T cell differentiation in autoimmune diseases
van der Graaff, W.L.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 9

Summary and general discussion
Chapter 9

The balance between different T cell subsets is believed to play a role in development or prevention of autoimmune diseases. Especially an imbalance in the mutually antagonizing type-1 and type-2 T cells could result in damage to the host. Type-1 cells are pro-inflammatory and it has been postulated that an overshoot type-1 immune response could lead to organ-specific autoimmune disease such as arthritis, multiple sclerosis, thyreoiditis and diabetes mellitus. Type-2 cells on the other hand are effective inducers of antibody production by B cells and can antagonize the effects of type-1 T cells. Unopposed type-2 reactivity could lead to antibody-mediated disease such as allergy and systemic lupus erythematosus. In this thesis it has been tested if the balance between T helper 1 and T helper 2 cells plays a role in human rheumatic diseases. Both cell types were identified by flowcytometry with antibodies against IFN-γ, a prototypical T helper 1 cytokine and IL-4, a marker for type-2 T cells.

As shown previously, synovial fluid (SF) T cells of rheumatoid arthritis patients are primed cells as they express CD45RO and CD95. However while both type-1 and type-2 cells can be found in the peripheral blood of rheumatoid arthritis patients, SF T cells have predominantly a type-1 phenotype. This finding is not specific for rheumatoid arthritis but can also be observed in reactive arthritis, undifferentiated arthritis and psoriatic arthritis (chapter 2).

Whether this is a result of a mechanism where type-1 T cells are preferentially homing from the blood to the inflamed synovium or that after entry, type-1 cells can further differentiate in the synovium while type-2 cells are inhibited in their differentiation process is not entirely clear, but support for both mechanisms can be found.

The possibility of selective homing is supported by the observation that type-1 T cells express the adhesion molecule CD49d (alpha4) (chapter 5) and chemokine receptors like CCR5 and CXCR-3 of which the ligands are abundantly expressed on endothelial cells and in the extracellular matrix of the inflamed synovium (VCAM-1, Fibronectin, RANTES, IP-10 and MIG, respectively).

Chapter five gives in vivo support for the selective homing of type-1 T cells to the rheumatoid synovium. The humanized monoclonal antibody CA2 blocks the activity of TNF-α and is shown to interfere with the inflammatory cascade in the joints. This results in the downmodulation of adhesion ligands like VCAM-1 and ICAM-1 on synovial endothelium thereby obstructing the process of adherence of peripheral blood T cells to the inflamed endothelium and subsequently migration into the synovium. Indeed, the lymphocytosis that can be seen in the blood three days after administration of the antibody to rheumatoid arthritis patients is a likely the result of T cell redistribution. We found that this increase in lymphocytes is caused by the increase of CD45RO positive T cells with a type-1 phenotype expressing CD49d suggesting that specifically these cells had lost the ability to adhere to the endothelium.

The second explanation for the enrichment of type-1 T cells in the inflamed synovium is local differentiation. Polarization into type-1 cells of synovium entering T cells can result from the presence of IL-12, IL-18 and IL-15.
The pro-inflammatory action of type-1 cells in the synovium is subsequently exerted by both IFN-gamma production and direct contact with macrophage type cells. Since this induces increased local production of TNF-α this leads to amplification of the inflammatory response that in turn attracts more type-1 T cells to the synovium resulting in chronic inflammation. The assumption of this amplifying circle is supported by the observation that the ratio between type-1 and type-2 CD4 cells in the synovial fluid and the extent of inflammation as estimated by the erythrocyte sedimentation rate is correlated (chapter 2). However it is still unclear how the vicious circle is initiated and which factors in non-rheumatoid individuals are involved in switching it off.

In contrast to the synovium the ratio between type-1 and type-2 cells in the peripheral blood is not correlated to inflammation (chapter 2, 8). While the ratio is significantly lower in the presumed type-2 disease SLE (chapter 3), in rheumatoid arthritis patients as well as in ankylosing spondylitis patients it is not different from healthy controls (chapter 2 and 4).

Even though treatment of arthritis patients during three months with DMARDS results in a reduction of disease activity, this is not accompanied by a comparable change in the type-1/type-2 ratio in the peripheral blood (chapter 6). This might mean that the ratio in peripheral blood is not only dependent on redistribution induced by inflammation, but that in longer time periods other mechanisms are involved. Since even in healthy controls substantial differences exist in this ratio in the peripheral blood, it can be argued that it is influenced by genetic factors as well as T cell responses to previously encountered pathogens.

In mice, it has been shown that the outcome of a T cell response to a particulate antigen is dependent on pathogen-derived signals as well as genetic factors of the host and that the possibility to develop a strong type-1 immune response can be essential in the resistance against certain pathogens. It might therefore be that the tendency to develop type-1 response is an advantage in the defence against intracellular pathogens, while the prize could be a higher susceptibility to chronic inflammatory conditions like rheumatoid arthritis.

This theory is supported by the observation of a decreased occurrence of atopic disease which is type-2 mediated in rheumatoid arthritis patients but contradicting data exist.

Rheumatoid arthritis is a multifactorial disorder and shows a wide spectrum of clinical phenotypes from mild disease to severe arthritis. Epidemiological studies have revealed that multiple genetic factors are involved in the susceptibility as well as the severity of the disease. In this thesis it is studied whether the type-1/type-2 ratio in the peripheral blood of rheumatoid arthritis patients, is related to disease severity. Again heterogeneity of rheumatoid arthritis is indicated in chapter 7 and 8. Although the measured type-1/type-2 ratio in the peripheral blood shows a relation with persistence of disease activity during one year (chapter 7), this seemed only to be true when a homogeneous group of patients was analysed (chapter 8). Nevertheless this suggests that a tendency to react with a type-1 immune response is unfavourable with respect to the course of rheumatoid arthritis. Because of the heterogeneity of rheumatoid arthritis the unpredictable clinical outcome and the increasing capability to prevent long term damage, there is a strong need for parameters to identify severe disease at an early stage. The data
obtained during our studies show that the T helper 1/T helper 2 ratio is not a strong enough predictor to be used in an unselected patient population. Still, it will be interesting to test its possible clinical relevance combined with other prognostic parameters or during longer follow-up periods.

References

2. Damle NK, Doyle LV. Ability of human T lymphocytes to adhere to vascular endothelial cells and to augment endothelial permeability to macromolecules is linked to their state of post-thymic maturation. J Immunol 1990;144:1233-1240


