HIF1α or HIF2α: Enhancing CD8$^+$ T-cell Fitness for Antitumor Immunity

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Adoptive T-cell therapy requires the transferred lymphocytes to adapt to the hypoxic tumor microenvironment. In this issue, Veliça and colleagues found that modified HIF2α expression in CD8$^+$ T cells increases antitumor efficacy.

See article by Veliça et al., p. 401

Hypoxia-inducible transcription factors (HIF) are critical regulators of cellular responses to low tissue oxygen tension. HIFs are heterodimers consisting of an oxygen-labile HIFα subunit, either HIF1α or HIF2α, and a constitutive HIF1β subunit. In the presence of oxygen, HIF1/2α is hydroxylated by specific prolyl hydroxylases (PHD), facilitating binding of von Hippel–Lindau protein (VHL), ubiquitylation, and proteasomal degradation. A second level of oxygen control is exerted by factor inhibiting HIF (FIH), an enzyme that hydroxylates a conserved asparagine residue in HIFα subunits, blocking association with the p300/CREB-binding protein (CBP) coactivator for transcription. Under hypoxic conditions, PHD and FIH activities are inhibited, leading to stabilization and translocation of HIF1/2α into the nucleus, where they heterodimerize with HIF1β and activate the transcription of hypoxia-responsive genes. Although the expression and function of HIF1α and HIF2α partially overlap, the two subunits play distinct context-dependent roles in many physiologic conditions and pathologic diseases (1). In cancer, deletion of HIF1α, but not HIF2α, in CD8$^+$ T cells reduces tumor infiltration and tumor-cell killing (2). However, there are substantial unanswered questions about the roles of HIF1α versus HIF2α and the roles of specific oxygen-regulating mechanisms that could be potentially important in T-cell engineering for adoptive T-cell therapy for cancer.

To elucidate the distinct roles of HIF1α and HIF2α and their susceptibility to oxygen regulation by PHD- versus FIH-dependent mechanisms in influencing CD8$^+$ T-cell cytotoxicity *in vitro* and antitumor efficacy *in vivo*, Veliça and colleagues (3) compared CD8$^+$ T cells expressing wild-type and mutant versions (resistant to PHD or FIH) of HIF1α and HIF2α. Strikingly, the authors found that HIF2α, but not HIF1α, induces broad transcriptional changes in CD8$^+$ T cells, leading to increased cytotoxicity against tumor targets. HIF1α and HIF2α share 48% amino acid–sequence identity and similar protein structure, and both are subjected to similar PHD- and FIH-dependent regulation. Although the exact mechanisms underlying the differential roles between HIF1α and HIF2α in T cells remain to be investigated, previous studies show that HIF1α and HIF2α have nonoverlapping target genes (4). In addition, HIF1α is activated during acute intense hypoxia (<0.1% O_2), whereas HIF2α can be active under prolonged mild hypoxia (<5% O_2) in neuroblastoma cells (5). Thus, it is possible that HIF2α functions better, with broader transcriptional activities, in the chronic hypoxic condition in the tumor microenvironment, and this may explain enhanced effector function in CD8$^+$ T cells expressing HIF2α.

One of the most interesting and important findings of the study by Veliça and colleagues is that a specific mutation (N851A), which eliminates the hydroxyl group acceptor site for FIH in HIF2α, gives rise to the most effective antitumor T cells *in vivo*. In contrast, HIF2α mutations causing resistance to PHD reduced cell proliferation, T-cell receptor expression, and IFNγ production. It is conceivable that persistent presence of HIF2α resistant to VHL-mediated proteasome degradation may cause detrimental effects on T cells due to sustained broad transcriptional activity. It is, however, most intriguing that the N851A mutation has such a profound role in T-cell function, as transcriptional profiles are similar between this mutant and the wild-type HIF2α in CD8$^+$ T cells *ex vivo*, and the consequence of this mutation is observed only *in vivo*. It will be interesting to investigate what signals in the microenvironment lead to the changes, for example, the signals that lead to activation of transcriptional cofactors that selectively interact with N851A-mutant HIF2α. Regardless of further exploration of mechanisms stimulated by these findings, the current study provides a means for enhancing CD8$^+$ T-cell fitness via expression of engineered HIF transcription factors for adoptive T-cell therapy.

Author's Disclosures

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