FOXO factor promotes survival of oxygen-deprived cancer cells

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Scientists report that an evolutionarily conserved transcription factor may have both positive and negative effects on the growth of tumors, depending on whether or not the tumor cells have enough oxygen. The research, published by Cell Press in the December 28th issue of *Molecular Cell*, provides critical new information about how normal cells and cancer cells survive under stress.

Dividing tumor cells are often deprived of oxygen as a result of their rapid expansion or aberrant blood vessels. Response to stressful low oxygen conditions, known as hypoxia, involves expression of several genes that enable cells to adapt to the oxygen deficit. This response is primarily mediated by the hypoxia-inducible transcription factors, HIF1 and HIF2.

HIF proteins play a key role in hypoxic tumor development and are often associated with poor patient prognosis. Hypoxic tumor cells exhibit decreased sensitivity to radiation and chemotherapy, and increased potential for invasion and metastasis. Interestingly, recent research findings have also revealed an anti-cancer role for HIF1 that is mediated by the initiation of programmed cell death, called apoptosis, in response to severe hypoxic stress. Although HIF1 has been linked to several pro-apoptotic target genes, specific mechanisms that regulate this particular function of HIF1 are not well understood.

Dr. Tak W. Mak from the Campbell Family Institute for Breast Cancer Research at Princess Margaret Hospital in Toronto and colleagues found that hypoxia stimulates an HIF1-dependent increase in a protein called FOXO3a. FOXO transcription factors are evolutionarily conserved proteins that are critical regulators of cell survival under stressful conditions. Recently, FOXO proteins have also been shown to act as tumor suppressors.

Dr. Mak's group observed that under hypoxic conditions, FOXO3a inhibited HIF-1 induced apoptosis in normal cells and breast cancer cells by stimulating the transcription of the HIF1 target gene CITED2. Activation of CITED2, known to exert a negative influence on HIF1 activity, resulted in reduced expression of pro-apoptotic HIF1 target genes.

"Our results reveal a pro-survival role for FOXO3a in normal cells and cancer cells that are adapting to hypoxic stress," explains Dr. Mak. "Targeting of this pathway may benefit cancer treatment. Tumorigenesis could possibly be inhibited by either very high levels of FOXO3a/CITED2 activity that would cause complete inhibition of HIF1 or very low levels that would permit HIF1- induced apoptosis under hypoxic stress."

Source: Cell Press