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CHAPTER 8

Determinants of Host Resistance

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Although some viruses can infect and cause disease in many species (i.e., they have a wide host range), many are host specific. Furthermore, within a susceptible host species there is often a striking difference between individual animals in their levels of resistance. What are the determinants of host susceptibility or resistance? Clearly, they are multifactorial. Within susceptible species, resistance varies not only with the genetic constitution of the host, but also with age, nutritional status, stress, and many other factors. Together, these genetic and physiological factors determine what is called the “nonspecific” or “innate” resistance of the host, in contrast to the immunologically specific resistance that results from the operation of the immune response, which is described in Chapter 9.

HOST SUSCEPTIBILITY AND VIRAL VIRULENCE

Susceptibility to infection, or its reciprocal, resistance, can be measured by determining the dose of virus required to cause infection or death in 50% of the test group: the 50% infectious dose (ID_{50}) or the 50% lethal dose (LD_{50}) (see Chapter 3). Different strains of inbred mice may vary many thousandfold in their susceptibility or resistance to a given
virus. The severity of an infection depends on the interplay between the virulence of the virus and the resistance of the host. One can regard an acute infection as a race between the ability of the virus to replicate, spread in the body, and cause disease, and the ability of the host to restrict and control these events. A highly virulent strain of virus is less lethal for a highly resistant animal than for a susceptible animal; conversely, a relatively avirulent strain of virus may be lethal for an unusually susceptible animal.

The variability in the response of individual animals to infection with a given virus is regularly observed during epizootics; for example, during an outbreak of Venezuelan equine encephalitis, one horse may die, another may merely develop a febrile disease, and a third may have a completely subclinical infection, the only evidence of which is a sharp rise in antibody and lifelong immunity to reinfection. The dose of infecting virus may be influential, but this is by no means the only factor. Both genetic and physiological factors can influence the outcome of exposure to a virus.

**GENETIC DETERMINANTS**

Genetic differences in susceptibility are most obvious when different animal species are compared. Common viral infections often tend to be less pathogenic in their natural host species than in certain exotic or introduced species. For instance, foot-and-mouth disease virus causes a severe disease in European cattle, but none in the African buffalo. Donkeys are more resistant to African horse sickness virus than are horses or mules, while zebras are refractory.

Accurate genetic data on resistance to infection is almost unobtainable in many species, because genetic, physiological, and environmental differences are generally confounded. Using inbred strains of mice, however, it has been possible to study the genetics of resistance to viral infection in some detail. For example, susceptibility to certain flaviviruses and to mouse hepatitis virus (a coronavirus) is under the control of a single gene which determines the capacity of macrophages to support the growth of virus.

**Cellular Receptors**

In a few instances it has been shown that the susceptibility of animals is dependent on the presence of the appropriate cellular receptor for the particular virus on cells of key target organs. The susceptibility of differ-
ent strains of chickens to Rous sarcoma virus is attributable to a single gene that codes for a cellular receptor; susceptibility is dominant.

Human polioviruses provide an example of the importance of cellular receptors at the species level. These viruses ordinarily infect only primates; mice and other nonprimates are not susceptible because their cells lack appropriate receptors. However, poliovirus RNA, when introduced into mouse cells \textit{in vivo} or in culture, can undergo a single cycle of replication. Since progeny virions from such an artificial infection face mouse cells lacking receptors, they are unable to initiate a second cycle of replication.

\textbf{Immune Response Genes}

Immunological responsiveness to particular antigens differs greatly from one strain of mouse to another, being under the control of specific \textit{immune response (Ir) genes}. There are many of these genes, most of them situated in the region known as the major histocompatibility complex (MHC) (see Chapter 9). Most other genetic determinants of virus susceptibility are not directly related to the immune response and map outside the MHC locus. Individuals with a genetically determined poor immune response to neutralizing epitopes on the surface proteins of a given virus would presumably have difficulty in controlling infection with that particular virus. In the mouse at least, absence of a specific response is generally recessive. Susceptibility of mice to infection with cytomegaloviruses, retroviruses, and lymphocytic choriomeningitis virus has been shown to be linked to particular MHC genotypes. Some breeds of domestic animals (e.g., sheep) are so inbred that particular viral susceptibility and resistance patterns have been found to be associated with specific immune responsiveness patterns.

\textbf{PHYSIOLOGICAL FACTORS}

\textbf{Malnutrition}

Malnutrition can interfere with any of the mechanisms that act as barriers to the replication or progress of viruses through the body. It has been repeatedly demonstrated that severe nutritional deficiencies will interfere with the generation of antibody and cell-mediated immune responses, with the activity of phagocytes, and with the integrity of skin and mucous membranes. However, often it is impossible to disentangle adverse nutritional effects from other factors such as poor husbandry.
Moreover, just as malnutrition can exacerbate viral infections, so viral infections can exacerbate malnutrition, thus creating a vicious cycle.

**Age**

The high susceptibility of newborn animals to many viral infections is of considerable importance in livestock husbandry. It can also be exploited for the laboratory diagnosis of viral diseases. Before cell culture techniques became available, foot-and-mouth disease virus isolation, titration, and neutralizing antibody assays were carried out in suckling mice. Infant mice are still useful for the isolation of togaviruses, flaviviruses, bunyaviruses, and rhabdoviruses.

