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12-11-2013

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Use of IRF-3 and/or IRF-7 Knockout Mice To Study Viral Pathogenesis: Lessons from a Murine Retrovirus-Induced AIDS Model

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Interferon regulatory factor (IRF) regulation of the type I interferon response has not been extensively explored in murine retroviral infections. IRF-3$^{-/-}$ and select IRF-3/7$^{-/-}$ mice were resistant to LP-BM5-induced pathogenesis. However, further analyses strongly suggested that resistance could be attributed to strain 129-specific contamination of the known retrovirus resistance gene *Fv1*. Therefore, caution should be taken when interpreting phenotypes observed in these knockout mice, as strain 129-derived genetic polymorphisms may explain observed differences.

The type I interferon (IFN) antiviral response (IFN-α and IFN-β) plays a major role in host innate immunity to RNA and DNA virus infections (1–12). This antiviral type I IFN response is tightly regulated, in part, by interferon regulatory factors (IRFs) via upstream signaling induction by various pattern recognition receptors (PRRs). Several studies utilizing knockout mice for IRF-3, IRF-7, and IRF-3/7 (DKO) have reported on the overall complexity and sometimes distinct roles of IRF-3 and IRF-7 in antiviral IFN-dependent and IFN-independent responses to multiple viral infections (1–3, 9, 10, 13–16). Although most retroviruses are relatively poor inducers of robust innate antiviral responses, there is growing evidence for the existence of retrovirus-induced type I IFNs; therefore, IRF-3 and/or IRF-7 may also be involved (17–23).

LP-BM5, a gammaretrovirus, causes murine AIDS (MAIDS) upon infection of susceptible mouse strains—e.g., wild-type C57BL/6 (B6) (24, 25). MAIDS is characterized by early activational parameters, followed by broad, profound immunodeficiency of both T- and B-cell responses and susceptibility to opportunistic microbial infection (24–34).

To determine the possible role of IRFs in retroviral pathogenesis, B6 background mouse strains with IRF-3$^{-/-}$, IRF-7$^{-/-}$, and DKO congenic status (10, 13, 35) were infected with 5×10^4 PFU of LP-BM5 retrovirus and were compared to MAIDS-susceptible B6 and MAIDS-resistant 129S1/SvImJ (129) mice (NCI, Bethesda, MD) (31, 36). Upon sacrifice, at 8 weeks postinfection (wpi), MAIDS was assessed (Fig. 1). The extent of pathogenesis was calculated from established disease parameters, and a disease index

Received 10 October 2013 **Accepted** 3 December 2013
Published ahead of print 11 December 2013
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doi:10.1128/JVI.02960-13

