

## Research group Reina Mebius

Generation of an immune response is dependent on efficient interaction of rare antigen-specific T cells with dendritic cells that present the antigen. The likelihood that these two infrequent cells encounter each other is greatly enhanced by the existence of lymph nodes which are organized to mediate efficient interaction of these cell subsets. Thus, lymph nodes are viewed as professional immune response factories. Moreover, they are formed during embryogenesis as a direct result of the interaction between stromal **organizer** cells and hematopoietic **inducer** cells. This leads to the production of chemokines and adhesion molecules by organizer cells, attracting more hematopoietic cells. Within inflammatory lesions that are characteristic of autoimmune disease, a similar interaction of organizer and inducer cells can be envisioned. Stromal fibroblasts can be viewed as organizer cells, which upon continuous triggering by activated lymphocytes, produce factors that recruit and retain other cells. This may lead to the formation of tertiary lymphoid structures, found in inflammatory lesions of autoimmune patients, which at times show a similar organization as seen in lymph nodes. It is likely that a high degree of organization will worsen the disease since efficient presentation of autoantigen enhances activation of autoreactive T cells.

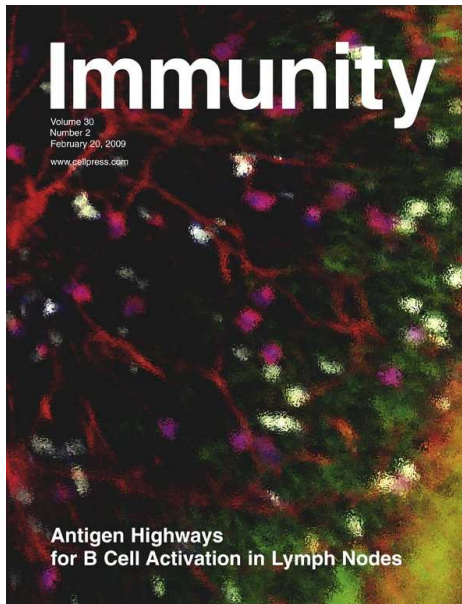
We are delineating the cellular and molecular mechanisms that initiate lymph node formation. Hereto we are defining the molecular mechanisms that mediate the differentiation of stromal cells towards organizing cells, allowing the attraction of hematopoietic cells to the developing lymph nodes. Furthermore, similar processes are studied during the development of tertiary lymphoid structures in chronic inflammatory diseases.

Within adult lymph nodes these stromal cells have been differentiated into reticular fibroblasts that enwrap the reticular fibers, which allow rapid transport of molecules such as antigens, chemokines, and cytokines to the inner part of the lymphoid organs. Many dendritic cells are covering these reticular fibroblasts and their interaction can be seen as an anchoring within the lymphoid tissues until they pick up antigen from the conduit that needs to be presented or receive stimulatory signals that mediate their maturation. One can envision that interaction of dendritic cells with stromal fibroblasts is not merely a means of attachment, but that reticular fibroblasts also provide cues to these dendritic cells for their functioning.

We are studying the influence of reticular fibroblasts on the ability of dendritic cells to induce either skin or gut homing molecules on lymphocytes. When antigen enters the body, it is taken up by dendritic cells (DCs), which present the antigen to lymphocytes in tissue draining lymph nodes (LNs). During this process DCs, coming from either peripheral or mucosal sites, are able to induce the expression of adhesion molecules and chemokine receptors on T cells to ensure that activated T cells, upon LN exit, will preferentially return to the site where DCs initially encountered the antigen. For homing of T lymphocytes to the gut, expression of gut homing molecules  $\alpha_4\beta_7$  and CCR9 is required. The expression of these molecules is induced by retinoic acid (RA), a vitamin A metabolite produced by retinal dehydrogenases (RALDHs), which are specifically expressed in DCs in gut associated lymphoid tissues (GALT).

By transplantation of mucosal lymph node to peripheral sites as well as in vitro cultures we have shown that reticular stromal cells are crucial for the induction of gut homing molecules and that cooperation of sessile LN stromal cells with mobile dendritic cells warrants the imprinting of tissue specific homing receptors on activated T cells.

## Highlights 2008/2009



On the cover: Pathways by which antigens reach sites of B cell activation in secondary lymphoid organs are only beginning to be explored. Roozendaal et al. (pages 264–276) show that follicular conduits of the lymph node channel small-molecular-weight antigens from the subcapsular sinus directly to B cells for immediate uptake and activation. The cover is an artistic rendition of an intravital micrograph depicting turkey egg lysozyme (red) entering a lymph node follicle through conduits and accumulating on lysozyme-specific B cells (blue), although entry of lysozyme conjugated to phycoerythrin (green) is delayed. Image by Thorsten Mempel. See also Preview by Harwood and Batista.