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Targeting HIF-α: when a magic arrow hits the bull's eye

Targeting hypoxia-inducible factor-α (HIF-α) for therapeutics has attracted a great deal of attention in recent years because of the pivotal role of HIF-α in oxygen homeostasis. Hypoxia – an oxygen deficiency in tissues – is the cause of ischemic diseases including heart attacks and stroke, and a culprit of tumor development and progression. Therefore, alteration of HIF-α activity could be therapeutically beneficial.

In ischemic tissues, therapeutic upregulation of HIF-α activity should induce angiogenesis and glycolysis, thereby alleviating the hypoxic stress. By contrast, in cancerous tissues, the pharmacological downregulation of HIF-α activity might prevent cellular adaptation to hypoxia, presumably inhibiting tumor growth.

In a recent issue of *Drug Discovery Today*, Hewitson and Schofield [1] provided an excellent review on targeting the HIF pathway in that regard, with an emphasis on the inhibition of HIF hydroxylase activity to prevent HIF-α degradation.

Some of the therapeutic agents in current clinical trials inhibit HIF-α activity by targeting the phosphorylation signaling pathways to downregulate HIF-α transcription and/or translation. Others do so by targeting pathways controlling HIF-α stability or transcriptional activity [2,3]. However, none of these targeted pathways have been elucidated in the regulation of HIF-α activity [4]. Interestingly, no therapeutic agent has been developed that targets the primary mechanism regulating HIF-α activation – hydroxylation signaled ubiquitin-proteasome proteolysis [4]. HIF-α is modified by the prolyl-4-hydroxylases, which use oxygen, ferrous iron and 2-oxoglutarate as co-factors. In the review by Hewitson and Schofield, use of 2-oxoglutarate analogues as inhibitors of hydroxylation and exploration of HIF-α specific hydroxylase targeting are extensively discussed.

Undoubtedly, key to the success of molecular targeting is finding and selecting the correct target, as epitomized by imatinib mesylate (Gleevec), a protein-tyrosine kinase inhibitor that inhibits the abnormal Bcr-Abl tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia. It is logical to aim at the phosphorylation and hydroxylation pathways that regulate HIF-α activity because no pharmaceutical has been identified that directly targets transcription factors. However, the pleitropic nature of these targets in signaling pathways could complicate or compromise the outcome, and therefore HIF-α specific targeting would be more desirable.

Moreover, upregulation of HIF-α activity increases angiogenesis and glycolysis, but heightened levels of HIF-1α also induce cell-cycle arrest [5], an unwanted effect in the treatment of ischemic diseases. It should be noted that HIF-1α induced cell-cycle arrest is independent of its DNA binding and transcriptional activity, a novel mechanism that is worth consideration as a new target. Furthermore, the distinct functionalities of HIF-1α and HIF-2α in biology and pathophysiology are emerging from more recent studies, even though the nuances of their regulatory mechanisms have yet to be fully appreciated. Differential targeting of HIF-1α and HIF-2α could improve drug specificity and thereby efficacy. In essence, the effectiveness of molecular targeting relies upon continued investigation of the mechanisms of action – the bull's eye – that will ultimately lead to the discovery of precision drugs.

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1359-6446/04/$ – see front matter PII: S1359-6446(04)03227-1