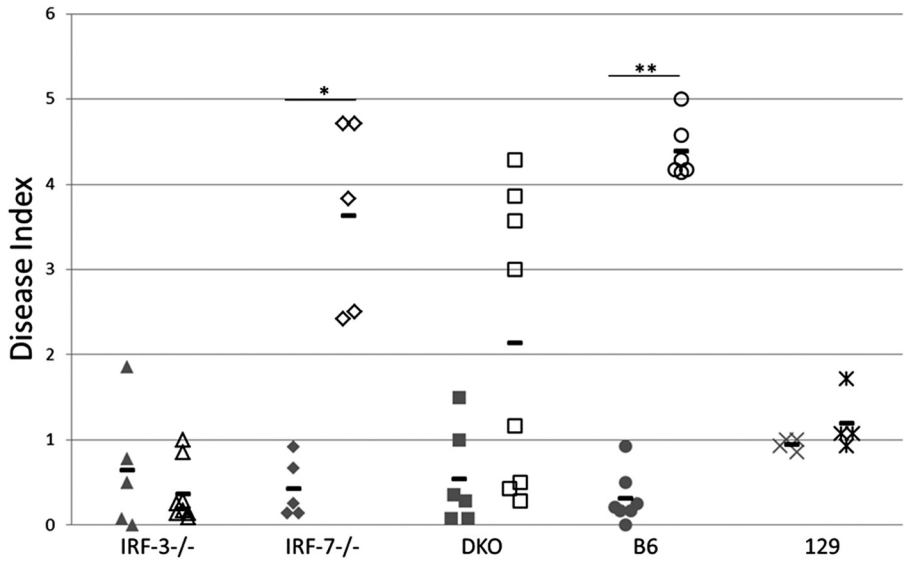

FIG 1 IRF-3$^{-/-}$ mice demonstrate increased MAIDS resistance. IRF-3$^{-/-}$, IRF-7$^{-/-}$, DKO, B6, and 129 mice were infected with LP-BM5, and MAIDS disease index was calculated: gray symbols, uninfected mice; open or black symbols, mice assayed 8 wpi. Solid gray horizontal lines indicate means. *, $P < 0.05$; **, $P < 0.01$ (Mann-Whitney test).

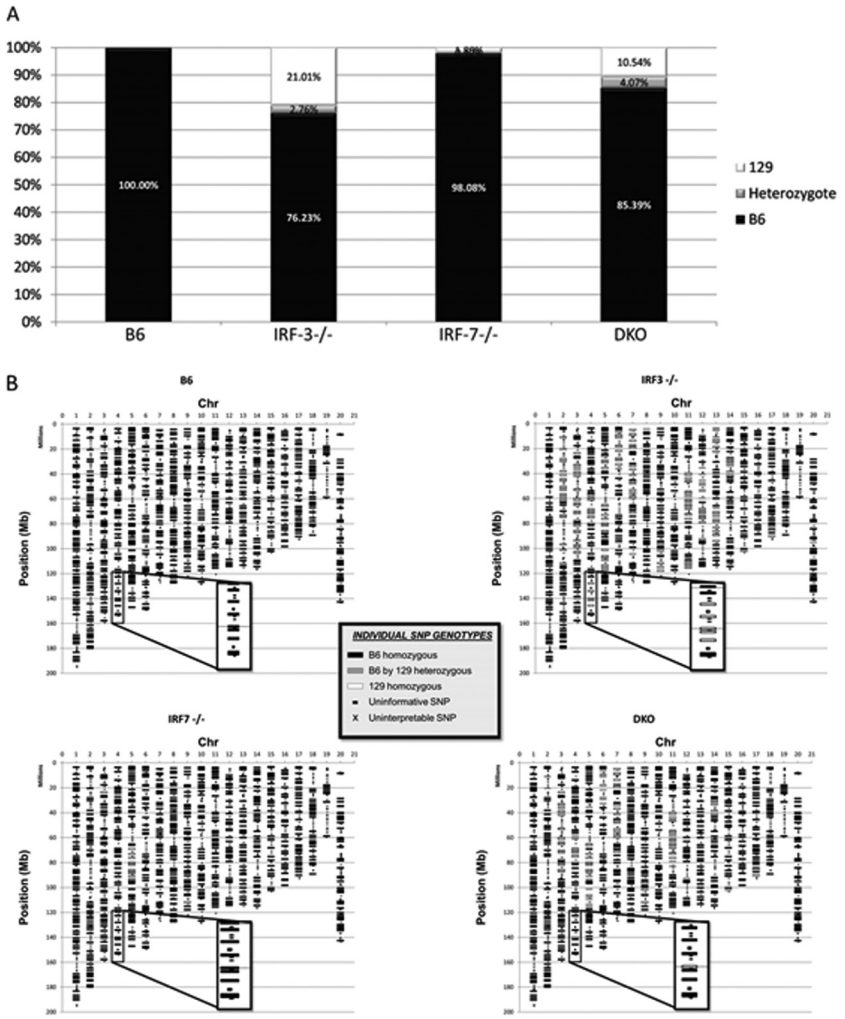

FIG 2 Strain 129 genetic contamination in IRF-3$^{-/-}$ and DKO mice. IRF-3$^{-/-}$, IRF-7$^{-/-}$, and DKO breeder mice were assessed at the DartMouse Speed Congenic Core Facility for overall genetic background in comparison to B6 and 129 mice (A) and SNP genetic analysis of individual chromosomes (Chr) (B). Additional strain 129 contamination on the distal portion of chromosome 4, the site of the *Fv1* gene (enlarged box), of IRF-3$^{-/-}$ and DKO mice is indicated.

