UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers identify mechanism that maintains stem-cell readiness, helps leukemia-cell growth

DALLAS – May 31, 2012 – An immune-system receptor plays an unexpected but crucially important role in keeping stem cells from differentiating and in helping blood cancer cells grow, researchers at UT Southwestern Medical Center report today in the journal *Nature.*

"Cancer cells grow rapidly in part because they fail to differentiate into mature cells. Drugs that induce differentiation can be used to treat cancers," said Dr. Chengcheng "Alec" Zhang, assistant professor in UT Southwestern's departments of physiology and developmental biology. "Our research identified a protein receptor on cancer cells that inhibits differentiation, and knowing the identity of this protein should facilitate the development of new drugs to treat cancers."

The family of proteins investigated in the study could help open a new field of biology integrating immunology with stem cell and cancer research, he added.

"The receptor we identified turned out to be a protein called a classical immune inhibitory receptor, which is known to maintain stemness of normal adult stem cells and to be important in the development of leukemia," he said.

Stemness refers to the blood stem cells' potential to develop into a range of different kinds of cells as needed, for instance to replenish red blood cells lost to bleeding or to produce more white blood cells to fight off infection. Once stem cells differentiate into adult cells, they cannot go back to being stem cells. Current thinking is that the body has a finite number of stem cells and it is best to avoid depleting them, Dr. Zhang explained.

Prior to this study, no high-affinity receptors had been identified for the family of seven proteins called the human angiopoetic-like proteins. These seven proteins are known to be involved in inflammation, supporting the activity of stem cells, breaking down fats in the blood, and growing new blood vessels to nourish tumors. Because the receptor to which these proteins bind had not been identified, the angiopoetic-like proteins were referred to as "orphans," he said.

The researchers found that the human immune-inhibitory receptor LILRB2 and a corresponding receptor on the surface of mouse cells bind to several of the angiopoetic-like proteins. Further studies, Dr. Zhang said, showed that two of the seven family members bind particularly well to the LILRB2 receptor and that binding exerts an inhibitory effect on the cell, similar to a car's brakes.

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In the case of stem cells, inhibition keeps them in their stem state. They retain their potential to mature into all kinds of blood cells as needed but they don't use up their energy differentiating into mature cells. That inhibition helps stem cells maintain their potential to create new stem cells because in addition to differentiation, self-renewal is the cells' other major activity, Dr. Zhang said. He stressed that the inhibition doesn't cause them to create new stem cells but does preserve their potential to do so.

In future research, the scientists hope to find subtle differences between stem cells and leukemia cells that will identify treatments to block the receptors' action only in leukemia.

Other UT Southwestern researchers involved in the study from the departments of physiology and developmental biology include postdoctoral researchers Dr. ChangHao Cui, Dr. Xiaoli Chen, Dr. Chaozheng Zhang, Dr. HoangDinh Huynh, and Dr. Xunlei Kang; senior research associates Robert Silvany and Jiyuan Li; and graduate student Xuan Wan. Researchers from the department of immunology include former technician Alberto Puig Cantó and Dr. E. Sally Ward, professor of immunology.

Former UT Southwestern researchers include lead author and former instructor of physiology Dr. Junke Zheng, now at Shanghai Jiao Tong University School of Medicine in Shanghai, China; Dr. Masato Umikawa, now at the University of Ryukyus in Okinawa, Japan; Dr. Huan-You Wang, now at the University of California, San Diego; and Dr. Jingxiao Ye, now at UT Dallas. Dr. Shu-Hsia Chen, from Mount Sinai School of Medicine in New York City, also collaborated in the study.

The study received funding from the National Institutes of Health; the American Society of Hematology Junior Faculty Award; March of Dimes Basil O'Connor Scholar Award; the Department of Defense; the Cancer Prevention and Research Institute of Texas; and the Gabrielle's Angel Foundation.

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