo et al., 2001; Eigen, 1996; Eigen and Biebricher, 1988; Eigen and Schuster, 1979; Nowak, 1992). Quasispecies was formulated as a general theory of molecular evolution by M. Eigen and colleagues to describe self-organization and adaptation of simple early replicons that could occur at early stages of the development of life (Eigen and Biebricher, 1988; Eigen and Schuster, 1979). Although the initial quasispecies theory involved mutant distributions in equilibrium, extensions of the theory to finite replicon populations subjected to environmental changes have been developed (Eigen, 2000; Wilke et al., 2001). Therefore, the quasispecies theory was instrumental in understanding the population structure and dynamics of RNA virus populations. Virologists use an extended definition of quasispecies to signify dynamic distributions of nonidentical but closely related mutant and recombinant viral genomes subjected to a continuous process of genetic variation, competition, and selection, and which act as a unit of selection (Domingo, 1999). It must be stressed that because of high mutation rates (Batschelet et al., 1976; Drake and Holland, 1999), each individual genome in a replicating population, which includes a number of distinctive mutations, has only a fleeting existence because new mutations are arising continuously, even in a single infected cell. Thus, an RNA virus genome population may be defined statistically but it is essentially indeterminate at the level of individual genomes (Domingo et al., 1978, 2001). Mutant swarms are subjected unavoidably to competition, and those mutant distributions best adapted to replicate in a given environment are those that dominate the population at a given time. Unfit mutant distributions are subjected to negative selection and kept at low (sometimes undetectable) levels in the population. Unfit mutant distributions in one environment may nevertheless be fit in a different environment, and a modulation of frequencies of genome subpopulations is the key to adaptability of RNA viruses. The biological relevance of the quasispecies nature of RNA viruses stems from the fact that mutant spectra may contain genomes with altered biological properties, including modified cell recognition capacity. Relevant parameters are the number of mutations per genome, genome length, and viral population size, as documented with several virus systems both in cell culture and in vivo (Table 1).
Despite the unlikely occurrence of generalized high mutation rates in complex DNA viruses, hot spots for variation at sequence repeats and extensive diversity among isolates of DNA viruses have been observed (Lua et al., 2002; Smith and Inglis, 1987). Furthermore, small DNA viruses, such as plant geminiviruses or animal paroviruses, show features of quasispecies dynamics, similar to RNA viruses (Isnard et al., 1998; Lopez-Bueno et al., 2003; reviewed in Domingo et al., 2001).

Diversification of viruses within infected organisms, even when it involves limited genetic change, is of consequence for viral pathogenesis and persistence. This is because one or a few mutations may suffice to change important biological properties of viruses (such as host cell tropism, resistance to antibodies, to cytotoxic T lymphocytes or to inhibitors, among other traits; Table I). Small numbers of mutations in components of mutant spectra are easily attainable by diversifying populations of viruses during acute or chronic infections. Even when a mutation that confers a phenotypic change results in a modest fitness decrease, compensatory mutations can have an opportunity to rescue genomes with normal or nearly normal fitness values (Cassady et al., 2002; Escarmís et al., 1999, 2002; Lázaro et al., 2002; Liang et al., 1998; Nijhuis et al., 1999; Wang et al., 1996; Yuan and Shih, 2000).

### TABLE I

| Relevant parameters                                                                 |   |
|-----------------------------------------------------------------------------------|---|
| 1. Average number of mutations per genome found in a viral population: typically it ranges from 1 to 100 |   |
| 2. Virus population size: very variable but can reach 10^9 to 10^{12} in some infections in vivo |   |
| 3. Genome length: 3 to 33 kb, with compact genetic information                      |   |
| 4. Mutations needed for a phenotypic change: one or few mutations, as documented amply in the text for changes in receptor recognition specificity |   |

Examples of phenotypic changes in RNA viruses dependent on one or few mutations

1. Antigenic variation (antibody-, CTL-escape)
2. Virulence
3. Altered pattern of gene expression
4. Resistance to antiviral inhibitors
5. Cell tropism and host range (the topic of this review)

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Based on many published studies reviewed in Domingo et al. (1985, 1999, 2001), Crandall (1999), Flint et al. (2000), and DeFilippis and Villarreal (2001).
Viral fitness determined *ex vivo* may be a relevant indicator of disease progression *in vivo* (Ball *et al.*, 2003). Within-host variation is the first step in the process of long-term diversification of viruses in successions of transmission events from infected to susceptible hosts. Comparison of consensus nucleotide sequences of independent isolates of the same virus originated from a single source of infection allows a calculation of the rate of evolution. As expected from the complex quasispecies dynamics, rates of evolution for RNA viruses are not constant with time (a “clock” does not operate) and are often in the range of $10^{-2}$ to $10^{-4}$ substitutions per nucleotide and year. These values can also vary for different genomic segments of the same virus. In sharp contrast, rates of evolution for cellular genes have been estimated in $10^{-8}$ to $10^{-9}$ substitutions per nucleotide and year. Interestingly, DNA viruses, even those with small genome size, display widely different rates of evolution. As an example, such rates have been estimated in $1.7 \times 10^{-4}$ substitutions per nucleotide and year for canine parvovirus and in the range of $1 \times 10^{-7}$ to $3 \times 10^{-8}$ substitutions per nucleotide and year for some papovaviruses (reviewed in Domingo *et al.*, 2001).

Genomic consensus sequences of independent isolates of a virus allow the establishment of phylogenetic relationships by the application of classical procedures of population genetics (Doolittle, 1996; Page and Holmes, 1998; Weiller *et al.*, 1995). Such procedures have confirmed the extensive diversity of extant viruses; it has not been possible to derive a genetic tree that relates the known viruses, not even DNA or RNA viruses separately. This, together with the disparate replication strategies exhibited by viruses, suggests multiple origins for the viruses we study today: viruses are polyphyletic. For viruses that infect distantly related host species, such as the herpesviruses, a parallelism between host phylogeny and virus phylogeny has been observed (McGeoch and Davison, 1999). This suggests a host–virus cospeciation, implying deep evolutionary roots of viruses with their hosts (Gorbalenya, 1995; McGeoch and Davison, 1999) (discussed further in Section V,D).

While we have attained some understanding of the mechanisms involved in the generation of diversity, little is understood of the forces that favor the dominance of some virus types over others in nature. According to the International Committee on Taxonomy of Viruses (van Regenmortel *et al.*, 2000), there are about 3600 virus species recognized and more than 30,000 different viruses, strains, and subtypes. Considering that each “individual” RNA virus circulates as a dynamic quasispecies, the diversity of viral genomes on earth is astonishing.
Each replication-competent component of a quasispecies distribution can, in principle, initiate a virus diversification process to generate a spectrum of genotypes and phenotypes. RNA replicons constitute a highly dynamic “RNA world” in a relatively more static [but only relatively! (Bushman, 2002)] DNA-based biosphere of differentiated organisms, as noted two decades ago by Holland and colleagues (1982). The central objective of this review is to examine the effect of virus variation on cell recognition and some of its biological consequences.

III. Nature of Viral Receptors

Viruses recognize target cells by binding to specific receptor molecules at the cell surface. Until the mid-1980s, the only virus receptors that were identified unequivocally were sialic acids for the myxoviruses and paramyxoviruses (Haywood, 1994). Since that time, there has been a deluge of new data about the nature of cell surface molecules participating in viral entry. The molecules that have so far been characterized as viral receptors belong to different families of proteins, carbohydrates, and lipids, often organized as cell surface complexes. Receptors are normally involved in critical cellular functions such as signal transduction, cell adhesion, immune modulation, enzymatic activities, and for some receptors no cellular function has been identified yet (Table II). It is not clear why some macromolecules and not others act as viral receptors. It has been suggested that one reason is their abundance and availability on the cell surface combined with their capacity to bind and/or internalize viruses while triggering initiation of the virus replication cycle. By participating in the first step of virus infection, receptors divert from their usual activity in cellular metabolism and provide yet another example of molecular parasitism, essential in the life cycle of viruses.

It has not been possible to predict the type of receptors likely to be used by a virus from its phylogenetic position, nor from its biological properties. The diversity of receptors is reciprocated by their unforeseeable exploitation by viruses, independently of their genome structure and replication strategy. The picornaviruses, which share structural features in their capsids, may use as receptors molecules as diverse as integrins, glycoproteins of the immunoglobulin gene superfamily, decay accelerating factor (DAF or CD55), or sialic acid or sialylated proteins or lipids (Table II). A survey of the more complex coronaviruses does not modify the picture: receptors for coronaviruses include aminopeptidase N, the sialic acid N-acetyl-9-O-acetylneuraminic acid, N-glycolylneuraminic
TABLE II

SOME CELL SURFACE COMPONENTS PROPOSED TO BE INVOLVED IN VIRUS ENTRY INTO CELLS

| Receptor class | Cellular structure |
|----------------|--------------------|
| Extracellular matrix components, sugar derivatives and lipids | Galactosylceramide |
| | Gangliosides |
| | Glycosaminoglycans (heparan and chondroitin sulfates) |
| | Phospholipids |
| | Sialic acid (N-acetylneuraminic acid, N-acetyl-9-O-acetylneuraminic acid and N-glycolylneuraminic acid) |
| | 3-O-sulfated heparan sulfate |
| Cell adhesion and cell–cell contact proteins | α-Dystroglycan |
| | Coxsackievirus-adenovirus receptor (CAR; Ig superfamily) |
| | CD4 (Ig superfamily) |
| | CEACAMs (including Bgp1a, Bgp2, and pregnancy-specific glycoprotein) |
| | Intercellular adhesion molecule type 1 (ICAM-1; Ig superfamily) |
| | Integrins |
| | Junction adhesion molecule (JAM) |
| | Laminin receptor (high affinity) |
| | MHC class I and β2-microglobulin |
| | Neural cell adhesion molecule (NCAM) |
| | Signaling lymphocyte activation molecule (SLAM or CDw150) |
| | Vascular adhesion molecule 1 (VCAM-1) |
| Chemokine receptors and G-protein-coupled receptors | CC chemokines subfamily: CCR1, CCR2, CCR3, CCR5 |
| | CXC chemokines subfamily: CX3CR1, CXCR4 (Fusin), CXCR6 (BONZO) |
| Complement control protein superfamily | G-protein-coupled receptor: GPR1, GPR15 (BOB) |
| | CD21 (CR2) |
| | CD46 |
| | CD55 (DAF) |
| | CD59 |
| Growth factor receptors | Epidermal growth factor receptor (EGFR) |
| | Fibroblast growth factor receptor (FGFR) |
| | Low-affinity nerve growth factor receptor |
| Low-density lipoprotein receptor-related proteins | Low-density lipoprotein receptor (LDLR) |
| | Very low-density lipoprotein receptor (VLDLR) |

(continues)
acid, and biliary glycoproteins, which belong to the carcinoembryonic antigen-cell adhesion molecule; CR, complement receptor; DAF, decay-accelerating factor; HIgR, herpesvirus immunoglobulin-like receptor; Hve, herpesvirus entry protein; HVEM, herpesvirus entry protein mediator; Ig, immunoglobulin; MHC, major histocompatibility complex; Prr, poliovirus receptor related.

At least three different receptors have been proposed to be involved in the entry of human hepatitis C virus (HCV) into liver cells: CD81, a member of the tetraspanin superfamily of proteins (Pileri et al., 1998),
the low-density lipoprotein receptor (LDLR) (Agnello et al., 1999), and the human scavenger receptor class B type I (hSR-BI) (Scarselli et al., 2002) (Table III). Binding of HCV to CD81 is strain specific, and the binding affinity can be modulated by hypervariable sequences in the envelope protein (Roccasecca et al., 2003). Other hepatitis viruses, despite sharing a specificity for hepatocytes as their main target cells, employ other receptor molecules. The human hepatitis A virus receptor HAVcr-1 is a mucine-like class I integral membrane glycoprotein, and the receptor for duck hepatitis B virus is the C domain of the carboxypeptidase D, gp180 (Urban et al., 2000).

As in the case of viruses with liver tropism, different viruses sharing preferences for other tissues (neural, lymphoid, etc.) do not generally use the same receptor sites. Each class of tissue offers a variety of molecules that can potentially act as virus receptors, and viruses make use of them presumably as the result of ancestral evolutionary processes. As discussed in Section V, analysis of the complete genomic nucleotide sequences of several prokaryotic and eukaryotic organisms, including the first draft of the human genome, has unveiled the presence of several types of mobile genetic elements, suggesting ancestral exchanges of modules among cells, in which viruses likely played an active role. Our present observations on how viruses can penetrate cells and replicate in them are just a snapshot that reflects an instant out of eons of fluid exchanges among cells and autonomous replicons (Bushman, 2002).

