IMBA Press Release

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Cause of congenital immunodeficiency in children identified

Scientists at the IMBA – Institute of Molecular Biotechnology at the Austrian Academy of Sciences have succeeded in simulating congenital immunodeficiency syndrome in mice and identifying a possibility for its treatment. The researchers have now published their findings in the renowned scientific journal Nature Genetics.

Post-doctoral researcher Gerald Wirnsberger, a member of Josef Penninger's team at IMBA, bred a mouse line with congenital immunodeficiency in which the function of neutrophil granulocytes in the blood was severely impaired. Neutrophil granulocytes are the most common white blood cells, and are necessary for a functional immune system. People born with severe congenital neutropenia, as it is called, often suffer serious infections because their bodies cannot defend themselves adequately against bacterial and fungal infections. The cause of this immunodeficiency is apparently a defect in gene JAGN1. That is the conclusion drawn by the doctors and scientists at the Dr. von Haunerschen Children's Hospital in Munich and the CeMM Research Center for Molecular Medicine in Vienna who found this genetic defect in 14 children.

"This research project is a great example of successful international collaboration," said Josef Penninger, scientific director at IMBA and last author of one of the two studies. His research partners Christoph Klein und Kaan Boztug succeeded in finding families affected and in identifying the genetic defect. "But our mouse model is what made it possible to study the disease systematically and in-depth, and then formulate a proposal for a possible new treatment," said Penninger in explaining the relevance of the fundamental genetic research.

The IMBA researchers were able to show that the immune systems of mice that have a defect in gene JAGN1 were just as ineffective in defending them from fungal infections as those in humans. After being infected with the Candida albicans fungus, which is also relevant for humans, the mice with this genetic defect died much earlier than healthy mice.

"We then tested available and potential medicines and made a promising discovery," explained Gerald Wirnsberger, first author of the IMBA study. G-CSF, the medication currently used, does not help children with a JAGN1 defect, leaving a bone marrow transplant as their only option. G-CSF is ineffective in the mouse bred for this study as well. But another medicine, GM-CSF, brought a breakthrough. Mice treated with GM-CSF were able to handle the fungal infection much better and were significantly more resistant. The scientists then tested the medication in patient bone marrow cells and achieved promising success. After treatment the cells were once again resistant to the fungus. That means that GM-CSF could work in patients with a JAGN1 genetic defect as well. This is now being investigated in clinical trials.

ÖAW Austrian Academy of Sciences

IMBA Institute of Molecular Biotechnology of the Austrian Academy of Sciences

The results of this research project will be presented in two publications in the renowned scientific journal Nature Genetics:

Wirnsberger, G. et al. Jagunal-homolog 1 is a critical regulator of neutrophil function in fungal host defense. Nat Genet. (2014).*

*Dr. Gerald Wirnsberger is a post-doctoral researcher in Josef Penninger's research group at IMBA and first author of the publication named above. The last author of this publication is Prof. Josef Penninger, scientific director at IMBA (Institute of Molecular Biotechnology at the AAS).

*Boztug, K.** et al. JAGN1 deficiency causes aberrant myeloid cell homeostasis and congenital neutropenia. Nat Genet. (2014).*

**Prof. Kaan Boztug, team leader at the CeMM Research Center for Molecular Medicine at the AAS, assistant professor in the department of pediatrics and adolescent medicine at the Medical University of Vienna, and first author of the publication named above. The last author of this publication is Prof. Christoph Klein, medical director of the children's hospital and children's polyclinic at the Dr. von Haunerschen Children's Hospital at the University of Munich Hospital.