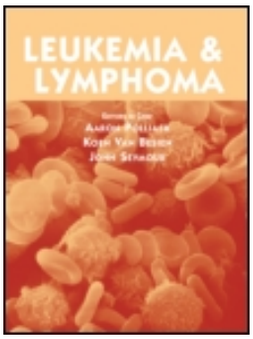

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COMMENTARY

Activation of hypoxia signaling is marker of poor prognosis in myelodysplasia

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Hypoxic-triggered signaling has been shown to lead to increased metastasis, drug resistance and poorer prognosis in cancer [1,2]. Chronic hypoxia can initiate a genetic transition to a more resistant phenotype and lead to adverse prognosis in these patients. Hematological malignancies are often characterized by alterations in the marrow microenvironment, which can trigger hypoxia-mediated signaling and activate transcription factors such as hypoxia-inducible factor-1α (HIF-1α). HIF-1α can enhance the ability of malignant cells to breach key cellular checkpoint mechanisms such as p53 targeting, apoptosis and autophagy during transformation [3]. Under normoxic conditions, phosphorylated HIF-1α (post-translational modification) interacts with a tumor suppressor VHL (Von Hippel–Lindau) gene which facilitates HIF-1α degradation by the "ubiquitin-proteosomal" pathway. Conversely in hypoxia, the lack of a phosphorylated moiety on HIF-1α circumvents its binding to VHL and leading to its stabilization and switching on a myriad of hypoxia-inducible genes. These genes enable the cancer cell to survive in a hypoxic environment. In parallel, hypoxia-independent mechanisms (growth factors) have also been shown to activate and increase synthesis of HIF-1α via the mitogen-activated protein kinase/phosphatidylinositol 3-kinase (MAPK/PI3K) and mammalian target of rapamycin (mTOR) pathways [4].

Myelodysplasia (MDS) is a well-known clonal heterogeneous bone marrow failure syndrome which spans across a spectrum ranging from bone marrow suppression in early stages to a higher-risk transformation into a leukemic subtype at later stages. Apart from the effect of inflammatory cytokines on the bone marrow niche, depletion of functionally reconsitutable hematopoietic stem cells, pancytopenia and leukemic blasts may also contribute to altered O_2 tension in the marrow and lead to activation of HIF-1α. This activation may contribute to the activation of proliferation pathways that may be important in the transformation of MDS into acute myeloid leukemia (AML). Thus, it is possible that chronic hypoxia may be critical for leukemic transformation by transactivation of notable hypoxia response elements (HREs) promoting cell proliferation, metastasis, drug resistance and, most importantly, vasculogenesis by vascular endothelial growth factor (VEGF) [5]. The current study shows that HIF-1α expression correlates with a more aggressive phenotype of MDS and indirectly supports this hypothesis.

The current study also shows that HIF-1α is a marker of adverse prognosis in MDS. The International Prognostic Scoring System (IPSS) has been the cornerstone of risk prognostication in patients with MDS [6]. However, in clinical practice, it is frequently seen that some patients with low IPSS scores may have a shortened survival. This has warranted a search for newer parameters with higher specificity, which may assist in better risk stratification and more prudent decision-making in the clinic. As reported in this issue by Dr. Tong and colleagues, a cohort of patients with MDS undergoing treatment with decitabine (hypomethylating agent) showed a statistically significant correlation between positive expression of HIF-1α and MDS subtype, with a greater propensity of occurrence with high-risk MDS, which has a proclivity toward a pre-leukemic morphogenesis [7]. Also, poorer survival trends were noted in those with high-risk MDS and positive HIF-1α versus their low-risk counterparts, which is similar to other studies linking HIF-1α to clinical profile and patient prognosis in solid tumors and hematological malignancies. However, to claim the role of decitabine in silencing the expression of only VHL is inconclusive, albeit it plays a critical role in HIF-1α ubiquitinylation. As is well known, most of the methyl transferases have a global effect, and are often redundant in its epigenetic silencing.

The inhibition of HIF-1α may have therapeutic potential also. Studies in renal cell cancer have shown that genomic loss in the VHL allele can result in high levels of HIF-1α and -2α. Using renal cancer cell lines, it has been shown that small molecule inhibitors of HIF-1α [8,9] can inhibit tumor growth *in vitro* and in xenografts. Thus, it is possible that HIF inhibitors may have a therapeutic role in MDS/AML also and need to be tested.

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