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The immune system – both weak and overreactive in the absence of CTLA4

The ability to recognise a pathogen and combat it effectively is certainly one of the most complex and sophisticated processes the human body has evolved. People with an immunodeficiency or autoimmune disease may have a genetic defect in one of the genes involved in the immune response. Working with immunologists from London, scientists Desirée Schubert and Prof. Dr. Bodo Grimbacher from the Centre for Chronic Immunodeficiency (CCI) at the Freiburg University Medical Centre discovered that a point mutation in the CTLA4 gene severely impairs the immune system. This is because the CTLA4 mutation affects different types of cells that have key immune defence functions.

Desirée Schubert in Prof. Dr. Bodo Grimbacher's research team is studying the function of the CTLA4 receptor.

The airways are afflicted with a severe infection and the immune system attacks its own organs (e.g. the intestines or the lungs). Paradoxically, both outcomes can occur concurrently in the same individual in cases where complex immunobiological processes function incorrectly. However, although not always successful, the human immune system has the important task of stopping the process before it gets that far. Its job is to recognise pathogens or altered body cells in order to start destroying them.

Way back in 1976, the immunologists Rolf Zinkernagel and Peter Doherty showed that T cells only recognised foreign antigenic peptides when they were presented on the cell surface by MHC (major histocompatibility complex) molecules. This ability is known as MHC restriction, and enables agents such as viruses or cancer cells to be recognised as harmful. The antigen-presenting cells (APC) thus provide the first signal required to initiate an immune response. The recognition of the antigen is mediated by the MHC-antigen complex binding to the T-cell receptor (TCR) of a conventional T cell, and – as a second, co-stimulatory signal - by the APC ligands CD80 and CD86

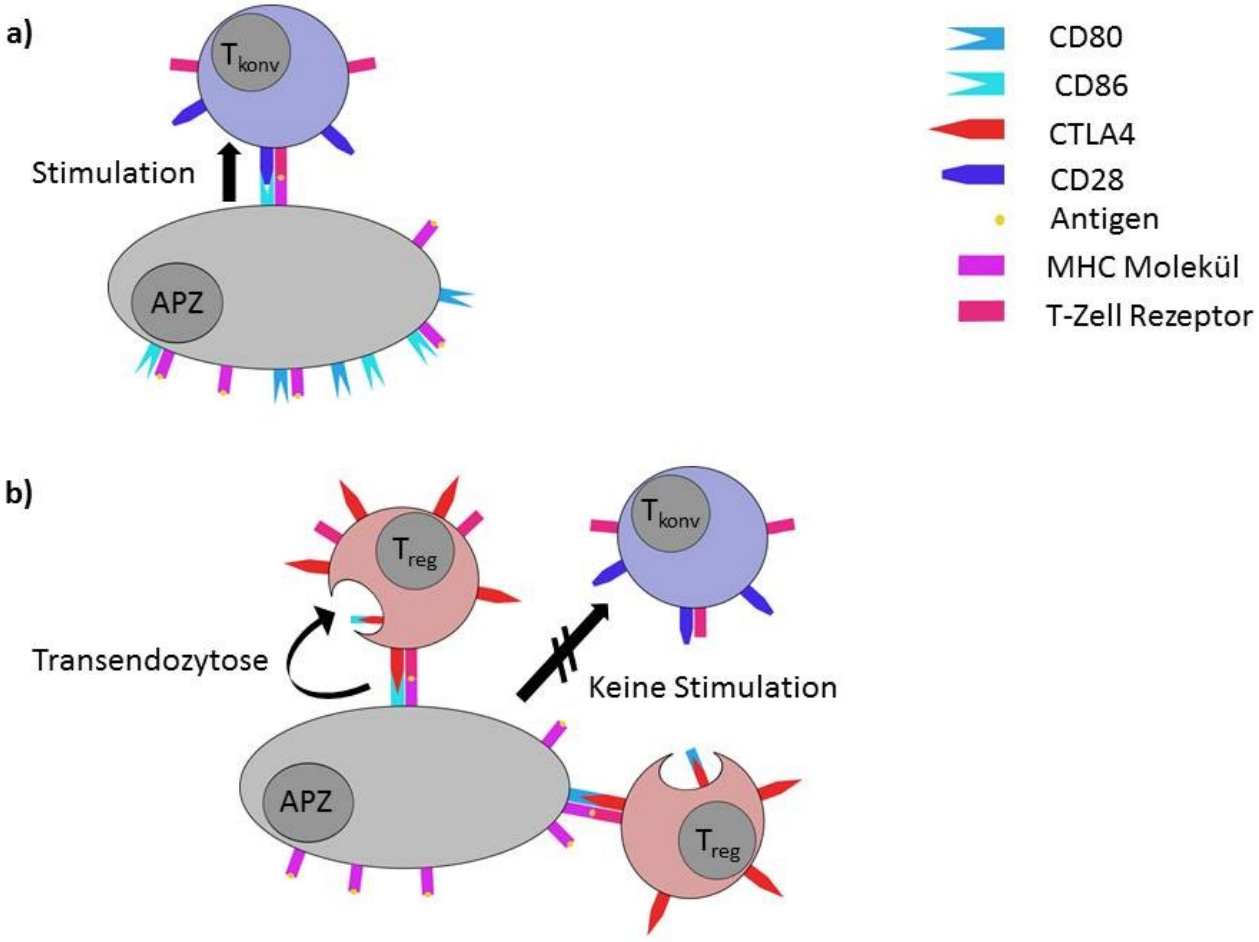
contacting the T-cell's CD28 receptor. Binding to CD28 enhances the maturation of T cells into T helper cells or cytotoxic T cells and also enables T cells to activate B cells. In other words, CD28 binding decreases the threshold for effective T-cell activation.

