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Loss of Molecular Handbrakes Compromises Immune System

Removing two small proteins that put the brakes on cell proliferation in separate tissues can have deadly consequences, according to HHMI investigator James Ihle and colleagues at St. Jude Children's Research Hospital.

The scientists speculate that one of the proteins, which controls the development and function of T cells, may play a role in some forms of leukemia. And, say the scientists, "slippage" of these two "handbrakes" due to subtle malfunctions in mutant forms of the gene may compromise immune system function.

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- James Ihle

In two articles in the September 3, 1999, issue of the journal *Cell*, Ihle and his colleagues show why eliminating two members of the "SOCS" family of genes in mice proves lethal. Ihle's group and other scientists had shown in several earlier research articles that eliminating one of the SOCS proteins causes lethality, but they did not know why until now. *SOCS*, which stands for suppressor of cytokine signaling, renders cells insensitive to substances called cytokines, which stimulate the growth of blood and immune system cells.

In one of the *Cell* articles, Ihle and his colleagues reported that the protein produced by the *SOCS1* gene appears to play several regulatory roles in T cells critical infection-fighting cells in the immune system. When the scientists knocked out the *SOCS1* gene in mice, they discovered that the gene regulates the differentiation of T cells in the thymus and affects the action of those cells elsewhere in the body.

The data from the experiments indicated that *SOCS1* performed three functions, said Ihle. "In the thymus, the gene probably plays a major role in the differentiation of T cells," he said. "And it may negatively regulate, or turn down, activated T cells in the bloodstream such that the gene's absence allows the T cells to begin cranking out the cytokine, interferon gamma." Interferon gamma is a powerful immune system stimulator produced by T cells.

Finally, explained Ihle, *SOCS1* also controls the response of various cells to interferon gamma, and its absence makes the cells highly sensitive to the substance. Given such broad regulatory functions, knocking out the *SOCS1* gene has devastating effects, said Ihle.

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In a second article, Ihle and his colleagues demonstrated that knocking out the related gene, *SOCS3*, triggered an enormous overproduction of red blood cells, which killed developing embryos. The researchers' knockout experiments revealed that the *SOCS3* protein was critical to normal regulation of red blood cell production in the liver.

"It was quite clear just by looking at the appearance of these blood cells that they were not going through their normal growth and differentiation processes," said Ihle. "Also, our experiments showed that the *SOCS3* gene is developmentally regulated, that is, it is almost exclusively expressed during the fetal stage of red blood cell formation."

According to Ihle, *SOCS3* likely became incorporated into the red blood cell formation process as an important brake on growth. "One can envision a situation in which, while the body needed to make the lot of red cells quickly at that stage, it may have acquired the ability to make too many," explained.

"Evolution selected a mechanism to slow the process down a bit.

"As we learn more about fetal liver blood cell formation, we realize there are a number of positive and negative checks and balances on this whole system."

Advances in understanding the functions of the *SOCS1* gene, in particular, may have important clinical implications, said Ihle. "For example, it's clear that in acute lymphocytic leukemia there is some alteration in how the immune system cells are responding and proliferating," he said. "So, obviously an important question is what has happened to this brake during transformation. We're now beginning to explore whether *SOCS1* is involved."

Also, he said, more subtle *SOCS1* malfunctions may powerfully affect the immune system. "When you knock out a gene, as we did with *SOCS1*, you see the black and white of its function. But what if there are people with mutations that make their *SOCS1* a little bit less efficient? Given this gene's critical role in controlling immune system development and response, even a ten percent change genetically might predispose a person to dramatically altered immune reactions."