In laboratory animals the first few weeks of life are a period of very rapid physiological change. For example, during this time mice pass from a stage of immunological nonreactivity (to many antigens) to immunological maturity. This change profoundly affects their reaction to viruses like lymphocytic choriomeningitis virus, which induces a persistent tolerated infection when inoculated into newborn mice, but an immune response in mice infected when over a week old. Most domestic animals are reasonably mature immunologically at the time of birth, but still very susceptible to infection with those viruses against which their dam has no antibody. If the umbrella of maternal antibody usually provided in mammals through colostrum or transplacental transfer is missing, the newborn animal is particularly vulnerable to infections with viruses such as canine distemper virus, canine parvovirus, hog cholera virus, bovine virus diarrhea virus, enteropathogenic coronaviruses, rotaviruses, and various herpesviruses during the first few weeks of life.

In humans, there are viruses that tend to produce more severe disease in adults than in children. For example, varicella virus, usually the cause of an uncomplicated disease in children, may produce severe pneumonia in adults; and mumps in adults may be complicated by orchitis. There are few parallels in domestic animals, but one example is bovine virus diarrhea virus, which generally infects calves subclinically, whereas older animals have a higher probability of developing clinical disease (see Chapter 25).

**Hormones, Pregnancy, and Stress**

There are few striking differences in the susceptibility of males and females to viral infections (except in the obvious instances of viruses with a predilection for tissues such as testes, ovaries, or mammary glands). Pregnancy significantly increases the likelihood of severe disease follow-
ing infection with certain viruses, e.g., Rift Valley fever virus in sheep.
Herpesvirus infections are often reactivated during pregnancy, contami-
nating the birth canal and leading to infection of the newborn.

The therapeutic use of corticosteroids exacerbates many viral infec-
tions; e.g., infections with infectious bovine rhinotracheitis, pseudorabe-
ries, or equine herpesvirus 1 viruses are often more severe in domestic animals receiving corticosteroids. The precise mechanism is not
understood, but corticosteroids reduce inflammatory and immune re-
sponses and depress interferon synthesis. It is also clear that adequate
levels of these hormones are vital for the maintenance of normal re-
sistance to infection. The stress of overcrowding and long-distance trans-
port is believed to contribute to shipping fever in cattle via adrenocortical
immunosuppression (see Chapter 10).

**Fever.** Almost all viral infections in domestic animals are accom-
panied by fever. The principal mediator of the febrile response appears
to be the macrophage product, interleukin-1 (previously known as en-
dogenous pyrogen). Interleukin-1 is induced by immunological mecha-
nisms, e.g., generalized antigen–antibody and cell-mediated immune
reactions. It is found in inflammatory exudates and acts on the tem-
perature-regulating center in the anterior hypothalamus. Interferons are
also pyrogenic when present in sufficiently high concentration; their
antiviral and immunomodulatory functions are discussed below.

Fever profoundly disturbs body functions. The increased metabolic
rate, by increasing the metabolic activity of phagocytic cells and the rate
at which inflammatory responses are induced, might be expected to
exert antiviral effects. *In vitro* experiments have shown that antibody
production and T-cell proliferation induced by interleukin-1 are greatly
increased when cells are cultured at 39°C rather than at 37°C. Further-
more, when fever was prevented in animals experimentally infected
with vaccinia virus or influenza virus, the ensuing disease was more
severe and very much more virus was excreted.

Lwoff suggested many years ago that fever constitutes a natural de-
fense against viruses, and that virulent strains of virus have evolved
with the ability to replicate in the host at temperatures achieved during
fever (indeed, latent infections with some herpesviruses are actually
reactivated by fever, hence the synonym "fever blisters" for recurrent
herpes simplex in humans). It was subsequently suggested that tem-
perature-sensitive (ts) viral mutants might therefore be expected to be
less virulent, and this correlation has now been observed with *ts* mu-
tants of many viruses, some of which are being used as vaccines (see
Chapter 14).
INTERFERONS

Interferons are proteins that are induced in virus-infected cells and interfere with the replication of viruses. Their properties and mode of action were described in Chapter 6; here we consider their role in the animal.

Production and Distribution in Vivo

It is difficult to determine which cell types, or even which tissues and organs, are responsible for most interferon production in vivo, but, extrapolating from findings with cultured cells, one can probably assume that most cells in the body are capable of producing interferons in response to viral infection. Certainly, interferons can be found in the mucus bathing epithelial surfaces such as the respiratory tract, and interferon is produced by most or all cells of mesenchymal origin. Lymphocytes, especially T cells, NK cells, and K cells, as well as macrophages, produce large amounts of interferons α and γ, and probably comprise the principal source of circulating interferon in viral infections characterized by a viremic stage.

Role in Recovery from Viral Infections

There are data supporting a central role for interferons in the recovery of animals and humans following at least some viral infections. The most telling evidence that interferon can indeed be instrumental in deciding the outcome of a natural viral infection is that mice infected with any of several nonlethal viruses, or with sublethal doses of more virulent viruses, die if antiinterferon serum is administered. In general, however, we know very little about the relative importance of the various interferons. While it is widely postulated that interferons constitute the first line of defense in the process of recovery from viral infections, it would be naive to believe that they are the only, or even the most important factor. If this were so, one might expect that a systemic infection with any virus, or indeed, immunization with a live vaccine, might protect an animal, for a period at least, against challenge with an unrelated virus. While some experimental data suggest that this may occur, the phenomenon cannot be generally demonstrated. Evidence is somewhat stronger that infection of the upper respiratory tract with one virus will provide temporary local protection against others. Perhaps this distinction provides the clue; the direct antiviral effect of interferons is limited in both time and space. Their main antiviral role may be to protect cells in the immediate vicinity of the initial focus of infection.
Further Reading

FURTHER READING

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