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ENGLISH SUMMARY

A hallmark of the immune system is its ability to efficiently respond to a wide range of foreign antigens without provoking an inappropriate response to self-antigens (body's own antigens). To achieve this, strategically positioned lymph nodes (LNs) provide the infrastructure for efficient immune cell surveillance and when necessary, for robust immune responses to foreign antigens. LNs have several important functions including filters for antigens, recruitment of antigen-presenting cells (APCs) and naïve lymphocytes, initiation of adaptive immune responses against foreign antigens and suppression of immune response against self-antigens. To manage these various activities within a LN, an additional layer of organization is required, which is achieved by non-hematopoietic lymph node stromal cells (LNSCs). LNSCs play a key role in migration and survival of lymphocytes, and suppression of self-reactive immune cells. Moreover, LNSCs organize the LN into functional niches that allow the separation of adaptive immune cells (T- and B-lymphocytes). These compartments facilitate the interaction of rare antigen-specific lymphocytes with their cognate antigen, resulting in an appropriate and fast adaptive immune response to foreign antigens.

Upon entry of infectious agents (viruses, bacteria etc.) into the body, dendritic cells (DCs) will capture these infectious agents at the site of infection and transport them to the nearest LN to initiate an adaptive immune response against these foreign antigens. However, DCs located in the skin need to first traverse and degrade a collagen-rich layer in the dermis to reach the lymphatics vessels. We showed in **chapter 2** that mice with altered collagen fibrillogenesis, resulting in thicker collagen fibers in the dermis, displayed a reduced DC migration from the skin towards the LNs. Consequently, the qualitative outcome of the adaptive immune response was significantly impaired in mice with altered collagen fibrillogenesis. We provided novel evidence, using a mouse model, that altered collagen fibrillogenesis has severe consequences for the initiation of an efficient adaptive immune response triggered in the skin.

However, DCs are also capable of carrying self-antigens to LNs. Activation of immune cells against self-antigens is dangerous as this may initiate autoimmunity. Therefore, strategic positioning of LNs is also required to suppress the activation of T cells ($CD8^+$ and $CD4^+$ T cells) that might be interacting with DCs carrying self-antigens. Here, LNSCs have been shown to control the activation of self-reactive $CD8^+$ and $CD4^+$ T cells by presenting self-antigens via major histocompatibility complex (MHC) class I and class II molecules respectively. Interestingly, it has been shown that the lack of MHC class II molecules on LNSCs results in the reduction of T regulatory (T_{REG}) cells. This is very important since T_{REG} cells are a subpopulation of T cells that control the immune system, by suppressing the immune response to self-antigens, and avoid autoimmune disease. Here in this thesis

in **chapter 3**, we provided additional novel mechanisms by which self-antigen presentation by murine LNSCs resulted in the conversion of self-reactive $CD4^+$ T cells into T_{REG} cells, thereby safeguarding the immune homeostasis by limiting immune reactivity. Moreover in **chapter 4**, we showed that LNSCs that drain different organs are functionally distinct. We demonstrated in **chapter 4** that skin-associated self-antigens are restricted to stromal cells in skin-draining LNs while gut-draining LNs lack the expression of such self-antigens. Consequently, conversion of self-reactive $CD4^+$ T cells into T_{REG} cells was restricted to skin-draining LNs. Furthermore, we showed that the regulatory function of LNSCs is hampered upon activation of LNSCs, as conversion of $CD4^+$ T cells into T_{REG} cells was completely diminished upon Lipopolysaccharide (LPS) stimulation of LNSC. This is very important since infectious agents are the major postulated environmental triggers that can initiate or exacerbate autoimmunity. It may thus be that LNSCs lose their immunosuppressive capacity upon pathogen invasion, and thereby contribute to the initiation of autoimmunity.

Nevertheless, the key problem in various autoimmune diseases such as Rheumatoid Arthritis (RA) is the production of autoantibodies by B cells years before the onset of disease. B cell growth, differentiation and survival is coordinated by a specialized subset of T helper cells known as T follicular helper (T_{FH}) cells. Upon T_{FH}-B cells interaction, T_{FH} and B cells migrate to the center of the B cell area and form a distinct substructure called germinal center (GC). T_{FH} cells are speculated to be the central players in the pathogenesis of autoimmune diseases by steering selective expansion of high-affinity self-reactive B cells. Using LN transplantations, we showed in **chapter 3** that expression of a defined self-antigen (i.e. Ovalbumin, Ova) by LNSCs restricts the expansion of self-reactive T_{FH} cells. As a consequence of the control over T_{FH} cells, the presentation of Ova as a self-antigen by LNSCs also restricted the development of self-reactive B cells against Ova within transplanted LNs. Overall, we showed that LNSCs can further control the activation of immune cells by generating T_{REG} cells and suppress the activation of autoreactive T_{FH} cells and B cells.

