Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Further Reading

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HOST GENETIC RESISTANCE

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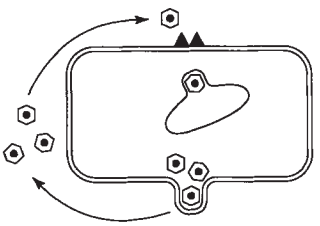

History

Genetic diversity is maintained among individuals of any noninbred species in order to provide the raw material to adapt to evolutionary forces. Although the species as a whole benefits from this diversity, individuals may not. Individuals may inherit certain genes or gene combinations that make them unusually susceptible to specific infectious or noninfectious diseases. In genetic terms, alleles, or alternative forms of the same gene, are the basis of variations in genetic resistance to diseases whether these variations are controlled by single or multiple loci. Developments in many fields but especially molecular genetics have facilitated the characterization of genes with multiple alleles that regulate disease resistance. Those polymorphous genes that regulate resistance to viral diseases are the subject of this entry.

In 1933, Webster was the first to observe that resistance to a disease caused by a virus could be inherited. The virus was yellow fever and the host was the laboratory mouse. He crossed strains of mice that were resistant and susceptible to the lethal effects of yellow fever virus and showed that segregant progeny expressed resistance according to predictions of Mendelian genetics. Other examples of genetic resistance in mice to what were then termed arboviruses were soon to follow. Today, polymorphous genes that regulate resistance to 11 genera of viruses have been reported.

Experimental results using laboratory mice needed corroboration in a natural population of another species. This came in the 1950s when the highly virulent myxoma virus was introduced into wild European rabbits in Australia to control burgeoning lagomorph populations. Although numerous factors conspired to attenuate initially high mortality rates, selection for resistant host genes was clearly an important factor. In humans, attempts to associate the severity of smallpox, poliomyelitis, congenital rubella and hepatitis B with various blood group and major histocompatibility antigens met with limited success. An impetus for this line of inquiry in humans came with Allison's discovery in 1964 of the relationship between resistance to falciparum malaria and heterozygosity of the sickle cell gene. Although this work did not deal with a viral infection, it established that genetic polymorphisms in humans regulate resistance to at least one microbial disease.

To date, the most systematic approach to the study of relationships between the severity of viral diseases and specific host genes remains comparisons of highly inbred strains of mice that vary in their susceptibility to a particular disease. Derivatives of resistant and susceptible strains such as bilineal congenic and recombinant inbred strains have been especially valuable in these studies. What has emerged from them is confirmation that polymorphous host genes are important regulators of the severity of many if not most viral infections, that single or multiple loci are involved, and that each locus appears to specify resistance to a particular genus of virus, or even a specific strain of virus within a genus. These studies have also shown that polymorphisms within the

major histocompatibility complex (MHC) may influence the course of viral infections, but that loci outside of the MHC are often more important.

During the past several years a number of viral disease resistance genes have been identified. In some cases their protein products or their mechanisms of action are known. In other cases their protein products and their functions are unknown but as they become more precisely mapped and eventually cloned 'reverse genetics' can be used to delineate their functions. Substantial homology between the murine and human genomes makes it possible to identify similar genetic resistance elements in humans. This has already been done for the *Mx1* locus on mouse chromosome 16 and human chromosome 21 which regulates susceptibility to influenza A and B viruses. The resistance loci that have been provisionally or definitively mapped are discussed here since this represents the most substantial progress in recent years (**Table 1**).

General Considerations

Viruses rely heavily upon products of host genes for their replication. Beginning with their interaction with host-encoded cell surface receptors and host factors involved in uncoating, continuing with their use of host transcription and translation factors, and ending with host-encoded post-translational enzymes, viruses require multiple products of host genes. The specific viral requirements differ depending on the replication strategy of the virus. In addition, viruses elicit protective responses in the host that are ultimately orchestrated by the host genome and these responses also vary depending on the virus. Any of these multiple points of interaction between the virus and products of the host genome have the potential to be sources of variation if alleles exist at these points within the host population and if the products of these alleles interact differently with the viral genome or its products.