was assigned, with disease severity ranging from 0 (no disease) to 5 (most-severe disease) (37–39). Infected IRF-3$^{-/-}$ mice were almost as resistant as MAIDS-resistant 129 mice, whereas IRF-7$^{-/-}$ mice developed disease equivalent to that seen with the susceptible B6 controls. Surprisingly, DKO mice succumbed to variable and intermediate disease, with some resistant mice, which was an unexpected result versus previous studies reporting increased susceptibility to infection with other viruses in IRF-3$^{-/-}$ and/or IRF-

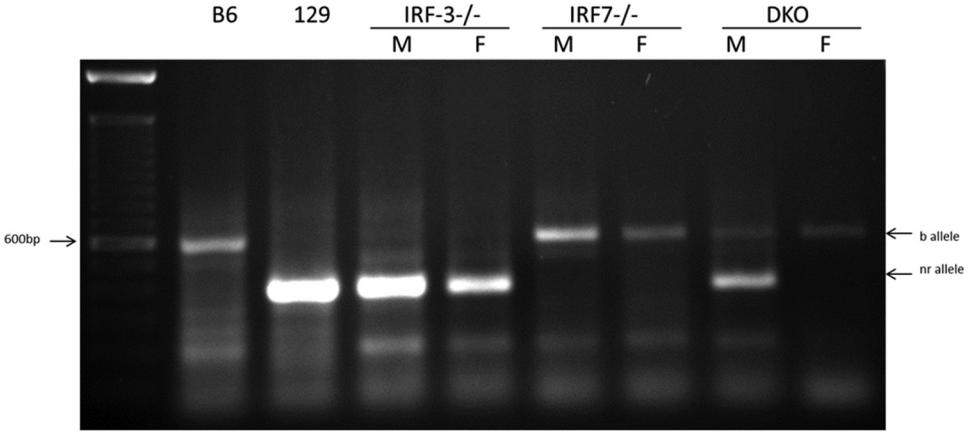

FIG 3 Strain 129-specific contamination of *Fv1* of IRF-3$^{-/-}$ and DKO mice. *Fv1* genotypes were determined with PCR and visualized by gel electrophoresis using genomic DNA from male (M) and female (F) B6, 129, IRF-3$^{-/-}$, IRF-7$^{-/-}$, and DKO breeder mice. Expected band lengths: *Fv1*^{b}, 621 bp; *Fv1*^{nr} allele, 406 bp.

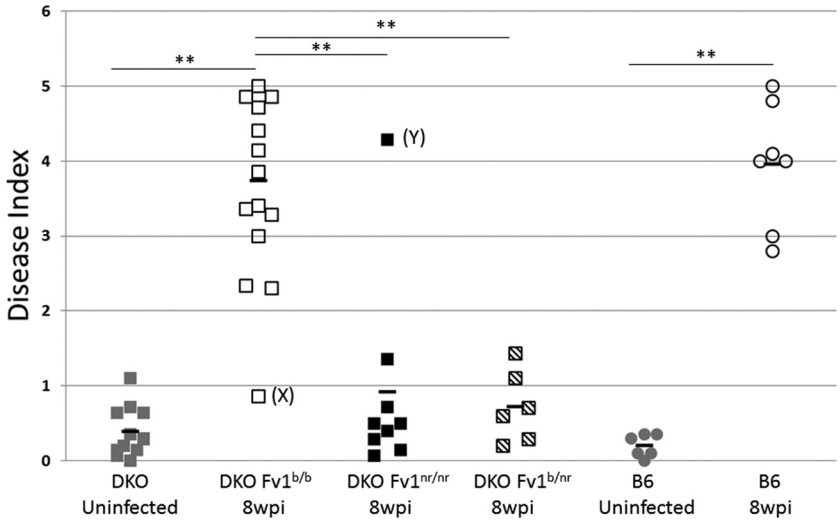

FIG 4 Presence of the *Fv1*^{nr} allele in DKO mice and resistance to MAIDS. DKO *Fv1*$^{b/b}$, DKO *Fv1*$^{nr/nr}$, DKO Fv1$^{b/nr}$, and B6 mice were infected with LP-BM5, and the disease index was calculated at 8 wpi. **, $P < 0.01$ (Mann-Whitney test). Outlier mice are indicated as "(X)" and "(Y)."