Regulatory T cells control immune response and tolerance to self

The intensity of an immune response needs to be constantly monitored to ensure that altered body cells and pathogens are destroyed, and that autoimmune response against own tissues is suppressed. This is the mission of the so-called regulatory T cells, which are able to suppress the activity of other T cells.

"A response to a pathogen will eventually come to an end, and the immune response must then be shut down," says Desirée Schubert from the Center for Chronic Immunodeficiency (CCI) of the Freiburg University Medical Centre. Desirée is a doctoral student in Prof. Dr. Bodo Grimbacher's team who is studying the genetic triggers that potentially cause immune diseases. She is specifically focused on an important inhibitory receptor on the surface of regulatory T cells. This receptor, which is called CTLA4 (cytotoxic t-lymphocyte-associated antigen 4), plays a crucial role in the regulation of immune responses: "CTLA4 binds to APC via the co-stimulatory molecules CD80 and CD86 and removes the latter from the cell surface," says Schubert. "The molecules are taken up by the regulatory cells in a process known as transendocytosis, and are subsequently degraded." This leads to a low number of co-receptors on the APC. "Depletion of CD80 and CD86 from APCs by CTLA4 via transendocytosis reduces APC-mediated activation of conventional T cells via CD28. This results in the suppression of T-cell activation and the immune response comes to an end," says Schubert. This process therefore plays a key role in preventing or stopping an immune response.

CTLA4 is an essential negative regulator of immune responses



Antigen-presenting cells (APC, here labelled as APZ) activate conventional T cells (Tkonv); b) regulatory C cells ensure that the co-stimulatory molecules are removed from the APC and transendocytosed.

Schubert believes that stealing recognition proteins from other cells and then internalising receptor and ligand is a somewhat unusual concept. But it is definitely one that works. It works because the binding of CTLA4 to its CD80 and CD86 ligands is closely linked to its function as CD28 co-stimulation competitor. CTLA4's affinity to CD80 and CD86 is far greater than that of CD28. When opposing immune regulators compete for CD80 and CD86 binding, inhibitory CTLA4 wins against stimulatory CD28, resulting in the suppression of T-cell activation. However, T-cell activation is crucial for maintaining an immune response. In mice, a lack of the negative regulator of immune responses, CTLA4, leads to drastically enhanced T-cell activation. This leads to an excessive production of lymphocytes, which then infiltrate all tissues. The overactivation of the immune system caused fatal immunity in three-week old mice. "Given that the immune system is overactive, you would think it could effectively fight off the pathogens. But this is not what happens," says Schubert. Overactive T cells are unable to keep viral intruders at bay. And since T cells also activate B cells that are important for fighting off bacterial pathogens, an effect cannot be expected here either.

Of mice and men

Schubert and Grimbacher analysed patients with similar clinical symptoms and found in 14 individuals from six families heterozygous, dominant point mutations in the CTLA4 gene. While regulatory T cells were present in elevated numbers in these individuals, their suppressive function

– CTLA-4 ligand binding and transendocytosis of CD80 – was severely impaired.

The disease is quite variable. However, the majority of affected individuals showed T-cell infiltrates into multiple organs and also presented with infections of the lungs and the upper respiratory airways as well as chronic inflammatory bowel diseases. Moreover, the researchers discovered reduced numbers of circulating B cells, and hence antibodies, in the majority of the patients examined. The researchers now expect this rare genetic defect to be diagnosed more frequently in future due to progress in diagnostic tools and methods. The idea is to also examine patients who present with rheumatoid arthritis or inflammatory bowel disease as initial symptoms in order to determine whether CTLA4 plays a role. The researchers also believe that it will be possible in future to show that diseases previously classified as neurological due to the presence of lymphocytes and inflammation in the brain are characterised by CTLA4 mutations. Further examinations will be carried out to substantiate these assumptions.

The researchers see CTLA4 as an interesting clinical target because it is possible to increase its effect artificially and therefore mitigate the effect of some autoimmune diseases. In the treatment of tumours, there is also the potential to mitigate the effect of CTLA4 in order to enable the immune system to fight off malignant melanomas more effectively. In fact, two CTLA4 fusion proteins, which bind to CD80 and CD86 and inhibit immune activation, have already been placed on the market for the treatment of rheumatoid arthritis and the prevention of organ rejection (e.g. renal implants). However, scientific evidence for the effect of CTLA4 has only now become available and the findings suggest that the drugs are in fact effective. Above all, it has become clear that CTLA4 plays a key role in immune defects and autoimmune diseases and might in future be used as basis for developing new therapies.

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