Polymorphous resistance genes may therefore be expressed at the level of the target cells if they control proteins that are necessary for virus replication or at the organismal level if they regulate antiviral effector mechanisms. The effects of the former can usually be demonstrated in primary cultures of target cells from genetically resistant and susceptible hosts because they are expressed at the cellular level. The effects of the latter cannot usually be demonstrated in pure populations of target cells in culture because they involve cell interactions which are orchestrated at the organismal level. There is at least one exception to this organizational paradigm, however, and that is the antiviral state that is induced in target cells by interferons. In this case, target cells express proteins, now numbering about 24, that inhibit rather than promote virus replication. Polymorphous resistance genes can be classified as follows based on their organizational level of expression and whether they are induced by the infection or are constitutively expressed:

1. Genes expressed at the target cell level:
   a. constitutive expression – these genes regulate proteins that are necessary for virus replication;
   b. inducible expression – these genes regulate interferon-dependent proteins.
2. Genes expressed at the organismal level: these genes regulate antiviral effector mechanisms.

Resistance Genes Constitutively Expressed in Target Cells

Two resistance genes listed in **Table 1** are constitutively expressed in target cells. These are the *H-2D* gene that controls resistance to the lethal effects of mouse cytomegalovirus (MCMV) infection and the *Hv-2* locus that regulates susceptibility to acute mortality caused by mouse hepatitis virus type 4 (MHV4).

Inbred strains of mice that carry the MHC $H\text{-}2^k$ haplotype are among the most resistant to acute mortality caused by MCMV, a herpesvirus. Mice that carry the $H\text{-}2^d$ or $H\text{-}2^b$ haplotypes are 10 times more susceptible to lethal cytomegalovirus infection and permit significantly more virus replication than mice of the same genetic background that carry the $H\text{-}2^k$ haplotype. This difference is determined by the class I gene, *H-2D*. Products of class I MHC genes are important in cellular immune responses. Class I antigens are expressed by a wide variety of cells and serve as recognition molecules for specific classes of T cells. In the case of cytomegalovirus infection, however, the role of *H-2D* in genetic resistance is independent of its role in immune recognition. Cells from $H\text{-}2D^k$ mice are highly insensitive to infection with MCMV. Class I heavy-chain antigens are covalently bound to a second cell surface antigen, β_2-microglobulin, which is believed to serve as a cytomegalovirus receptor. The *H-2D* antigen is therefore directly involved with virus binding or it regulates the affinity of β_2-microglobulin for the virus antireceptor. In the case of $H\text{-}2D^k$ antigen the affinity of mouse cytomegalovirus for β_2-microglobulin is markedly reduced.

The *Hv-2* locus controls susceptibility of mice to the lethal effects of MHV4, a coronavirus. Like *H-2D* in the MCMV system, its effects are readily seen in

Table 1 Mapped or tentatively mapped polymorphous resistance genes

Virus	*Disease*	*Gene*	*Mouse chromosome*	*Linkage marker*	*Homologous human chromosome*	*Resistant genotype (carrier)*	*Susceptible genotype (carrier)*	*Dominant phenotype*	*Gene action*
Coxsackie-virus B3	Chronic myocarditis	*amd*	14	*Tcrα*	14q	amd^r (C57BL/6)	amd^s (A, DBA/2)	R	Effector
	Acute myocarditis	*H*-2-linked	17	*H-2*	6p	(A.CA)	(A.BY, A.SW)	Unknown	Unknown
		H-2-linked	17	*H-2*	6p	(B10, B10.A)	(B10.Q, B10.BR)	Unknown	Unknown
Ectromelia virus	Acute mortality	*Rmp*-2	2	*Hc*	9q	$Rmp\text{-}2^r$ (C57BL/6)	$Rmp\text{-}2^s$ (DBA/2)	R	Unknown
		Rmp-3	17	*H-2*	6p	$Rmp\text{-}3^r$ (C57BL/6)	$Rmp\text{-}3^s$ (DBA/2)	R	Unknown
Influenza A virus	Acute mortality	*Mx*1	16	*Ets*-2	21	$Mx\text{-}1^+$ (A2G)	$Mx\text{-}1^-$ (BALB/c)	R	Inducible
Mouse cytomegalo-virus	Acute mortality	*Cmv*-1	6	*Prp*	12p	$Cmv\text{-}1^l$ (C57BL/6)	$Cmv\text{-}1^h$ (BALB/c)	R	Unknown
		H-2D	17	*H-2*	6p	$H\text{-}2D^k$ (BALB.K)	$H\text{-}2D^d$ (BALB/c)	S	Constitutive
Mouse encephalomyelitis virus	Chronic demyelination	–	6	*Tcrβ*	7q	(BALB/c)	(SJL)	R/S	Effector
		–	3	*Car*-2	8q	(C57BL/c)	(DBA/2)	R	Effector
		H-2D	17	*H-2*	6p	$H\text{-}2D^b$ (C57BL/6)	$H\text{-}2D^d$ (DBA/2)	R	Effector
		H-2D	17	*H-2*	6p	$H\text{-}2D^b$ (C57BL/10)	$H\text{-}2D^s$ (SJL)	R	Effector
Mouse hepatitis virus	Acute mortality					$Hv\text{-}2^r$	$Hv\text{-}2^s$		
		Hv-2	7	*Svp*-2	19q	(SJL)	(C57BL/10)	S	Constitutive
		H-2-linked	17	*H-2*	6p	(A.CA)	(A/Sn)	R/S	Unknown
	Chronic demyelination	*H*-2-linked	17	*H-2*	6p	(A.CA)	(A.BY)	R	Unknown