The presence on the cell surface of a protein that has been identified as the receptor for a given virus may not be sufficient for a productive viral infection, and there may be multiple mechanisms behind such restrictions: functional domains of the receptor may be blocked in some cellular context, additional proteins (or other cofactors) may be needed, or cells may exhibit impediments for completion of the infection cycle, despite an initial successful interaction with a functional receptor. Mice that are transgenic for the functional form of the poliovirus receptor (PVR or CD155) become susceptible to poliovirus and, upon infection, develop the typical limb paralysis. However, the tissue and organ distribution of the PVR mRNA does not correspond to the sites where virus replicates (Nomoto et al., 1994; Ren and Racaniello, 1992; Ren et al., 1990). Likewise, the N-acetyleneuraminic acid (sialic acid), which is the receptor for human influenza virus, is common on glycosylated molecules on cell surfaces. As a consequence, influenza viruses can bind to many cell types and yet productive infection occurs generally in the epithelial cells of the respiratory tract when the virus causes disease.
| Virus                        | Cell surface molecules                                      |
|-----------------------------|-------------------------------------------------------------|
| **Double-stranded DNA viruses** |                                                             |
| Adenoviridae                |                                                             |
| Human adenovirus            | CAR (except subgroup B Ad3 and Ad7; and subgroup D Ad8 and Ad37) (Bergelson et al., 1997; Tomko et al., 1997; Roelvink et al., 1998; 1999; Bewley et al., 1999; Freimuth et al., 1999); murine CAR (Tomko et al., 1997; Bergelson et al., 1998); integrins αvβ3, αvβ5 (Wickham et al., 1993; Mathias et al., 1998; Chiu et al., 1999), αvβ1 (Li et al., 2001); MHC class I (α2 domain), but not allele HLA-A*0201 (Hong et al., 1997; Davison et al., 1999); HS-GAG (Dechecchi et al., 2000, 2001) |
| Human adenovirus 8, 19a, 37 | Sialic acid (α2,3-linked) (Arnberg et al., 2000a, 2000b, 2002) |
| Canine adenovirus 2         | CAR (Soudais et al., 2000)                                  |
| Avian adenovirus CELO       | CAR (Tan et al., 2001)                                      |
| **Herpesviridae, alphaherpesvirinae** |                                                             |
| HSV-1/HHV-1                 | HS-GAG and CS-GAG (WuDunn and Spear, 1989; Shieh et al., 1992; Banfield et al., 1995); 3-O-sulfated HS (HSV-1 only) (Shukla et al., 1999a; Trybala et al., 2000); HveA/HVEM (Montgomery et al., 1996; Whitbeck et al., 1997; Mauri et al., 1998); nectin-1 alpha/Prr1α/HveC, beta/Prr1β/HIgR, and gamma (Cocchi et al., 1998; Geraghty et al., 1998; Lopez et al., 2001; Milne et al., 2001); nectin-2 alpha/Prr2α/HveB and delta/Prr1δ (HSV-1 mutant Rld and HSV-2) (Warner et al., 1998; Lopez et al., 2000); murine HveA and HveC (Menotti et al., 2000); porcine HveC (Milne et al., 2001) |
| HSV-2/HHV-2                 |                                                             |
| VZV/HHV-3                   | HS-GAG (Zhu et al., 1995); manose-6-phosphate-dependent receptor (Zhu et al., 1995) |
| BHV-1                       | HS-GAG (Okazaki et al., 1991); nectin-1 alpha/Prr1α/HveC and beta/Prr1β/HIgR (Geraghty et al., 1998; Spear et al., 2000); porcine HveC (Milne et al., 2001); murine HveC (Menotti et al., 2000); PVR/CD155 (Geraghty et al., 1998) |
### TABLE III (continued)

| Virus | Cell surface molecules |
|-------|------------------------|
| PrV   | HS-GAG *(Mettenleiter et al., 1990)*; nectin-1 alpha/Prr1α/HveC *(Geraghty et al., 1998)*; nectin-2 alpha/Prr2α/HveB *(Warner et al., 1998)*; murine HveB *(Shukla et al., 1999b)*; porcine HveC *(Milne et al., 2001)*; murine HveC *(Menotti et al., 2000)*; PVR/CD155 *(Geraghty et al., 1998)* |
| HCMV/HHV-5 | HS-GAG *(Compton et al., 1993)*; APN/CD13 *(Soderberg et al., 1993)*; MHC class I via β2-microglobulin *(Grundy et al., 1987)* |
| HHV-6 | CD46 *(Santoro et al., 1999)* |
| HHV-7 | HS-GAG *(Secchiero et al., 1997; Skrincosky et al., 2000)*; CD4 *(Lusso et al., 1994)* |
| KSHV/HHV-8 | HS-GAG *(Akula et al., 2001; Birkmann et al., 2001; Wang et al., 2001)*; integrin α3β1 *(Akula et al., 2002)* |
| MCMV | MHC class I (H-2Dd and Kb) *(Wykes et al., 1993)* |
| EBV/HHV-4 | CD21/CR2 *(Fingeroth et al., 1984; Frade et al., 1985; Nemerow et al., 1985)*; MHC class II (HLA-DR, -DP, -DQ) *(Reisert et al., 1985; Li et al., 1997; Haan et al., 2000; Haan and Longnecker, 2000)* |
| BHV-4 | HS-GAG *(Vanderplaschen et al., 1993)* |
| Papillomaviridae | α6 integrins *(Evander et al., 1997; McMillan et al., 1999)*; HS-GAG *(Giroglou et al., 2001)* |
| Murine polyomavirus | Sialic acid (N-acetyl neuraminic acid) *(Stehle et al., 1994; Stehle and Harrison, 1996)*; integrin α4β1 *(Caruso et al., 2003)* |
| SV40 | MHC class I *(Atwood and Norkin, 1989; Breau et al., 1992)* |
| Poxviridae | Vaccinia virus | HS-GAG and CS-GAG *(Chung et al., 1998; Hsiao et al., 1999)* |
| Myxoma virus | CCR1, CCR5, CXCR4 *(Lalani et al., 1999)* |
| Parvoviridae | AAV2 | HS-GAG *(Summerford and Samulski, 1998; Qiu et al., 2000)*; FGFR 1 *(Qing et al., 1999)*; integrin α6β3 *(Summerford et al., 1999)* |

(continues)
| Virus                          | Cell surface molecules                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------|
| Human virus B19               | Erythrocyte P antigen (globoside) ([Brown et al., 1993; Chipman et al., 1996])          |
| Bovine parvovirus             | Sialic acid, glycophorin A ([Thacker and Johnson, 1998])                               |
| Canine parvovirus             | Sialic acid ([Barbis et al., 1992]); human, feline and canine TfR ([Parker et al., 2001; Hueffer et al., 2003]) |
| Feline parvovirus             | Sialic acid ([Barbis et al., 1992]); human and feline TfR ([Parker et al., 2001])      |

DNA and RNA reverse transcribing viruses

*Hepadnaviridae*

| Virus                          | Cell surface molecules                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------|
| HBV                           | Sialic acid ([Komai et al., 1988]); asialoglycoprotein receptor ([Treichel et al., 1994]); endonexin II ([Hertogs et al., 1993]) |
| Duck hepatitis B virus        | Carboxypeptidase D ([Breiner et al., 1998; Urban et al., 1998; Tong et al., 1999; Urban et al., 2000]) |

*Retroviridae (alpharetrovirus)*

| Virus                          | Cell surface molecules                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------|
| ALV-A                         | Tva ([Bates et al., 1993; Connolly et al., 1994])                                      |
| ALV-B, -D                     | CAR1 ([Brojatsch et al., 1996; Adkins et al., 2001])                                   |
| ALV-E                         | TEF ([Adkins et al., 1997])                                                             |

*Retroviridae (betaretrovirus)*

| Virus                          | Cell surface molecules                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------|
| MMTV                          | MTVR/mouse TfR-1 ([Ross et al., 2002])                                                 |
| JSRV, ONAV                    | HYAL2 ([Rai et al., 2001; Miller 2003])                                                |
| SRV (receptor group 1)        | RDR/R-receptor/ATB<sup>9</sup>/ASCT2/Na<sup>+</sup>-dependent neutral amino acid transporter type 2 ([Kewalramani et al., 1992; Koo et al., 1994; Rasko et al., 1999; Tailor et al., 1999b]) |

*Retroviridae (gammaretrovirus)*

| Virus                          | Cell surface molecules                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------|
| BaEV (receptor group 1)       | RDR/R-Receptor/ATB<sup>9</sup>/ASCT2/Na<sup>+</sup>-dependent neutral amino acid transporter type 2 ([Kewalramani et al., 1992; Koo et al., 1994; Rasko et al., 1999; Tailor et al., 1999b]) |
| FeLV-B (receptor group 5)     | Pit1/Glvr ([Takeuchi et al., 1992; Miller, 1996]; Pit2 /Ram-1/Glvr-2 (mutants of FeLV-B only) ([Sugai et al., 2001]) |
| FeLV-C (receptor group 4)     | FLVCR ([Tailor et al., 1999e])                                                         |
| FeLV-T                        | Pit1/Glvr; FeLIX ([Anderson et al., 2000; Lauring et al., 2001])                        |
| GALV (receptor group 5)       | Pit1/Glvr ([O’Hara et al., 1990; Miller and Miller, 1994; Miller, 1996])               |

(continues)
| Virus                      | Cell surface molecules                                                                 |
|---------------------------|----------------------------------------------------------------------------------------|
| MLV-A (receptor group 2)  | Pit2 /Ram-1/Glvr-2 ([Miller et al., 1994; Miller and Miller, 1994; van Zeijl et al., 1994]) |
| MLV-10A1                  | Pit1/Glvr; Pit2 /Ram-1/Glvr-2 ([Miller and Miller, 1994; Miller, 1996])                |
| MLV-E                     | MCAT-1/REC-1 /ecoR/ATRC-1 ([Albritton et al., 1989; Wang et al., 1991a])               |
| MLV-X (receptor group 3)  | XPR1 /X-receptor/Rmc-1/sxv ([Battini et al., 1999; Tailor et al., 1999a; Yang et al., 1999]) |
| P-MLV (receptor group 3)  | XPR1 /X-receptor/Rmc-1/sxv ([Battini et al., 1999; Tailor et al., 1999a; Yang et al., 1999]) |
| RD114 (receptor group 1)  | RDR/R-receptor/ATB⁰/ASCT² /Na⁺-dependent neutral amino acid transporter type 2 ([Kewalramani et al., 1992; Koo et al., 1994; Rasko et al., 1999; Tailor et al., 1999b]) |
| REV (receptor group 1)    | RDR/R-receptor/ATB⁰/ASCT² /Na⁺-dependent neutral amino acid transporter type 2 ([Kewalramani et al., 1992; Koo et al., 1994; Rasko et al., 1999; Tailor et al., 1999b]) |
| **Retroviridae (deltaretrovirus)** |                                                                                           |
| BLV (receptor group 6)    | BLVRcp1/Blvr ([Ban et al., 1993])                                                       |
| HTLV-I (receptor group 7) | MHC class I; interleukin 2 receptor ([Clarke et al., 1983; Lando et al., 1983; Kohtz et al., 1988]) |
| **Retroviridae (lentiviruses)** |                                                                                           |
| FIV-A, -B                 | CXCR4/fusin ([Willett et al., 1997; Poeschla et al., 1998; Richardson et al., 1999; Frey et al., 2001]; feline homologue of CD9 ([Willett et al., 1994]) |
| HIV-1 (receptor group 8)  | HS-GAG ([Patel et al., 1993; Roderiquez et al., 1995; Saphire et al., 2001]; CD4 ([Dalgleish et al., 1984; Klatzmann et al., 1984; Maddon et al., 1986; McDougal et al., 1986]; CXCR4/ Fusin; CCR5/CC-CXR5; CCR2b/CC-CXR2b; CCR3/CC-CXR3; CCR8/Chem-1; BOB/GPR15; Bonzo/CXCR6/STRL33/TYMSRT; GPR1; APJ ([Alkhatib et al., 1996; Choe et al., 1996; Deng et al., 1996, 1997; Doranz et al., 1996; Dragic et al., 1996; Feng et al., 1996; Lapham et al., 1996; Liao et al., 1997; Loetscher et al., 1997; Rucker et al., 1997; Choe et al., 1998; Edinger et al., 1998a,b; Shimizu et al., 1999]; US28 ([Pleskoff et al., 1997; Rucker et al., 1997]; BLTR ([Owman et al., 1998]; CD8 ([Saha et al., 2001]); GalCer ([Bhat et al., 1991; Fantini et al., 1993]; integrin αβ₃ ([Lafrenie et al., 2002]) |

(continues)


TABLE III (continued)

| Virus                               | Cell surface molecules |
|-------------------------------------|------------------------|
| HIV-2 (receptor group 8)            | CD4; CXCR4/fusin; CCR5/CC-CKR5; CCR8/Chem-1; GPR1 (Owen et al., 1998; Reeves et al., 1999; Shimizu et al., 1999; Liu et al., 2000); GalCer (Hammache et al., 1998); US28 (Pleskoff et al., 1997) |
| SIV (receptor group 8)              | CD4; CCR3/CC-CKR3; CCR5/CC-CKR5; CCR8/Chem-1; BOB/GPR15; Bonzo/CXCR6/STRL33/TYMSRT; GPR1; APJ (Alkhatib et al., 1997; Deng et al., 1997; Farzan et al., 1997; Rucker et al., 1997; Choe et al., 1998; Edinger et al., 1998b; Liu et al., 2000) |
| Visna virus                         | Ovine MHC class II (Dalziel et al., 1991) |
| Double-stranded RNA Viruses         |                        |
| Reoviridae                          |                        |
| Reovirus type 1                     | JAM (Barton et al., 2001a, 2001b); carbohydrate (unknown nature) (Lerner et al., 1963; ChapPELL et al., 2000); EGFR (Strong et al., 1993; Tang et al., 1993) |
| Reovirus type 3                     | JAM (Barton et al., 2001a, 2001b); sialic acid (Gentsch and Pacitti, 1987; Paul et al., 1989; ChapPELL et al., 2000); type A glycoporin (Paul and Lee, 1987); β-adrenergic receptor (Co et al., 1985b; Choi and Lee, 1988; Donta and Shanley, 1990) |
| Group A human rotavirus             | Integrins α<sub>4</sub>β<sub>3</sub> (Guerrero et al., 2000); α<sub>2</sub>β<sub>1</sub> (VLA-2) (Ciarlet et al., 2002) |
| Group A simian rotavirus            | Sialic acid (not RRV variant nar 3) (Yolken et al., 1987; Willoughby and Yolken, 1990; Mendez et al., 1993, 1999; Ciarlet and Estes, 1999), gangliosides (Superti and Donelli, 1991; Srnka et al., 1992; Delorme et al., 2001); integrins α<sub>2</sub>β<sub>1</sub> (VLA-2), α<sub>4</sub>β<sub>1</sub> (VLA-4) (Hewish et al., 2000; Zarate et al., 2000; Ciarlet et al., 2002), α<sub>4</sub>β<sub>3</sub> (Guerrero et al., 2000) |
| Group A porcine rotavirus           | Gangliosides (Rolsma et al., 1994, 1998); integrins α<sub>2</sub>β<sub>1</sub> (VLA-2) (Coulson et al., 1997; Ciarlet et al., 2002) |
| Negative-sense, single-stranded RNA viruses |                        |
| Arenaviridae                        |                        |
| LCMV                                | α-Dystroglycan (Cao et al., 1998; Kunz et al., 2001) |
| Lassa fever virus                   | α-Dystroglycan (Cao et al., 1998) |
| New World arenavirus                | α-Dystroglycan (Spiropoulou et al., 2002) |
| (clade C, but not clade A and B viruses) |                        |
Table III (continued)

| Virus                        | Cell surface molecules                                                                                                                                 |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Bunyaviridae**             |                                                                                                                                                       |
| Hantaviruses                 | $\beta 3$ integrins (Gavrilovskaya et al., 1998, 1999)                                                                                                 |
| **Filoviridae**              |                                                                                                                                                       |
| Ebola virus                  | FR-$\alpha$ (Chan et al., 2001)                                                                                                                        |
| Marburg virus                | FR-$\alpha$ (Chan et al., 2001); asialoglycoprotein receptor (Becker et al., 1995)                                                                     |
| **Orthomyxoviridae**         |                                                                                                                                                       |
| Influenza A, B               | Sialic acid ($N$-acetylneuraminic acid, $\alpha 2,3$ and $\alpha 2,6$-linked) (Paulson et al., 1979; Weis et al., 1988; Eisen et al., 1997); mannose receptor (Reading et al., 2000) |
| Influenza C                  | Sialic acid ($N$-acetyl-9-O-acetylneuraminic acid) (Herrler et al., 1985; Rosenthal et al., 1998)                                                       |
| **Paramyxoviridae, Paramyxovirinae** |                                                                                                                                               |
| Human parainfluenza virus 1, 3 | Sialic acid residues on gangliosides glycolipids (Suzuki et al., 2001)                                                                                       |
| Measles virus                | CD46 (Dorig et al., 1993; Naniche et al., 1993; Schneider-Schaullies et al., 1995; Horvat et al., 1996; Buckland and Wild, 1997; Buchholz et al., 1997; Niewiesk et al., 1997); SLAM (Tatsuo et al., 2000b) |
| Sendai virus                 | Sialic acid residues on glycoporin and gangliosides GD1a, GT1b, GQ1b (glycolipids) (Markwell and Paulson, 1980; Wu et al., 1980; Markwell et al., 1981, 1986; Wybenga et al., 1996); asialoglycoprotein receptor (Markwell et al., 1985; Bitzer et al., 1997) |
| NDV                          | Sialic acid (Crennell et al., 2000)                                                                                                                       |
| Rinderpest virus             | SLAM (Tatsuo et al., 2001)                                                                                                                               |
| Canine distemper virus       | CD9 (Loffler et al., 1997); SLAM (Tatsuo et al., 2001)                                                                                                                                                         |
| **Paramyxoviridae, pneumovirinae** |                                                                                                                                               |
| HRSV                         | Iduronic acid-containing glycosaminoglycans (heparan sulfate and chondroitin sulfate B) (Feldman et al., 1999; Hallak et al., 2000; Martinez and Melero, 2000); CX3CR1 (Tripp et al., 2001) |
| **Rhabdoviridae**            |                                                                                                                                                       |
| Rabies virus                 | Acetylcholine receptor (Lentz et al., 1982, 1984; Hanham et al., 1993; Gastka et al., 1996); NCAM (Thoulouze et al., 1998); low-affinity nerve growth factor receptor p75NTR (Tuffereau et al., 1998, 2001); sialylated gangliosides |

