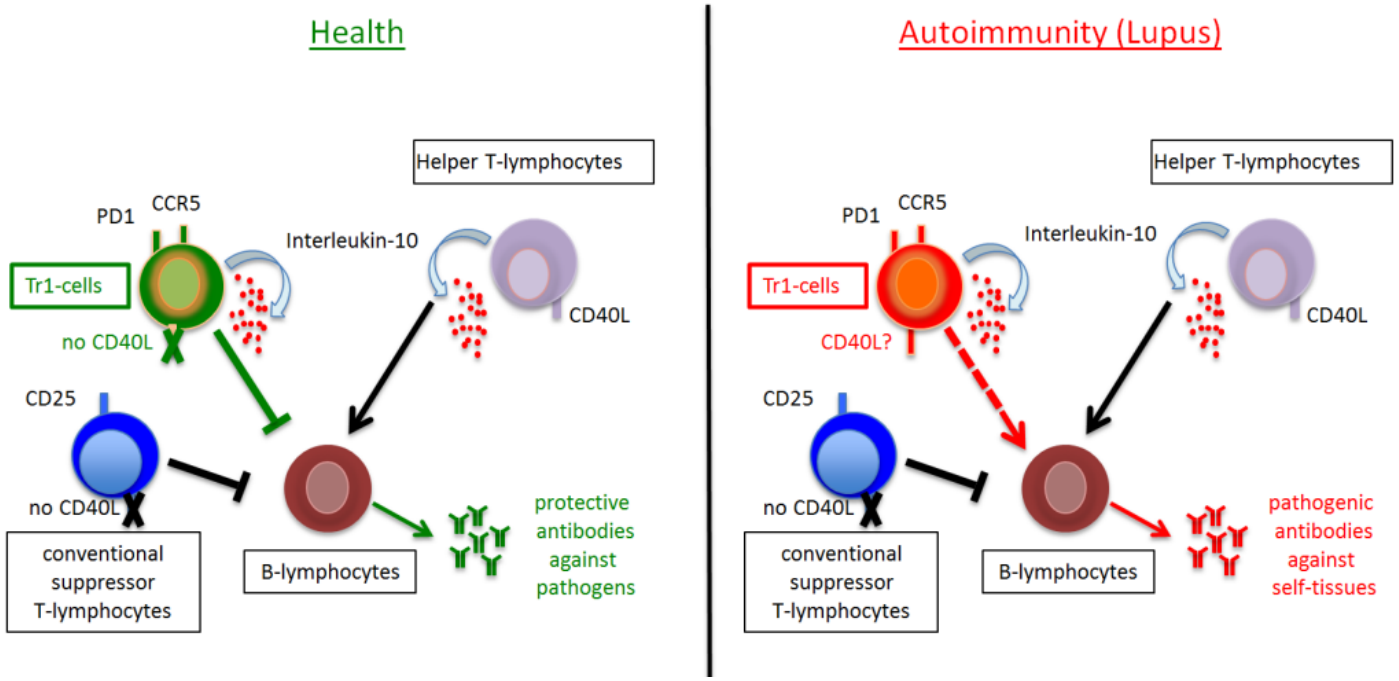
A functional defect of unconventional suppressor T-lymphocytes might lead to disease progression in lupus autoimmune patients

A healthy immune system discriminates between pathogenic invaders that have to be eliminated, and the body's own tissues that have to be protected. Central to this role are immune cells called lymphocytes. B-lymphocytes are particularly important, because they produce proteins called antibodies that can neutralize pathogenic invaders and thus protect from infections. Antibody production by B-lymphocytes is however tightly controlled by other immune cells, the T-lymphocytes. There are two different classes of T-lymphocytes that regulate antibody production, which have completely opposing functions: On the one hand helper T-lymphocytes that interact with B-lymphocytes induce antibody production, and this help is required for most protective immune responses against infections. On the other hand suppressor T-lymphocytes inhibit antibody production and are required to prevent aberrant autoimmune responses against healthy tissues.

