IMP Press Release

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IMP
Research Institute of Molecular Pathology

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Defect in Ikaros gene mimics human B cell leukemia

Meinrad Busslinger and colleagues from the IMP in Vienna find dramatic effects of a mutation in the Ikaros gene during early development of immune cells.

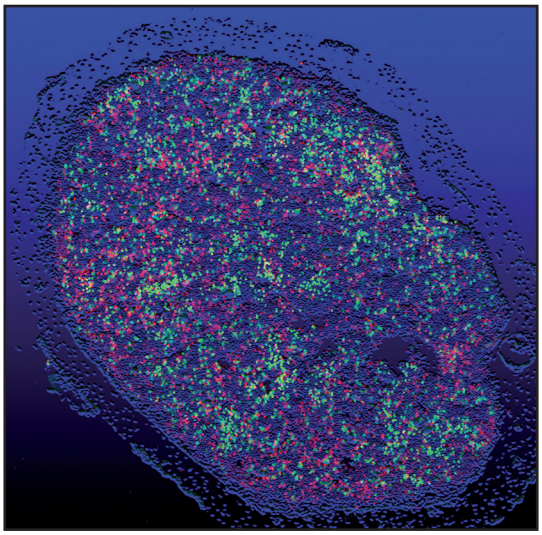
Vienna, 2014-02-10 - Meinrad Busslinger and his team from the Institute of Molecular Pathology (IMP) investigate the differentiation of stem cells to mature B cells. They now present for the first time molecular details on the role of the Ikaros gene during early B cell development. A defect in Ikaros function causes an early block in B-lymphopoiesis and prevents the development of mature B cells. The cells stay in an aberrant state, which closely resembles that of cells in B-ALL, a special form of human B cell leukemia. The results of this study are published in the current Advance Online edition of Nature Immunology (doi; 10.1038/ni.2828).

The immune system consists of a complex structure of organs, cell types and cell-cell interactions which protects the organism from harmful intruders as well as aberrant cells within the body. Two mechanisms of immunological defense can be distinguished – innate and adaptive immunity. Cells from the adaptive immune system recognize specific structures of invaders and develop defense mechanisms accordingly. B and T cells from the group of white blood cells represent the main players of the adaptive immune defense.

Role of Ikaros in B cells is no longer a myth

B cells are derived from blood stem cells in the bone marrow. By differentiating through several stages of lymphopoiesis, these stem cells give rise to fully functional, mature B cells. This process is tightly controlled by a group of regulatory proteins called transcription factors. “We already know several transcription factors that play a central role in B cell differentiation. Pax5 for example represents a critical factor which activates the B cell-specific program in precursor cells and simultaneously suppresses alternative cell fates”, Busslinger explains. ”For Ikaros we did not know until now what this factor is doing during early B cell development”.

The researchers from Busslinger’s team therefore analyzed mice specifically lacking Ikaros from an early stage of B cell development on. They found that Ikaros deficiency arrested B cell development in an aberrant “pro-B” cell stage and prevented further differentiation. Without Ikaros, the cells were not able to transmit certain signals via their cell surface receptors. Furthermore, they showed increased cell adhesion and reduced migration compared to normal cells.



Caption: Cross-section through the bone marrow of a mouse lacking the Ikaros protein. In the absence of Ikaros, an important early checkpoint of B-lymphopoiesis is no longer functional. As a consequence, early B cell development is arrested at an aberrant “pro-B” cell stage. Staining of the sections visualizes the arrested pro-B cells (green), myeloid cells (red) and nuclei (blue). Copyright: IMP

European grant allows comprehensive analyses

In 2011, Busslinger was awarded one of the prestigious „ERC Advanced Grants“ from the European Union. This generous financial support made it possible to tackle a large scope project - the systematic analysis of transcription factors in the immune system. Busslinger and his team use the technology of biotin-tagging to add a “molecular label” to transcription factors for their studies. This facilitates the isolation of these proteins from murine B cells. Despite the huge effort that comes with this method, Busslinger and his co-workers have already labelled and analysed about ten transcription factors using biotin-tagging. In most cases, they were successful with this approach. For Ikaros, this meant gaining fundamental new insights into the molecular way of action. The researchers identified a large number of genes that are controlled by this transcription factor during early B cell development.

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Striking similarity to human tumor cells

The Ikaros gene is a so-called tumor-suppressor gene that protects cells from becoming tumorigenic under normal conditions. Loss of the function of this gene has been associated with the development of "B-ALL", a certain form of human leukemia, which requires further genetic alterations in addition to the Ikaros gene mutation. As in mice with a mutated Ikaros gene, B cells from human B-ALL patients are arrested at an early checkpoint of B cell development.

Due to the striking similarity between the defect in the mouse model and human cancers, this study may help to understand how leukemia develops at the molecular level. In the future, the findings might be valuable in devising new concepts for the prevention or therapy of blood cancer.

Original Publication

TA Schwickert, H. Tagoh, S. Gültekin, A. Dakic, E. Axelsson, M. Minnich, A. Ebert, B. Werner, M. Roth, L. Cimmino, RA Dickins, J. Zuber, M. Jaritz and M. Busslinger. „Stage-specific control of early B cell development by the transcription factor Ikaros", Nature Immunology 15, doi; 10.1038/ni.2828.

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Illustration

An illustration can be downloaded from the IMP Website and used free of charge in connection with this press release: http://www.imp.ac.at/pressefoto-Ikaros

About Meinrad Busslinger

Meinrad Busslinger was born in Switzerland in 1952. He studied Biochemistry at the ETH Zürich and obtained a doctorate in molecular biology from the University of Zürich. Following postdoctoral studies at the MRC Institute Mill Hill, London, he became a group leader at the University of Zürich. In 1987, he followed Max Birnstiel as a Senior Group Leader to the newly founded IMP in Vienna. Busslinger is Director of Academic Affairs at the IMP, and since 2013 also scientific Deputy Director of the institute.
Busslinger is Professor at the University of Vienna and a full member of the Austrian Academy of Sciences and of the European Molecular Biology Organisation. He has published over 160 papers in peer-reviewed journals and serves on editorial boards of several scientific journals. Busslinger was awarded the Wittgenstein prize of the Austrian Government in 2001 and the Virchow Medal by the University of Würzburg in 2010.

About the IMP

The Research Institute of Molecular Pathology (IMP) in Vienna is a basic biomedical research institute largely sponsored by Boehringer Ingelheim. With over 200 scientists from 30 nations, the IMP is committed to scientific discovery of fundamental molecular and cellular mechanisms underlying complex biological phenomena. Research areas include cell and molecular biology, neurobiology, disease mechanisms and computational biology.

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