The HIF-1α-c-Myc pathway and tumorigenesis: Evading the apoptotic gatekeeper

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The imbalance between oxygen delivery and consumption results in hypoxia (low oxygen concentration), a hallmark of human cancers that contributes to resistance to radiation therapy and chemotherapy and ultimately to poor patient prognosis. The master regulator of the adaptive response to oxygen deprivation is hypoxia-inducible factor-1 (HIF-1), a transcription factor that operates by activating the expression of genes related to angiogenesis, glycolytic metabolism, oxygen consumption, migration and invasion.[1] HIF-1 protein complex consists of a β subunit, which is constitutively expressed, and a HIF-α subunit that is oxygen responsive and regulated by ubiquitin-proteasomal degradation. HIF-1α is frequently overexpressed in human cancers and is an attractive target for therapy.[2]

HIF-1α has also been implicated in a non-canonical pathway that does not require DNA binding activity and counteracts the effects of c-Myc on gene expression. Indeed, work from Huang's laboratory has provided evidence that the PAS (Per-ARNT-Sim)-B domain of HIF-1α is responsible for inhibiting the c-Myc-dependent expression of *MSH2* and *NBS1*, enzymes involved in DNA mismatch and double-strand break repair, respectively.[3] Thus, the HIF-α-c-Myc pathway seems to act as an essential component in mediating genetic instability in a hypoxic environment that promotes tumor progression.[4]

These results, however, raised the important question as to whether normal tissues would respond differently to the selection pressure toward genetic instability exerted by the hypoxic environment. In the July 15th issue of *Cell Cycle*, Hayashi and her colleagues pursued this question by looking at one of the major features of cancer, evasion of apoptosis and whether non-cancerous cells would experience similar accumulation of genetic alterations induced by the HIF-1α-c-Myc pathway, or whether these normal cells would somehow be protected.[5] Indeed, they found that hypoxia or HIF-1α expression inhibited DNA repair and induced DNA damage in all malignant and benign mouse cells tested. However, only apoptosis-deficient malignant cells accumulated DNA damage and acquired anchorage-independent growth and features consistent with epithelial-mesenchymal transition (EMT), implicating a protective function of apoptosis against HIF-1α-induced malignant development. Furthermore, the growth advantage observed was further associated with resistance to etoposide treatment, at least in part attributed to increased Akt activity and inhibition of autophagy, thus, once again, implicating the HIF-1α-c-Myc pathway in promoting the survival of apoptosis-deficient malignant cells. Taken together, Hayashi et al. provide evidence that normal cells proficient in apoptosis are, for the most part, safe under hypoxic stress, and genetic alteration produced by HIF-1α is largely cell-context dependent.

The contribution of HIF to tumor progression is largely attributed to its ability to induce the expression of genes whose products contribute to essential features of the malignant phenotype, including metabolic reprogramming, angiogenesis and metastasis. The elegant work of Hayashi and his colleagues extends the involvement of HIF-1α in tumorigenesis by implicating a non-canonical mechanism of action that counteracts c-Myc effects on gene expression. However, to what extent this pathway is active in the presence of deregulated or oncogenically activated c-Myc remains to be established. Indeed, under these circumstances, the interaction between HIF and c-Myc appears to be much more complex.[6] For instance, HIF-1 and c-Myc can cooperate for the induction of glycolytic enzymes or angiogenic factors, and HIF-2 enhances c-Myc transcriptional activity in renal cell carcinogenesis.[7]

The work published by Hayashi et al. in the July 15th issue of *Cell Cycle* is consistent with a model in which apoptosis proficiency is a gatekeeper to limit the potential damaging genetic changes effected by a hypoxic microenvironment. Indeed, evidence has been provided that HIF-1α may induce apoptosis, although the context in which this occurs and the pathways implicated are still poorly understood. Evasion of apoptosis is a hallmark of human cancers and selection of genetically altered, apoptosis-resistant clones by hypoxia has been previously suggested.[8] The interplay between cell-autonomous genetic changes and the selection pressure exerted by the tumor microenvironment is crucial to fully execute the tumorigenic program. Hayashi and colleagues provide further experimental evidence to corroborate a critical role played by the HIF-1α-c-Myc pathway in tumorigenesis.

References

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