VIRUS-RESISTANCE GENES: THE MOUSE MODEL.

GENES DE RESISTÊNCIA VIRAL: O MODELO MURINO.

Pedro Faísca[1]

1) ULHT – Universidade Lusófona de Humanidades e Tecnologias; faiscapedro@netcabo.pt

Abstract: *Human and animals differ widely in their responses to virus infections. Viruses may induce barely discernible symptoms in some of them and severe, life-threatening illness in others.*
Evidence is accumulating that genetic background is one of the major factors involved, thus, identifying genes that control the response to virus infection is a crucial step in elucidating how they might affect the pathophysiological processes underlying the severity of the disease induced.
In this review, it's illustrated how mouse-virus systems are being used to identify candidate virus-resistance genes, and how they provide the probes to detect functional homologues of resistance genes that are shared by rodent and other species.

Resumo: *Os Homens e os animais diferem grandemente nas suas respostas às infecções virais. Os vírus podem induzir, em alguns, sintomas ligeiros, enquanto que em outros podem provocar patologias graves mesmo mortais.*
Acumulam-se evidências que o património genético é um dos factores primordiais a condicionar e contribuir para a complexidade das interações vírus-hospedeiro. A identificação de genes com papel na resposta à infecção viral tornou-se pois o tema de investigação de muitos laboratórios, com o objectivo de elucidar os processos fisiopatológicos que regem e determinam esse tipo de resposta.
Neste artigo de revisão pretende-se ilustrar como o modelo murino têm sido utilizado para a identificação de genes de resistência viral, e como estes podem funcionar como base para a descoberta de genes homólogos em outras espécies. na elucidação dos mecanismos de resistência, e em novos componentes da reunir todos os genes de resistência viral descobertos em murganhos

INTRODUCTION

Virus-Host Interactions

Human and animals differ widely in their responses to virus infections. Viruses may induce barely discernible symptoms in some of them and severe, life-threatening illness in others [1, 2, 3, 4, 21]. These differences reflect both the complex, intimate, and multifaceted nature of virus-host interactions and the variables that can influence these interactions. Viruses elicit a complex temporal sequence of stringently regulated innate and adaptive immune responses. These responses are essential for recovery, but they also contribute to disease symptoms. Optimal innate and adaptive immune responses are therefore balanced at a narrow interface between ineffectual and overly aggressive. Variables of age, gender, immune status, and genetic background influence the availability and form of the host metabolites on which viruses depend as well as the magnitude and effectiveness of the ensuing host response [11]. Evidence is accumulating that genetic background is one of the major factors involved, thus, identifying genes that control the response to virus infection is a crucial step in elucidating how they might affect the pathophysiological processes underlying the severity of the disease induced [1, 2, 3, 4].

The mouse model

The large size and complexity of the human and domestic animals genome, have limited the identification and functional characterization of components of the innate immune system that play a critical role in front-line defence against invading virus. However, the advent of new technologies and resources, including the complete sequence of mammalian genomes, has had a dramatic impact on the genetic analysis of susceptibility to infections. Besides that, the study of the genomic organization and content of widely divergent vertebrate species has shown a remarkable degree of evolutionary

conservation, which enables the cross-species comparison and analysis of newly discovered genes.

Application of comparative genomics to host resistance will rapidly expand our understanding of human and domestic animals immune defence by facilitating the translation of knowledge acquired through the study of model organisms [9, 28, 38, 47].

The mice have been for quite a long the model of choice [20, 21, 34], more is known now about genetic control of resistance to viruses in mice than any other animal. They own this success to the low costs incurred, the existence of thousands of inbred strains, and the fact that the mouse is the species with the greatest density of known genetic markers, which facilitates the tracing of the alleles partly or wholly responsible for complex phenotypes [34].

VIRUS-RESISTANCE GENES

The Mx

The mouse genome contains two related interferon-regulated genes, Mx1 and Mx2.

The Mx1 was both the first virus-resistance gene to be cloned and the first to be used to identify a human homologue, it encodes a type I interferon inducible nuclear protein that affords specific protection against influenza viruses. Only three mouse strains, A2G, SL/NiA and T9, express the antiviral form of protein; other mouse strains have deletions in the Mx1 gene that result in truncated proteins that are devoid of antiviral activity [45].

