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Press Release

The mystery of the third signal

In COPD, several mechanisms, which normally protect the lungs from the body's own immune cells, cease to function properly

At least three protective mechanisms defend the lungs against erroneous attacks by the body's own immune system. This was discovered by the Immuneregulation research group headed by Professor Dunja Bruder at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany. In the case of chronic obstructive pulmonary diseases, briefly COPD, a group of common diseases, whose etiology has been linked to smoking or an individual's prolonged exposure to harmful dust particles, these mechanisms apparently cease to function properly. The researchers have now published their findings in the current issue of the American Journal of Respiratory Cell and Molecular Biology.

The lung surfaces separate the body from the external environment. It is particularly important that, here, the immune system is able to recognize and fight off harmful substances while sparing the body's own structures. When a certain type of immune cells - called T cells – is produced in the body, the unfortunate by-product is the development of dysfunctional T cells capable of attacking the body itself. Before they become active in the body, a control mechanism selects and destroys dysfunctional T cells. On a quite regular basis, however, some of these cells, called autoreactive T cells, evade detection by the control mechanisms and thus end up staying in the body, where they can pose a threat on the different tissues. As it turns out, in the case of COPD, autoreactive T cells play a rather important - and previously underestimated - role.

COPD is by now the fourth most common cause of death in industrialized countries. An effective COPD therapy, however, does not yet exist. Smokers and those exposed to badly polluted air have an increased risk of developing the disease. Among other factors, the smouldering hearths in closed rooms, which are still being used for cooking and heating in developing countries, should be mentioned here. "It is certainly true that, for development of COPD, which is commonly known as 'smoker's cough', smoking and dust exposure are two important risk factors. The inflammation which results, could, however, lead to T cells attacking the lung tissue, ultimately resulting in the development of an autoimmune disorder," explains HZI scientist Marcus Gereke.

Gereke is part of a team of HZI scientists that, together with colleagues from the Free University Berlin, the University Hospital Essen, and the Otto-von-Guericke University Magdeburg, has been studying the lungs' inherent protective mechanisms that ward off potential attacks by a person's misguided immune system. In the process, they discovered that autoreactive T cells, which recognize "self" lung tissue, do not by themselves automatically trigger COPD, but that other factors also play a role. The researchers are especially interested in a subgroup of T cells, which is normally in charge of recognizing and destroying infected cells to prevent pathogens from spreading. They are part of the acquired immune response, which adapts to newly introduced pathogens throughout a person's life, targeting them for destruction. A year ago, the scientists were already able to show that the cells in question also attack chronically inflamed lung alveoli.

To understand the role of T cells in the etiology of COPD, the researchers conducted experiments in mice, in which they were able to specifically evoke autoimmunity by introducing autoreactive T cells into the murine lungs. Against expectations, however, they found that the mere presence of cells that are viewed as "non-self" did not by itself provoke an attack by autoreactive T cells. Instead, it appears that, besides erroneously recognizing a tissue as "non-self," the autoreactive T cells require an additional signal to prompt their differentiation into cells capable of attacking "self" cells. To their surprise, the scientists found that the T cells became activated only temporarily once the scientists delivered an additional, second signal by triggering the innate immune response - a kind of "body alarm system" that switches on the entire immune defense. "It seems that a third signal is needed to completely turn on these cells. Once we find out what this third signal actually is, we will have taken an important step forward in our understanding of COPD. This would then allow us to intervene therapeutically and prevent the progress of the disease," emphasizes Dunja Bruder the relevance of their results. The researchers' investigations point to the fact that chronic infections may be responsible for producing the third signal. Infections lead to inflammation of the lungs, which then completely turns on the autoreactive T cells.

The researchers assume that similar processes may occur in a smoker's lungs. Certain substances in cigarette smoke damage the mucosa of the lungs. This in turn exposes structures that are then recognized by immune cells. The innate immune system is constantly being activated and licenses the autoreactive T cells to attack and destroy the lung tissue. In the chronically inflamed lung tissue of heavy smokers, the protective mechanisms are effectively shut down. All too often, the outcome is the development of COPD.

Original publication:

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CD8+ T cells responding to alveolar self-antigen lack CD25 expression and fail to precipitate autoimmunity
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The research group "Immuneregulation" at the HZI explores the immune system under extreme situations. These can be parallel infections with different pathogens or the erroneous attack of parts of the own body by the immune system.