SOUTHWESTERN NEWS

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SCIENTISTS UNCOVER MOLECULAR BASIS OF FATAL CHILDHOOD IMMUNODEFICIENCY DISORDER

DALLAS – December 3, 1999 – Scientists at UT Southwestern Medical Center at Dallas have found that a rare but fatal genetic disorder in children is caused by defects in the protein perforin. It's a finding that could improve understanding of how the human immune system is regulated and lead to treatments and cures for diseases like lupus and multiple sclerosis.

Dr. Vinay Kumar, professor of pathology, graduate student Susan Stepp and colleagues report in today's issue of *Science* that their study of familial hemophagocytic lymphohistiocytosis (FHL) showed that perforin, found in white blood cells of the human immune system, is not only necessary for the destruction of abnormal cells but is also implicated in the down-regulation of activated immune defense cells.

"Through the study of these patients, we have uncovered an extremely important mechanism by which the human immune system is regulated. This information has broad implications for our understanding of other diseases of immune dysregulation, including diseases that are not due to inherited defects in perforin," said senior author Kumar.

The authors believe that knowing that perforin-containing immune cells have important regulatory functions will improve understanding of autoimmune diseases like lupus and multiple sclerosis, in which the immune system destroys normal tissues.

FHL is characterized by an acute deregulation of the immune system. Previously healthy infants and young children suddenly become sick with fever, enlarged spleens and livers, and blood and neurological abnormalities. Patients accumulate overactivated immune-system cells and signaling proteins that affect the behavior of other cells. Children can be treated with immunosuppressive agents, but a bone-marrow transplant is the only cure.

Previous research by the French and Swedish co-authors had shown that most of the

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patients' have a genetic defect linked to chromosome 10.

Kumar and collaborators studied eight unrelated chromosome 10-linked FHL patients. Because perforin was previously mapped to chromosome 10 in the same region as the chromosome 10-linked FHL cases, they analyzed the deoxyribonucleotide sequence of the patients' perforin genes. They found defects in all.

"We believe that the primary inherited defect of FHL is the inability of the cells containing perforin to destroy activated immune cells and thereby regulate the immune system's response to certain childhood infections," said Stepp, the paper's lead author. "In the absence of such regulation, the uncontrolled activation and proliferation of the immune cells results in FHL."

Other UT Southwestern investigators participating in the study were Dr. Michael Bennett, professor of pathology, and Sadhna Bhawan, a summer student from Boston University. Researchers from the University of North Texas Health Science Center, Fort Worth; Sweden's Karolinska Institutet; and France's Unité de Recherches sur le Dévelopment Normal et Pathologigue du Système Immunitaire INSERM were co-authors of the study.

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