infected cells in primary cultures. The mechanism of action of *Hv-2* is currently disputed. Only one strain of mouse, SJL, is known to carry the *Hv-2*^{r} allele. Mendelian genetics of resistance to the lethal effects of MHV4 in crosses between SJL and various susceptible strains indicate that one gene controls resistance. It has been shown that SJL mice fail to express a 110K cell surface glycoprotein that binds MHV4, whereas susceptible strains of mice do. These data suggest that *Hv-2* encodes the viral receptor. *Hv-2* was defined on the basis of differences in the replication of MHV4 in macrophages from resistant and susceptible mice. In macrophages from *Hv-2*^{r} and *Hv-2*^{s} mice, the virus replication diverges at a point after the virus is internalized and after transcription of viral genes. This suggests that *Hv-2* does not encode the virus receptor but a protein that functions subsequent to binding. There is evidence that *Hv-2* encodes the host protease that activates the viral S glycoprotein which serves as the antireceptor. This virus–host interaction is necessary for the infection to spread and could explain why the infection fails to spread in macrophage cultures from *Hv-2*^{r} mice.

Resistance Genes Inducible in Target Cells

The single example of this class of resistance gene is *Mx1* which regulates resistance to diseases caused by influenza A and B viruses. This is the most thoroughly examined resistance gene, having been mapped, cloned and sequenced. Its protein product is known although the exact mechanism whereby it inhibits influenza virus replication has not been determined. Its inhibitory action occurs after virus uncoating and before translation. *Mx1* is an interferon-inducible nuclear protein with an M_r of 72000. Interferons α and β but not γ induce the synthesis of *Mx1*$^+$ mRNA. Most laboratory strains of mice have deletion or point mutations in the *Mx1* gene resulting in a potential coding capacity for the inactive N-terminal half of the *Mx1* protein only.

Resistance Genes Expressed Through Host Antiviral Effectors

Five of the genes listed in **Table 1** are expressed at the organismal level through antiviral effectors. All of these examples are believed to regulate specific immune responses that are involved in virus clearance or in immunopathic injury. Four of these genes regulate susceptibility to Theiler's mouse encephalomyelitis virus (TMEV), a picornavirus. Mice that are inoculated intracerebrally with certain laboratory-adapted strains of TMEV may develop one of several diseases, depending on their genotype. The most intensively studied disease occurs after the acute phase of infection and is characterized by progressive paralysis in association with chronic demyelination of the central nervous system. This disease is immunologically mediated and is associated with viral persistence in the white matter oligodendrocytes and infiltrating macrophages. The genes that mediate susceptibility to viral persistence and myelin breakdown in this system vary with the strain of mouse. In susceptible DBA/2 mice, demyelination is mediated by the *H-2D*^{d} allele of the MHC and a second allele at a locus near the *Car-2* gene on chromosome 3. In susceptible SJL mice, disease is mediated by an allele on a gene located near the structural gene for the T cell receptor β-chain constant region on chromosome 6. The *H-2D*^{s} allele of the MHC of SJL mice also appears to mediate susceptibility in SJL mice but its effects have not been seen in all studies.

