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Adenoviruses are used extensively to deliver genes into mammalian cells, particularly where there is a requirement for high-level expression of transgene products in cultured cells, or for use as recombinant viral vaccines or in gene therapy (reviewed in Ref. 1). The boundaries between the latter two applications are somewhat blurred, as the use of viral vectors as vaccines (e.g. for immunotherapy of cancer) is not fundamentally different from their use in mammalian cells for the development of recombinant viral vaccines and for delivery of therapeutic genes.

Characteristics such as versatility, stability and high-level expression make adenovirus vectors invaluable tools for the expression of transgenes in mammalian cells for the development of recombinant viral vaccines and for delivery of therapeutic genes.

Fig. 1b. From the perspective of adenovectorology, the most important regions are the early regions and 3 (E1 and E3). E3 is nonessential and can be deleted without interfering with the ability of the virus to replicate, and E1, although essential, can also be deleted, resulting in a defective virus that is propagated in E1-expressing cells such as 293 cells (Ad5-transformed human embryonic kidney cells).

The most commonly used vectors are those containing deletions of E1 and E3, with inserts of foreign DNA in E1. Such vectors, which are generally referred to as first-generation (FG) vectors, are defective for replication in normal cells but can efficiently transduce most cells. FG vectors are particularly useful for gene transfer into cultured cells and for gene therapy applications that require transient gene expression. FG vectors are not suitable for long-term expression because they retain most viral genes and express them at low levels, resulting in an immune response against transduced cells in vivo. Currently, the best available adenovirus vectors for long-term expression in vivo are ones from which all viral genes have been deleted. These fully deleted (FD) adenoviruses have been deleted.
vectors must be propagated in the presence of a helper virus that provides all the viral functions and virion capsid proteins needed in trans for virus replication, and are often referred to as ‘helper-dependent’ vectors.

Applications

FG vectors are easy to engineer, propagate and purify, and have numerous uses where efficient gene delivery and high-level expression are desired. Thus, they are excellent research tools, and will be used increasingly as novel genes are discovered and their products become a subject for investigation. Because the vectors can deliver genes encoding antigens and express them at high levels in vivo in any mammalian species, they are excellent candidates as recombinant viral vaccines. Indeed, vectors capable of immunizing animals against rabies, herpes viruses, rotaviruses and coronaviruses have all been developed. FG vectors are particularly suited for use in cancer immunotherapy strategies because of the ability of the vector to transduce most cell types, including nondividing cells, and its ability to express transgene products to high levels. In these regimens, transient expression is preferred over long-term expression, and the inflammatory response and cytotoxic T lymphocyte (CTL) activity associated with administration of FG vectors may be advantageous. Several FG vectors have been produced that express a variety of cytokines and other immunomodulatory proteins. These have yielded encouraging results when tested in tumour models in animals and some have been used in clinical trials.

FD vectors are technically more difficult to engineer, propagate and purify than FG vectors but have a much higher therapeutic index and give much longer expression in vivo. Thus, FD vectors may find use in ‘classical’ gene therapy such as enzyme replacement, where the desired outcome is permanent expression of the transgene product.

Concluding remarks

In summary, adenovirus vectors come in many forms and have great versatility and high efficacy when designed and used appropriately. They will play an increasingly important role as agents for gene transfer into mammalian cells.

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In recent years, there has been an increasing interest in the role of natural killer (NK) cells in primary host defense and their connection with adaptive immunity. NK-cell recognition of pathogen-infected cells and tumors is based on the expression of multiple cell-surface receptors that bind either major histocompatibility complex (MHC) class I or non-MHC ligands and transduce either inhibitory or activating signals. MHC class I receptors normally inhibit NK-cell activation when engaged by self-MHC, while allowing effector responses to occur when class I molecules are downregulated by viruses or transformation. Other receptors recognize ligands that have yet to be defined and trigger lysis and cytokine production. The balance of all these signals controls NK-cell activation.

Receptors for MHC class I molecules

Studies over the past ten years have led to the discovery of two families of MHC class I receptors. Immunoglobulin (Ig) superfamily (Ig SF) receptors include the human killer cell Ig-like receptor (KIR) and the human Ig-like transcript 2 (ILT2)/leukocyte inhibitory receptor 1 (LIR-1). KIR and ILT/LIR recognize groups of class I allotypes rather than individual MHC class I–peptide complexes. In particular, KIRs with two Ig-like domains (KIR2D) recognize groups of MHC class I alleles rather than individual MHC class I–peptide complexes. KIRs and the ILT molecules.

A recent conference* brought together scientists from 18 countries to discuss advances in our understanding of development, target-cell recognition, signal transduction, and effector mechanisms of natural killer (NK) cells.

The interaction of KIRs with MHC class I

In a new and exciting development in the study of the interaction of KIRs with class I, Peter D. Sun (Rockville, MD, USA) presented a recent study of the interaction of KIRs with class I–peptide complexes. KIRs and the ILT molecules.

Institute of Canada (NCIC), and by Merck Research Laboratories.

Frank L. Graham (graham@mcmaster.ca) is at the Depts of Biology and Pathology and Molecular Medicine, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4K1.

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*The 18th International Workshop on Natural Killer Cells was held in Giens, France, on 5–9 May 2000.