(continues)
TABLE III (continued)

| Virus                        | Cell surface molecules                                                                 |
|------------------------------|----------------------------------------------------------------------------------------|
| (Superti et al., 1986); phospholipids (Superti et al., 1984) |                                                                                       |
| VSV                          | Phosphatidylserine (Schlegel et al., 1983); phosphatidylinositol (Mastromarino et al., 1987) |
| **Positive-sense, single-stranded RNA viruses** |                                                                                       |
| **Arteriviridae**            |                                                                                       |
| Lactate dehydrogenase virus  | Mouse Ia antigens (Inada and Mims, 1984)                                               |
| **Coronaviridae**            |                                                                                       |
| HCoV-229E                    | Human APN (CD13) (Yeager et al., 1992; Lachance et al., 1998); feline APN (Tresnan et al., 1996) |
| HCoV-OC43                    | Sialic acid (N-acetyl-9-O-acetyleneuraminic acid) (Vlasak et al., 1988)                 |
| TGEV                         | Porcine APN (Delmas et al., 1992); feline APN (Tresnan et al., 1996); canine APN (Benbacer et al., 1997); bovine APN (Benbacer et al., 1997); sialic acid (N-glycolyneuraminic acid) (Schultze et al., 1995, 1996) |
| BCV                          | Sialic acid (N-acetyl-9-O-acetyleneuraminic acid) (Vlasak et al., 1988; Schultze et al., 1991; Schultze and Herrler, 1992) |
| FIPV                         | Feline APN (Tresnan et al., 1996); canine APN (Benbacer et al., 1997)                    |
| CCV                          | Canine APN (Benbacer et al., 1997); feline APN (Tresnan et al., 1996)                    |
| MHV                          | CEACAMs (Dveksler et al., 1991; Williams et al., 1991a; Compton et al., 1992; Yokomori and Lai, 1992; Dveksler et al., 1993; Chen et al., 1997a), including biliary glycoproteins (Bgp1a, Bgp2) (Nedellec et al., 1994) and pregnancy-specific glycoprotein (Chen et al., 1995) |
| **Flaviviridae**             |                                                                                       |
| Dengue virus                 | HS-GAG (Chen et al., 1997b; Germi et al., 2002)                                          |
| Yellow fever virus           | HS-GAG (Germi et al., 2002)                                                            |
| HCV                          | LDLR protein family (Agnello et al., 1999; Monazahan et al., 1999); CD81 (Pileri et al., 1998; Flint et al., 1999); tamarin CD81 (Allander et al., 2000); human SR-BI (Scarselli et al., 2002) |
| BVDV                         | LDLR protein family (Agnello et al., 1999)                                             |
| GB virus C/hepatitis G virus | LDLR protein family (Agnello et al., 1999)                                             |
| CSFV                         | HS-GAG (Hulst et al., 2000, 2001)                                                       |

(continues)
### TABLE III (continued)

| Virus                        | Cell surface molecules                                                                 |
|------------------------------|----------------------------------------------------------------------------------------|
| **Picornaviridae (aphthovirus)** |                                                                                         |
| FMDV                         | HS-GAG (Jackson et al., 1996; Sa-Carvalho et al., 1997; Fry et al., 1999; Baranowski et al., 2000); integrins $\alpha_v\beta_3$ (Fox et al., 1989; Berinstein et al., 1995; Jackson et al., 1997; Neff et al., 1998), $\alpha_v\beta_6$ (Jackson et al., 2000b), $\alpha_v\beta_1$ (Jackson et al., 2002), $\alpha_5\beta_1$ (Jackson et al., 2000a) |
| **Picornaviridae (cardiovirus)** |                                                                                         |
| EMCV                         | VCAM-1 (Huber, 1994); sialylated glycoporin A (Allaway and Burness, 1986)                |
| **Picornaviridae (enterovirus)** |                                                                                         |
| Coxsackievirus A9            | Integrin $\alpha_v\beta_3$ (Roivainen et al., 1991; Roivainen et al., 1994; Berinstein et al., 1995; Triantafilou et al., 1999); GRP78 (Triantafilou et al., 2002); MHC class I via $\beta_2$-microglobulin (Triantafilou et al., 1999) |
| Coxsackievirus B1-6          | CAR (Bergelson et al., 1997; Shafran et al., 1997c; Tomko et al., 1997; Martino et al., 2000; He et al., 2001); murine CAR (Tomko et al., 1997; Bergelson et al., 1998) |
| Coxsackievirus B1, B3, B5    | DAF (Bergelson et al., 1995; Shafran et al., 1995; Martino et al., 1998); integrin $\alpha_v\beta_6$ (Agrez et al., 1997) |
| Coxsackievirus A21           | DAF (Shafran et al., 1997b); ICAM-1 (Shafran et al., 1997a,b, 1997b; Xiao et al., 2001) |
| Echovirus 1, 8                | Integrin $\alpha_2\beta_1$ (VLA-2) (Bergelson et al., 1992, 1993; King et al., 1995) |
| Echovirus 9Barty              | Integrin $\alpha_v\beta_3$ (Nelsen-Salz et al., 1999)                                    |
| Echovirus 3, 6, 7, 11–13, 20, 21, 24, 29, 33 | DAF (Bergelson et al., 1994; Ward et al., 1994; Powell et al., 1997); MHC class I via $\beta_2$-microglobulin (Ward et al., 1998); HS-GAG (Goodfellow et al., 2001); CD59 (Goodfellow et al., 2000) |
| Enterovirus 70                | DAF (Karnauchow et al., 1996)                                                             |
| TMEV strains BeAn, DA         | Sialic acid (Zhou et al., 1997, 2000)                                                    |
| TMEV strain GDVII             | UDP-galactose transporter (or galactose containing glycoprotein) (Hertzler et al., 2001); HS-GAG (Reddi and Lipton, 2002) |
| Poliovirus 1–3                | PVR (Mendelsohn et al., 1989; Racaniello, 1996; Belnap et al., 2000; He et al., 2000) |
| Swine vesicular disease virus | CAR (Martino et al., 2000)                                                               |

(continues)
| Virus                        | Cell Surface Molecules                                      |
|-----------------------------|------------------------------------------------------------|
| **Picornaviridae (Hepatovirus)** |                                                             |
| Hepatitis A virus            | HAVcr-1 (Kaplan et al., 1996; Feigelstock et al., 1998)    |
| **Picornaviridae (Rhinovirus)** |                                                             |
| Major group HRV              | ICAM-1 (Greve et al., 1989; Staunton et al., 1989; Tomassini et al., 1989; Olson et al., 1993; Kolatkar et al., 1999) |
| Minor group HRV              | VLDLR (Hofer et al., 1994; Marlovits et al., 1998; Hewat et al., 2000); avian homologues of the mammalian LDLR (Gruenberger et al., 1995) |
| HRV 87                      | Sialic acid (Uncapher et al., 1991)                        |
| **Picornaviridae (Parechovirus)** |                                                             |
| Human parechovirus 1/echovirus 22 | Integrins $\alpha_v\beta_1$ and $\alpha_v\beta_3$ (Triantafilou et al., 2000) |
| **Togaviridae**              |                                                             |
| Sindbis virus                | High-affinity laminin receptor (Wang et al., 1992); HS-GAG (Byrnes and Griffin, 1998; Klimstra et al., 1998) |

a Abbreviations of virus names: AAV2, adeno-associated virus type 2; Ad, adeno-virus; ALV, avian leukemia virus; BaEV, baboon endogenous retrovirus; BCV, bovine coronavirus; BHV, bovine herpesvirus; BLV, bovine leukemia virus; BVDV, bovine viral diarrhea virus; CCV canine coronavirus; CSFV classical swine fever virus; EBV, Epstein–Barr virus; EMCV, encephalomyocarditis virus; FeLV, feline leukemia virus; FIPV, feline infectious peritonitis virus; FIV, feline immunodeficiency virus; FMDV, foot-and-mouth disease virus; GALV, gibbon ape leukemia virus; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HCoV, human coronavirus; HHV, human herpes virus; HIV, human immunodeficiency virus; HRV, human respiratory syncytial virus; HRV, human rhinovirus; HSV, herpes simplex virus; HTLV, human T-cell leukemia virus; JSRV, Jaagsiekte sheep retrovirus; KHSV, Kapośi’s sarcoma-associated herpesvirus; LCMV, lymphocytic choriomeningitis virus; MCMV, murine cytomegalovirus; MHV, mouse hepatitis virus; MLV-A, amphotropic murine leukemia virus; MLV-E, ecotropic murine leukemia virus; MLV-X, xenotropic murine leukemia virus; MMTV, mouse mammary tumor virus; NDV, Newcastle disease virus; ONAV, ovine nasal adenocarcinoma virus; P-MLV, polytropic murine leukemia virus; PrV, pseudorabies virus; RD114, cat endogenous retrovirus; REV, reticuloendotheliosis virus; SIV, simian immunodeficiency virus; SRV, simian retrovirus; SV40, simian virus 40; TEF, name given to the receptor for subgroup E of avian leukosis virus; TGEV, transmissible gastroenteritis virus; TMEV, Theiler’s encephalomyelitis virus; VSV, vesicular stomatitis virus; VZV, varicella zoster virus.

b Abbreviations of cellular structures: APJ, name given to a ligand-unknown “orphan” seven transmembrane domain receptor of the central nervous system; APN, aminopeptidase N; BLTR, leukotriene B4 receptor; BLVR, bovine leukemia virus receptor; Bgp, biliary glycoprotein; CAR, coxsackievirus-adenovirus receptor; CAR1, name given to the receptor for subgroups B and D avian leukosis virus; CCR, CC-chemokine receptor; CEACAM, carcinoembryonic antigen-cell adhesion molecule; CR, complement receptor; CS-GAG, chondroitin sulfate glycosaminoglycan; CXCR, CXC-chemokine receptor; DAF,
A. A Virus May Use Different Receptor Types

Some viruses apparently use only a single receptor to infect their target cells, whereas others are able to exploit several alternative receptors to initiate their replication in different cell lines or even to enter the same cell type (Table III). Evidence shows that foot-and-mouth disease virus (FMDV) may employ integrins $\alpha_v\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_6$ as receptors. Recognition of these integrins is dependent on an Arg-Gly-Asp (RGD) triplet found in the surface G-H loop of capsid protein VP1, and this triplet is very conserved among natural isolates of the seven FMDV serotypes (Domingo et al., 1990, 1992; Mateu, 1995). However, several studies suggest the use of alternative receptors by FMDV, both in cell culture and in vivo. Upon adaptation of FMDV to cell culture, mutations may occur that result in the acquisition of positively charged amino acids at key residues of the capsid surface that allow FMDV to enter cells via heparan sulfate (HS) and possibly other receptors (Baranowski et al., 1998, 2000; Escarmis et al., 1998; Fry et al., 1999; Jackson et al., 1996; Sa-Carvalho et al., 1997; Sevilla et al., 1998; Zhao et al., 2003). Following this seminal observation with FMDV, studies with other viruses have demonstrated that passage in cell culture results in evolutionary changes that allow the viruses to use HS for cell entry. Examples include Sindbis virus adapted to BHK cells (Klimstra et al., 1998), classical swine fever virus propagated in swine kidney cells (Hulst et al., 2000), and variants of human rhinovirus 89 adapted to HEp2 cells (Reischl et al., 2001; Vlasak et al., 2002) (Section II,B).
A well-documented case of use of multiple receptors is that of lentiviruses HIV-1, HIV-2, and simian immunodeficiency virus (SIV). Almost all strains described to date require interactions with two molecules on the cell surface. One of them acts as an attachment receptor, with which viral glycoprotein gp120 interacts. This interaction promotes conformational changes that expose the fusogenic peptide of gp41, which, in turn, interacts with the fusion receptor. This is essential for the fusion of viral and cellular membranes and therefore allows the viral capsid to enter the host cell. The group of cellular molecules involved in lentivirus fusion are referred to as coreceptors. It has been suggested that those strains shown to use only the fusion receptor have already undergone, at least partially, the conformational changes normally induced by the attachment receptor (Berger et al., 1999).

