Researchers link cell division and oxygen levels

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Cells grow abundant when oxygen is available, and generally stop when it is scarce. Although this seems straightforward, no direct link ever has been established between the cellular machinery that senses oxygen and that which controls cell division. Now, in the June 10 issue of *Molecular Cell,* researchers at Johns Hopkins report that the MCM proteins, which promote cell division, also directly control the oxygen-sensing HIF-1 protein.

"It's always been a mystery why a vast excess of MCM proteins is present in cells, but now we have discovered at least one reason," says Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of Medicine, director of the vascular program in Hopkins' Institute for Cell Engineering and a member of the McKusick-Nathans Institute of Genetic Medicine. "Our data indicate that MCMs mediate crosstalk between the cell division machinery and proteins that help cells react to changes in their surroundings."

Since discovering HIF-1 in the 1990s, Semenza's team has been studying how it works to sense oxygen levels and turn on genes that help cells survive when oxygen is low. To find proteins that HIF-1 physically interacts with, the team went on a biochemical fishing expedition and, using HIF-1 as bait, pulled out MCM7. MCM7 is a member of a larger group of related proteins that are known to bind to DNA and start its duplication when a cell gets ready to divide. Using a different protein-binding technique, the team then found that HIF-1 also binds to MCM3.

When it senses low oxygen levels, HIF-1 turns on genes that enable cells to adapt, such as genes that stimulate the growth of new blood vessels and genes that alter a cell's metabolism to change how much oxygen it consumes for energy generation. To understand what MCM proteins do to or with HIF-1, the researchers examined how well HIF-1 turns on genes in the presence and absence of MCM3 or 7. They found when the levels of MCM proteins were increased, the activity of HIF-1 went down, while reducing the levels of MCMs, led to increased HIF-1 activity. "HIF-1 instructs cells not to divide, since more cells will consume more oxygen, making any shortage of oxygen even worse, while the role of MCMs is to trigger cell division" says Semenza. "So it's not surprising that MCMs would oppose the action of HIF-1."

The team also noticed that there seemed to be less MCM7 present when cells were exposed to low oxygen for 24 hours. To see if this had anything to do with HIF-1, they first turned up HIF-1 levels in cells--by either exposing them to low oxygen or treating them with a drug that boosts HIF-1 production--and found a decrease in the levels of MCM proteins 24 hours later. Separately, they removed HIF-1 from cells, then exposed the cells to low oxygen and found no change in MCM protein levels, allowing the group to conclude that HIF-1 controls MCM proteins as well, so that the MCMs and HIF-1 oppose each other's action. "It's like a tug of war," says Semenza. "When oxygen and nutrients are plentiful, MCMs win, and cells divide. When oxygen is low, HIF-1 wins and cell division is prevented. The mutual antagonism may be critical for tightly controlling cell growth based on oxygen availability."

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