The Mx2 gene is non-functional in all laboratory mice strains examined, since its open reading frame (ORF) is interrupted by an insertional mutation and a subsequent frameshift mutation. However, the Mx2 mRNA of cells from feral mouse strains NJL(Mus musculus musculus) and SPR (Mus spretus) that differs from that of the laboratory mouse strains tested is expressed upon interferon treatment and inhibits vesicular stomatitis virus, and hantavirus replication [30, 31].

The Hv2

Hv2, another mouse virus-resistance gene, controls resistance to mouse hepatitis virus (MHV), a large-enveloped RNA virus that is distantly related to human enteric and respiratory coronaviruses. As natural pathogens of mice, MHV strains may cause either localized intestinal infections or generalized infections that emanate from the respiratory tract. All MHV strains appear to use members of the biliary glycoprotein subfamily as receptor proteins [19]. The principal receptors for MHV are several isoforms encoded by the biliary glycoprotein 1 (Bgp1) gene on the proximal end of mouse chromosome 7 [39].

The SJL inbred mouse strain, unlike almost all other inbred strains, is highly refractory to MHV infection. The Bgp1b (Hv2r) allele of SJL mice contains divergent sequences in the N-terminal virus-binding domain [33], particularly in the critical residues 38-43 [39]. The altered Bgp1b isoform remains a functional virus receptor, but its affinity for MHV is reduced by one to two orders of magnitude [37].

The Flv

Innate resistance to flavivirus, which includes human pathogens such as yellow fever, Dengue, and West Nile virus was demonstrated in mice in the 1920s as a monogenic autosomal dominant inheritance. The alleles that determined resistance and susceptibility were designated Flvr and Flvs, respectively [27]. Resistant mice are susceptible to infections with other types of viruses but are resistant to all flaviviruses [44]. Resistant mice can be infected by flaviviruses, but the virus titers in their tissues are lower by 1,000-10,000 times than those in the tissues of susceptible animals, and the spread of the infection in resistant mice is slower [17, 26]. Most commonly used inbred laboratory mouse strains have a homozygous flavivirus-susceptible genotype. Only the Det, BSVR, BRVR, CASA/Rk, CAST/Ei, MOLD/Rk, and PRI inbred strains have the resistant allele [7].

The Cmv1

Murine cytomegalovirus (MCMV) is a natural pathogen of mice that has been widely used as a model of human cytomegalovirus infection. Differences in susceptibility were observed among inbred mouse strains, being the

C57BL/6 resistant and BALB/c susceptible to MCMV infection [41]. MCMV titers in the spleens of susceptible mice were inversely correlated with their ability to mount an effective Natural Killer (NK) cell response [41, 42] suggesting an important role of those cells in the innate control of cytomegalovirus infection. Later on, this has been demonstrated in humans with a rare disorder characterized by complete absence of NK cells and in genetically deficient mice lacking NK cells or being depleted of those cells by treatment with anti-NK cell antibodies [7]. A single dominant locus, named Cmv1, located in the natural killer gene complex on mouse chromosome 6 controls the NK efficient response and consequently the resistance to MCMV infection in mice [18, 24, 41, 42, 43]. The alleles of the Cmv1 locus can confer either susceptibility (Cmv1s, a recessive allele) or resistance (Cmv1r, a dominant allele) to MCMV.

The Rmp

Ectromelia virus, is a naturally occurring pathogen of mice and belongs to the Poxviridae family. Orthopoxviruses cause localized or generalized infections in a variety of species. Systemic infections which include smallpox (variola) in human beings are among the most lethal infections known [22, 23].

Most inbred strains of mice are highly susceptible to the lethal effects of ectromelia virus infection, but C57BL and AKR strains are highly resistant [9, 13]. Susceptible strains succumb to the acute necrotizing effects of ectromelia virus on liver, spleen, and bone marrow, whereas resistant strains develop mild, transient inflammatory changes in target organs [12].

Resistance to mousepox is inherited as a polygenic trait [14, 48]. At least four autosomal dominant genes, named Rmp-1, Rmp-2, Rmp-3, and Rmp-4, control resistance to mousepox in C57BL mice. The genes that control resistance to mousepox are of interest because they are dominant over ectromelia virus genes that encode virokines and other virulence factors and because they may be some of the best examples of mouse genes that have responded to selection pressure by a highly lethal naturally occurring virus.