The helper T-cell differentiation antigen CD4 is an important attachment receptor for HIV-1, HIV-2, and SIV, but other cell surface molecules, including galactosyl ceramide (GalCer), syndecans, and other glycosaminoglycans, have been found to play a role in the attachment of these viruses (Baba et al., 1988; Ito et al., 1987; Saphire et al., 2001; Zhang et al., 2002). The preferential use of some attachment receptors over others is thought to be influenced by their relative abundance on the cell surface. Thus, on macrophages, CD4 is scarce and HIV attachment takes place mainly through HS proteoglycans, especially syndecans (Saphire et al., 2001). It has been reported that integrin αvβ3 is involved in the infection of macrophages that have differentiated in vitro (Lafrenie et al., 2002); certainly, the significance of this interaction in vivo deserves further study. HIV infection of colon epithelia in vivo is CD4–independent and is believed to take place through GalCer (Bhat et al., 1993; Fantini et al., 1993). Neuronal cells and intestinal epithelia are rarely infected in vivo, but binding of HIV envelope glycoproteins to GalCer contributes to the selection of CCR5-binding variants following vertical transmission (Meng et al., 2002). This GalCer-mediated selection may also contribute to pathogenesis, e.g., in the gastrointestinal disorders associated with HIV infection and in neuronal dysfunction in AIDS dementia. HIV populations that acquired the capacity to bind CD8 and replicate in CD8+ T cells have been recovered from a patient at a late stage of the infection (Saha et al., 2001). A wide variety of molecules from different structural and functional families can act as fusion receptors (or coreceptors). The most important is the chemokine receptor superfamily, for many of its members can bind HIV and/or SIV. A related protein is a β-chemokine receptor US28, encoded by human cytomegalovirus (Pleskoff et al., 1997). There are also other coreceptors, such as the
leukotriene B₄ receptor (BLTR) (which has structural homology with chemokine receptors) (Owman et al., 1998) and an orphan receptor of the central nervous system (APJ). Usually, most HIV strains evolve in vivo from using mainly CCR5 (R5 viruses) to using mainly CXCR4 (X4 viruses), but many other coreceptors can be used simultaneously.

An example in which the functional receptor for a virus is a complex of several cell molecules that the virus uses in a multistep process is found among Reoviridae (Mendez et al., 1999). Rotaviruses are important viral agents of acute gastroenteritis in young children and in many animal species. Rotavirus strains differ in their requirement of sialic acid for initial binding to the cell surface: a minority of animal rotaviruses require the presence of sialic acid residues on the cell surface for efficient binding and infectivity (Arias et al., 2001; Zarate et al., 2000), but most animal and human rotaviruses do not. However, binding to sialic acid is not an essential step for rotavirus infection, as confirmed by the isolation of sialic-independent variants from a sialic-dependent strain (Mendez et al., 1993). The existence of a postattachment cell receptor common to most, if not all, rotavirus strains has been proposed. Integrin αᵥβ₃ blocks the infectivity, although not the binding, of the sialic acid-dependent rhesus rotavirus (RRV), its sialic acid-independent mutant nar3, and the sialic acid-independent human rotavirus strain WA, suggesting that αᵥβ₃ interacts with both neuraminidase-sensitive and neuraminidase-resistant rotaviruses at a postbinding, probably penetration, step (Guerrero et al., 2000). Other integrins, such as α₂β₁, α₄β₁, and αₓβ₂, have also been reported to play a role in rotavirus entry (Ciarlet et al., 2002; Coulson et al., 1997; Hewish et al., 2000; Londrigan et al., 2000).

Cell recognition by herpesviruses offers a classical example of complexity in virus–receptor interactions. The initial contact of herpes simplex virus 1 (HSV-1), the prototype of the Alphaherpesvirinae subfamily, with cells is usually the binding of virus to HS proteoglycans (Shieh et al., 1992; Shukla and Spear, 2001; WuDunn and Spear, 1989), mediated by glycoprotein gC and, to a lesser extent, by gB. Then, glycoprotein gD can interact with at least three different classes of molecules that can act as entry mediators for HSV-1. These molecules include HveA (which belongs to the family of tumor necrosis receptor proteins), nectin-1 (HveC) and nectin-2 (HveB) (two members of the immunoglobulin superfamily), and 3-O-sulfated HS (reviewed in Spear et al., 2000; Shukla and Spear, 2001). The binding of gD to one of these different receptors initiates fusion between the viral envelope and the cell membrane. The related Epstein–Barr virus (EBV), a transforming virus of the gammaherpesvirinae subfamily,
displays a marked B-cell lymphotropism associated with the expression of receptor CD21 (or CR2). EBV has been associated with a number of human proliferative diseases, including B-cells lymphomas, a clinical condition encountered in immunocompromised hosts (Krance et al., 1999). However, EBV can replicate in differentiated epithelial cells that do not express CD21, suggesting that other receptors may be involved in EBV infections (reviewed in Schneider-Schaulies, 2000).

Studies with vaccinia virus revealed that two different forms of the same virus can bind to different cellular receptors. Intracellular mature virus and extracellular enveloped virus are two antigenically and structurally distinct infectious virions that bind to unidentified and possibly different cellular receptors (Vanderplasschen and Smith, 1997). Other examples of the use of several receptor types by a virus include adenoviruses, coronaviruses, hepatitis C virus, influenza virus, measles virus, and rabies virus (references and additional examples in Table III and Section IV).

B. A Receptor Type Can Be Used by Several Viruses and Other Microbial Pathogens

Early evidence that viruses can share receptors was obtained in studies on interference in cell binding between different viruses (Lonberg-Holm et al., 1976). Many receptor types are used by viruses of different families, and several examples can be identified by examining Table III (Baranowski et al., 2001). A remarkable example is the shared use of coxsackievirus adenovirus receptor (CAR) by some human and animal adenoviruses and by some picornaviruses of different genera (Bergelson et al., 1997). These viruses belong to immeasurably distant families and are associated with unrelated diseases. Adenoviruses 2 and 5 are agents of respiratory disease in children, whereas coxsackieviruses B1 to B6 may be associated with febrile illness, meningitis, and some types of cardiopathies.

Other examples of shared receptors by viruses include cell surface components belonging to a wide range of receptor classes such as cell adhesion and cell–cell contact proteins (CD4, ICAM-1, integrins, MHC I), chemokine receptors (CXCR4), members of the complement control protein superfamily (CD46, DAF), low-density lipoprotein receptor and poliovirus receptor-related proteins, transporter proteins, and aminopeptidase N, as well as extracellular matrix components and sugar derivatives (references and additional examples in Table III and Section IV) (Baranowski et al., 2001).
Ubiquitous extracellular matrix components such as HS glycosaminoglycans are the preferential class of receptors employed by many viruses (Table III). The abundance of such molecules at the cell surface may facilitate initial contact with the virus, but subsequent interactions with more specific receptors may be needed. For many viral systems, attachment to HS is not an absolute requirement for infection, and cells devoid of HS can be infected, although with a reduced efficiency. Binding to heparin is a phenotypic trait displayed by several viruses propagated in cell culture, presumably because the interaction with HS residues may provide a selective advantage for viruses evolving in cultured cells (Section IV,B). Microbial pathogens that bind to cell surface HS proteoglycans include numerous intracellular (Borrelia burgdorferia, Chlamydia trachomatis, Listeria monocytogenes, Mycobacterium spp., Neisseria gonorrhoeae) and extracellular (Bordetella pertussis, Haemophilus influenzae, Helicobacter pylori, Staphylococcus aureus, Streptococcus spp.) bacteria, fungi, and other cellular parasites (Leishmania spp., Plasmodium spp., Trypanosoma cruzi) (reviewed in Bernfield et al., 1999).

Integrins have several features that make them attractive portals of entry for pathogens (reviewed in Krukonis and Isberg, 1997; Mims et al., 2001; Parkes and Hart, 2000). Interaction of adenovirus with αv integrins has been reviewed (Nemerow and Stewart, 1999; Nemerow, 2000) (Table II). A variety of bacterial pathogens also use integrin receptors to either adhere to or enter into host cells. Yersinia pseudotuberculosis is a gram-negative enteropathogen, which infects cells of the gut wall via binding to β1 integrins (Isberg and Leong, 1990), and Yersinia enterocolitica uses integrins to bind to cells of the intestinal epithelium. The interaction of Yersinia with host surface integrins induces activation of the cytoskeleton and the rearrangement of actin into pseudopods that engulf the bacteria (Krukonis and Isberg, 1997). A number of microbial pathogens, including B. pertussis, Coxiella burnetti, E. coli, Histoplasma capsulatum, Legionella pneumophila, Leishmania spp., and Rhodococcus equi, make use of integrins αMβ2 and αXβ2, also known as complement receptors (CR3 and CR4), to enter the macrophage and avoid the host microbicidal oxidative burst (Aderem and Underhill, 1999; Capo et al., 1999; Krukonis and Isberg, 1997; see review of cell entry mechanisms by diverse pathogens in Mims et al., 2001).

Another recently described example of a receptor type used by several microbial pathogens is CD81, a putative receptor for HCV (Pileri et al., 1998), which is required on hepatocytes for Plasmodium falciparum and yoelii sporozoite infectivity (Silvie et al., 2003).
C. Virus–Receptor Interactions Revealed by Structural Studies

The specific interactions between a viral protein or glycoprotein and receptor molecules are amenable to structural studies, and such studies are providing essential new information for the understanding of virus–receptor interactions. Enveloped viruses, such as HIV, attach to host cells by means of spike-like membrane glycoproteins, whereas most nonenveloped viruses, such as picornaviruses, attach by means of specialized domains integral to their capsids. Some viruses cannot be assigned to one of the two binding modes. For example, adenoviruses are nonenveloped particles, but have trimeric fibers projecting from the vertices of their icosahedral capsid, which terminate in a globular knob domain responsible for the specific interactions with the cellular receptors (Nemerow, 2000). The interaction of the surface hemagglutinin of human influenza virus with N-acetylneuraminic acid and the conformational alterations associated with the pH-dependent membrane fusion stand as one of the best characterized virus entry processes at both functional and structural levels. The entry of human influenza virus into human cells has been reviewed (Skehel and Wiley, 2000) and is not treated here except as an illustration of some concepts in following sections. Viral receptor-binding sites typically comprise highly conserved amino acid residues (Rossmann et al., 1985), a requirement that appears to guarantee survival of the virus. Early crystallographic studies of picornaviruses indicated that these and other viruses may shield their receptor-binding sites in cavities or surface depressions (“canyons”) that are inaccessible to antibody molecules, and this inaccessibility would confer viruses a selective advantage (Rossmann et al., 1985). Subsequent studies with other viruses have shown that receptor-binding sites may also occur in highly exposed regions of the viral surface (He et al., 2002; Hewat et al., 2000; Verdaguer et al., 1995). It may be predicted that when receptor-binding sites and neutralizing antibody-binding sites overlap at the virus surface, amino acid replacements needed for antibody escape may be deleterious as they affect receptor recognition. However, in line with the dynamics of RNA virus populations (Section II,B), this conflict is just one of the several instances in which negative selection may act to maintain variants at low levels and to rescue fit viruses through compensatory mutations. There is no strict requirement that surface residues involved in receptor recognition be entirely shielded from immune attack. Another proposed mechanism to compensate for possible adverse effects of amino acid replacements regarding cell
recognition is provided by the water buffer hypothesis, discussed at the end of this section.

Cryoelectron microscopy (cryo-EM) and image reconstruction methods allow direct visualization of virus–receptor complexes, which are usually too large and unstable to be amenable to analysis by high-resolution X-ray crystallography. In addition, when high-resolution structures of the virus and receptor domains are known, a pseudo-atomic model of the virus–receptor complex can be reproduced by docking the atomic structures together using the cryo-EM density map as a guide. Cryo-EM analyses of the major group rhinoviruses 16 and 14 (HRV16, HRV14) in complex with intracellular adhesion molecule-1 (ICAM-1 or CD54) (Kolatkar et al., 1999; Olson et al., 1993) and of the enteroviruses poliovirus type 1 Mahoney (PV1) in complex with poliovirus receptor (PVR or CD155) (Belnap et al., 2000; He et al., 2000; Xing et al., 2000), coxsackievirus A21 (CAV21) in complex with ICAM-1 (Xiao et al., 2001) and coxsackievirus B3 (CBV3) in complex with the coxsackie-adenovirus receptor (CAR) (He et al., 2001) have revealed how various receptors bind differently to structurally similar canyons found on the surface of virus particles (Fig. 1) (reviewed in Rossmann et al., 2002).

ICAM-1, PVR, and CAR are membrane-anchored glycoproteins that belong to the Immunoglobulin (Ig) superfamily. Their extracellular regions comprise five, three, and two domains, respectively, each with Ig-like folds consisting of a β barrel in which all β strands run parallel or antiparallel to the long axis of the domain (Fig. 1). In the three cases, the amino-terminal domain D1 contains the virus recognition site. This may reflect the steric capacity of the N-terminal Ig domain to penetrate into the picornaviral canyon. All the various receptor molecules utilized by picornaviruses are long, thin, and articulated at hinges between domains, and their properties are consistent with the requirement that the receptor be a molecule able to flex sufficiently to recognize additional sites on the viral surface once the first receptor site has been bound.

The interaction of ICAM-1 with the major group HRVs and with CAV21 and of PVR and CAR with PV1 and CBV3 indicates a common core of partially conserved residues on the canyon of those viruses (He et al., 2001; Rossmann et al., 2000; Xiao et al., 2001). However, the orientation of the receptor molecules is different for each virus–receptor complex (Fig. 1). The orientation of domain D1 is approximately radial in all cases except for poliovirus. The canyon of poliovirus is wider than that of CBVs and HRVs, allowing the tangential binding of PVR into the PV canyon (Belnap et al., 2000;
He et al., 2000; Xing et al., 2000). Therefore, the shape and size of the
canyon may be important factors that dictate the docking orientation
of the receptors. Receptor binding to major group HRVs and enteroviruses is localized within the canyon, at a site adjacent to a hydrophobic pocket within the VP1 β barrel containing an as yet unidentified “pocket factor.” Kinetic analyses of the virus–receptor interaction have shown for both HRVs (Casasnovas and Springer, 1995) and polioviruses (McDermott et al., 2000) that there are two distinct modes of binding whose relative abundance varies with temperature. The binding modes observed in the cryo-EM reconstructions are likely to be the most stable intermediates, although the nature of the interaction may depend on the specific virus–receptor complex.

In contrast to observations with the major group rhinoviruses, cryo-EM reconstructions of the complex between HRV2 and the first three ligand-binding repeats of the very low-density lipoprotein (VLDL) receptor revealed that the receptor for minor group rhinoviruses binds to a star-shaped dome on the five-fold axis and not in the canyon (Hewat et al., 2000). The footprint of V1-3 includes only residues of VP1. Close to the receptor attachment site is the virus-neutralizing immunogenic site A, located within the BC loop of VP1. Because the receptor-binding site of HRV2 is on a protruding domain of the capsid, it is not hidden from immune surveillance. It is remarkable that the receptor-binding site of major group HRVs is very similar to that of enteroviruses, which belong to a different genus, but is essentially different from that of minor group HRVs, which belong to the same genus. Minor group HRVs, which do not bind ICAM-1, are not obviously phylogenetically or structurally distinct from major group HRVs. Furthermore, HRV14, a major group serotype, is more distantly related to another major group serotype, HRV16, than to the minor group representative HRV2. Nevertheless, the residues of HRV2 corresponding to the ICAM-1 footprint on HRV14 or HRV16 lack the charge complementarity observed for major group HRVs (Kolatkar et al., 1999; Verdaguer et al., 2000). In addition, receptors of major group HRVs and enteroviruses both cause virus destabilization, unlike the receptor of minor group HRVs. This is an example of the adaptability to different receptors and the variety of receptor-binding sites exhibited by members of the picornavirus family. A comparison of receptor interactions and entry pathways of different picornaviruses suggests that those receptors that bind into canyons or pits of the capsid induce partial capsid destabilization through displacement of the “pocket factor,” which contributes to capsid stability. This type of receptor-mediated destabilization occurs in poliovirus, some coxsackieviruses, and the
major group rhinoviruses, which utilize molecules of the Ig superfamily as receptors. In contrast, those receptor molecules that do not bind into the canyon often do not contribute to virus destabilization and may condition the nature of subsequent steps in the entry process (a destabilizing, acid-mediated step in endosomes, etc.). Examples include the binding of VLDV receptor to the five-fold axis region of the minor group of HRV-2, echovirus 7 binding to DAF and FMDV binding to integrins or other receptor molecules (Table III). It has been suggested that viruses that do not use molecules of the Ig superfamily as receptors may be more variable at receptor recognition sites, facilitating shifts in receptor usage, with consequences for virus pathogenesis (Rossmann et al., 2002).