7$^{-/-}$ mice and equal or greater susceptibility in DKO mice (3, 10, 13, 14).

Therefore, the genetic backgrounds of breeder knockout mice were assessed for strain 129 genetic material originating from the original knockout construction (27, 40, 41). Upon high-density single nucleotide polymorphism (SNP) analysis (42), IRF-7$^{-/-}$ mice exhibited ~2% strain 129 contamination, consistent with full, standard backcrossing (Fig. 2A). However, IRF-3$^{-/-}$ (15% to 25%) and DKO (10% to 20%) mice had substantial 129 contamination (Fig. 2A): the intermediate contamination level of the DKO mice expected from their derivation by crossing IRF-3$^{-/-}$ and IRF-7$^{-/-}$ mice (10).

The *Fv1* gene restricts murine leukemia viruses (MLVs), including LP-BM5 (27, 40, 43, 44), with the *Fv1*^{b}, *Fv1*^{n}, and *Fv1*^{nr} alleles restricting N-tropic, B-tropic, and B- and N-tropic MLVs, respectively (27, 41, 45, 46). To ensure successful B-tropic LP-BM5 infectivity, our studies were performed with homozygous *Fv1*$^{b/b}$ (B6) mice. SNP analysis of IRF-3$^{-/-}$ and DKO mice identified 129 contamination, in part, at chromosome 4 (distal) in the area of *Fv1* (Fig. 2B) (47, 48). Engineered PCR primers specific for *Fv1* alleles allowed definition of IRF-7$^{-/-}$ breeders as uniformly *Fv1*$^{b/b}$; in contrast, IRF-3$^{-/-}$ breeders were defined as *Fv1*$^{nr/nr}$, marking these strains as permissive versus nonpermissive, respectively, to LP-BM5 infection (Fig. 3). DKO breeders were mixed, with *Fv1*$^{b/b}$ (susceptible) versus *Fv1*$^{b/nr}$ and *Fv1*$^{nr/nr}$ (resistant) DKO progeny (Fig. 3).

DKO progeny mice from controlled matings were produced to allow segregation of the *Fv1*^{b} and *Fv1*^{nr} alleles, genotyped, and infected with LP-BM5 to potentially correlate susceptibility and resistance phenotypes with the *Fv1* genotype rather than with knockout of *IRF-3* (Fig. 4). The disease index determined at 8 wpi, in comparison to susceptible B6 mice, demonstrated that (i) DKO *Fv1*$^{b/b}$ mice displayed equivalent disease and equal viral load (ecotropic *gag* and defective *gag*) (data not shown); (ii) infected DKO *Fv1*$^{nr/nr}$ and DKO *Fv1*$^{b/nr}$ mice, each with at least one resistant *Fv1*^{nr} allele, displayed significantly less disease; and (iii) there was a single outlier mouse in each ("X" with less disease and "Y" with more disease) for which SNP analysis revealed (~15%) 129 contamination within the range of DKO mice as a whole (data not shown) (Fig. 4). These DKO data thus strongly associate MAIDS pathogenesis with the observed strain 129 contamination and *Fv1* allelism in a manner independent of the status of the *IRF-3* gene.