The Fv-1, Fv-4

In 1957, Charlotte Friend described a novel retroviral disease in mice characterized by splenic enlargement, erythroleukemia, and death [25]. This rapidly progressive disease, now known as Friend disease, has provided a powerful tool for the study of multistage carcinogens and, most recently, has provided major insights into the molecular mechanisms of leukemia resistance.

A number of host genes have been identified that affect the susceptibility of mice to Friend virus–induced erythroleukemia. These genes can be divided into several groups based on their proposed mechanism of resistance: group 1: interference with retroviral infection (Fv1, Fv4); group 2: altered immune response (Fv3, Rfv1, Rfv2, Rfv3); and group 3: regulators of erythroid cell proliferation and differentiation (Fv2, Fv5, Kit, and Mgf) [5].

In terms of virus-resistance genes only the first group, that consists of genes that dominantly interfere with the infection of target cells by the virus, will be mencioned. We have then, the Fv1 gene that encodes a Gag-related protein, which interferes with the retroviral life cycle [6] and the Fv4 gene that encodes a protein which blocks ecotropic viral receptors [29].

Differences in susceptibility among mouse strains allowed the identification of those genes. In the Fv1 gene, two alleles were discovered by this way: Fv1n and Fv1b. These alleles are able to block specific subclasses of MLV [8]. Fv1n, found in NIH Swiss mice, is able to block replication of B-tropic MLV while allowing replication of N-tropic virus, and Fv1b, found in BALB/c mice, acts vice versa. In the Fv4 gene, the dominant allele was first described in a G stain of laboratory mouse, and subsequently, in several wild mouse populations in Japan, Southeast Asia and western North America [36, 46] as a single dominant gene for the resistance against MLV infection, independent of Fv1.

H-2 class I genes

Theiler's virus causes a persistent and demyelinating infection of the central nervous

system of the mouse, which is one of the best animal models to study multiple sclerosis.

All inbred mouse strains inoculated intracranially with Theiler's virus present with early encephalomyelitis. However, not all of them remain persistently infected. The C57BL/6 strain clear the infection after approximately 2 weeks. On the contrary, the susceptible strains (SJL and FVB/N) remain infected for life [15, 16, 40].

The susceptibility of the mouse to persistent infection is multigenic. H2 class I genes have a major effect [32], While most of the non-H2 susceptibility genes group control viral load during persistence by modulating the immune response. Among several non-H2 susceptibility loci, Tmevp3 appears to regulate the expression of important cytokines [10].

CONCLUSION

These examples illustrate how mouse-virus systems are being used to identify candidate virus-resistance genes. They provide the probes to detect functional homologues of resistance genes that are shared by rodent and other species. They delineate novel genetic mechanisms of resistance and highlight specific genetically complex and polymorphic components of the innate immune system as sources of variation in responses to viruses. Other benefits are likely to emerge as more mouse virus-resistance genes are identified and characterized. Clearly, not all details of virus-restriction pathways are conserved between mice and other species, but even where differences exist, functional similarities may be enough to guide genetic studies of resistance to viruses.

REFERENCES

1. Abel L, Demenais F, Prata A, Souza AE, and Dessein A. Evidence for the segregation of a major gene in human susceptibility/resistance to infection by Shistosoma mansoni. Am J Hum Genet 48: 959-970, 1991.

2. Abel L, Vu DL, Oberti J, Nguyen VT, Van VC, Guilloud-Bataille M, Schurr E, and Lagrange PH. Complex segregation analysis of leprosy in southern Vietnam. Genet Epidemiol 12: 63-82, 1995.

4. Alcais A, Abel L, David C, Torrez ME, Flandre P, and Dedet JP. Evidence for a major gene controlling susceptibility to tegumentary leishmaniasis in a recently exposed Bolivian population. Am J Hum Genet 61: 968-979, 1997.

5. Axelrad A. Genetic and cellular basis of susceptibility or resistance to Friend leukemia virus infection in mice. Can Cancer Conf. 8: 313-343, 1969.

6. Best S, Le Tissier P, Towers G, Stoye JP. Positional cloning of the mouse retrovirus restriction gene Fvl. Nature. 382: 826-829, 1996.

7. Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. Annu Rev Immunol. 17: 189-220, 1999.

8. Bishop KN, Bock M, Towers G, Stoye JP. Identification of the Regions of Fv1 Necessary for Murine Leukemia Virus Restriction J Virol. 75: 5182-5188, 2001.

