HFI-1 gene has key role in both oxygen sensing, heat shock pathway

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University of Oregon researchers have found an unexpected regulatory link between cellular responses to hypoxia and heat shock. Central to the discovery is a gene known as Hypoxia-Inducible Factor-1 (HIF-1) that is critical for both normal and pathological changes, making it a potential target for both health promotion and cancer therapies.

In their study, researchers used microarray technology to observe the activity of genes found in the genome of the fruit fly (Drosophila). With it, they watched as the activity of heat shock proteins was turned on under conditions of low oxygen, or hypoxia. A microarray allows researchers to place tens of thousands of genes on 1.5-inch-square slides and study them under a microscope.

"These are proteins that were previously known to turn up under conditions of heat shock," said Eric Johnson, a professor in the UO Institute of Molecular Biology. "Now they are coming into view in hypoxia conditions as well."

When Johnson's team manipulated the genes to knock out the activity of HIF-1, the change dramatically lowered the presence of heat shock proteins. Over-activation of HIF-1 is often seen in a wide variety of cancers.

"We've found that there is more complexity to how a cell responds to a change in the environment than what we had long suspected," he said. "Instead of having a simple sensing and response process, there are

sensing, calibrations, fine-tuning and responses that occur. These connections can now be targeted for therapies."

The findings of the research, which was supported by an American Cancer Society Research Scholar Grant to Johnson, appear online in advance of regular publication in the *Journal of Biological Chemistry*.

"This HIF-1 activity was somewhat surprising, because people in the past have often thought that these different pathways that sense environmental change have been separate entities," Johnson said. "It has been assumed that different pathways responded to different conditions, but we've found that the regulator of low oxygen response, HIF-1, actually goes over and cranks up the regulator to the heat shock response."

Understanding and targeting the role of HIF-1 could prove beneficial in turning away oxygen from cancerous cells, choking them off by not allowing oxygen in, Johnson said. The rush of oxygen back into cells after a period of hypoxia also works against wound healing.

In healthy cells, the researchers theorize, HIF-1's turning on of heat shock proteins is beneficial, because the proteins appear to prepare the cell for the return of oxygen, which can cause proteins in the cell to unfold. The heat shock proteins activated by HIF-1 help to refold proteins to ensure a healthy cellular response. "It's a very clever system," Johnson said. "Instead of targeting one of the heat shock proteins, we should consider targeting HIF-1, which controls all of their activity during hypoxia."

Source: University of Oregon