Thus, on the basis of comparisons to LP-BM5-infected IRF-7$^{-/-}$ and B6 mice, we describe increased MAIDS resistance in infected IRF-3$^{-/-}$ and certain DKO mice, apparently a result of strain 129-derived contamination of the *Fv1*^{nr} allele in purportedly fully backcrossed (to B6) congenic IRF-3$^{-/-}$ mice. The inconsistent degrees of B6 genetic background in IRF-3$^{-/-}$, IRF-7$^{-/-}$, and DKO mice provide a cautionary note that results seen with these mice, in our studies and in those of others, may not be indicative solely of the knockout of the *IRF* gene(s) itself. The DKO mice have been bred at least three times independently from the single knockout mice, according to previous reports (3, 10, 13, 15, 35), and were previously reported to be of 91% B6 background, versus 97% for the IRF-7$^{-/-}$ mice, via analysis of microsatellite markers (15). These levels of contamination are similar to the B6 background levels observed here by SNP analyses: >98% in IRF-7$^{-/-}$, 75% to 85% in IRF-3$^{-/-}$, and 80% to 90% in DKO mice. The incomplete backcrossing to B6 of the IRF-3$^{-/-}$ mice and the 129-derived restrictive *Fv-1*^{nr} inheritance notwithstanding, the results from the two outlier DKO mice (Fig. 4) suggest the presence of additional strain 129-derived genetic elements that may also affect LP-BM5 infectivity or pathogenesis.

ACKNOWLEDGMENTS

We thank David Leib, Edward Usherwood, Jim Gorham, Cynthia Stevens, Kathy Green, Jessica Rastad, Matthew Ranson, Patrick Lizotte, Torrey Gallagher, Eugene Demidenko, and Sarah Hosford for many helpful discussions and technical assistance. We also thank David Leib for generously providing the IRF-3$^{-/-}$, IRF-7$^{-/-}$, and DKO mice to be used in these studies.

This work was supported by National Institutes of Health RO1 grant CA50157 to W.R.G. and a NIH T32 training grant (AI007363), which supported M.A.O. Flow cytometry was performed in the DartLab Flow Cytometry and Immune Monitoring Laboratory, which was established by the NIH Shared Instrument Program, and the Geisel School of Medicine at Dartmouth, which is supported in part by a Core Grant (CA23108) from the National Cancer Institute to the Norris Cotton Cancer Center and by NIH/NCRR NIGMS COBRE P20 (RR16437) and P30

(GM103415) grants from the Center of Biomedical Research Excellence in Molecular, Cellular, and Translation Immunological Research (principal investigator, W.R.G.), which also supports the DartMouse Speed Congenic Core Facility.