Mouse data has shown the importance of LNSCs in suppressing the activation of self-reactive T cells, while such studies for human LNSCs and their potential role in autoimmunity such as RA are lacking. To ultimately cure or prevent this destructive disease it is essential to understand the earliest changes in the immune system. Therefore, we started to collect and study unique human LN biopsies obtained during the preclinical and earliest phases of RA and study the regulatory function of LNSCs in these patients. Our characterization of human LNSCs, described in **chapter 5**, showed an effect of human LNSCs on T cell proliferation which was ratio-dependent and altered in LNSCs obtained from RA patients. This suggests that the immunoregulatory functions of stromal cells in the LNs of (pre-clinical) RA patients are altered and that LNSCs from (pre-clinical) RA patients may create a microenvironment that contribute to the early activation

of self-reactive T- and B-cells within LNs at the initiation phase of the disease. Moreover, our results presented in **chapter 6** showed that human LNSCs, similar to mouse LNSCs, possess antigen presentation machineries and express various self-antigens, therefore they have the ability to present self-antigens in the context of MHC class I or II to T cells.

The capacity of LNSCs to control self-reactive T cells may also be used to manipulate the antitumor response, as interfering with this function of LNs could allow a productive adaptive immune response to tumor antigens, which are often self-antigens. In **chapter 7** we show that we indeed observed an elevated frequency of T_{REG} cells in the tumor draining-LNs in different tumor models, which correlated with an increase in MHC class II expressing LNSC when compared to WT mice that lacked tumors. Therefore, we can speculate that alterations in the frequency of antigen presenting LNSCs may alter the T_{REG} cell frequencies, resulting in either a more productive suppression or activation of the adaptive immune responses against self-antigens, depending on the changes in LNSCs (Figure 1).

Overall, this hypothesis will require future studies, using mouse and human experimental models, to decipher the mechanism by which LNSCs control T cell mediated B cell responses. This may ultimately lead to the identification of innovative targets for immunomodulation and treatment of RA.

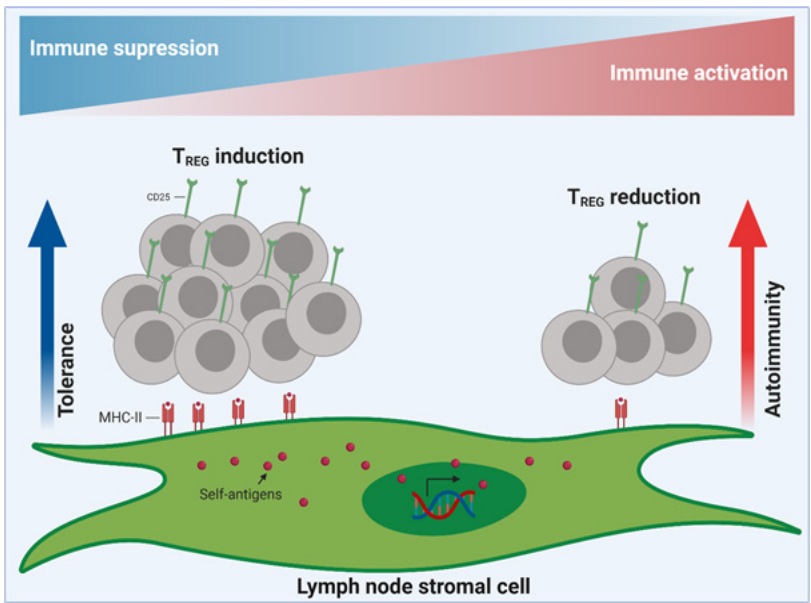

Figure 1. The hypothetical immuneregulatory function of lymph node stromal cells (LNSCs) in inducing or reducing regulatory T (T_{REG}) cells. Increased expression of self-antigens and MHC class II by LNSCs might result in the induction of T_{REG} cells against self-antigens therefore forming a suppressive microenvironment within the LNs. Decreased expression of self-antigens and MHC class II might reduce T_{REG} cells and increase the activation of self-reactive T cells against self-antigens.