Other cryo-EM studies have provided indirect evidence about the location of the receptor-binding sites of reoviruses, alphaviruses, adenoviruses, and the picornavirus FMDV. For example, studies on the structure of VP4, the 88-kDa receptor recognition protein of rotavirus,
FIG 1. (A) Representation and comparison of the domain structure of ICAM-1 (CD54), the receptor for the major group rhinoviruses, and the poliovirus receptor (PVR or CD155). The immunoglobulin-like domains (labeled D1–D5 or D1–D3) are represented schematically by a circle closed by one or two disulfide bonds. The different Ig domains are linked by a flexible peptide chain. Hinge points are indicated by arrows. (B) Cryo-EM reconstruction showing the complex of HRV16 with its ICAM-1 receptor (from Kolatkar et al., 1999) virus is represented as a gray-scale surface. D1 and D2 domains of ICAM-1 are colored red. (C) Cryo-EM reconstruction of the complex of PV1(M) (gray) with PVR (yellow) (from Xing et al., 2000). (D) ICAM-1 and PVR-binding modes. Stereoview of the ICAM-1 (red) docked onto one icosahedral asymmetric unit of HRV16 (gray) using the cryo-EM map as a guide (PDB accession code 1D3E). The structure of PVR in complex with PV1 (M) (PDB accession code 1DGI) was superimposed for comparison (yellow). ICAM-1 contacts primarily the floor and south wall of the HRV16 canyon. In contrast, PVR overlaps the north and south walls, as well as the floor of the canyon, making additional contacts with the viral surface.
have documented that 60 dimers of VP4 ("spikes") extend 100 Å above the viral capsid surface in a uniform arrangement that appears to facilitate the binding interaction with cellular receptors (Prasad et al., 1988, 1990). The distal ends of the spikes are believed to contain the receptor-binding sites, as neutralizing antibodies that bind near the distal ends inhibit viral penetration (Prasad et al., 1990). Cryo-EM and three-dimensional reconstructions have been valuable tools for identifying putative receptor-binding sites on the E2 glycoproteins of two alphaviruses, Sindbis virus and Ross River virus (Smith et al., 1995). This strategy has also facilitated the examination of a highly mobile, Arg-Gly-Asp (RGD)-containing antigenic loop on the adenovirus 2 and 12 particles (Stewart et al., 1997; Chiu et al., 1999) and on the picornavirus FMDV capsid (Hewat et al., 1997; Verdaguer et al., 1999), which harbor integrin-binding sites (Fig. 2).

Detailed understanding of virus–receptor interactions will ultimately require structural analyses at high resolution. Crystallographic studies of interactions between FMDV O1 and HS have shown that the binding site is a shallow depression, of positive electrostatic charge, on the virion surface, contributed by the three external capsid

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**Fig 2.** (A) Ribbon representation of a CS8c1 pentamer subunit (VP1, blue; VP2, green; VP3, red). The mobile antigenic G-H loop of VP1 (residues 130–160) is highlighted in yellow in a position corresponding to that found in the complex with the neutralizing antibody SD6 (Hewat et al., 1997) and in cyan for the position determined in the crystallographic structure of the reduced FMDV-O1BFS (Logan et al., 1993). The RGD integrin-binding triplet is depicted as sticks. (B) The structure of FMDV in complex with heparin (Fry et al., 1999). Heparin coordinates for five sugars are shown as yellow ball and sticks.
proteins VP1, VP2, and VP3 (Fry et al., 1999) (Fig. 2). The crystal structure revealed that the heparin molecule makes ionic interactions with the viral residues using two sulfates (GlcN-2-2-N-SO$_3$ and GlcN-4-6-O-SO$_3$). Amino acid Arg-56 in VP3 plays a central role in organizing the sulfate groups, making interactions with both. Further polar residues that belong to all three major capsid proteins play a subsidiary role in heparin binding via bridging water molecules. The nonionic interactions observed include van der Waals stacking contact among, His-195 of VP1, the central L-iduronic acid (Idu) ring, and the apolar patch of GlcN-4. The virus surface remained essentially unchanged to accommodate the sugar, suggesting that the shape complementarity may contribute to receptor specificity.

Crystallographic studies of interactions between the HIV gp120 in complex with its receptors (Kwong et al., 1998; Wyatt et al., 1998) and the structurally unrelated adenovirus 12 knob with CAR (Bewley et al., 1999) allowed the identification of key determinants of receptor-binding specificity. These structures revealed that the receptor-binding faces are surface loops exposed to immune selective pressure. Both viruses bury a similar amount of surface area to create an atypical virus–receptor interface because of the presence of a shape mismatch in the surface topography that creates large cavities or channels. The lack of van der Waals interactions between the two protein surfaces may be partially compensated by the presence of solvent molecules filling the cavities. These water molecules would act as a bridge mediating hydrogen bonds between the backbone atoms of the viral protein and the receptor. The viral residues in contact with this water-filled cavity show important sequence variability, whereas surrounding this patch are highly conserved residues, the substitution of which may affect receptor binding. Thus, the observed interfacial cavities may serve a dual purpose as a water buffer between the viral protein and the receptor, and as molecular glue through the establishment of hydrogen bonds between backbone and conserved atoms. The tolerance for variation in the surface of the protein associated with this cavity produces a variational island, which is centrally located between regions required for receptor binding and may help the virus escape from antibodies. By using a noncomplementary interface that traps water molecules, the virus can maintain its receptor specificity while altering its amino acid sequence. This type of interface observed in two very different viruses such as HIV and adenovirus supports the water buffer hypothesis as a new general mechanism by which viruses can complete the first stage.
of infection successfully. The trapping of water molecules may allow receptor recognition to be less influenced by amino acid substitutions at the relevant sites of the virus surface, minimizing the adverse effects of high mutational pressure (Section II,B) on an essential step in the virus life cycle.

IV. QUASISPECIES AND SHIFTS IN RECEPTOR USAGE

A. Minimal Changes in Viral Genomes May Modify Receptor Recognition or Cell Tropism

There are several cases of minimal changes in viral genomes that result in the alteration of receptor specificity or affinity (Baranowski et al., 2001). Early studies with influenza virus identified key residues of virus hemagglutinin (HA) that confer specificity for sialic acid linked to galactose by either an α-2,3 or an α-2,6 linkage. Human H3 influenza viruses bind preferentially to sialic acid linked to galactose by an α-2,6 linkage, whereas avian and equine viruses show a preference for the α-2,3 linkage (Matrosovich et al., 1997; Rogers and Paulson, 1983). Human H1 and H2 viruses, as well as swine H1 viruses, also show preferentially a specificity for Neu5-Acα-2,3Gal. It was established that a single substitution in the 226 position of the HA changed the receptor specificity, which suggests that HAs that differ in the recognition of one sialic acid or another differ in amino acid 226 (Rogers et al., 1983a). Further studies indicated that two mutations in residues 226 and 228 of a human HA allowed replication in ducks. The mutations resulted in a receptor-binding site sequence identical to the known avian influenza virus sequences (Naeve et al., 1984). Other studies on receptor specificity in human, avian, and equine H2 and H3 influenza virus isolates showed that residues 226 and 228 are leucine and serine in human isolates and are glutamine and glycine in avian and equine isolates (Connor et al., 1994), confirming the key role of these two residues in determining the receptor specificity of influenza viruses.

Picornaviruses provide additional examples. Single replacements (Val-160 to Ile in VP1 or Met-62 to Ile in VP4) allow the primate-restricted P1/Mahoney strain of poliovirus to paralyze mice (Colston and Racaniello, 1995). The mutation in VP4 may render the virus accessible to a molecule that acts as a virus receptor and which is located on the surface of neurons of the mouse spinal cord. This molecule does not seem to be expressed in the mouse brain (Jia et al., 1999). A mutant
of encephalomyocarditis virus termed variant D is usually asymptomatic for rodents, but it can induce diabetes in mice through the destruction of pancreatic β cells. The diabetogenic variant includes amino acid replacement Thr-776 to Ala along the capsid pit, likely affecting receptor interaction and cell tropism (Bae and Yoon, 1993). Important determinants of tropism and pathogenesis of Theiler’s murine encephalomyelitis virus (TMEV) have been mapped at various positions on capsid protein VP1, including positions adjacent to the putative virus receptor-binding site. TMEV mutants harboring single amino acid substitutions at these particular VP1 positions displayed altered neurovirulence in susceptible mice and produced only mild symptoms during the acute phase of the infection or were highly attenuated regarding the development of chronic demyelinating disease (Jnaouï et al., 2002; Lin et al., 1998; McCright et al., 1999; Wada et al., 1994). Amino acid residues flanking the RGD integrin-binding motif of FMDV have been shown to influence the selectivity of integrin binding (Jackson et al., 2000a, 2002).

Research on the Edmonston vaccine strain of measles virus (MV) led to the identification of CD46 (a group of determinants whose function is to protect cells from complement-mediated lysis) as a receptor for this virus. Transgenic mice expressing CD46 may show typical pathogenic manifestations of the virus (Oldstone et al., 1999). Marmosets lacking CD46 were susceptible to several isolates of MV, but not to the Edmonston vaccine strain. Some natural isolates of MV do not enter cells through CD46, instead they use the signaling lymphocyte activation molecule (SLAM or CDW150), a glycoprotein expressed on some types of B and T lymphocytes, as a receptor (Hsu et al., 2001; Tatsuo et al., 2000a, 2000b). Although wild-type MV interacts with SLAM with high affinity, it can also interact with CD46 with low affinity (Masse et al., 2002). A single amino acid replacement in the surface hemagglutinin of the MV envelope determines the ability of the virus to bind CD46 with high affinity (Hsu et al., 1998). Additional receptors may be involved in MV infection (Hashimoto et al., 2002; Oldstone et al., 2002). Despite its relative antigenic stability, it has been estimated that MV mutates at an average rate of $9 \times 10^{-5}$ substitutions per base copied (Schrag et al., 1999). Therefore, point mutations of the type that led to binding of CD46 should occur frequently during MV replication.

Another example of minimal change in a viral genome that affects receptor recognition, tropism, and pathogenesis is afforded by substitutions in the E2 surface glycoprotein of Sindbis virus. The presence of Arg at position 172 impaired neurovirulence through a decrease of
binding to a receptor on neural cells (Tucker and Griffin, 1991); the opposite occurred when position 172 was a Gly. Also, position 55 of E2 is critical for binding to neurons under certain environmental conditions (in media with a similar ionic strength and degree of sulfation than found in interstitial fluid). While Gln-55 increases binding to neurons, His-55 (a substitution that entails a single nucleotide mutation) stabilizes the interaction between Sindbis virus and the surface of neural cells, contributing to a greater neurovirulence (Lee et al., 2002).

Studies on HIV coreceptor usage in cell culture revealed that the presence of either Lys or Arg at position 306, or Lys at position 322 within the variable V3 loop of gp160, led to a switch from using CCR5 to CXCR4 to enter cells (De Jong et al., 1992; Fouchier et al., 1995). In vivo, the change to using the CXCR4 coreceptor was also linked to a number of mutations that implied an acquisition of positive charges and loss of a N-glycosylation site, modifications that clustered between amino acids 190 and 204 of gp160. In other cases, substitutions to nonbasic amino acids at position 440 of gp160 were also linked to the R5 or X4 phenotypes (Hoffman et al., 2002). Furthermore, changes that confer a highly basic character (on loop V3) allow the virus to also use glycosaminoglycans as attachment factors for cell entry, which results in a 10-fold increase in viral production in cell culture (Zhang et al., 2002).

The cellular tropism of another lentivirus, feline immunodeficiency virus (FIV), may be affected by mutations in the V3 region of the surface glycoprotein SU. A change of cell tropism in cell culture was associated with replacement Glu-407 to Lys (Verschoor et al., 1995). Crandell feline kidney (CRFK) cells were transfected with an FIV molecular clone that was unable to infect them. However, high-dose DNA transfection resulted in the recovery of an FIV mutant capable of replicating in these cells. A single point mutation in the SU protein was responsible for this change in viral tropism (Vahlenkamp et al., 1997). In another study, a variant of FIV emerged after the passage of wild-type virus in cell culture. The variant displayed a phenotype markedly different from that of the parental virus, including the capacity to productively infect previously refractory cell lines and the induction of large syncytia. This phenotype could be attributed to the combination of two amino acid substitutions (Gln-224 to Pro, Thr-470 to Pro) in glycoprotein SU and to a premature stop codon that resulted in a truncated transmembrane protein (Lerner and Elder, 2000).

Cases of amino acid replacements affecting cell recognition have also been described in small and complex DNA viruses. Modifications of the
host range of paroviruses have been associated with amino acid substitutions on the viral capsid (Parrish and Truyen, 1999). Binding affinity to the transferrin receptor correlated only partially with the host range displayed by the virus (Hueffer et al., 2003). Remarkable changes in adenovirus (Ad) host cell tropism can be observed upon minimal alterations of virus fiber sequences. Amino acid substitution Glu-240 to Lys in the distal domain of Ad19p fiber conferred binding to human conjunctival cells, whereas the reverse substitution abrogated cell binding when introduced into the phylogenetically distant Ad37 (Huang et al., 1999). The presence of a Lys residue at position 240 of the adenovirus fiber was associated with an outbreak of epidemic keratoconjunctivitis.