REFERENCES

1. **Daffis S, Samuel MA, Keller BC, Gale M, Jr, Diamond MS.** 2007. Cell-specific IRF-3 responses protect against West Nile virus infection by interferon-dependent and -independent mechanisms. PLoS Pathog. **3:**e106. http://dx.doi.org/10.1371/journal.ppat.0030106.
2. **Daffis S, Samuel MA, Suthar MS, Keller BC, Gale M, Jr, Diamond MS.** 2008. Interferon regulatory factor IRF-7 induces the antiviral alpha interferon response and protects against lethal West Nile virus infection. J. Virol. **82:**8465–8475. http://dx.doi.org/10.1128/JVI.00918-08.
3. **Daffis S, Suthar MS, Szretter KJ, Gale M, Jr, Diamond MS.** 2009. Induction of IFN-beta and the innate antiviral response in myeloid cells occurs through an IPS-1-dependent signal that does not require IRF-3 and IRF-7. PLoS Pathog. **5:**e1000607. http://dx.doi.org/10.1371/journal.ppat.1000607.
4. **Fu XY, Schindler C, Improta T, Aebersold R, Darnell, Jr, JE.** 1992. The proteins of ISGF-3, the interferon alpha-induced transcriptional activator, define a gene family involved in signal transduction. Proc. Natl. Acad. Sci. U. S. A. **89:**7840–7843. http://dx.doi.org/10.1073/pnas.89.16.7840.
5. **Hiscott J, Pitha P, Genin P, Nguyen H, Heylbroeck C, Mamane Y, Algarte M, Lin R.** 1999. Triggering the interferon response: the role of IRF-3 transcription factor. J. Interferon Cytokine Res. **19:**1–13. http://dx.doi.org/10.1089/107999099314360.
6. **Honda K, Taniguchi T.** 2006. IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. Nat. Rev. Immunol. **6:**644–658. http://dx.doi.org/10.1038/nri1900.
7. **Levy DE, García-Sastre A.** 2001. The virus battles: IFN induction of the antiviral state and mechanisms of viral evasion. Cytokine Growth Factor Rev. **12:**143–156. http://dx.doi.org/10.1016/S1359-6101(00)00027-7.
8. **Lin R, Heylbroeck C, Pitha PM, Hiscott J.** 1998. Virus-dependent phosphorylation of the IRF-3 transcription factor regulates nuclear translocation, transactivation potential, and proteasome-mediated degradation. Mol. Cell. Biol. **18:**2986–2996.
9. **Menachery VD, Leib DA.** 2009. Control of herpes simplex virus replication is mediated through an interferon regulatory factor 3-dependent pathway. J. Virol. **83:**12399–12406. http://dx.doi.org/10.1128/JVI.00888-09.
10. **Murphy AA, Rosato PC, Parker ZM, Khalenkov A, Leib DA.** 2013. Synergistic control of herpes simplex virus pathogenesis by IRF-3, and IRF-7 revealed through non-invasive bioluminescence imaging. Virology **444:**71–79. http://dx.doi.org/10.1016/j.virol.2013.05.034.
11. **Reich NC.** 2007. STAT dynamics. Cytokine Growth Factor Rev. **18:**511–518. http://dx.doi.org/10.1016/j.cytogfr.2007.06.021.
12. **Zimmerer JM, Lesinski GB, Radmacher MD, Ruppert A, Carson WE, 3rd.** 2007. STAT1-dependent and STAT1-independent gene expression in murine immune cells following stimulation with interferon-alpha. Cancer Immunol. Immunother. **56:**1845–1852. http://dx.doi.org/10.1007/s00262-007-0329-9.
13. **Honda K, Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, Shimada N, Ohba Y, Takaoka A, Yoshida N, Taniguchi T.** 2005. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature **434:**772–777. http://dx.doi.org/10.1038/nature03464.
14. **Schilte C, Buckwalter MR, Laird ME, Diamond MS, Schwartz O, Albert ML.** 2012. Cutting edge: independent roles for IRF-3 and IRF-7 in hematopoietic and nonhematopoietic cells during host response to Chikungunya infection. J. Immunol. **188:**2967–2971. http://dx.doi.org/10.4049/jimmunol.1103185.
15. **Steinberg C, Eisenächer K, Gross O, Reindl W, Schmitz F, Ruland J, Krug A.** 2009. The IFN regulatory factor 7-dependent type I IFN response is not essential for early resistance against murine cytomegalovirus infection. Eur. J. Immunol. **39:**1007–1018. http://dx.doi.org/10.1002/eji.200838814.
16. **Thackray LB, Duan E, Lazear HM, Kambal A, Schreiber RD, Diamond MS, Virgin HW.** 2012. Critical role for interferon regulatory factor 3 (IRF-3) and IRF-7 in type I interferon-mediated control of murine norovirus replication. J. Virol. **86:**13515–13523. http://dx.doi.org/10.1128/JVI.01824-12.
17. **Beignon A-S.** 2005. Endocytosis of HIV-1 activates plasmacytoid dendritic cells via Toll-like receptor-viral RNA interactions. J. Clin. Invest. **115:**3265–3275. http://dx.doi.org/10.1172/JCI26032.