All mice that are susceptible to paralytic TMEV infection share augmented delayed-type hypersensitivity responses to the virus when compared to resistant mice. Their susceptibility is therefore believed to result from inappropriate cell-mediated immune responses to the virus which allow it to persist and which mediate tissue injury. Consistent with this interpretation is the fact that most of these loci map to regions that are known to regulate immune responses. The localization of one gene to the vicinity of the T cell receptor β-chain structural gene is of special interest because the T cell receptor repertoire has been implicated as an etiology in certain autoimmune diseases.

Another example of an inappropriate immune response underlying genetic susceptibility to a virus-induced disease is that which occurs after infection with coxsackievirus B3 (CVB3). In this case, however, the immune response that is triggered by the infection is not directed at the virus, but rather at a host protein in the tissue where the virus replicates.

CVB3 is a common cause of infectious myocarditis in humans. CVB3 causes acute and chronic myocarditis in inbred mice depending on the strain of mice. The chronic myocarditis results from an autoimmune response to cardiac myosin that is triggered by viral replication in and injury to the heart of susceptible mice. Both *H-2*-linked and non-*H-2*-linked genes control susceptibility to chronic myocarditis. One form of the disease is mediated by IgG antibodies specific for cardiac myosin. This form is seen in DBA/2 and A mice and is modulated by a gene that is located on chromosome 14 in the vicinity of structural loci for the T cell receptor α-chain and the cardiac myosin α-heavy chain. Associations between the T cell receptor repertoire and autoimmune

diseases has been previously mentioned in the context of TMEV-induced chronic demyelination. The possibility that allelic differences in cardiac myosin may account for the observed chromosomal localization of the susceptibility gene is also being considered. However, the susceptible phenotype has been shown to correlate with susceptibility to autoimmune myocarditis after immunization with cardiac myosin, suggesting that allelic differences in cardiac myosin are not the basis of susceptibility.

Resistance Genes Expressed Through Unknown Mechanisms

Seven of the genes listed in **Table 1** exert their effects through unknown mechanisms. Five of these are linked to the MHC and six regulate susceptibility to acute viral diseases. The associations with the MHC suggest that some of these genes regulate specific immune responses. However, the temporal divergence of phenotypes of mice with resistance and susceptibility alleles for some of these genes occurs before effects of specific immune mechanisms are likely. For this reason the *H-2*-linked genes that regulate susceptibility to acute effects of ectromelia virus (mouse-pox), CVB3 and MHV are more likely to be expressed through early, nonspecific effectors than through specific immune responses. These early effectors include activated natural killer cells, interferon and acute-phase reactants.

There is evidence that *Cmv-1,* which regulates resistance to the lethal effects of MCMV, is expressed through the early inflammatory response. This gene limits virus replication, prevents virus-induced splenic necrosis within 72h of infection, and appears to be expressed at the organismal level. Allelic differences at this locus are correlated with differences in the phenotypic character of the early inflammatory infiltrate. There is preliminary evidence that resistance to the lethal effects of ectromelia virus, an orthopoxvirus is regulated by a gene (not among the two listed in **Table 1**) that maps to the same region of mouse chromosome 6 as *Cmv-1*. Other similarities between these two loci are that they are expressed in the spleen, they regulate virus-induced splenic necrosis, they regulate the influx of cells into the spleen or the proliferation of cells already present, and their resistance alleles are expressed by the same strains of mice. Should these turn out to be the same locus, it would be the first example of a polymorphous gene active against more than one genus of virus.

Future Perspectives

Genetically determined variations in responses to viral infections are important determinants of disease severity in all species, including humans. The difficulty in identifying modifying genes directly in genetically heterogeneous populations has retarded efforts to identify such loci in humans. The continuing success in identifying these genes in mice and the extensive genetic homology between mice and humans provides a means for identifying resistance genes for specific viruses in humans. In some cases, allelic differences at these loci will modulate the severity of human viral illnesses as they do in mice. A thorough understanding of how these polymorphisms modulate viral infections will lead to more enlightened approaches to the therapy of viral diseases and the identification of individuals at risk to develop serious sequelae.

See also: **Genetics of animal viruses; Immune response: General features; Interferons: General features; Pathogenesis: Animal viruses; Replication of viruses; Viral receptors; Virus–host cell interactions.**

Further Reading

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