Single amino acid substitutions in glycoprotein gD of herpes simplex 1 (HSV-1) can alter receptor preferences (reviewed in Spear et al., 2000). Although wild-type HSV-1 strains can enter cells via HveA (but not via human nectin-2), Rid mutants, which differ from the wild type by an amino acid substitution at position 25 or 27 of gD, can use human nectin-2 (but not human HveA). Studies with the swine alphaherpesvirus pseudorabies virus (PrV) further documented the important potential of herpesviruses to explore alternative mechanisms of cell recognition (Nixdorf et al., 1999; Schmidt et al., 1997, 2001). Although glycoprotein gD is critically involved in PrV entry into susceptible cells, the expression of gD is not required for direct viral cell to cell spread and PrV mutants deleted in the gD gene can be propagated in MDBK cells by cocultivating infected and noninfected cells. While infectivity was found to be strictly cell associated in early passages, repeated passaging resulted in the appearance of infectivity in the supernatant, reaching titers as high as $10^7$ PFU/ml. Mutations in viral glycoproteins gB and gH were found to correlate with the capacity of PrV to interact with alternative receptors and the development of a gD-independent mode of entry.

This by no means exhaustive list of examples underscores the biological relevance for RNA viruses of quasispecies dynamics regarding alterations in host cell tropism and pathogenic manifestations of viral infections. The weight of single nucleotide substitutions in the phenotype of RNA viruses must be considered in relation to the additional three parameters indicated in Table I (number of mutations per genome, virus population size, and genome length). The fact that a single replacement can have profound biological consequences for an RNA virus was one of the triggers of interest in quasispecies (review of early observations in Domingo et al., 1985). To what extent complex DNA viruses may incorporate mutations at some genomic sites
involved in cell recognition, with the flexibility of RNA viruses, is largely unknown. Because of several implications for the biology and uses of DNA viruses (discussed in Section V), this problem certainly deserves further investigation (compare with Section II,B).

B. Changes in Receptor Specificity upon Virus Evolution in Cell Culture and in Vivo

A modification of receptor specificity of FMDV was observed on the long-term passage of FMDV C-S8c1 [a biological clone derived from natural isolate C-Sta Pau Sp/70, representative of serotype C FMDV (Sobrino et al., 1983)] in BHK-21 cells. The parental clone C-S8c1 enters BHK-21 cells via an RGD-dependent integrin, as documented by both inhibition of cell entry by synthetic peptides and site-directed mutagenesis of an infectious cDNA clone to modify the RGD (Baranowski et al., 2000). Passage of FMDV C-S8c1 in BHK-21 cells resulted in the dominance of viruses with several amino acid replacements on the capsid surface (Fig. 3). These replacements resulted in an expansion of host cell tropism in cell culture, with the acquired capacity to infect a number of primate and human cell lines, a capacity that was absent in the parental C-S8c1 (Baranowski et al., 2000; Ruiz-Jarabo et al., 2002). As expected, some of the amino acid replacements conferred to the multiply passaged virus the capacity to bind heparin.

Fig 3. Flexibility in receptor usage by FMDV. Passage of FMDV in BHK-21 cells resulted in acquisition of amino acid replacements in the capsid, which expanded receptor usage (HS, heparan sulfate; integrin αvβ3; X, an unidentified receptor). Replacements are depicted as Van der Waals spheres in yellow (VP1, blue; VP2 green; VP3, red).
However, these viruses did not need to use HS as a receptor, as mutants deficient in heparin binding (that were selected from the multiply passaged quasispecies) were equally infectious in cell culture (Baranowski et al., 2000). Therefore, a third entry pathway, which is independent of HS and of RGD-dependent integrins, must have been acquired by FMDV C-S8c1 upon repeated passage in BHK-21 cells. The selective changes underlying such cell recognition conversion are not known (Baranowski et al., 2000, 2001).

The acquisition of a third entry pathway by FMDV did not abrogate a potential use of RGD-dependent integrins. Indeed, using the mutants from the multiply passaged FMDV C-S8c1 that were deficient in heparin binding, it was documented that RGD containing peptides (but not the same peptides with RGG instead of RGD) inhibited the infection of BHK-21 cells (Baranowski et al., 2000). Therefore, when HS binding was impaired, the virus used the RGD-dependent pathway for cell entry. These results prove that modifications in receptor recognition can be produced readily by modest evolutionary transitions and that a virus can maintain the capacity to penetrate the same cell type via three alternative entry pathways (Baranowski et al., 2000, 2001) (Fig. 3).

Some lines of evidence suggest that the use of alternative receptors for FMDV also occurs in vivo. Variants of FMDV harboring replacements within the RGD or at some neighboring positions documented to be critical for integrin binding have been isolated in vivo. One of the relevant experiments involved vaccination of 138 cattle with synthetic peptides representing B-cell and T-cell epitopes of FMDV C3 ARg-85 (Taboga et al., 1997; Tami et al., 2003). The animals were protected only partially as a result of the immune response to the synthetic peptide constructs and, upon challenge with virulent FMDV C3 Arg-85, several of them developed viremia and vesicular lesions. Virus from several lesions included amino acid substitutions within the RGD or at neighboring positions (Fig. 4). It is not clear whether such variant viruses would be able to reinitiate infection of cattle and, if they did, whether they would be stable through the completion of infectious cycles in vivo. Passage of FMDV O/CHN/90 (a type O FMDV used for vaccine production in China) in BHK-21 cells resulted in viruses that displayed altered tropism. Cell culture adaptation of the Cathay prototype foot-and-mouth disease virus from China results in altered tissue culture host range and pathogenic phenotype in pigs (Zhao et al., 2003). This altered virus caused mild disease in swine. Despite this evidence for flexibility in receptor usage, variants of FMDV selected to bind heparan sulfate were attenuated in
cattle (Sa-Carvalho et al., 1997). This and other observations suggest that RGD-dependent integrins may be a major class of receptors employed by FMDV in vivo (Neff et al., 1998), although the flexibility of the virus to modify receptor usage in vivo is an open question.

Variants of the arenavirus lymphocytic choriomeningitis virus (LCMV) arise during long-term persistent infections in mice (Ahmed et al., 1984; reviewed in Sevilla et al., 2002). Some of the variants had different biological properties, expected from the tissues from which they were isolated. One type of variant predominated in the central nervous system (CNS), whereas another type was dominant in lymphocytes and macrophages. Most CNS isolates caused acute infection when injected intravenously into immunocompetent adult mice. These variants evoked a potent immune response and infection was cleared with the active participation of anti-LCMV CD8+ cytotoxic T lymphocytes (CTLs). In contrast, most LCMV variants from lymphocytes and macrophages evoked a generalized immunosuppression in the animals. Interestingly, these critically different phenotypes

![Fig 4. Selection of FMDV variants in peptide-immunized cattle. In lesions from the immunized animals challenged by a cloned virus, variants with amino acid replacements within or near the RGD integrin receptor-binding triplet were isolated. The position of the RGD in an open turn between a β strand and an helical region of VP1 is indicated in the box (VP1, blue; VP2, green; VP3, red) above the sequence alignment, indicating the amino acid replacements.](image)
of LCMV relate to alterations in the affinity for α-dystroglycan, a receptor for LCMV, lassa fever, and clade C new world arenaviruses (Cao et al., 1998; Spiropoulou et al., 2002). A single amino acid substitution in the glycoprotein GP1 of LCMV alters its affinity for α-dystroglycan; high-affinity binding is associated with immunosuppression and viral persistence in mice, whereas low-affinity binding results in clearance of infection (Cao et al., 1998; Sevilla et al., 2000, 2002; Smelt et al., 2001).

HIV-1 coreceptor usage changes during infection in humans. Most primary isolates belong to the coreceptor specificity R5, but as infection progresses, dualtropic (R5X4) and X4 variants arise and often become dominant (Section III,A). The emergence of X4 HIV-1 strains in infected individuals has been associated with an increase in pathogenic manifestations and development of AIDS. Evolution of coreceptor usage (R5, multitropic, X4) seems to be the rule with HIV-1 subtypes A, B, D, and E during progressive disease. Subtype C apparently does not follow this trend in that the great majority of isolates obtained at different geographic sites are R5 monotropic regardless of the severity of the HIV infection (Fenyő, 2001). There are variants proven to be able to use other coreceptors as well, such as CCR2b, CCR3, CCR8, BOB, Bonzo, US28, and BLTR (B₄ leukotriene receptor), but their relevance for HIV infection in vivo is not clear (Fenyő, 2001). The host range of HIV-2 in human cells is similar to that of HIV-1, yet differences exist in the use of coreceptors. Primary isolates of HIV-2 use CCR5, but they may simultaneously use a wide variety of other coreceptors, such as CCR1, CCR2b, CCR3, CCR5, and BOB (Table III), despite the main coreceptor being CCR5. Variants that can use CXCR4 become dominant at late stages of the infection (Morner et al., 1999). Multitropic HIV-2 and SIV strains can infect CD4-negative cells (Liu et al., 2000). SIVsm is closer phylogenetically to HIV-2 than to HIV-1 and behaves similarly in several ways. As HIV-2, SIVsm can use a wide variety of different coreceptors, such as CCR3, CCR5, CXCR4, BOB, and Bonzo. They are multitropic, and several isolates can infect CD4-negative cells (this is also true for a small number of HIV-1 strains). Coreceptor usage, in contrast to what it is observed with HIV-1, narrows with time, and as the infection progresses, HIV-2 isolates tend to use only coreceptor CXCR4, and SIV only CCR5 (Vodros et al., 2001).

Feline leukemia virus A (FeLV-A) is the form of FeLV that is transmitted from cat to cat, and for this reason it is called the ecotropic form. It does not cause acute disease and is restricted to grow on feline cells. The receptor for this group of viruses has not been isolated. FeLV-Bs evolve from FeLV-A by recombination with endogenous FeLV-like
(enFeLV) envelope sequences, which results in a change to Pit1 receptor specificity. Pit1 is a classic multiple membrane-spanning receptor molecule. Recombinant forms of FeLV-B differ in the amount of envelope surface unit (SU) that is derived from enFeLV, and this may affect whether the virus can also use Pit2 (which has 62% structural identity with Pit1) as a receptor (Anderson et al., 2001; Sommerfelt, 1999; Sugai et al., 2001; Tailor et al., 1999b). Viruses that use Pit1 and Pit2 as receptors use the latter with lower efficiency (Boomer et al., 1997). FeLV-C and -T evolve by mutation of FeLV-A. In contrast to group A, groups B, C, and T FeLVs show an expanded host range, which includes infection of human cells (Sommerfelt, 1999; Sugai et al., 2001). FeLV-C viruses use a protein called feline leukemia virus subgroup C receptor (FLVCR), and the use of this receptor is associated with amino acid replacements within the 15 to 20 amino acids of the first variable region (V1) of SU. FeLV-C strains differ from FeLV-A in a Lys-to-Arg substitution in V1, but additional substitutions in SU must be involved in the use of FLVCR and the expanded host range (Brojatsch et al., 1992; Sommerfelt, 1999). FeLV-T (a T-cell tropic feline leukemia virus) is the first naturally occurring type C retrovirus that cannot infect cells unless both Pit1 and a second coreceptor or entry factor are present. This second receptor component, called FeLIX, is a cellular protein that is closely related to a portion of the FeLV envelope protein. This cellular protein can function either as a transmembrane protein or as a soluble component to facilitate infection (Anderson et al., 2000; Lauring et al., 2001). The most important feature to confer T-cell tropism seems to be an insertion of four to six amino acids in the C-terminal portion of SU, although additional amino acids could also be involved in this phenotype.

Friend virus is a nonneuropathogenic ecotropic murine leukemia virus. Variant PVC-211 isolated after 30 passages of Friend virus in BALB/c mice caused a rapidly progressive hind limb paralysis when injected into newborn rats and mice and displayed an expanded tropism in tissue culture. The two mutations responsible for the altered phenotype were Glu-116 to Gly and Glu-129 to Lys in the surface protein of the virus (Kai and Furuta, 1984; Masuda et al., 1992, 1996a, 1996b).

C. Nature of the Selective Forces That Drive the Selection of Virus Variants

It is very difficult to identify the selective pressures that act on viruses during an infectious process, not only because of the complexity of host influences involved, but also because selective pressures may vary
due to physiological alterations that often accompany the infection. HIV infections, with their erosive effects on the immune system, offer a relevant case. Adaptation of HIV to a changing cellular environment could contribute to the selection of variants with different cell tropism and different pathogenicity (Viscidi, 1999). This can be regarded as a positive selection directed by the immune system, resulting in modifications of host cell tropism of HIV (Crandall, 1999). For example, in the late stages of HIV infection, CD4^+ cells are depleted, and variants that use CD8 to enter CD8^+ cells arise (Saha et al., 2001). Thus, subpopulations of cells involved in the human immune response, whose abundance may be modified by HIV-1 infection, may in turn become a key selective force for HIV evolution (Crandall, 1999).

The relative availability of chemokine receptor ligands may also be a selective pressure involved in HIV evolution in vivo. Stromal-derived factor 1 (SDF-1), a chemokine that is a CXCR4 ligand, is expressed constitutively by mucosal epithelial cells at sites of HIV transmission and replication (Agace et al., 2000), and this may be one of the factors implicated in the selective transmission of R5 HIV-1 strains. Individuals whose peripheral blood lymphocytes produce high levels of CCR5 ligands (such as RANTES, MIP1α, and MIP1β) are relatively resistant to infection (Garzino-Demo et al., 1998; Paxton et al., 1996; Zagury et al., 1998). Selection by receptor ligands is also supported by experiments using a mouse model in which a modified form of RANTES, a natural ligand for CCR5, selected HIV mutants that used CXCR4 as a coreceptor (Mosier et al., 1999). Also, AMD3100, a bicyclam that is a selective antagonist of CXCR4, led to the complete suppression of X4 variants in cell culture and prevented the switch from the less pathogenic R5 HIV to the more pathogenic X4 strains (Este et al., 1999).

Multiplication in a given type of cell may also be a likely trigger of a tropism alteration. Measles virus isolated on marmoset B-cell lines infected some primate B- and T-cell lines and retained pathogenicity for monkeys. This was not the case for measles virus isolated on Vero cells, as such isolates manifested a different tropism and host range (Tatsuo et al., 2000a, 2000b), suggesting that the type of cell used for measles virus isolation exerted a selective force on the virus. Likewise, the host cell selected an avian retrovirus variant with an expanded host range, consisting of recognition of a receptor on chicken cells and a distinct receptor on quail cells (Taplitz and Coffin, 1997). This evidence must make virologists aware that when they isolate a virus from a biological specimen by passage in an established cell line, a virus with different biological properties (cell tropism or other) than
the natural virus may be selected. Variants of LCMV with profoundly different biological properties have been isolated from different organs of infected mice (Section IV,B), emphasizing the impact of quasispecies dynamics during infections in vivo (Sevilla et al., 2002). In most cases summarized in this section, the precise nature of the selective force that acts to perturb mutant distribution is not well understood in molecular terms. In many other cases, even the types of selective constraints that mediate changes in host cell tropism are not obvious. This is perhaps one of the areas of research in evolutionary virology that necessitates efforts because of the multiple implications of variations of host cell tropism for the control of viral disease. Model experiments in cultured cells (that attempt to match the type of cells found in vivo), with the aim of relating variations in the nucleotide sequence (and in the corresponding structure of encoded proteins) with alteration in cell recognition, may provide information on the molecular basis for tropism specificity and tropism changes.

