Sensitive balance in the immune system

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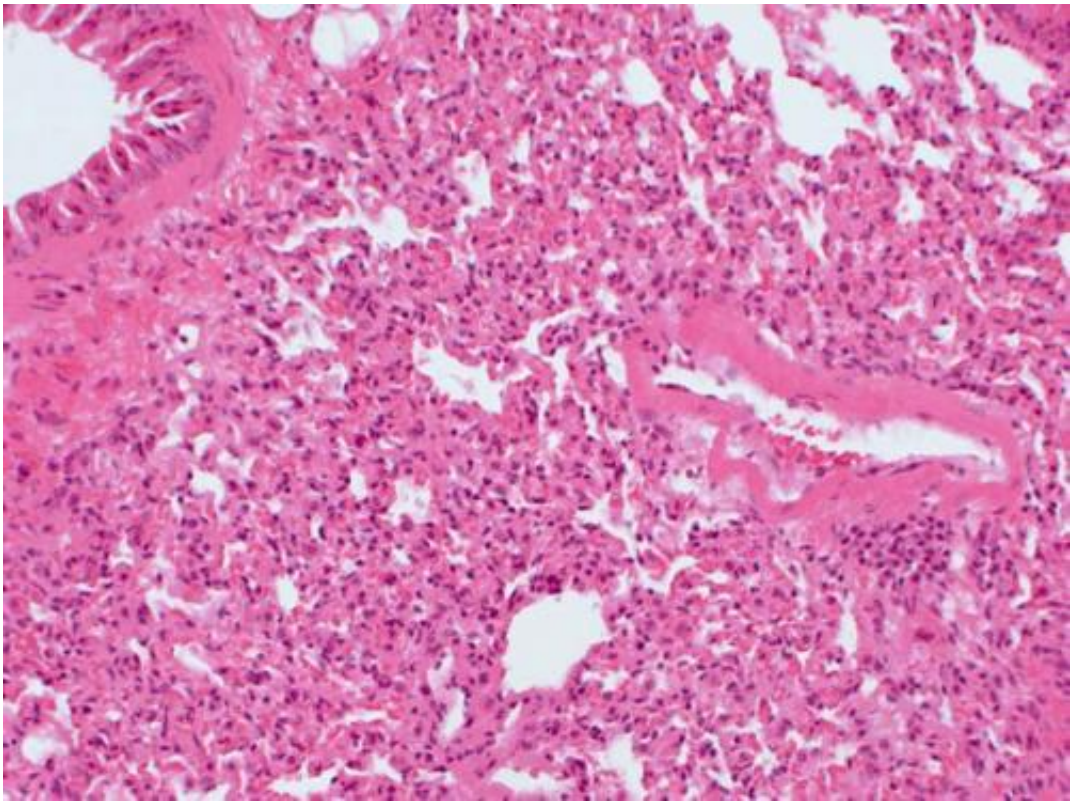

The image shows inflammed lung tissue with immune cells that have migrated into the lungs. Their nuclei are stained blue. Credit: Helmholtz Association of German Research Centres

Apoptosis is used by cells that are changed by disease or are simply not needed any longer to eliminate themselves before they become a hazard to the body—on a cellular level, death is part of life. Disruption of this process can lead to cancer or immunodeficiencies, but also to

autoimmune diseases, in which cells attack their own body.

HZI scientist Prof Ingo Schmitz and his team investigate the regulation of apoptosis in the immune system. In collaboration with researchers of the Otto von Guericke University Magdeburg and the Helmholtz Zentrum München, they elucidated the role of a central protein in this process. The researchers published their results in *Cell Death & Disease*. So-called c-FLIP proteins inhibit signaling cascades that can lead to apoptosis. This is important temporarily in the response to pathogens to ensure that lymphocytes, a type of immune cells, can proliferate sufficiently. Towards the end of the immune response, once the lymphocytes completed their tasks and successfully eliminated the pathogen, c-FLIP is usually degraded. As a result, apoptosis is enabled again, the lymphocytes die and the equilibrium in the immune system is restored.

The HZI researchers then took a closer look at the exact function of a certain variant of the protein, called c-FLIPR. They used mice to investigate what happens if this protein is always present in lymphocytes and other blood cells. Whereas the apoptosis inhibitor caused no anomalies in young mice, the scenario in older mice was quite different: "The composition of the lymphocytes was changed significantly," says Schmitz. "Furthermore the immune cells were strongly activated."

The overactivation is easily apparent in the body. The researchers found immune molecules, called autoantibodies, which attack the body's own tissue in the kidneys and lung. In addition, they detected harmful protein deposits in the kidneys. The changes in the lung tissue are also indicative of the immune system attacking its own body in the presence of too much c-FLIPR. "Immune cells migrate into the lung and attack the lung tissue," says Schmitz. Physicians usually see these symptoms in a human autoimmune disease called systemic lupus erythematosus

The HZI scientists discovered already last year that cells can fight bacterial infections better if c-FLIPR is turned on permanently. This means that inhibiting the suicide of cells has beneficial effects in acute infections, but leads to autoimmune reactions in the long run. "c-FLIPR is important for the balance of the immune system. It might be possible to intervene with suitable therapeutic agents if the equilibrium of the immune system is disrupted," says Schmitz.

More information: Frida Ewald, Michaela Annemann, Marina C. Pils, Carlos Plaza-Sirvent, Frauke Neff, Christian Erck, Dirk Reinhold, Ingo Schmitz, Constitutive expression of murine c-FLIPR causes autoimmunity in aged mice, *Cell Death & Disease*, 2014

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