18. **Browne EP.** 2011. Toll-like receptor 7 controls the anti-retroviral germinal center response. PLoS Pathog. **7:**e1002293. http://dx.doi.org/10.1371/journal.ppat.1002293.
19. **Browne EP.** 2013. Toll-like receptor 7 inhibits early acute retroviral infection through rapid lymphocyte responses. J. Virol. **87:**7357–7366. http://dx.doi.org/10.1128/JVI.00788-13.
20. **Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, Lipford G, Wagner H, Bauer S.** 2004. Species-specific recognition of single-stranded RNA via Toll-like receptor 7 and 8. Science **303:**1526–1529. http://dx.doi.org/10.1126/science.1093620.
21. **Lee H, Komano J, Saitoh Y, Yamaoka S, Kozaki T, Misawa T, Takahama M, Satoh T, Takeuchi O, Yamamoto N, Matsuura Y, Saitoh T, Akira S.** 2013. Zinc-finger antiviral protein mediates retinoic acid inducible gene I-like receptor-independent antiviral response to murine leukemia virus. Proc. Natl. Acad. Sci. U. S. A. **110:**12379–12384. http://dx.doi.org/10.1073/pnas.1310604110.
22. **Meier A, Alter G, Frahm N, Sidhu H, Li B, Bagchi A, Teigen N, Streeck H, Stellbrink HJ, Hellman J, van Lunzen J, Altfeld M.** 2007. MyD88-dependent immune activation mediated by human immunodeficiency virus type 1-encoded Toll-like receptor ligands. J. Virol. **81:**8180–8191. http://dx.doi.org/10.1128/JVI.00421-07.
23. **Yu P, Lübben W, Slomka H, Gebler J, Konert M, Cai C, Neubrandt L, Prazeres da Costa O, Paul S, Dehnert S, Döhne K, Thanisch M, Storsberg S, Wiegand L, Kaufmann A, Nain M, Quintanilla-Martinez L, Bettio S, Schnierle B, Kolesnikova L, Becker S, Schnare M, Bauer S.** 2012. Nucleic acid-sensing Toll-like receptors are essential for the control of endogenous retrovirus viremia and ERV-induced tumors. Immunity **37:**867–879. http://dx.doi.org/10.1016/j.immuni.2012.07.018.
24. **Cerny A, Hügin AW, Hardy RR, Hayakawa K, Zinkernagel RM, Makino M, Morse HC, III.** 1990. B cells are required for induction of T cell abnormalities in a murine retrovirus-induced immunodeficiency syndrome. J. Exp. Med. **171:**315–320. http://dx.doi.org/10.1084/jem.171.1.315.
25. **Morse HC, III, Yetter RA, Via CS, Hardy RR, Cerny A, Hayakawa K, Hugin AW, Miller MW, Holmes KL, Shearer GM.** 1989. Functional and phenotypic alterations in T cell subsets during the course of MAIDS, a murine retrovirus-induced immunodeficiency syndrome. J. Immunol. **143:**844–850.
26. **Buller RM, Yetter RA, Fredrickson TN, Morse HC, III.** 1987. Abrogation of resistance to severe mousepox in C57BL/6 mice infected with LP-BM5 murine leukemia viruses. J. Virol. **61:**383–387.
27. **Hartley JW, Rowe WP, Huebner RJ.** 1970. Host-range restrictions of murine leukemia viruses in mouse embryo cell cultures. J. Virol. **5:**221–225.
28. **Ho O, Green WR.** 2006. Cytolytic CD8+ T cells directed against a cryptic epitope derived from a retroviral alternative reading frame confer disease protection. J. Immunol. **176:**2470–2475.
29. **Khan IA, Green WR, Kasper LH, Green KA, Schwartzman JD.** 1999. Immune CD8(+) T cells prevent reactivation of Toxoplasma gondii infection in the immunocompromised host. Infect. Immun. **67:**5869–5876.
30. **Klinman DM, Morse HC, III.** 1989. Characteristics of B cell proliferation and activation in murine AIDS. J. Immunol. **142:**1144–1149.
31. **Klinken SP, Fredrickson TN, Hartley JW, Yetter RA, Morse HC, III.** 1988. Evolution of B cell lineage lymphomas in mice with a retrovirus-induced immunodeficiency syndrome, MAIDS. J. Immunol. **140:**1123–1131.
32. **Mayrand SM, Schwarz DA, Green WR.** 1998. An alternative translational reading frame encodes an immunodominant retroviral CTL determinant expressed by an immunodeficiency-causing retrovirus. J. Immunol. **160:**39–50.
33. **Mosier DE, Yetter RA, Morse HC, III.** 1985. Retroviral induction of acute lymphoproliferative disease and profound immunosuppression in adult C57BL/6 mice. J. Exp. Med. **161:**766–784. http://dx.doi.org/10.1084/jem.161.4.766.
34. **Mosier DE, Yetter RA, Morse HC, III.** 1987. Functional T lymphocytes are required for a murine retrovirus-induced immunodeficiency disease (MAIDS). J. Exp. Med. **165:**1737–1742. http://dx.doi.org/10.1084/jem.165.6.1737.
35. **Sato M, Suemori H, Hata N, Asagiri M, Ogasawara K, Nakao K, Nakaya T, Katsuki M, Noguchi S, Tanaka N, Taniguchi T.** 2000. Distinct and essential roles of transcription factors IRF-3 and IRF-7 in response to

