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Quieting cells' low-oxygen alarm stops flare-ups in rare bone disorder

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The cellular response to the lack of oxygen fans the flames of flare-ups in a rare bone disorder. In fibrodysplasia ossificans progressiva (FOP), a mutation triggers bone growth in muscles, which limits motion, breathing, and swallowing, among a host of progressive symptoms.

Scientists from the Center for Research in FOP and Related Disorders at the Perelman School of Medicine at the University of Pennsylvania and colleagues examined the critical role of tissue hypoxia, or oxygen starvation, in the induction and amplification of FOP lesions, also called flare-ups.

The research team, led by Haitao Wang, PhD, a senior research investigator, Robert Pignolo, MD, PhD, an associate professor in the division of Geriatrics and the Ian Cali Distinguished Clinician-Scientist at the Center, and Frederick S. Kaplan, MD, the Isaac & Rose Nassau Professor of Orthopaedic Molecular Medicine and Chief of the division of Molecular Orthopaedic Medicine, published their findings in the *Journal of Bone and Mineral Research* this month.

They showed that cells from FOP lesions in humans and in a mouse model of FOP are markedly oxygen-starved and that this hypoxia triggers a molecular alarm orchestrated by the HIF-1α protein. Surprisingly, HIF-1α dramatically amplifies the already mutant bone morphogenetic protein (BMP) signaling in the oxygen-starved cells and stimulates heterotopic ossification, the abnormal metamorphosis of muscle to bone that occurs in FOP. Most importantly, when the team

disabled the HIF-1α cellular alarm, BMP signaling in human FOP bone progenitor cells was restored to levels comparable to cells in normal oxygen. This adjustment profoundly reduced heterotopic ossification and the resulting disability in the FOP mouse.

A Tantalizing Lead

In 2006, Penn researchers led by Kaplan and Eileen Shore, PhD, the Cali-Weldon Professor of FOP Research and a co-author on the current study, discovered how a mutation in the gene for a BMP receptor called Activin Receptor A type I (ACVR1) occurs in all individuals who have classic FOP. The mutation in ACVR1 (mACVR1) causes the ACVR1 protein, a cell surface receptor, to be mildly overactive, thereby stimulating the BMP pathway continuously, like a faucet that drips water when it should be turned off. However, despite the presence of mACVR1 in all FOP patients, individuals with FOP do not form bone continuously but rather episodically during flare-ups, an important clue that suggested that something else fuels the process of lesion formation.

A tantalizing lead came from studying FOP lesions themselves. Importantly, all FOP flare-ups, whether spontaneous or triggered by trauma, are associated with inflammation, also a well-known cause of oxygen starvation in cells.

"Hypoxia can occur for many reasons, but in early FOP flare-ups, we speculated that hypoxia might result from the inflammatory microenvironment in lesions," Kaplan said. "This happens when oxygen supply to the damaged tissue is impaired and oxygen demand by the damaged cells greatly exceeds its supply."

Indeed, every cell continuously produces HIF-1α but rapidly destroys it when the cell has an adequate supply of oxygen. When a cell is oxygen starved, the enzymes that inactivate HIF-1α instantly cease to function,

allowing HIF-1α to escape destruction, enter the nucleus of the cell, and trigger an alarm that instructs genes to adapt to a low-oxygen microenvironment. This chain of events allows the cell to survive.

The current study showed that HIF-1α inhibitors, specifically the cancer drug imatinib (Gleevec), the natural product apigenin, and the small molecule PX-478, potently inhibit dysregulated BMP signaling induced by HIF-1α in cells, as well as heterotopic ossification following tissue injury in a mouse model of FOP.

"The implications for targeted clinical trials and for compassionate clinical use of HIF-1α inhibitors in the treatment of FOP flare-ups are promising, however we need more data on dosing, duration, timing, rebound, resistance and long-term safety," Pignolo said.

"Our study provides profound insight into the role of cellular hypoxia in FOP flare-ups and shows that cellular oxygen sensing through HIF-1α is a critical regulator of the BMP pathway and heterotopic ossification in FOP," Kaplan said.

The findings support the hypothesis that FOP lesions thrive in a hypoxic microenvironment, not simply due to oxygen deprivation, but also because of a maladaptive response to hypoxia by the HIF-1α molecular alarm, similar to that seen in cancer. Most importantly for individuals with FOP, the study identifies HIF-1α as a therapeutic target—knowledge that will likely contribute to the development of more effective treatments for FOP and related common disorders of heterotopic ossification.

Provided by University of Pennsylvania School of Medicine

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