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Researchers unravel protein's elusive role in embryo and disease development

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Reporting in *Nature,* scientists from Thomas Jefferson University have determined that a single protein called FADD controls multiple cell death pathways, a discovery that could lead to better, more targeted autoimmune disease and cancer drugs.

Twelve years ago, internationally-known immunologist Jianke Zhang, Ph.D., an associate professor in the Department of Microbiology and Immunology at Thomas Jefferson University, realized FADD, which stands for Fas-Associated protein with Death Domain, played an important role in embryonic development and the onset of some diseases, but he didn't know exactly why until now.

In the paper published online March 2, Dr. Zhang and researchers show this protein regulates not one but two types of cell deaths pivotal for embryo and disease development. It is now known that FADD causes apoptosis, the "healthy" cell death, while keeping necrosis, the "toxic" one, at bay.

Understanding this pathway is instrumental in developing drugs with selectivity and fewer side effects, said Dr. Zhang, a member of the Kimmel Cancer Center at Jefferson,

"This work has direct impact on our understanding of diseases: cancer, autoimmune disease, immune-deficiency disease," he said. "This is the one gene that regulates these two processes in cells, so now we can find targeted drugs to control the cell death process."

The research suggests that with the absence or variation in expression of this one protein, an embryo may not develop properly or a person may develop disease later in life.

"This breakthrough is a testimony to Dr. Zhang's research acumen and dogged determination to solve a longstanding mystery regarding the regulation of cell death pathways," said Tim Manser, Ph.D., professor and chair of the Department of Microbiology and Immunology at Jefferson. "It is gratifying to know that Thomas Jefferson University provides the research infrastructure that allows outstanding researchers like Dr. Zhang to make seminal discoveries, such as those reported in the Nature paper."

FADD's importance in embryogenesis and lymphocyte death response has been known, but the mechanism that underlies these functions in FADD has remained elusive.

Researchers found that mice that did not express FADD contained raised levels of RIP1, Receptor-Interacting Protein 1, an important protein that mediates necrosis and the apoptotic processes, and their embryonic development failed due to massive necrosis.

"When the FADD-mediated death process is deregulated, we will produce white bloods cells that will attack our own tissue, which is the cause of auto-immune diseases, such as arthritis and lupus," said Dr. Zhang. "And without the necessary cell deaths that are required for tumor surveillance, humans could develop cancer."

There are drugs currently under development today that activate TNF-a-related apoptosis-inducing ligand (TRAIL) death receptor signaling, which induces apoptosis through FADD in cancer cells specifically, but its mechanisms are not well understood and the treatment not perfected. There are also tumor cells that are resistant to TRAIL-induced apoptosis

for unknown causes.

"The killing of these tumor cells is not efficient, and this paper actually figured out why," said Dr. Zhang. "We now know that the FADD protein , while required for apoptotic death, is inhibiting necrotic death in tumor cells."

Provided by Thomas Jefferson University