Systemic lupus erythematosus is an autoimmune disease in which the immune system erroneously attacks the body's own tissues. It affects primarily young women, has a global disease rate between 20-70/100.000 and there is still no cure available. Lupus is characterized by the uncontrolled production of antibodies by B-lymphocytes that react with molecular structures of healthy tissues, and these autoantibodies can damage the kidneys and drive disease. Since the relative contributions of helper and suppressor T-lymphocytes is determining if B-lymphocytes produce antibodies or not, a disturbed balance between these populations is a likely reason for autoantibody production in lupus patients.



Proposed model how loss of suppressor functions by Tr1-cells could lead to uncontrolled autoantibody production in lupus autoimmune disease. In healthy individuals CD40L+ helper T-lymphocytes that produce B-helper cytokines like Interleukin-10 induce protective antibody secretion by B-lymphocytes against pathogenic invaders like viruses or bacteria. CD40L- suppressor T-lymphocytes – conventional ones and Tr1-cells – prevent the inappropriate induction of autoantibodies against the body's own tissues. In contrast, in autoimmune diseases like lupus Tr1-cells loose their suppressive functions and this is likely to contribute to the aberrant production of pathogenic antibodies against healthy tissues. Since Tr1-cells produce B-helper cytokines like Interleukin-10 they might even directly induce autoantibodies when they acquire CD40L expression.

The helper function of T-lymphocytes depends on a surface receptor called CD40L that is expressed on most T-lymphocytes, as well as on soluble mediators, known as cytokines, which can be released by T-lymphocytes upon interaction with B-lymphocytes. Only the combined action of CD40L and cytokines induce B-lymphocytes to differentiate into antibody-producing cells. Among the factors that stimulate B-lymphocytes to produce antibodies the cytokine Interleukin-10 is particularly important in lupus. However, Interleukin-10 has also strong inhibitory effects on other immune cells and is therefore paradoxically characteristic for a peculiar population of suppressor T-lymphocytes called Tr1-cells. This enigmatic population is increasingly recognized to be important to prevent autoimmune diseases. However, while conventional suppressor T-lymphocytes can be easily identified by the expression of a surface receptor named CD25, how to track Tr1-cells is unclear. This is a major hurdle for the study of Tr1-cells in lymphoid organs, the place where B-lymphocytes interact with T-lymphocytes and differentiate into antibody-producing cells.

We identified a combination of surface markers, i. e. CCR5 and PD-1, which identified Tr1-cells in human lymphoid organs and allowed their purification to assess their role in antibody production. We found that Tr1-cells, similar to conventional suppressor T-lymphocytes, lacked CD40L expression and were therefore unable to induce antibodies. Moreover, they had a dominant inhibitory effect on antibody production induced by helper T-lymphocytes. An important difference between Tr1-cells and conventional suppressor T-lymphocytes was however that the provision of CD40L was sufficient to revert suppression by Tr1-cells. We then analyzed the characteristics of Tr1-cells in lupus patients. We observed that Tr1-cells were more abundant in lupus patients, but had lost their suppressive functions and even induced antibodies in some patients. In contrast, conventional suppressor T-lymphocytes were not increased and had normal suppressive functions.

In summary, we described a strategy how to identify this peculiar population of suppressive Tr1-cells in lymphoid organs. We showed that they lack CD40L and can consequently suppress antibody production similar to conventional suppressor T-lymphocytes. However, since Tr1-cells secrete B-helper cytokines their suppressive functions can be easily reverted, and presumably for this reason lupus patients have a selective functional defect in Tr1-cells. A possible future therapeutic approach in lupus is therefore to infuse patients with suppressive Tr1-cells as was recently performed in colitis patients.

Publication

IL-10-producing forkhead box protein 3-negative regulatory T cells inhibit B-cell responses and are involved in systemic lupus erythematosus.
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