V. BIOLOGICAL IMPLICATIONS OF MODIFICATIONS IN RECEPTOR USAGE

A. Coevolution of Receptor Usage and Antigenicity

Structural studies have shown in many cases that there is an overlap between the amino acid residues on a viral capsid or envelope that are involved in cell recognition and those that recognize neutralizing antibodies (Section III,C) (Table IV). The structure of the complex between the G-H loop of VP1 of FMDV with monoclonal antibody 4C4 has clear resemblance with the complex that can be modeled between the virus and its integrin receptor (Fig. 5). A change in receptor specificity could involve a modification in binding to antibodies or vice versa. Furthermore, an antigenic domain that coincides with a receptor-binding site may lose constraints for variation once a different receptor that interacts with other capsid residues becomes operational. The latter possibility can be illustrated with results obtained with FMDV.

The capacity of FMDV to use multiple alternative receptors for entry even into the same cell type (Section IV,C) confers to this virus the potential to modulate receptor usage in response to selective constraints (Baranowski et al., 2000), which has considerable implications for the evolution of virus antigenicity. Because the RGD triplet located at the surface G-H loop of capsid protein VP1 is a key part of several epitopes recognized by neutralizing antibodies (Mateu, 1995; Verdaguer et al., 1995), dispensability of the RGD integrin-binding
### TABLE IV
**Examples of Overlap between Antibody and Receptor-Binding Sites in Viruses**

| Viral system      | Main observations                                                                                                                                 |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| **Adenoviridae**  |                                                                                                                                                  |
| Adenovirus        | Synthetic peptides representing fiber knob of Ad-3 present cell receptor-binding sites and antigenic epitopes (Liebermann *et al*., 1998)              |
| **Coronaviridae** |                                                                                                                                                  |
| Murine coronavirus | Mab recognized epitopes involved in the binding of virions to cellular receptors (Kubo *et al*., 1993, 1994)                                        |
| **Flaviviridae**  |                                                                                                                                                  |
| BVDV              | Anti-idiotype antibodies mimicking viral antigens bind to cellular receptors (Xue and Minocha, 1993; Minocha *et al*., 1997)                         |
| Dengue virus      | Amino acid residues critical for mouse neurovirulence are involved in antibody binding (Hiramatsu *et al*., 1996)                                     |
| Yellow fever virus| Amino acid residues critical for virus neurotropism are involved in antibody binding (Jennings *et al*., 1994)                                       |
| **Hepadnaviridae**|                                                                                                                                                  |
| Duck hepatitis B virus | Residues critical for virus neutralization are involved in the interaction with cells (Tong *et al*., 1995; Li *et al*., 1996; Sunyach *et al*., 1999) |
| Hepatitis B virus | Anti-idiotype antibodies mimicking viral antigens bind to cellular receptors (Petit *et al*., 1992; Hertogs *et al*., 1994; Budkowska *et al*., 1995)     |
|                   | Anti-idiotype antibodies mimicking cellular structures bind to small hepatitis B surface antigen (Neurath *et al*., 1986)                          |
|                   | A synthetic peptide analogue is recognized by both cell receptors and anti-HBV antibodies (Neurath *et al*., 1986)                                  |
| **Herpesviridae** |                                                                                                                                                  |
| BHV-1             | Anti-idiotype antibodies mimicking viral antigens bind to cellular receptors (Thaker *et al*., 1994; Varthakavi and Minocha, 1996)                   |
| HCMV              | Anti-idiotype antibodies mimicking viral antigens bind to cellular receptors (Keay *et al*., 1989; Keay and Baldwin, 1991)                           |
| HSV               | Anti-idiotype antibodies mimicking viral antigens bind to cellular receptors (Huang and Campadelli-Fiume, 1996)                                      |
|                   | Overlap between major neutralizing antigenic site and a receptor-binding domain of gD (Whitbeck *et al*., 1999)                                        |

(continues)
Orthomyxoviridae

| Viral system | Main observations |
|--------------|-------------------|
| Influenza virus | Amino acid residues within the sialic acid-binding pocket of virus hemagglutinin are accessible to neutralizing antibodies (Stewart and Nemerow, 1997) |
| | Antigenic and hemagglutinin variants selected upon egg adaptation (Robertson et al., 1987) |
| | Low-affinity neutralizing antibody response selected for receptor-binding variants of influenza virus HA (Laeeq et al., 1997) |
| | Amino acid changes at residues involved in antibody binding can modulate the hemagglutinating activity of influenza C virus (Matsuzaki et al., 1992) |
| | Passage of influenza C virus in HMV-II cells resulted in selection of antigenically distinct variants, which have an advantage in binding to the cell surface receptors (Umetsu et al., 1992) |
| | Hemagglutinin variants displayed increased resistance to neutralization (Nohinek et al., 1985) |
| | The receptor-binding specificity of the hemagglutinin can markedly influence the antigenic analysis obtained with monoclonal antibodies in HI tests (Yamada et al., 1984) |

Picornaviridae

| Viral system | Main observations |
|--------------|-------------------|
| FMDV | Overlap of integrin- and antibody-binding sites (Verdaguer et al., 1995) |
| | Monoclonal antibodies selected variants with altered integrin recognition (Martinez et al., 1997; Baranowski et al., 2000; Ruiz-Jarabo et al., 2003) |
| | Adaptation to cell culture may result in antigenic variation (Curry et al., 1996; Sa-Carvalho et al., 1997; Baranowski et al., 2000) |
| | Some amino acid residues involved in heparin-binding map at antigenic sites (Sa-Carvalho et al., 1997; Fry et al., 1999; Baranowski et al., 2000) |
| | Antigenic variants with altered receptor specificity can be selected in vivo (Taboga et al., 1997; Tami et al., 2003) |
| Poliovirus | Receptor recognition influenced by residues of antigenic sites (Murray et al., 1988; Harber et al., 1995) |
| | The exposed BC loop of capsid protein VP1 plays a critical role in receptor interactions in the mouse central nervous system (Yeates et al., 1991) |
| HRV | Neutralizing antibody to human rhinovirus 14 penetrates the receptor-binding canyon (Smith et al., 1996) |

(continues)
motif for cell entry expanded the repertoire of antigenic variants of FMDV greatly and prompted the isolation of viable antibody-escape mutants with profoundly altered antigenicity that contained mutations at the RGD triplet (Martinez et al., 1997; Ruiz-Jarabo et al., 1999). Mutants with RED, RGG, and even GGG instead of RGD were isolated. Viable viruses were obtained when the relevant mutations were engineered in an infectious clone with the sequence context of the capsid of the multiply passaged C-S8cl; RNA transcripts did not give rise to variable virus when the same mutations were engineered in the sequence context of the parental clone C-S8cl (Baranowski et al., 2000). Studies with FMDV containing RGG showed impaired reactivity with monoclonal antibodies specific for the relevant antigenic sites and with polyclonal antibodies raised in swine and guinea pigs using the wild-type virus as immunogen (Ruiz-Jarabo et al., 1999).

| Viral system         | Main observations                                                                                                                                 |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| TMEV                 | Neutralization epitopes map close to the putative receptor binding region (Sato et al., 1996)                                                      |
|                      | Mutations associated with adaptation to some culture cells map in antigenic sites (Jnaoui and Michiels, 1998)                                      |
| Reoviridae           | Anti-idiotypic antibodies mimicking viral antigens bind to cellular receptors (Xu et al., 1997)                                                   |
| Bluetongue virus     | Anti-idiotypic antibodies mimicking viral antigens bind to cellular receptors (Co et al., 1985a; Gaulton et al., 1985; Williams et al., 1988, 1989, 1991b) |
| Reovirus             | Anti-idiotypic antibodies mimicking viral antigens bind to cellular receptors (Hanham et al., 1993)                                               |
| Rhabdoviridae        | Anti-idiotypic antibodies mimicking viral antigens bind to cellular receptors (Ubol and Griffin, 1991; Wang et al., 1991b; Strauss et al., 1994)     |
| Rabies virus         | Amino acid residues critical for virus neurotropism are involved in antibody binding (Coulon et al., 1998)                                       |
| Togaviridae          | Anti-idiotypic antibodies mimicking viral antigens bind to cellular receptors (Smith et al., 1995)                                               |
| Sindbis virus        | Several antibodies bind to regions of the virions implicated in cell-receptor recognition (Smith et al., 1995)                                    |
| Ross River virus     | Several antibodies bind to regions of the virion implicated in cell-receptor recognition (Smith et al., 1995)                                    |
The genomic changes that can endow FMDV with the capacity to use alternative mechanisms of cell recognition (Section V.A) are minimal, and viruses with alterations in the RGD and with unusual receptor-binding specificities are likely to be present in the mutant spectrum of FMDV replicating in the animal host (Taboga et al., 1997) (described in Section IVB). The antigenic alterations produced by replacements at or around the RGD suggest that the emergence of these particular FMDV mutants in vivo was the result of selection of antigenic variants that escaped neutralization by anti-FMDV antibodies in peptide-vaccinated cattle (Fig. 4). A study analyzing the genetic changes selected during the adaptation of FMDV to guinea

![Figure 5](image-url)
pig documented the progressive dominance of an unusual amino acid replacement (Leu-147 to Pro) affecting the antigenic structure of the G-H loop of capsid protein VP1 in the course of adaptation of FMDV to this new host (Núñez et al., 2001). Construction of infectious cDNA clones of FMDV confirmed that this Leu-147 was essential for virus interaction with integrin receptor molecules expressed in BHK cells and various other cell lines used commonly to propagate FMDV and that mutants with Pro-147 do not form plaques on BHK-21 cells (Núñez et al., 2001). The isolation of FMDV mutants displaying altered cell tropism in association with antigenic changes illustrates the important adaptive potential of FMDV and the capacity of this virus to explore new antigenic/receptor recognition structures upon replication in its hosts.

A mutant of rabies virus harboring changes Lys-330 to Asn and Arg-333 to Met at antigenic site III of its surface glycoprotein manifested a modification in both cell tropism and antigenicity (Coulon et al., 1998). This double mutant, selected by the successive use of two neutralizing antiglycoprotein monoclonal antibodies, was not pathogenic for adult mice and could not penetrate the nervous system either by the motor or by the sensory routes. In vitro experiments showed that the double mutant was able to infect BHK cells, neuroblastoma cells, and freshly prepared embryonic motoneurons, albeit with a lower efficiency than the parental strain CVS. Upon further incubation at 37°C, the motoneurons became resistant to infection by the mutant while remaining permissive to infection by the CVS strain (Coulon et al., 1998). Thus, rabies virus can use different types of receptors: a molecule that is expressed ubiquitously at the surface of continuous cell lines and that is recognized by both CVS and the double mutant and a neuron-specific molecule that is not recognized by the double mutant.

One of the first lines of evidence of coevolution of receptor usage and antigenicity in viruses was documented with human influenza type A with single amino acid replacements in the hemagglutinin, which modified receptor specificity or receptor-binding affinity (Robertson et al., 1987; reviewed in Skehel and Wiley, 2000). Additional cases of an overlap of receptor-binding and antigenic sites are given in Table IV.

B. Use of Soluble Receptor Analogs and Receptor Ligands, and Selection of Resistant Viruses

Ever since viral receptors were discovered, antiviral therapies have been designed based on the administration of soluble receptors and receptor ligands. The discovery that chemokine receptors act as cofactors essential for HIV entry into target cells identified new targets for
antiretroviral therapy. Viral entry can be inhibited in vitro by the natural ligands for CXCR4, the CXC chemokine SDF-1, and CCR5, the CC chemokines RANTES, MIP-1\(\alpha\) and MIP-1\(\beta\). Several peptidic compounds have been identified as CXCR4 antagonists that display anti-HIV activity, and the HIV-1 tat protein has been described as a “natural” CXCR4 antagonist with anti-HIV-1 activity. The bicyclam derivatives are among the most potent and specific CXCR4 antagonists described and they block X4 HIV replication very efficiently (De Clercq and Schols, 2001). Mutants resistant to CCR5 antagonists have been isolated. This resistance is not mediated by a change in coreceptor usage, but rather by the ability to use CCR5 despite the presence of the inhibitor (Trkola et al., 2002). However, much remains to be learned about the possible physiological impact of the administration of receptor analogs and receptor ligands. The multitude of different receptors involved in HIV entry into cultured cells and their important physiological roles in vivo, together with their implications in distinct pathogenic processes, have added further complexity to this field of research (Heveker, 2001).

One of the most obvious potential difficulties with the use of receptor analogs as an antiviral therapy is the selection of soluble receptor-resistant mutants from the quasispecies swarms. This was illustrated with the avian sarcoma-leukosis virus subgroup A (ASLV-A), in which virus with a six amino acid deletion in the heterogeneous region 1 of the surface protein (SU) was selected by a soluble receptor in cell culture (Holmen and Federspiel, 2000). In some other instances, soluble receptors were capable of inducing conformational changes in viral envelopes, and nonsusceptible cells became susceptible to viral infection. In the case of ASLV-A, soluble Tva could activate SU and convert it to a fusogenic conformation-competent form capable of mediating the fusion of viral and cellular membranes, even when the membranes did not harbor viral receptors (Damico and Bates, 2000). This has also been observed with murine leukemia viruses (Lavillette et al., 2000), with mouse hepatitis virus (Taguchi and Matsuyama, 2002), and with HIV-1 in that CD4 on the surface of a cell could be used by the virus to fuse to neighboring cells, provided the latter had a coreceptor (even in the absence of CD4) (Speck et al., 1999).

There is no solid reason to assume that the selection of viruses resistant to receptor analogs or to receptor ligands should be substantially more difficult than the selection of antibody- or inhibitor-resistant mutants in the course of viral replication, selections that have been documented profusely not only for HIV but for many other RNA viruses (Table I) (reviewed in Domingo et al., 2001). From the
mechanisms exploited by viruses to escape antibodies, CTLs, or inhibitors and from the molecular basis of fitness gain, a number of pathways for the selection of mutants resistant to soluble receptors (or analogs) are plausible. Viral mutants could be selected that display an increased affinity for the receptor attached to the cell surface, and not for its soluble form (or analog). A completely independent pathway could be the selection of mutants able to use an unrelated receptor, as this has already been described even for viruses not subjected to the presence of receptor analogs (Section V,A). Yet another possibility is the selection of mutants capable of binding both the cellular receptor and the authentic receptor on the cell, with a slight affinity bias to permit cell entry, among other conceivable variations of these mechanisms.

