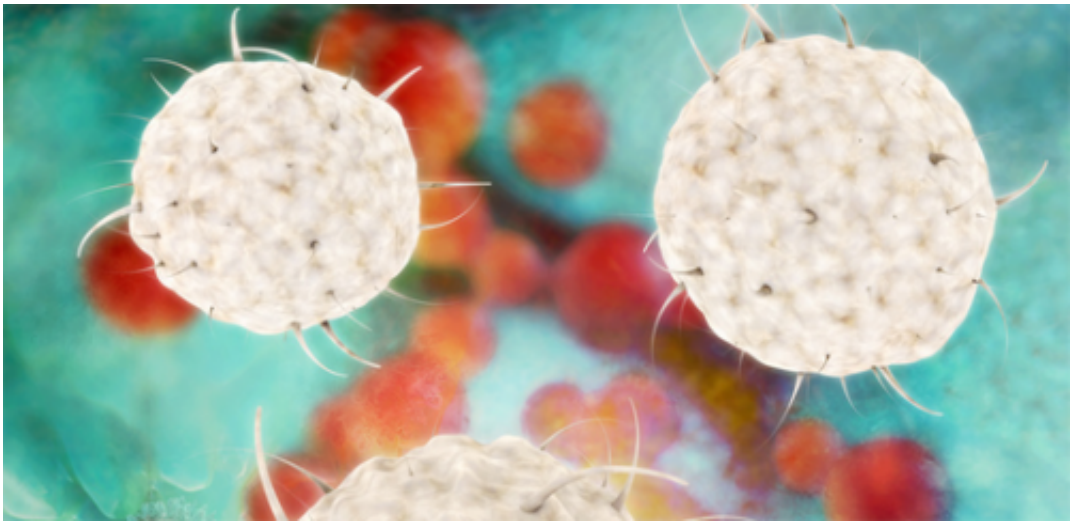
Mutation disables innate immune system

August 29 2014



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A Ludwig Maximilian University of Munich team has shown that defects in the JAGN1 gene inhibit the function of a specific type of white blood cells, and account for a rare congenital immune deficiency that increases vulnerability to life-threatening infections.

An LMU research team has pinpointed the genetic variant responsible for a rare form of hereditary immune deficiency. Klein and his colleagues have shown that mutations in the gene that codes for the protein Jagunal-1 disrupt the differentiation of a particular class of leukocytes in the blood, the so-called neutrophil granulocytes. These cells are required for the destruction of invading microorganisms

recognized by the innate immune system, but in patients who carry two defective copies of the Jagunal-1 gene not enough granulocytes are produced, and those that do differentiate are functionally impaired. In the absence of adequate numbers of these cells, the immune system is unable to eliminate bacterial and fungal infections. The LMU investigators, together with collaborators at the CeMM Research Center for Molecular Medicine and the Medical University in Vienna, report their results in *Nature Genetics*.

"The findings demonstrate how clinical observations and clinical care of children with rare diseases can open up new perspectives in basic research and point to new approaches to the effective treatment of these conditions," says Christoph Klein. In a sample of 14 children from all over the world who display severe congenital neutropenia, i.e. neutrophil deficiency, the researchers found that all had alterations in the gene for Jagunal-1. The Korean word 'jagunal' means 'small egg', and refers to the fact that, in female fruit flies in which this gene is inactivated, the egg cells (oocytes) fail to reach their normal size, because the uptake of yolk proteins by the growing oocyte is inhibited. The international collaboration led by Professor Klein has now shown that the human version of the fly protein, Jagunal-1, is required for the formation and normal function of neutrophil granulocytes.

Many patients who suffer from congenital neutropenia can be successfully treated with G-CSF, a factor which stimulates the differentiation of granulocytes. However, G-CSF does not alleviate the immune deficiency in children whose JAGN1 gene is mutated. The reason for this is that the G-CSF receptor expressed by their immune cells is functionally compromised. The LMU team, together with Professor Josef Penninger's group in Vienna, has now shown in an animal model that a different hematopoietic differentiation factor, GM-CSF, which promotes differentiation of macrophages (another type of phagocytic cells) as well as neutrophils, enables jagn1 mutant mice to

effectively combat a fungal infection. Clinical studies are now planned to determine whether patients with defects in JAGN1 also respond to treatment with GM-CSF.

More information: "JAGN1 deficiency causes aberrant myeloid cell homeostasis and congenital neutropenia." Kaan Boztug, et al. *Nature Genetics* (2014) DOI: 10.1038/ng.3069. Received 26 January 2014 Accepted 25 July 2014 Published online 17 August 2014

"Jagunal homolog 1 is a critical regulator of neutrophil function in fungal host defense." Gerald Wirnsberger, et al. *Nature Genetics* (2014) DOI: 10.1038/ng.3070. Received 27 January 2014 Accepted 25 July 2014 Published online 17 August 2014

Provided by Ludwig Maximilian University of Munich