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New evidence from mice study explains what happens when cell signaling goes awry

Study clarifies how intercellular signaling mechanism influences cell development, and absence may figure in developmental disorders and fetal death

Unraveling the signaling mechanisms that regulate the development and interaction of cells inside the human body is fundamental to understanding what happens when things go wrong. This week, an international team of RIKEN-led researchers reported that they now better understand a key player in certain cellular interactions - two protein kinases on the surface of B cells that help regulate early-stage cell development.

B cells are lymphocytes that play a large role in the body's immune response. They make antibodies against antigens and are an essential component of the adaptive immune system of mammals. But there is growing indication that they also have a crucially important role in regulating cell differentiation, development and activity. The answers sought by the RIKEN-led team were several, with interest particularly focused on how B cells influence other cells. Among their findings reported this week in the online journal *Immunity* was evidence that specific signaling factors, when absent, can lead to the death of developing cells and failure of progenitor cells to differentiate into other cell types.

In molecular biology, extracellular signal-regulated kinases (Erks) are protein kinase intracellular signaling molecules involved in the regulation of cell development and the functioning of differentiated cells. As part of the RIKEN research, two such kinases, Erk1 and Erk2, were of special interest in the mice studies.

Targeted disruption of Erk2 was already shown by earlier research to result in embryonic lethality due to defective placental development. Thus, in order to examine the effect of the double deficiency of Erk1 and Erk2 on B cell development and function, the RIKEN researchers additionally erased Erk1 in laboratory mice. Two weeks later, the treated mice showed a reduction in the number of pre-B cells to just 7% of control mice and a corresponding decrease in immature B cells in their bone marrow.

The scientists found that deletion of both Erk1 and Erk2 kinases was associated with defective expansion of B cells as well as interrupted transition of the cells in their normal developmental process. While the other studies had already investigated Erk2, the descriptions of intermediate stage signals and genetic transcription modulators were 'poorly characterized,' the authors said. Their new findings provide previously unrevealed indication, they said, of 'a crucial role for Erk kinases in regulating B cell development by initiating the transcriptional regulatory network and thereby pre-B cell receptor-mediated cell expansion.' In fact, the double-deficiency was found to lead to worse disruption than the absence of either protein kinase alone.

As part of a growing body of research by the authors and others, these findings could lead to new approaches on how to predict and treat certain developmental disorders. If so, among other possible applications, a 'genetic fix' might be useful in boosting the body's sagging natural defenses by raising the expression levels of the intracellular regulatory signals.

The study was conducted by a research team including Tomohiro Kurosaki at the RIKEN Research Center for Allergy and Immunology, in cooperation with the Institute of Signaling, Developmental Biology and Cancer Research (Nice, France), Tokyo Medical and Dental University Graduate School, and the Department of Biochemistry, Mie University School of Medicine. Published in the peer-reviewed journal *Immunity*, the article and supplementary data can be viewed online at http://www.immunity.com.

Original work:

Yasuda, T., Sanjo, H., Pagés, G., Kawano, Y., Karasuyama, H., Pouysségur, J., Ogata, M., Kurosaki, T. Erk Kinases Link Pre-B Cell Receptor Signaling to Transcriptional Events Required for Early B Cell Expansion. *Immunity (2008)*, published online on Mar. 20, 2008

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