If an antiviral therapy based on soluble receptors, receptor analogs or receptor ligands is to be pursued, it may be necessary—in line with antiviral strategies based on combination therapy—to administer simultaneously several types of soluble analogs when potential alternative receptors for the virus have been identified. An obvious problem is the possible physiological impact of such a combination of receptors or their analogs. These difficulties should also be evaluated carefully if strategies employing combinations of inhibitors, receptor analogs, and immunotherapy are considered. Viruses have learned to confront many selective constraints over extended periods of coevolution with their hosts (Sections I and V) and it is not known whether artificial constraints may be found that would suppress viral replication in a way as to prevent selection of escape mutants.

C. Emergence and Reemergence of Viral Diseases

The emergence and reemergence of infectious diseases are increasing concerns for human and animal health and for a number of economically significant activities related to agriculture and farming. More than 40 emergent and reemergent human viral diseases have been described over the last two decades, and the adaptive potential of viruses, including changes in host range, undoubtedly has played a very relevant role (reviewed in Brault et al., 2002; Leitmeyer et al., 1999; specific recent examples in Morse, 1993; Morse, 1994). However, a complex set of interconnected influences are involved in viral disease emergence. These include environmental and climatic changes, socioeconomic and political factors, agricultural practices, and technological developments. The recent reemergence of the foot-and-mouth disease in Europe illustrates how a number of rather unpredictable and complex factors can produce a devastating animal
disease epizootic (Samuel and Knowles, 2001; Sobrino and Domingo, 2001). Additional examples have been documented and discussed (Domingo et al., 2001; Mahy, 1997; Morse, 1993, 1994; Murphy and Nathanson, 1994). These multiple influences have, as a net result, an alteration of viral traffic and of the demography of viral vectors and susceptible hosts (Morse, 1994), with the many implications of alterations of viral ecology (Hurst, 2000).

A majority of the emergent and reemergent viral diseases are associated with RNA viruses, and frequently those displaying high recombination rates. Examples are the expansion of dengue fever and dengue hemorrhagic fever (Gubler, 1998), recent outbreaks of poliomyelitis (Kew et al., 2002), and the appearance of severe acute respiratory syndrome (SARS). The emergence of HIV stands as the most significant introduction of a retrovirus into the human population, likely from several simian virus ancestors, and the virus is evolving continuously through mutation and recombination (Crandall, 1999). Poliovirus variation has been signaled as a major problem for the successful eradication of poliovirus (Nomoto and Arita, 2002). Furthermore, poliovirus and the C-cluster coxsackie A viruses are grouped together based on phylogenetic analyses. It has been suggested that if polioviruses were eradicated, some coxsackie A viruses may have an opportunity to modify their receptor specificity from ICAM-1 to CD155 (Table II) and evolve toward a polio-like virus (Nomoto and Arita, 2002).

Avian and equine hemagglutinins bind preferentially to N-acetyl sialic acid linked to galactose by α-2,3 linkages (Neu5-Acα-2,3Gal), whereas most human HAs bind preferentially to Neu5-Acα-2,6Gal. Changes in binding sites have been reported to cause host range switches among different hosts (Aytay and Schulze, 1991; Matrosovich et al., 1997, 1999, 2000; Naeve et al., 1984; Rogers et al., 1983a, 1983b). The receptor-binding specificity of the avian influenza hemagglutinin was altered early after the transmission to humans and pigs (Matrosovich et al., 2000), constituting a case of positive selection by the recipient host.

Modifications in host cell tropism need not be associated with a modification in receptor specificity. As discussed in Section VA, adaptation of a FMDV clone to the guinea pig resulted in the dominance of FMDV mutants with replacement Leu-147 to Pro in the G-H loop of VP1, which altered integrin recognition by the virus. However, the critical amino acid replacement for FMDV to cause disease in guinea pig was located in nonstructural protein 3A (Núñez et al., 2001). It is not known what is the actual contribution of Pro-147 in VP1 to the
pathogenesis of FMDV in guinea pigs, but this model study with FMDV illustrates yet another possibility in a cascade of adaptive events: a virus may emerge as pathogenic in a new species without a strict requirement for a shift in receptor recognition, but in the course of replication in the new host, additional mutations that entail modifications in receptor recognition become permissible and perhaps favored (Núñez et al., 2001).

D. Gene Flow and Gene Therapy: Role of Viruses

The growing list of complete genomic nucleotide sequences of many cellular organisms and viral genomes suggests that all life forms share some basic functional motifs (Mount, 2001). No viral functions that depart in any outstanding way from similar cellular functions have been identified. This includes similarities between viral and cellular proteins involved in genome replication, proteolytic activities, and general patterns of genome organization and expression. These important advances in molecular genetics suggest that the exchange of modules, together with mutation, has contributed to the coadaptation of cells and autonomous replications over long evolutionary periods (DeFilippis and Villarreal, 2001; Domingo, 2003; Domingo et al., 1999; Gorbalenya, 1995; Holland and Domingo, 1998). In cases in which viruses infect multiple host species, convergent phylogenies of viruses with their host can sometimes be seen (Gibbs and Weiller, 1999; McGeoch and Davison, 1999). Some of the features of variation of cell tropism discussed in Sections III,A and IV,A may not be foreign to differentiated organisms. The insertion of two amino acids into ectodysplasin—a member of the tumor necrosis-binding family—resulted in a change of its cellular receptor specificity, and the differential expression of the two forms of ectodysplasin plays a role in epidermal morphogenesis (Yan et al., 2000). Not only functional modules but also biological strategies are shared among viruses and cells.

In the case of viruses, the capacity to use alternative receptors and to change receptor specificities by modest genetic variation (involving short genetic distances) may represent an adaptation of viruses to cope with increasingly differentiated organisms. The absolute requirement of a cellular environment for virus replication (one of the definitive features of viruses; Section II,A) implies a permanent coexistence of cellular and viral genomes. The uptake of cellular genes by viruses has been documented in transducing bacterial viruses, RNA and DNA tumor viruses and, as remarkable cases, in cytopathic variants of the flavivirus bovine viral diarrhea virus, and defective viruses that have acquired host
sequences by nonhomologous recombination events (examples reviewed in Domingo et al., 1999; Bushman, 2002; Domingo 2003).

The elucidation and interpretation of the complete genomic sequences of an increasing number of prokaryotic and eukaryotic organisms indicate that a substantial part of many of these genomes consist of mobile genetic elements or their relics (reviewed in McClure, 1999; Mount, 2001; Bushman, 2002). It has been estimated that this part of the human genome is 40% of the total! The process by which cells from one organism have captured DNA fragments from another organism is known as horizontal gene transfer. This transfer appears to be particularly frequent in prokaryotes, but it does also occur in eukaryotes. In addition to virus infection, lateral gene transfers are mediated by conjugative plasmids and several classes of mobile elements. Transfers are affected by viral infection (transduction), conjugation, and transformation. The transposition of sequences may occur within the DNA of the same cell.

Virus receptor specificity and its variations (as discussed in previous sections) may facilitate the access of cellular genes to specific cell types in tissues and organs. The human body comprises 50 trillion cells organized in hundreds of organs, tissues, and classes of cell subpopulations. Viruses may spread differentially within organs. As an example, the dissemination of neurotropic viruses in the brain is used increasingly to define connections among subsets of neurons (Card, 2001). To complete its incorporation into a new host cell, the transferred DNA must integrate into the recipient chromosome by some type of molecular recombination event. In this respect, integrative bacteriophages and retroviruses provide the adequate mechanisms as an integral part of their life cycles (Coffin et al., 1997). The retroviral reverse transcriptases must jump strands to complete the synthesis of cDNA, and this property may favor the capture of cellular sequences for transfer to other cells. The mechanisms that mediate the integration of lysogenic bacteriophage DNA, retroviral cDNAs, and a class of transposons termed non-LTR retrotransposons are different, as are the proteins involved (reviewed in Ptashne, 1992; Bushman, 2002; Coffin et al., 1997). Nonidentical requirements for integration may have broadened the possibilities of DNA flow among cells in the course of evolution. About 8% of the human genome appears to have been derived from retroviral-like sequences. Retroviral-mediated gene transfer can have deep phenotypic consequences for cells, such as a variety of disease manifestations in differentiated organisms (McClure, 1999), including alterations of cell growth control, and in some cases of infertility in humans (Sun et al., 2000). Estimates using mice suggest that 40% of
DNA insertion events may have phenotypic consequences for the animal (reviewed in Bushman, 2002).

This brief account of the extensive evidence of lateral gene transfers in the cellular world underscores the profound evolutionary implications of the rapid changes in receptor specificities that viruses can undergo. Indeed, many of the viruses referred to in previous sections may infect multiple host species, and through genetic change they may acquire the potential to infect other host species, therefore permitting gene transfers among distant host species and, perhaps occasionally, also among taxa. Many lines of evidence (too numerous to be reviewed here) have clearly documented DNA transfers among distant domains of life (bacteria to plants, bacteria to animal cells, etc.) (reviewed in Bushman, 2002). It is not known how many DNA transfer events are initiated and never completed, and of those in which the transfer is completed, how many lead to viable genotypes. Perhaps the sorting of viable recombinant genomes is parallel on long evolutionary times to the sorting of viable RNA genomes subjected to mutational pressure that occurs over infinitely short evolutionary time scales (Section II,B). In both cases, negative selection may eliminate many nascent mutant and recombinant forms to leave a surviving minority endowed with a minimally required relative fitness value. Genetic disease in differentiated organisms may be viewed as an unavoidable price to pay to ensure a source of genome fluidity for long-term survival.

Gene therapy is a growing field of research in molecular medicine, whose aim is the supply of a functional gene into human cells for the treatment of inherited or acquired genetic disorders (Lemoine, 2000). The application of DNA recombinant techniques, together with an understanding of the life cycle of viruses, has permitted the development of virus vectors for the transport of foreign genes into target cells. This technology takes advantage of one of the natural tendencies of viruses to act occasionally as agents of horizontal gene transfers, although for therapeutic purposes, viruses must be modified carefully to act as safe and efficient vectors. Viruses that have been used as gene vectors include adenoviruses, parvoviruses (adeno-associated viruses), herpesviruses, retroviruses (simple and complex lentiviruses such as HIV), SV40, and some RNA viruses such as Sindbis virus (reviewed in Pfeifer and Verma, 2001). Viral vectors are engineered to have the foreign "transgene" replace deleted viral genes, while maintaining the cis-acting elements to form virions and to integrate the transgene. Packaging cells or plasmids provide in trans those proteins required for particle formation. A number of safety features (that necessitate
different approaches for the different vector types) must be introduced to avoid the spread of replication-competent viruses in the organism, cytotoxic effects, or undesired gene damage due to unrestricted and random integration of transgene into human DNA. Important difficulties encountered in viral-mediated gene therapy are the immune response (antibody or cellular responses evoked by the vector or preexistent in the human recipient), vector stability, dependence of the transduction efficiency on the metabolic state, and cell cycle phase of the target cells, among others. From the point of view of targeting the desired target cells, the receptor specificity of the viral vectors is an essential element of vector safety and efficacy, and many of the considerations discussed in previous sections concerning variations in receptor specificity are relevant to the design of viral vectors, both regarding the basal amplitude of host range afforded by each vector type and the possibilities of engineered alterations in the vector surface proteins to attain a more defined cellular specificity. Vectors based on adeno-associated virus type 2 or retroviral pseudotypes containing the surface glycoprotein of vesicular stomatitis virus display a broad host cell tropism. In contrast, vectors based on murine leukemia virus or HIV-1 often show restricted tropism, imposed by the receptors recognized by their surface envelope proteins (receptor types utilized by some viruses used for vector construction are listed in Table III). For some vectors, the host range can be expanded by replacing surface proteins (or subdomains) by heterologous counterparts, such as heterologous envelope proteins of retroviral vectors (Pfeifer and Verma, 2001).

VI. CONCLUSIONS AND OVERVIEW

The picture beginning to form from genome analyses of viruses, unicellular organisms, and multicellular organisms is that viruses have shared functional modules with cells. A process of coevolution has probably involved exchanges of genetic information between cells and viruses for long evolutionary periods. From this point of view, it is perhaps not surprising that present-day viruses show flexibility in receptor usage and a capacity to alter through mutation their receptor recognition specificity. Shifts in receptor usage have been documented for a variety of DNA and RNA viruses, and the list is increasing continuously. This is just one facet of the fluidity exhibited by cells and viruses regarding exchanges and variation of their genetic material. This is particularly spectacular for RNA viruses because they cannot replicate without producing mutants. The mutation rates, mutation
frequencies, and population dynamics of DNA viruses during short-term evolution have been investigated far less than those of RNA viruses. For this reason, it is not possible to anticipate at present whether some DNA viruses may share with RNA viruses a rapid adaptation to using new receptors. It is possible that for the complex DNA viruses, due to a likely limited tolerance to generalized high mutation rates, modifications in receptor specificity will be less frequent than for RNA viruses, albeit with similar biological consequences once they occur.

RNA viruses consist essentially of pools of mutants, and minority components of such pools may rise to dominance under appropriate environmental conditions. Just by exploring constellations of modest numbers of amino acid substitutions in their capsid or envelopes, viruses can extend the range of receptors they can utilize or cointilize to enter the same cell type, a means for the virus to secure its survival. Different receptors, or allelic forms of one receptor, may be used with different efficiency, and receptor affinities are probably modified by mutation and selection. Receptor abundance and its affinity for a virus may modulate not only the efficiency of infection, but also the capacity of the virus to diffuse toward other sites of the organism.

The acquired ability of an RNA virus to enter a new cell type may have yet another consequence for the biological behavior of the virus progeny due to the new intracellular environment encountered by the virus in which the subsets of genomes undergoing positive or negative selection may be different than those that underwent the same processes in the previous host cell type. Therefore, a change in receptor specificity represents biological novelty not only in that a new cell type is infected, but also because the new environment may alter the mutant repertoire participating in subsequent rounds of infection. The application of microarray-based gene expression screening methods suggests considerable variation in expression patterns not only between different tissues and organs but also, on occasion, among cells of the same tissue. Thus, there is a great potential for environmental heterogeneity to modulate the composition of quasispecies swarms.

The main conclusion of this review is that receptors may be shared by different, unrelated viruses and that one virus may use several receptors and may expand its receptor specificity in ways that, at present, are largely unpredictable. We have suggested that this may have consequences for viral pathogenesis, coevolution of cell receptor specificity and antigenicity, a number of possible medical applications of receptor analogs and receptor ligands, the host range of viruses, the emergence of viral disease, and the application of viral vectors for viral therapy. Most of the studies on which we have based our arguments have been
carried out with a single virus isolate, clone, or reference strain. Find-
ings may be dependent on a particular sequence context of the viral 
genome in view of the compactness of information in viral genomes 
and the connections among genomic regions. It would not be surprising 
if similar studies with other representatives of the same virus genus 
yielded different results in the detail of the specific mutations associated 
with a phenotypic change regarding receptor recognition. However, we 
would also expect that the results would still convey the same general 
concepts and conclusions, as they derive from the phenotypic flexibility 
resulting from high mutation rates and quasispecies dynamics.

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