9. Bonhomme F, Guenet JL, Dod B, Moriwaki K, Bulfield G. The polyphyletic origin of laboratory inbred mice and their rate of evolution. Biol J Linn Soc. 30: 51–58, 1987.

10. Brahic M, Bureau JF, Michiels T. The Genetics of the Persistent Infection and Demyelinating Disease Caused by Theiler's Virus. Annu Rev Microbiol. 59: 279-298, 2005.

11. Brinton MA. Viral pathogenesis. Lippincott-Raven Publishers, Philadelphia, 1997, p 303-328.

12. Brownstein DG, Bhatt PN, Gras L. Ectromelia virus replication in major target organs of innately resistant and susceptible mice after intravenous infection. Arch Virol. 129: 65–75, 1993.

13. Brownstein DG, Bhatt PN, Gras L, Budris T. Serial backcross analysis of genetic resistance to mousepox, using marker loci for Rmp-2 and Rmp-3. J Virol. 66: 7073-7079, 1992.

14. Brownstein DP, Bhatt N, Jacoby RO. Mousepox in inbred mice innately resistant or susceptible to lethal infection with ectromelia virus. V. Genetics of resistance to the Moscow strain. Arch Virol. 107: 35–41, 1989.

15. Bureau J-F, Montagutelli X, Lefebvre S, Gu´enet J-L, Pla M, Brahic M. The interaction of two groups of murine genes determines the persistence of Theiler's virus in the central nervous system. J Virol. 66: 4698–4704, 1992.

16. Clatch RJ, Melvold RW, Miller SD, Lipton HL. Theiler's murine encephalomyelitis virus (TMEV) induced demyelinating disease in mice is influenced by the H-2D region: correlation withTMEV-specific

delayed-type hypersensitivity. J Immunol. 135: 1408–1413, 1985.

17. Darnell MB, Koprowski H, Lagerspetz K. Genetically determined resistance to infection with group B arboviruses. I. Distribution of the resistance gene among various mouse populations and characteristics of gene expression in vivo. J Infect Dis. 129: 240–247, 1974.

18. Depatie C, Muise E, Lepage P, Gros P, Vidal SM. High-resolution linkage map in the proximity of the host resistance locus Cmv1. Genomics 39: 154-163, 1997.

19. Dveksler GS, Dieffenbach CW, Cardellichio CB, McCuaig K, Pensiero MN , Jiang GS, Beauchemin N. Several members of the mouse carcinoembryonic antigen related glycoprotein family are functional receptors for the coronavirus mouse hepatitis virus-A59. J Virol 67: 1-8, 1993.

20. Faisca P, Tran Anh DB, Thomas A, Desmecht D. Suppression of pattern-recognition receptor TLR4 sensing does not alter lung responses to pneumovirus infection. Microbes Infect 8: 621-627, 2006

21. Faisca P, Tran Anh DB, Desmecht D. Sendai virus-induced alterations in lung structure/function correlate with viral loads and reveal a wide resistance/susceptibility spectrum among mouse strains. Am J Physiol Lung Cell Mol Physiol 289: 777-787, 2005.

22. Fenner F, Wittek R, Dumbell KR. The orthopoxviruses. Academic Press: New York, 1989, p. 269–302.

23. Fenner, F., R. Wittek, and K. R. Dumbell. The orthopoxviruses. Academic Press, New York, 1989, p 198-226.

24. Forbes CA, Brown MG, Cho R, Shellam GR, Yokoyama WM, Scalzo AA. The Cmv1 host resistance locus is closely linked to the Ly49 multigene family within the natural killer cell gene complex on mouse chromosome 6. Genomics 41: 406-413, 1997.

25. Friend C. Cell-free transmission in adult swiss mice of a disease having the character of a leukemia. J Exp Med. 105: 307-318, 1956.

26. Goodman GT, Koprowski H. Macrophages as a cellular expression of inherited natural resistance. Proc Natl Acad Sci. 48: 160–165, 1962.

27. Green MC. Catalog of mutant genes and polymorphic loci. In: Green M. C. (Ed.), Genetic Variants and Strains of the Laboratory Mouse. Gustav Fischer Verlag: New York, 1981, p-137.

