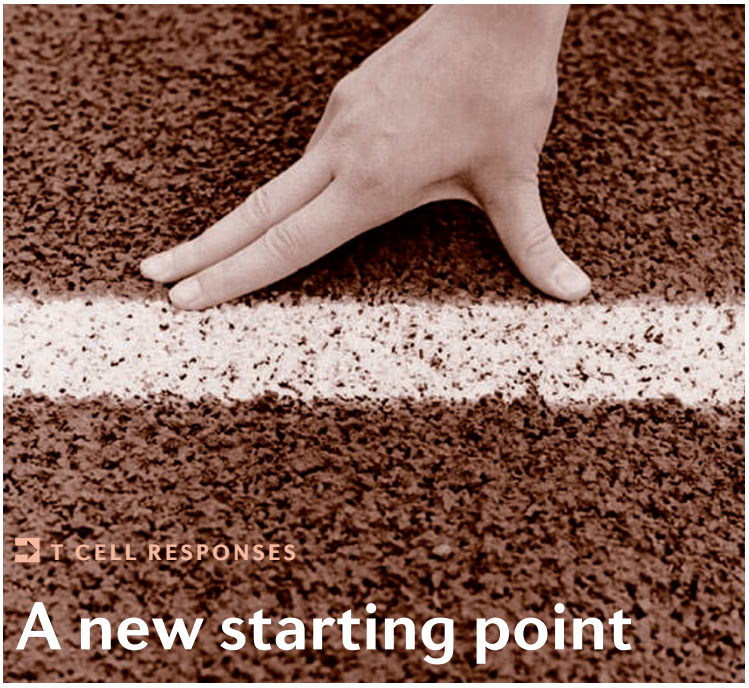

T CELL RESPONSES

A new starting point

A study published in *PLoS Biology* has challenged current dogma on the importance of lymph nodes in the initiation of adaptive immune responses. It shows that the induction of T cell responses, but not B cell priming and affinity maturation, can occur in the liver in the absence of lymphoid tissues.

Because alymphoplasia (*aly/aly*) mice — which are devoid of lymph nodes and Peyer's patches and have structural defects in the spleen and thymus — have severe immune defects and do not respond to immunization, it was thought that lymphoid tissues are essential for the initiation of adaptive immune responses. The defect in *aly/aly* mice is due to a point mutation in the essential component of the non-canonical nuclear factor-κB (NF-κB) pathway NIK (NF-κB-inducing kinase), which is required for CD40 and lymphotoxin-β receptor signalling in some cell types.

The authors found that experimental autoimmune encephalomyelitis (EAE) could not be initiated in *aly/aly* mice in response to subcutaneous immunization with myelin oligodendrocyte glycoprotein (MOG) peptide in complete Freund's adjuvant (CFA). However, immunization of bone marrow chimeric mice (*aly/+→aly/aly* mice) that retain the lymphoid tissue defects but have normal haematopoietic cells resulted in the induction of T cell-mediated EAE. Furthermore, EAE still developed in splenectomized *aly/+→aly/aly* mice, indicating that the immune defect in *aly/aly* mice is not due the loss of lymphoid tissues but due to the underlying genetic defect in haematopoietic cells. However, in contrast to control (*aly/+→aly/+*) mice, splenectomized *aly/+→aly/aly* mice did not develop high-affinity, class-switched MOG-specific antibodies, indicating (among other observations) that lymph nodes are essential for B cell activation.

But how is a T cell-mediated immune response to subcutaneous antigen initiated in the absence of lymphoid tissues? The authors showed that antigen delivered subcutaneously is transported by antigen-presenting cells to the liver of splenectomized *aly/+→aly/aly* mice. In addition, massive leukocyte infiltration and accumulation following MOG–CFA immunization was observed in the liver, and these neo-lymphoid aggregates could support $CD4^+$ T cell proliferation. Interestingly, proliferating $CD4^+$ T cells were also observed in the liver of control mice following immunization, albeit at much lower numbers. In addition to $CD4^+$ T cell activation, potent vaccination-induced antitumour cytotoxic $CD8^+$ T cell responses could also be initiated in the liver in the absence of lymphoid tissues.

Finally, immunization of *plt/plt* mice — which have severely disrupted lymph node T cell zones but intact B cell zones owing to a defect in T cell- and dendritic cell-homing to lymphoid organs — with MOG–CFA resulted in the formation of lymphoid aggregates in the liver and the (delayed) induction of EAE. This observation confirmed that the liver is an alternative site for T cell priming.

Given the importance of the fetal liver as a primary lymphoid organ during development and the fact that lymphocytes accumulate in the liver of some cold-blooded vertebrates following immunization, the authors propose that the liver is an evolutionarily conserved natural extra-lymphoid tissue for the initiation of cell-mediated immune responses.

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ORIGINAL RESEARCH PAPER Greter, M., Hofmann, J. & Becher, B. Neo-lymphoid aggregates in the adult liver can initiate potent cell-mediated immunity. *PLoS Biol.* **7**, e1000109 (2009)