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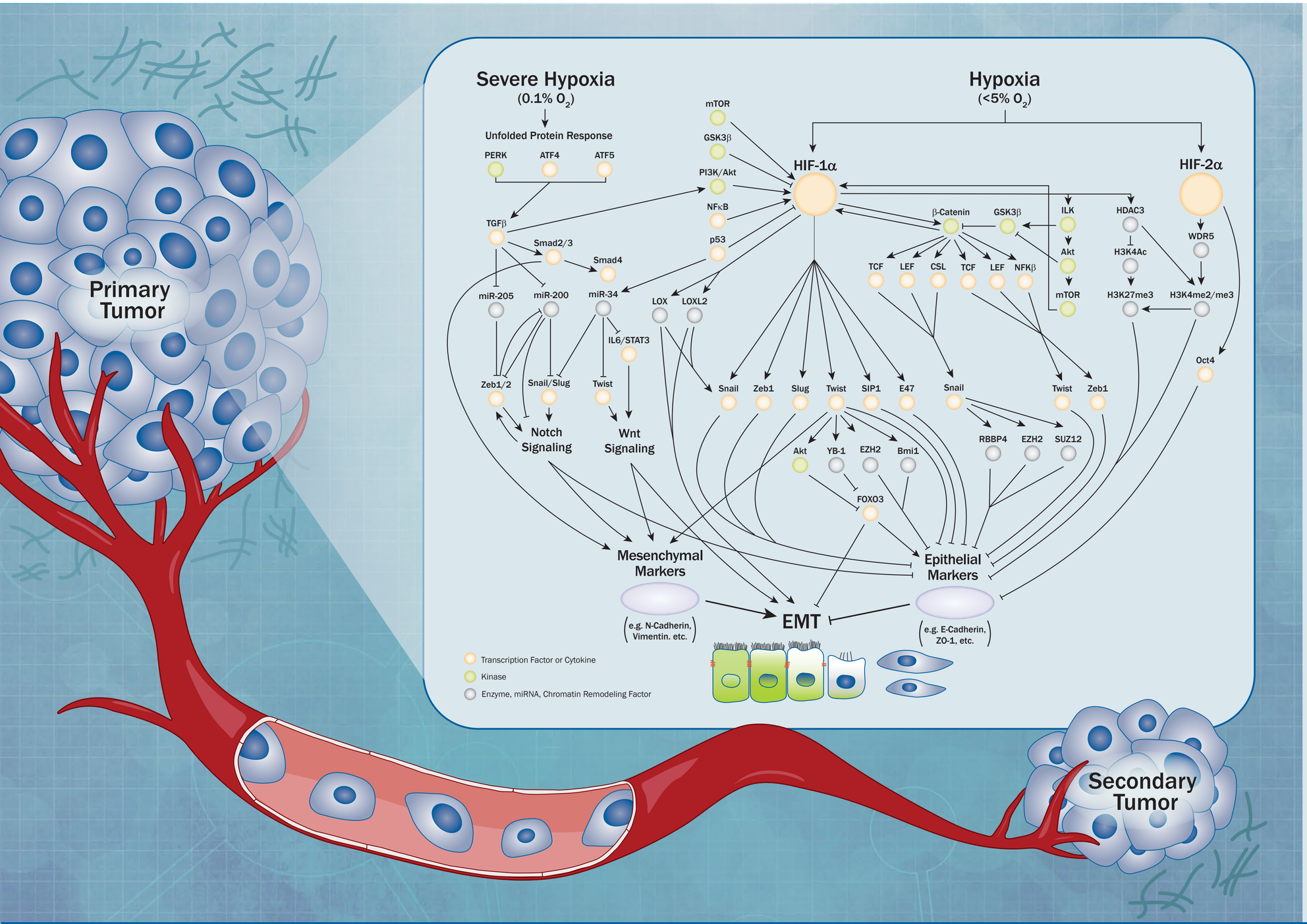
# Tumor Hypoxia and Epithelial-Mesenchymal Transition




## Tumor Hypoxia and Epithelial-Mesenchymal Transition (EMT)

EMT is characterized by the loss of cell-cell adhesion and apical-basal polarity. During EMT, epithelial cells lose E-cadherin expression, a hallmark of EMT, and obtain mesenchymal markers, such as vimentin and fibronectin. There are three types of EMT: type 1 occurs in embryogenesis and organ development, type 2 is important for tissue regeneration and organ fibrosis, and type 3 is associated with cancer progression and cancer stem cell properties. The changes in gene expression that contribute to the EMT process involve master regulators, including SNAIL, TWIST, and ZEB transcription factors. Their expression is activated early in EMT, and thus they have central roles in development, fibrosis, and cancer. These transcription factors have distinct expression profiles, and their contributions to EMT depend on the cell or tissue type involved and the signaling pathways that initiate EMT. EMT has been known to be an important process during tumor progression. EMT promotes invasion, which is considered an initial and critical step for metastasis.

Hypoxia in the tumor environment can promote EMT through hypoxia-inducible factor 1α (HIF1α), which activates the expression of TWIST, SNAIL and other EMT inducers. In epithelial cells undergoing EMT, TGFβ activates AKT through PI3K, which results in the activation of mammalian TOR complex 1 (mTORC1) and mTORC2. TWIST is a direct transcriptional target of HIF-1α, whereas SNAIL is regulated by hypoxia at the post-transcriptional level. TWIST is critical for hypoxia mediated EMT and metastasis, and plays a non-redundant role in relation to other EMT regulators under hypoxia. HIF-1α promotes EMT and stemness in cancer cells through the TWIST1–BMI1 axis. Members of the LOX/LOXL2 family are also upregulated in a hypoxic environment and can contribute to metastasis. Other EMT inducers (ZEB1/2) are also up-regulated by hypoxia and can potentially collaborate with TWIST–SNAIL in invasion and metastasis.

Studies have shown that the hypoxic tumor microenvironment contributes to the stabilization of HIF-1α, which functions to activate the Wnt, Notch, and TGF-β signaling pathways, inducing both EMT and stemness. In addition, HIF-2α activates the expression of Oct-4, a factor contributing to stemness. Recent research also reported that unfolded protein response (UPR) proteins such as PERK, ATF4, and ATF6 potentiate the EMT of cancer cells under conditions of severe hypoxia.