Genes that suppress tumors are vital to regulating blood precursor cells, study finds

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By Kim Irwin - UCLA stem cell scientists have found that two common tumor-suppressor genes — TSC and PTEN — are vital to regulating the stem cell–like precursor cells that create the blood supply in Drosophila, the common fruit fly.

Julian Martinez-Agosto

"We wondered how an organism knows how many blood cells to make and when to make them in the context of injury and repair to tissue," said UCLA's Dr. Julian A. Martinez-Agosto, the senior author of the study. "In particular, we wondered how the blood progenitor cells sense that change and know when it's time to make more blood cells."

To answer this question, Martinez-Agosto, an assistant professor of human genetics and pediatrics and a researcher with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, and his colleagues examined a signaling pathway called TOR that the cells use to gauge nutrition levels and stress.

"We found that the TOR pathway uses these two genes to regulate its function and, when activated, it expands or increases the number of blood progenitor cells in the fly's blood," Martinez-Agosto said.

The study was published Sept. 5 in the advance online issue of the peer-reviewed journal Development.

Michelle Dragojlovic-Munther, a graduate student in Martinez-Agosto's laboratory and the first author of the study, found that increased TOR activity gives cells a competitive advantage, allowing them to divide and make more of themselves so that they can make blood. These progenitors, Dragojlovic-Munther found, also have high levels of reactive oxygen species (ROS) — ions or very small molecules that include free radicals — which are known to damage cells and can predispose humans to aging and heart disease. But in this case, the ROS proved valuable.

The precursors, Martinez-Agosto said, were producing ROS all the time, and when TOR was activated, the levels increased dramatically. Too much ROS caused them to divide more than normal. The researchers found that if they treated the flies with antioxidants, which reduce ROS levels, the cells would develop normally.

The finding could be important because the TOR pathway is abnormally activated in many cancers, and it may be possible to target the levels of ROS, which may help regulate the pathway.

"What this study may be telling us is that too much ROS is causing more cells to divide, and we may be able to target therapies that reduce ROS to significantly improve the condition," Martinez-Agosto said, adding that specifically targeted antioxidants might be a potential treatment in certain subsets of blood disorders.

"Sometimes that pathway is working more than it should, and we need the right amount of ROS for balance," he said. "It's like Goldilocks — there can't be too little or too much. We need it just right."

Going forward, Martinez-Agosto and his team will try to determine w[Translate]are coming from and perhaps discover an enzyme that may be a good target for therapeutics. They know that the higher ROS levels in blood progenitors are not coming from mitochondria, the cell's power source, but have not yet identified how they are being produced.

"This study highlights mechanistic differences between TSC and PTEN on TOR function and demonstrates the multifaceted roles of a nutrient-sensing pathway in orchestrating proliferation and differentiation of myeloid-specific blood progenitors through regulation of ROS levels and the resulting myeloproliferative disorder when deregulated," the study states.

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The Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research:
UCLA's stem cell center was launched in 2005 with a UCLA commitment of $20 million over five years. A $20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the center. With more than 200 members, the Broad Stem Cell Research Center is committed to a multidisciplinary, integrated collaboration among scientific, academic and medical disciplines for the purpose of understanding adult and human embryonic stem cells. The center supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed toward future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine at UCLA, UCLA's Jonsson Cancer Center, the UCLA Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science.

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