Compromised immune system can be re-activated

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Failure of the immune system during blood poisoning (sepsis) can be reversed by a specific sugar. This restores the ability of immune cells to respond effectively to infections. This week, researchers from Radboud University and Radboudumc published an article on this topic in *Cell*. These insights can lead to improved treatment of sepsis.

Sepsis is a life threatening complication during infections that occurs when the immune system is unable to gain control of the infection-causing microorganism. Afterwards, the immune system of many sepsis patients (30%-40%) becomes compromised. This can continue for several weeks to several months. As a result, the immune system can no longer respond to new infections, and sepsis patients have a high risk of additional complications and death due to a second infection.

In an article that was published on 17 November in the journal *Cell*, the molecular biologist Henk Stunnenberg of Radboud University, in cooperation with internist-infectiologist Mihai Netea and other colleagues at Radboudumc, shows that this immune paralysis can be reversed. This is good news for sepsis patients, for whom treatments are currently lacking in efficiency.

In developed countries, each year approximately 2 to 30 people in every 10000 get sepsis. In the Netherlands, an estimated annual 9000 patients are admitted to the intensive care unit (ICU) with severe sepsis. Sepsis can lead to serious, permanent complications, and 20% of the sepsis patients die in the ICU.

The role of sugars

In the bloodstream, monocytes – a type of white blood cell – play a key role in the defense against infections. Monocytes can become macrophages, which remove harmful invaders. In 2014, the Nijmegen researchers showed that differentiation of monocytes into macrophages can be controlled by the environment. Monocytes that are exposed to a lipopolysaccharide (LPS), a molecule from the outer cell membrane of specific bacteria, mature into macrophages with a greatly reduced capacity to fend off foreign cells. This reflects sepsis-induced immunosuppression. The opposite occurs upon exposure to beta glucan, a sugar found in fungal cell walls.

At the molecular level, Stunnenberg then looked at the epigenetic setting of these different types of macrophages. The epigenome is involved in regulating gene expression; it varies by cell type and person and can change due to nutrition, stress and illness.

As a result, he discovered one of the "control switches" of the immune system that is driven by a sugar, beta-glucan. "By adding beta-glucan to blood samples of trial subjects with a disabled immune system, the macrophages were re-activated".

Time for a clinical trial

Stunnenberg tested the effects of beta glucan in blood in the laboratory. "A clinical trial with patients is an obvious step for the near future. We could begin with blood samples of people who have been admitted to the ICU with sepsis" says Mihai Netea.

Prospects

Now that the researchers have an indication of how they can reactivate a disabled immune system, they also hope to determine how they can temper an overactive system. Autoimmune diseases such as rheumatism, or inflammatory disorders such as Crohn's disease, are the result of an overactive immune system.

The article in *Cell* is one of the many publications from the BLUEPRINT project. This week alone, four papers were published in Cell and another nine papers were published in other *Cell* journals. BLUEPRINT investigated the epigenome of hundreds of types of blood cells and focused on the mystery of cell specialization. The five-year project involved 54 research teams from 12 countries (the Netherlands, UK, Italy, Spain, Belgium, Germany, Austria, Switzerland, Israel, France, Denmark and Sweden).

The epigenome is involved in regulating gene expression; it varies by cell type and person and can change due to nutrition, stress and illness. When the human genome was unraveled, it quickly became clear that the genetic code by itself was inadequate to understand how we are put together. Although each cell in the body has the same DNA, there are major differences between our cells. Moreover, cells change due to environmental influences, aging and disease. Consequently, the DNA is always used differently.

More information: Boris Novakovic et al. β-Glucan Reverses the Epigenetic State of LPS-Induced Immunological Tolerance, *Cell* (2016). DOI: 10.1016/j.cell.2016.09.034

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