Pathogenic maternal Ig

The role of maternally transmitted islet-reactive autoantibodies in the development of autoimmune diabetes mellitus is unclear. In *Nature Medicine*, Greeley *et al.* blocked maternal transmission, in NOD mice, of an Ig that reacts with islet β cells in order to investigate its influence on the susceptibility of progeny to diabetes. In the first of three strategies, NOD mice that lacked B cells (and, hence, maternal antibodies) were studied. In another approach Ig-transgenic mice were used to exclude autoreactive Ig specificities. Finally, NOD embryos were implanted into nonautoimmune pseudopregnant mice. In all cases, NOD progeny were protected from spontaneous diabetes. Thus, transmission of maternal Ig could play a potentially pathogenic role in the development of diabetes in susceptible individuals.

Nature Med. **8**, 399–402 (2002)

Critical B cell adapter

BCAP is an adapter protein that regulates BCR-mediated PLC-γ2 and PI3K activation *in vitro.* In the *Journal of Experimental Medicine*, Yamazaki *et al.* investigate the role played by BCAP in B cell development and function by generating BCAP-deficient mice. BCAP-deficient mice were viable but showed decreased numbers of mature B cells and B1 cell deficiency. The BCAP-deficient mice produced less serum IgM and IgG3 compared to wild-type mice and exhibited impaired responses to T cell–independent type II antigens. In addition, splenic BCAP-deficient B cells showed reduced Ca^{2+} mobilization and poor proliferative responses after BCR cross-linking. These results suggest that BCAP plays a critical immunoregulatory role in B cell activation and maturation.

J. Exp. Med. **195**, 535–545 (2002)

IS independence

The immunological synapse (IS) is thought to concentrate TCRs in the center of the T cell–APC contact interface and facilitate sustained TCR signaling for up to 20 h. In *Science*, Shaw and colleagues show that T cell engagement and activation begin before the IS is fully formed. Lck and ZAP-70 signaling in naïve T cells occurred primarily in the periphery of the synapse and was largely abated before the mature synapse had formed. This was consistent with the observation that TCRs were rapidly lost from the synapse after 30 min and that activation of naïve T cells only required 2 h of T cell–APC contact. Therefore, the clustering of TCRs *via* the IS is not required to initiate or sustain TCR signaling as previously thought.

Science **295**, 1539–1542 (2002)

Key AID for modification

Ig genes can undergo further genetic changes, including somatic hypermutation and isotype switching, upon B cell encounter with cognate antigen. Both processes are blocked in activation-induced deaminase (AID)-deficient individuals. In *Nature*, Honjo and colleagues expressed AID in fibroblasts containing artificial Ig switch substrates. Switch recombination occurred on transcriptionally active templates and exhibited features first characterized in B cells. Thus, AID appears to be the only B cell–specific factor required for the class switch recombination machinery. In *Science*, Arakawa *et al.* show AID is also required for Ig gene conversion, the major means of Ig diversification in chickens. AID is highly expressed in the bursa of Fabricus where gene conversion occurs. Disruption of the AID gene blocked Ig diversification in a chicken B cell line; this defect was repaired by transfection of AID cDNA. Still unresolved is how AID effects these Ig gene modifications.

Nature advance online publication, 3 March 2002 (DOI: 10.1038/nature727); *Science* **295**, 1301–1306 (2002)

Artemis opens RAG hairpins

RAG-mediated DNA cleavage of V(D)J recombination signal sequences (RSS) generates blunt-ended RSS that form signal joints and hairpin coding ends that can undergo further diversification before ligation to form coding joints. The physiologically relevant enzymes responsible for DNA hairpin opening were unknown. In *Cell*, Ma *et al.* show that Artemis complexes with the catalytic subunit of DNA-dependent protein kinase, DNA-PK. Artemis by itself has 5′ to 3′ exonuclease activity, but DNA-PK phosphorylates Artemis, converting it into an endonuclease that can cleave RAG-generated hairpin ends in Mg^{2+} buffers. Artemis mutants share the phenotype exhibited by DNA-PK mutants–hypersensitivity to DNA double-stranded breaks and an absence of B and T cells. Thus, the Artemis-DNA-PK complex may be responsible for hairpin opening *in vivo* during V(D)J recombination.

Cell immediate early publication, 1 March 2002 (DOI 10.1016/S0092867402006712)

Context sensitivity

Activation of MHC class II transcription relies on recruitment of CIITA and the MHC class II enhanceosome organizer RFX. In the *EMBO Journal*, Masternak and Reith show promoter-context sensitive differences in MHC locus expression. Quantitative ChIP assays of human B cells deficient for either CIITA or RFX indicated that their respective contributions vary in their ability to direct pretranscriptional initiation steps at the closely related MHC class II genes *DRA*, *DPB*, *DMB* and *Ii*. At the latter two promoters, RFX supports CIITA-independent acetylation of core histones and recruitment of general transcription factors, indicating that RFX is not merely a landing pad for CIITA for MHC class II expression. However, CIITA plays additional post-assembly roles to activate transcription of these genes.

EMBO J. **21**, 1379–1388 (2002)

RIP2 links innate to T_H1

Receptor-interacting protein 2 (RIP2) is a serine-threonine kinase previously associated with the generation of innate immune responses to LPS and intracellular bacterial pathogens. Two reports in *Nature* reveal that RIP2 also plays a role in activating T_H1 responses. Chin *et al.* generated $RIP2^{-/-}$ mice that display impaired NF-κB responses, decreased resistance to Listeria infections and defects in mounting T_H1 responses. IFN-γ, but not IL-4, production was impaired in $RIP2^{-/-}$ lymphocytes. Kobayashi *et al.* show reduced cytokine production by $RIP2^{-/-}$ cells in response to TLR2, TLR3 and TLR4, but not TLR9, and to IL-1, IL-18 and NOD signals. RIP2 was required for optimal T cell activation. Thus, RIP2 transduces signals necessary for both innate and adaptive immune responses.

Nature **416**, 190–194 & 194–199 (2002)