Toll recognition of viral RNA

The innate immune response to viral infection involves recognition of double-stranded RNA (dsRNA) by intracellular molecules, including the dsRNA-dependent protein kinase PKR. However, PKR-deficient cells can respond to the dsRNA analog poly(I:C), which suggests the existence of additional pathways for dsRNA recognition. In *Nature*, Flavell and colleagues show that mammalian TLR3 recognizes dsRNA. TLR3-deficient mice showed reduced responses to poly(I:C) and viral genomic dsRNA. In addition, these mice were resistant to poly(I:C)-induced shock upon D-galactosamine sensitization and reduced production of inflammatory cytokines. TLR3-induced cytokine production after poly(I:C) recognition was MyD88-dependent, whereas poly(I:C)-induced NF-κB, MAPK and dendritic cell activation was MyD88-independent. The relevance of TLR3 in the antiviral response remains to be determined.

Nature **413**, 732–738 (2001)

Protection against prion diseases

As the incidence of variant Creutzfeldt-Jacob disease rises, the development of prophylactic treatment will be important. However, vaccines may be ineffective against prion diseases because endogenous cellular prion proteins (PrP^cs) are poor immunogens. In *Science*, Heppner *et al.* circumvent this problem by expressing an anti-PrP immunoglobulin μ chain in PrP-deficient mice. These mice developed sustained anti-PrP titers, which were not suppressed by introduction of the $Prnp^+$ allele. No prion infectivity could be detected in the mice after inoculation of the brain and spleen with scrapie prions. Resistance was not due to down-regulation of Prp^c in the brain and spleen, which suggests acquired immunity was responsible for protection. These results show that *in vivo* immunological protection against prion diseases is possible.

Science **294**, 178–182 (2001)

The origin of HSCs

The origin of hematopoietic stem cells (HSCs) is a matter of much controversy because both the yolk sac and the intraembryonic region of vertebrate embryos show hematopoietic activity. In *Immunity*, two groups have identified the origins of HSCs. Cumano *et al.* and Tavlan *et al.* separated mouse and human yolk sac (YS) and intraembryonic splanchnopleura (Sp), respectively, before circulation was established. Cells from explanted mouse YS and Sp were transferred into alymphoid mice. Sp-derived precursors generated muti-lineage hematopoietic progeny in adult mice, whereas YS cells provided short-term myeloid reconstitution. Explanted human embryonic tissues were cultured in the presence of stromal cells to promote myeloid and B cell differentiation and with mouse fetal thymus tissue to analyze the T cell potential. Again, only human Sp cells generated muti-lineage lymphomyeloid progenitors. These results show that HSCs originate from intraembryonic human and mouse tissue.

Immunity **15**, 477–485 and 485–497 (2001)

Nef is Bad

The HIV Nef protein is an important virulence factor that has several functions including the enhancement of virus replication. Nef can bind and activate p21-activated kinase (PAK), but its specific role in Nef function is unclear. In *Nature Medicine*, Wolf *et al.* show that Nef-mediated PAK activation plays a role in blocking T cell apoptosis. Nef-mediated PAK activation was dependent on PI3K, which was also bound and activated by Nef. The Nef-associated PI3K-PAK complex induced phosphorylation of the pro-apoptotic Bad protein in a PKB kinase–independent manner. Bad phosphorylation blocked T cell apoptosis induced by HIV replication. Thus, these results show a molecular function for Nef-associated PAK. The anti-apoptotic effects of Nef may be crucial for HIV replication in the host and ultimately to disease pathogenesis.

Nature Med. **7**, 1217–1224 (2001)

Memory CTL requirements

How memory cytolytic T cells (CTLs) arise remains controversial. In the *Journal of Clinical Investigation* Manjunath and colleagues show memory CTL development is largely dependent upon the cytokine *mileau* that antigen-activated $CD8^+$ T cells encounter. Both IL-15 and low doses of IL-2 generated memory T cells from T-GFP–transgenic $CD8^+$ cells that recognized the LCMV peptide GP33–41. IL-15 could also redirect memory CTL development in cells that were activated with high doses of IL-2, which normally induce effector CTLs. Unambiguous characterization of the memory or effector CTL response was based upon multiple functional and phenotypic traits, including *in vivo* recall and homing preferences. This use of IL-15 in generating memory CTLs yields the promise of more effective vaccination strategies.

J. Clin. Invest. **108**, 871–878 (2001)

Knotty solution for IL-17

Activated T cells express isoforms of the pro-inflammatory cytokine IL-17, which regulates the cartilage and extracellular matrix turnover that characterize joint destruction in rheumatoid arthritis. In the *EMBO Journal*, Hymowitz *et al.* report the solution of the structure of human IL-17F, which was resolved to 2.85 Å. IL-17F induces fibroblast synthesis of IL-8 and G-CSF as well as IL-6 production and proteoglycan shedding in human and porcine joint explants. Although the biological effects of IL-17F were observed at nanomolar concentrations, no binding to known IL-17A receptors was observed at higher concentrations, suggesting other molecules conferred high-affinity binding. The IL-17F structure showed a surprising similarity to neutrophilins, such as NGF, and other cysteine knot proteins. This structural analogy leads the way for designing therapeutic compounds that might lessen the tissue damage that ensues in inflammatory joint diseases.

EMBO J. **20**, 5332–5341 (2001)

Catch and release by mast cell FYB

The Fyn-binding adaptor protein FYB, also known as SLAP-130, regulates TCR signaling. In the *Proceedings of the National Academy of Science, USA*, Geng *et al.* report FYB expression in mast cells, where it regulates integrin-mediated adhesion and mediator release upon FcεRI receptor cross-linking. Overexpression of FYB led to increased adhesion to fibronectin without altering integrin expression. Similarly, increases in wild-type FYB resulted in enhanced secretory molecule release. But, unlike the potentiation of adhesion, FYB mutants lacking the COOH-terminal SH3 domain failed to trigger increased secretion. Thus, distinct domains in FYB link FcεRI signaling to adhesion and mediator release.

Proc. Natl Acad. Sci. USA **98**, 11527–11532 (2001)