viruses for IFN-alpha/beta gene induction. Immunity **13:**539–548. http://dx.doi.org/10.1016/S1074-7613(00)00053-4.
36. **Green KA, Noelle RJ, Green WR.** 1998. Evidence for a continued requirement for CD40/CD40 ligand (CD154) interactions in the progression of LP-BM5 retrovirus-induced murine AIDS. Virology **241:**260–268. http://dx.doi.org/10.1006/viro.1997.8970.
37. **O'Connor MA, Green WR.** 2013. The role of indoleamine 2,3-dioxygenase in LP-BM5 murine retroviral disease progression. Virol. J. **10:**154. http://dx.doi.org/10.1186/1743-422X-10-154.
38. **Rutkowski MR, Ho O, Green WR.** 2009. Defining the mechanism(s) of protection by cytolytic CD8 T cells against a cryptic epitope derived from a retroviral alternative reading frame. Virology **390:**228–238. http://dx.doi.org/10.1016/j.virol.2009.05.003.
39. **Rutkowski MR, Stevens CA, Green WR.** 2011. Impaired memory CD8 T cell responses against an immunodominant retroviral cryptic epitope. Virology **412:**256–268. http://dx.doi.org/10.1016/j.virol.2010.11.013.
40. **Pincus T, Hartley JW, Rowe WP.** 1971. A major genetic locus affecting resistance to infection with murine leukemia viruses. I. Tissue culture studies of naturally occurring viruses. J. Exp. Med. **133:**1219–1233.
41. **Steeves R, Lilly F.** 1977. Interactions between host and viral genomes in mouse leukemia. Annu. Rev. Genet. **11:**277–296. http://dx.doi.org/10.1146/annurev.ge.11.120177.001425.
42. **Trask H, Tomlinson C, Fiering S, Gorham JD, Muirhead K.** 2010. Introducing DartMouse: the mouse speed congenic facility at Dartmouth Medical School. J. Biomol. Tech. **21:**S70.
43. **Stoye JP.** 1998. Fv1, the mouse retrovirus resistance gene. Rev. Sci. Tech. **17:**269–277.
44. **Pincus T, Hartley JW, Rowe WP.** 1975. A major genetic locus affecting resistance to infection with murine leukemia viruses. IV. Dose-response relationships in Fv-1-sensitive and resistant cell cultures. Virology **65:**333–342.
45. **Hartley JW, Fredrickson TN, Yetter RA, Makino M, Morse HC, III.** 1989. Retrovirus-induced murine acquired immunodeficiency syndrome: natural history of infection and differing susceptibility of inbred mouse strains. J. Virol. **63:**1223–1231.
46. **Kozak CA.** 1985. Analysis of wild-derived mice for Fv-1 and Fv-2 murine leukemia virus restriction loci: a novel wild mouse Fv-1 allele responsible for lack of host range restriction. J. Virol. **55:**281–285.
47. **Rowe WP, Sato H.** 1973. Genetic mapping of the Fv-1 locus of the mouse. Science **180:**640–641. http://dx.doi.org/10.1126/science.180.4086.640.
48. **Taylor BA, Bedigian HG, Meier H.** 1977. Genetic studies of the Fv-1 locus of mice: linkage with Gpd-1 in recombinant inbred lines. J. Virol. **23:**106–109.