ANTIVIRAL IMMUNITY

Immune control of endogenous retroviruses

The Stock Solution

Endogenous retroviruses (ERVs) are non-functional remnants of ancient viral infections and constitute a substantial proportion of the mammalian genome. Some mouse strains are prone to ERV-induced pathologies, including tumour formation, whereas other mouse strains, such as the C57BL/6 strain, are resistant. Two studies published in *Immunity* and *Nature* now describe mechanisms involving Toll-like receptor 3 (TLR3), TLR7, TLR9 and antibodies that control ERV infectivity.

The sensing of exogenous retroviruses in the cytoplasm by nucleic acid-sensing TLRs has an important role in controlling these viruses, so Yu *et al.* sought to determine whether these TLRs also have a role in the response to ERVs. Indeed, the emergence of infectious ERVs was observed in aged triple-deficient *Tlr3*$^{-/-}$*Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ C57BL/6 mice. TLR7 was shown to have a central role in the control of ERV viraemia, with indirect roles for TLR3 and TLR9. Furthermore, the loss of TLR3, TLR7 and TLR9 resulted in the premature death of aged mice owing to the development of pre-T cell acute lymphoblastic leukaemia (T-ALL). By generating a T-ALL tumour cell line (termed Baki-1 cells) from *Tlr3*$^{-/-}$*Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice, the authors showed that retroviral integration into genomic DNA led to dysregulation of T cell-specific oncogenes, giving rise to T cell transformation.

But how does TLR signalling inhibit ERVs in wild-type mice? Exogenous infection of C57BL/6 mice with ERVs isolated from Baki-1 cells resulted in the expression of genes encoding acute-phase proteins in a TLR-dependent manner. Furthermore, ERV-resistant mouse strains expressed high levels of ERV-specific neutralizing antibodies, whereas these antibodies were absent in susceptible mouse strains, including in *Tlr3*$^{-/-}$*Tlr7*$^{-/-}$*Tlr9*$^{-/-}$ mice. The production of these antibodies was shown to be TLR7 dependent.

Young *et al.* also describe a role for antibodies in the control of infectious ERVs. In this study, the authors first determined the role of the adaptive immune system in preventing the establishment of infectious viruses derived from ERVs. They found that *Rag1*$^{-/-}$ mice (which lack functional B and T cells), but not wild-type C57BL/6 mice, harboured infectious ecotropic murine leukaemia viruses (eMLVs) that were transmitted vertically to progeny.

Next, the authors showed that the presence of infectious eMLVs in these mice was due to a defect in antibody production. Of note, the expression of eMLV genes was markedly increased in *Tlr7*$^{-/-}$ mice. Similar to the observations in the study by Yu *et al.*, aged *Rag1*$^{-/-}$ mice had increased morbidity compared with wild-type mice owing to the development of retrovirus-induced lymphomas.

Both studies associated distinct innate and adaptive immune deficiencies with the establishment of pathogenic infectious MLVs. However, in contrast to the study by Yu *et al.*, the study by Young *et al.* suggested that innate and adaptive immune components were controlling exposure to unrelated environmental microorganisms. The authors suggested that immune deficiency increased the translocation of microbial products from intestinal bacteria into the systemic circulation, which in turn activated ERVs. This was supported by the observation that neither *Rag1*$^{-/-}$ nor *Tlr7*$^{-/-}$ mice lost control of their ERVs if they were housed under conditions in which microbial exposure was reduced or prevented.

Together, these studies highlight the importance of the innate and adaptive immune system for the control of ERVs in mice with selective immune deficiencies.

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> “mechanisms involving Toll-like receptor 3 (TLR3), TLR7, TLR9 and antibodies that control ERV infectivity”

ORIGINAL RESEARCH PAPERS Yu, P. *et al.* Nucleic acid-sensing Toll-like receptors are essential for the control of endogenous retrovirus viremia and ERV-induced tumors. *Immunity* 8 Nov 2012 (doi:10.1016/j.immuni.2012.07.018) | Young, G. R. *et al.* Resurrection of endogenous retroviruses in antibody-deficient mice. *Nature* 24 Oct 2012 (doi:10.1038/nature11599)
FURTHER READING Duggal, N. K. & Emerman, M. Evolutionary conflicts between viruses and restriction factors shape immunity. *Nature Rev. Immunol.* **12**, 687–695 (2012)