Researchers solve a molecular mystery in muscle

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The muscle-building abilities of hormones known as insulin-like growth factors (IGFs) are legendary. Just do an online search and you'll find not only scientific papers discussing the effects of IGFs on the cells that give rise to muscle tissue, but also scores of ads touting the purported benefits of IGF supplements for bodybuilding.

But in spite of widespread interest in these potent molecules, key details about how IGFs work on muscle cells have been lacking.

A research by a team led by University of Michigan molecular biologist Cunming Duan has cleared up a longstanding mystery about the workings of IGFs. The team's findings, scheduled to be published online this week in the Proceedings of the National Academy of Sciences, could lead to new treatments for muscle-wasting diseases and new ways of preventing the muscle loss that accompanies aging.

And because IGFs also are implicated in the growth and spread of malignant tumors, the new insights may have implications in cancer biology.

Like other peptide and protein hormones, IGFs work by binding to receptors on the cells they target. The binding then sets off a cascade of reactions that ultimately direct the cell to do something. You might think that a given hormone, binding to a particular receptor, would always elicit the same response from the cell, but that's not what happens in the case of IGF and myoblasts (immature cells that develop into muscle

tissue).

During muscle formation, the binding of IGF to its receptor can prompt either of two very different responses in myoblasts, said Duan, a professor in the Department of Molecular, Cellular and Developmental Biology. Some of the cells are stimulated to divide, while others interpret the very same signal as an order to differentiate (become specialized).

"These are opposite and mutually exclusive cellular events---once a muscle cell divides, it can't differentiate, and once it differentiates, it can never divide again," Duan said. How activation of the same receptor by the same hormone can elicit two such distinctly different responses has been one of the most puzzling questions about IGF, but Duan and colleagues have found the answer.

"The myoblasts' response is controlled by oxygen availability," said Duan. When oxygen levels are normal, IGF promotes muscle cell differentiation; when oxygen levels are below normal, IGF promotes muscle cell division. Teasing out the molecular details, the researchers discovered that low oxygen activates an intermediary called the HIF-1 complex, which reprograms the cascade of steps that ultimately controls the cell's response.

The findings not only reveal how muscle cells respond to varying oxygen levels during normal development, but also have implications for human disease, Duan said. "For example, a major reason that muscle atrophy occurs as people get older is that the IGF signal gets weaker. If we can find a way to affect IGF signaling, we may be able to stop or reverse the loss." Although manipulating the oxygen levels in living cells could be difficult, it may be possible to manipulate HIF-1 in ways that would mimic changing oxygen levels.

The work also could help scientists better understand the processes

involved in cancer progression and spread. It's known that IGF can promote tumor cell division and survival and also that oxygen levels are often lower in tumor tissue than in normal tissue. Finding the link between IGF activity and oxygen levels may lead to new strategies for cancer treatment.

More information: www.pnas.org/

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