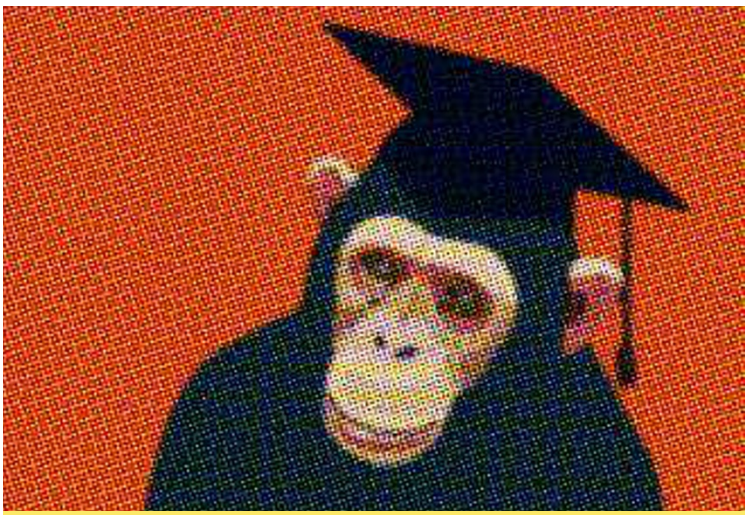

HIV

Learning from a monkey!

Why are some primates, such as sooty mangabeys, able to live with simian immunodeficiency virus (SIV) infection, whereas others, such as rhesus macaques, succumb to an AIDS-like disease? Understanding how sooty mangabeys resist disease could help to explain the mechanisms underlying HIV pathogenesis in humans. New research indicates that susceptibility or resistance to AIDS progression may stem from species-specific differences in the ability of plasmacytoid dendritic cells (pDCs) to produce interferon-α (IFNα) following exposure to the virus.

Although SIV establishes high levels of viraemia in infected sooty mangabeys, it does not cause the excessive, generalized immune activation that is associated with the development of AIDS in SIV-infected rhesus macaques and HIV-infected humans. To investigate the reasons behind this difference, Mandl *et al.* compared immune responses in the two monkey species. First, they found that the maturation and activation of pDCs (which have a key antiviral role by producing IFNα and inducing adaptive immune responses) was lower in infected sooty mangabeys than in infected rhesus macaques, such that pDCs did not migrate to lymph nodes in infected sooty mangabeys. Natural killer cells and $CD8^+$ T cells also showed limited expansion in infected sooty mangabeys.

Next, functional analyses revealed that, in contrast to pDCs from rhesus macaques and humans, pDCs from sooty mangabeys do not produce large amounts of IFNα on triggering of Toll-like receptor 7 (TLR7) and TLR9 signalling by several ligands, including inactivated virus. By contrast, the production of pro-inflammatory cytokines, such as interleukin-12, downstream of TLR7- and TLR9-mediated activation of nuclear factor-κB was the same in pDCs from both monkey species. This indicates that the defect in IFNα production in sooty mangabeys might involve the IFN-regulatory factor 7 (IRF7) pathway, which is specifically required for induction of IFNα expression. Consistent with this idea, sequence polymorphisms were identified in the transactivation domain of IRF7 in sooty mangabeys, whereas TLR7 and TLR9 sequences were highly conserved between the two monkey species and humans.

Based on these observations, the authors propose that the attenuated IFN response to SIV in sooty mangabeys is an evolutionary adaptation that enables them to avoid generalized immune activation during chronic virus infection.

Lucy Bird

ORIGINAL RESEARCH PAPER Mandl, J. N. *et al.* Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and nonpathogenic AIDS virus infections. *Nature Med.* **14**, 1077–1087 (2008)
FURTHER READING O'Connell, K. & Siliciano, R. F. Immune alteration fends off AIDS. *Nature Med.* **14**, 1016–1018 (2008)