New clues to help patients with immune deficiency disease

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Infection researchers at Umea University have uncovered a new disease mechanism in patients with Chronic Granulomatous Disease (CGD) in an international clinical collaboration with the Children's Hospital in Zurich. Their new findings are published in the *Journal of Allergy and Clinical Immunology*.

Fungal infections can cause life-threatening health problems for patients with immune deficiency. Their health is weakened by infections and they cannot undergo the treatment or surgery they need to survive. An example is Aspergillus infection which is life threatening for these patients. In this condition, the immune system is not able to kill the pathogen and the mould propagates from the lungs and respiratory tract into the whole body.

Chronic Granulomatous Disease (GDC) is a heritable severe immune deficiency disease that occurs at a frequency of one in 200,000 humans per year worldwide. Children with CGD often suffer life-threatening microbial infections with bacteria and fungi and die at young age without treatment. Particularly, infections with Aspergilli fungi often kill CGD patients, before bone marrow transplantations or gene therapy can be performed.

Scientists at the Swedish Laboratory for Molecular Infection Medicine (MIMS) in Umeå have now found new treatment of CGD patients.

While healthy individuals' white blood cells, also called neutrophils, release oxygen intermediates to kill and digest invading pathogens, the immune cells in CGD patients lack the ability to kill the microbes.

Constantin Urban, research group leader at the MIMS laboratory in Umea is studying mechanisms of fungi infections. In earlier studies of Candida infections, he found with his colleagues that neutrophils form extracellular structures, called neutrophil extracellular traps or NET, which catch microbes and fungi.

"NET is a very smart tool," says Urban. "It is comparable with a spider's web, catching and killing the trapped pathogen. We found in earlier studies that these web-like structures are made of chromatin and decorated with antimicrobial proteins. They also release oxygen intermediates and an antifungal substance called calprotectin."

In collaboration with clinical researchers at the Children's Hospital in Zurich, the scientists from Umea found new details behind CGD. They compared the function of a CGD patient's neutrophils before and after gene therapy.

"Our results clearly show that calprotectin is also important for the neutrophils immune defence against Aspergillus infection," says Constantin Urban.

Together with PhD student Maria Joanna Niemiec in his group at MIMS and medical doctors in Zurich, Constantin Urban found that neutrophils from the CGD patient did not form NETs trap and were not able to release calprotectin. This was the reason why the neutrophils were not able to kill and digest Aspergillus cells anymore.

"We found that after gene therapy the neutrophils could produce calprotectin at a normal level and even the NET structure was formed again," says Maria Joanna. "Our experiment showed that calprotectin is a key player for the neutrophils' defence against Aspergillus infection. We are now convinced that calprotectin can be used as a "molecular support" to compensate the neutrophils cell defect in CGD patients."

"We are confident that our study may lead to new treatment of CGD patients in the beginning of their life and prevent them from infections until they have the possibility to receive gene therapy or bone

marrow transplantation, which are more sustainable treatments," says Constatin Urban. "This possible treatment for CGD patients may also be an opportunity in the future for patients with other immune deficiency diseases."

More information: Matteo Bianchi, MSc, Maria J Niemiec MSC, Ulrich Siler, Constantin F. Urban, and Janice Reichenbach: Restoration of anti-Aspergillus defense by neutrophil extracellular traps in human chronic granulomatous disease after gene therapy is calprotectin-dependent. *Journal of Allergy and Clinical Immunology*, online publication, 4th march 2011, doi: 10.1016/j.jaci.2011.01.021

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