28. Hill AV. Genetics and genomics of infectious disease susceptibility. Br Med Bull 55: 401-413, 1999.

29. Ikeda H, Laigret F, Martin MA, Repaske R. Characterization of a molecularly cloned retroviral sequence associated with Fv-4 resistance. J Virol. 55:768-777, 1985.

30. Jin HK, Takada A, Kon Y, Haller O, Watanabe T. Identification of the murine Mx2 gene: interferon-induced expression of the Mx2 protein from the feral mouse gene confers resistance to vesicular stomatitis virus. J Virol 73: 4925-4930, 1999.

31. Jin HK, Yoshimatsu K, Takada A, Ogino M, Asano A, Arikawa J, and Watanabe T. Mouse Mx2 protein inhibits hantavirus but not influenza virus replication. Arch Virol 146: 41-49, 2001.

32. Lipton HL, Melvold RW. Genetic analysis of susceptibility to Theiler's virus induced demyelinating disease in mice. J Immunol. 132: 1821–1825, 1984

33. Kubo H, Yamada YK, Taguchi F. Localization of neutralizing epitopes and the receptor-binding site within the amino-terminal 330 amino acids of the murine coronavirus spike protein. J Virol 68: 5403 5410, 1994

34. Malakoff, D. The rise of the mouse, biomedicine's model mammal. Science 288: 248-253, 2000.

35. Malo D, Skamene E. Genetic control of host resistance to infection. Trends Genet 10: 365-371, 1994.

36. Odaka T, Ikeda H, Yoshikura H, Moriwaki K, Suzuki S. Fv4: gene controlling resistance to NB-tropic Friend murine leukemia virus. Distribution in wild mice, introduction into genetic background of BALB/c mice, and mapping of chromosomes. J Natl Cancer Inst. 67: 1123-1127, 1981.

37. Ohtsuka N, Yamada YK, Taguchi F. Difference in virus-binding activity of two distinct receptor proteins for mouse hepatitis virus. J Gen Virol 77:1683 1692, 1996.

38. Qureshi ST, Skamene E, Malo D.Comparative genomics and host resistance against infectious diseases. Emerg Infect Dis 5: 36-47, 1999.

39. Rao PV, Kumari S, Gallagher TM. Identification of a contiguous 6-residue determinant in the MHV receptor that controls the level of virion binding to cells. Virology 229: 336-348, 1997.

40. Rodriguez M, Leibowitz J, David CS. Susceptibility to Theiler's virus induced demyelination. Mapping of the gene within the H-2D region. J Exp Med. 163: 620–631, 1986.

41. Scalzo AA, Fitzgerald NA, Simmons A, La Vista AB, Shellam GR. Cmv-1, a genetic locus that controls murine

cytomegalovirus replication in the spleen. J Exp Med. 171: 1469-1483, 1990.

42. Scalzo AA, Fitzgerald NA, Wallace CR, Gibbons AE, Smart YC, Burton RC, Shellam GR. The effect of the Cmv-1 resistance gene, which is linked to the natural killer cell gene complex, is mediated by natural killer cells. J Immunol. 149:581-589, 1992.

43. Scalzo AA, Lyons PA, Fitzgerald NA, Forbes CA, Yokoyama WM, Shellam GR. Genetic mapping of Cmv1 in the region of mouse chromosome 6 encoding the NK gene complex-associated loci Ly49 and musNKR-P1. Genomics 27: 435-441, 1995.

44. Shellam GR, Sangster MY, Urosevic N. Genetic control of host resistance to flavivirus infection in animals. Rev Sci Tech. 17, 231–248, 1998.

45. Staeheli P, Gob R, Meier E, Sutcliffe JG, Haller O. Influenza virus-susceptible mice carry Mx genes with a large deletion or a nonsense mutation. Mol Cell Biol 8: 4518-4523, 1988.

46. Suzuki S, Tsuji K, Moriwaki K. Friend murine leukemia virus resistance in Japanese wild mice: possible allelism with Fv4 in FRG mice. J Natl Cancer Inst. 66: 729-731, 1981.

47. Tuite A, Gros P. The impact of genomics on the analysis of host resistance to infectious disease. Microbes Infect 8: 1647-1653, 2006.

48. Wallace GD, Buller RML, H. C. Morse HC. Genetic determinants of resistance to ectromelia (mousepox) virus-induced mortality. J Virol. 55: 890–891, 1985