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SIRT3 Controls Cancer Metabolic Reprogramming by Regulating ROS and HIF

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In this issue of *Cancer Cell*, Finley and coworkers report that the genetic loss of the deacetylase SIRT3 leads to metabolic reprogramming toward glycolysis. This shift is mediated by an increase in cellular reactive oxygen species (ROS) generation that amplifies HIF- α stabilization and HIF-dependent gene expression, thereby driving the tumor phenotype.

In cancer cells, reprogramming of cellular metabolism drives substrate utilization toward a dependence on glucose. First described by Otto Warburg (Warburg, 1956), the significance of this response for tumor growth has been controversial. However, it appears that this glycolytic shift is necessary to provide a source of substrates for the synthesis of amino acid, lipids, and nucleic acids that are needed for proliferation (Vander Heiden et al., 2009). Indeed, enhanced glucose uptake by tumor cells forms the basis for the clinical detection of tumors by imaging regions exhibiting increased uptake of the glucose analog ¹⁸F-fluorodeoxyglucose. While the association between cancer and the Warburg metabolic shift is well established, the cellular mechanisms regulating this response are not fully understood.

Posttranslational modifications of proteins are important for regulating their function in health and disease. Critical roles for protein deacetylases are also

emerging in cancer. For example, Kim et al. (2010) identified a role for SIRT3, a member of the seven-member sirtuin family, as a tumor suppressor. They showed that genetic deletion of SIRT3 pushes the cell in the direction of oncogenic transformation. While activation of two oncogenes (such as Myc and Ras) is needed to transform an immortalized fibroblast into a tumor-forming cell, genetic deletion of SIRT3 reduced that number to one. Thus, SIRT3 functions as a tumor suppressor (Schumacker, 2010). The mechanistic basis for SIRT3's tumor-suppressive role seems to reside in its ability to regulate reactive oxygen species (ROS) generation or clearance by the cell. Kim et al. (2010) noted that ROS levels were increased in SIRT3^{-/-} cells, as a consequence of a decreased expression of antioxidant enzymes such as catalase and MnSOD. The transcription factor FOXO3a plays an important role in regulating the expression of MnSOD and other antioxidants, and SIRT3-mediated deacetylation of

FOXO3a promotes its nuclear localization (Jacobs et al., 2008). Thus, the loss of SIRT3 activity suppresses FOXO3a, leading to an increase in cellular ROS signaling. Enhanced ROS levels have been linked to cancer, and Kim et al. (2010) observed an increase in the incidence of mammary tumors in the SIRT3 knockout mice. They suggested that the chronic increase in mitochondrial ROS stress might result in mitochondrial or genomic DNA damage, but that mechanism was not directly tested. Nevertheless, their study identified an important pathway by which SIRT3 suppresses tumor cell survival and proliferation through its effects on cellular ROS regulation.

But even the best studies leave many questions unanswered. The principal issue left in the wake of the Kim et al. (2010) study related to how the increase in ROS (caused by loss of SIRT3) mediates the enhanced tumor phenotype of cells. The answer to that question arrives in the article by Finley et al. (2011) in this

issue of *Cancer Cell*. While confirming that the genetic loss of SIRT3 leads to an enhanced tumor phenotype in a ROS-dependent manner, they move the field forward in a profound way by showing that this occurs because the ROS enhance HIF-1 α stabilization. HIF-1 and HIF-2 are hypoxia-responsive transcription factors that regulate the altered expression of more than 200 genes in responses to hypoxia (Semenza, 2010a). Upregulation of HIF activity is strongly linked to the survival and proliferation of tumor cells, because some HIF-dependent genes such as glucose transporters and glycolytic enzymes, and vascular endothelial growth

factor (VEGF) are critical for cell survival when chronically exposed to a hypoxic microenvironment in the tumor. Other HIF-dependent genes affect metabolic reprogramming, apoptosis, cell migration, remodeling of the extracellular matrix, iron metabolism, pH regulation, vascular reactivity, and other functions that are intimately involved in tumor progression and metastasis (Semenza, 2010b). Finley et al. (2011) made this connection by comparing the gene expression profile in brown adipose tissue of wild-type and SIRT3 knockout mice, and noting that the loss of SIRT3 led to a response that mimicked the change when cells were exposed to low oxygen. The mechanism underlying the response to SIRT3 deletion appears to involve an increase in ROS-dependent inhibition of prolyl hydroxylase (PHD) (Figure 1). This mechanism is consistent with previous studies demonstrating that mitochondrial ROS signals regulate HIF- α stability in hypoxia (Chandel et al., 1998). Interestingly, the loss of SIRT3, via enhanced HIF expression,

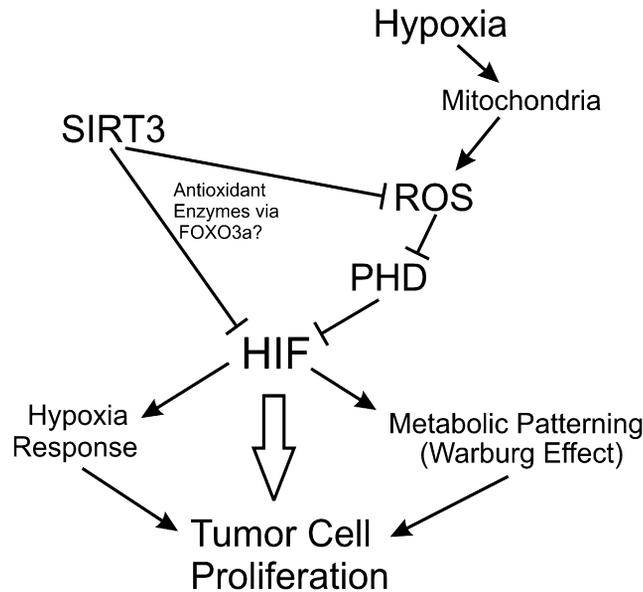


Figure 1. Regulation of Tumor Cell Phenotype by SIRT3

mediates the Warburg shift in metabolism in fibroblasts, driving them toward enhanced glucose utilization that is required for the enhanced growth properties they exhibit.

The loss of SIRT3 appears to drive HIF activation even under basal normoxic conditions, and to enhance the HIF response to hypoxia through a ROS-dependent mechanism. They report that treatment of SIRT3 knockout cells with the antioxidant N-acetyl cysteine (NAC) returns the normoxic HIF to wild-type levels while it abolishes the increased rate of proliferation and metabolic reprogramming. In vivo, NAC treatment repressed the hypoxia-associated gene expression profile in brown adipose tissue, without affecting expression patterns in wild-type animals. By contrast, overexpression of SIRT3 shifts the cell away from the Warburg effect and suppresses the hypoxic response, although the role of ROS in that response was not directly investigated.

Impressively, Finley et al. (2011) go on to provide correlative evidence showing

an association between the loss of SIRT3 in human breast cancers and the enhanced expression of HIF-1-dependent genes. Whether or not the loss of SIRT3 is a causative agent in cancer initiation or whether subsequent loss of SIRT3 in an existing tumor cell helps to drive its glycolytic and proliferative phenotype are questions that still need to be addressed. It seems likely that both events may occur in different conditions. In either case, the finding that SIRT3 loss can enhance the HIF-dependent response in cancer opens therapeutic opportunities for drug targets while it underscores the potential importance of identifying agents that can selectively

inhibit ROS signaling and HIF activity in cancer.

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