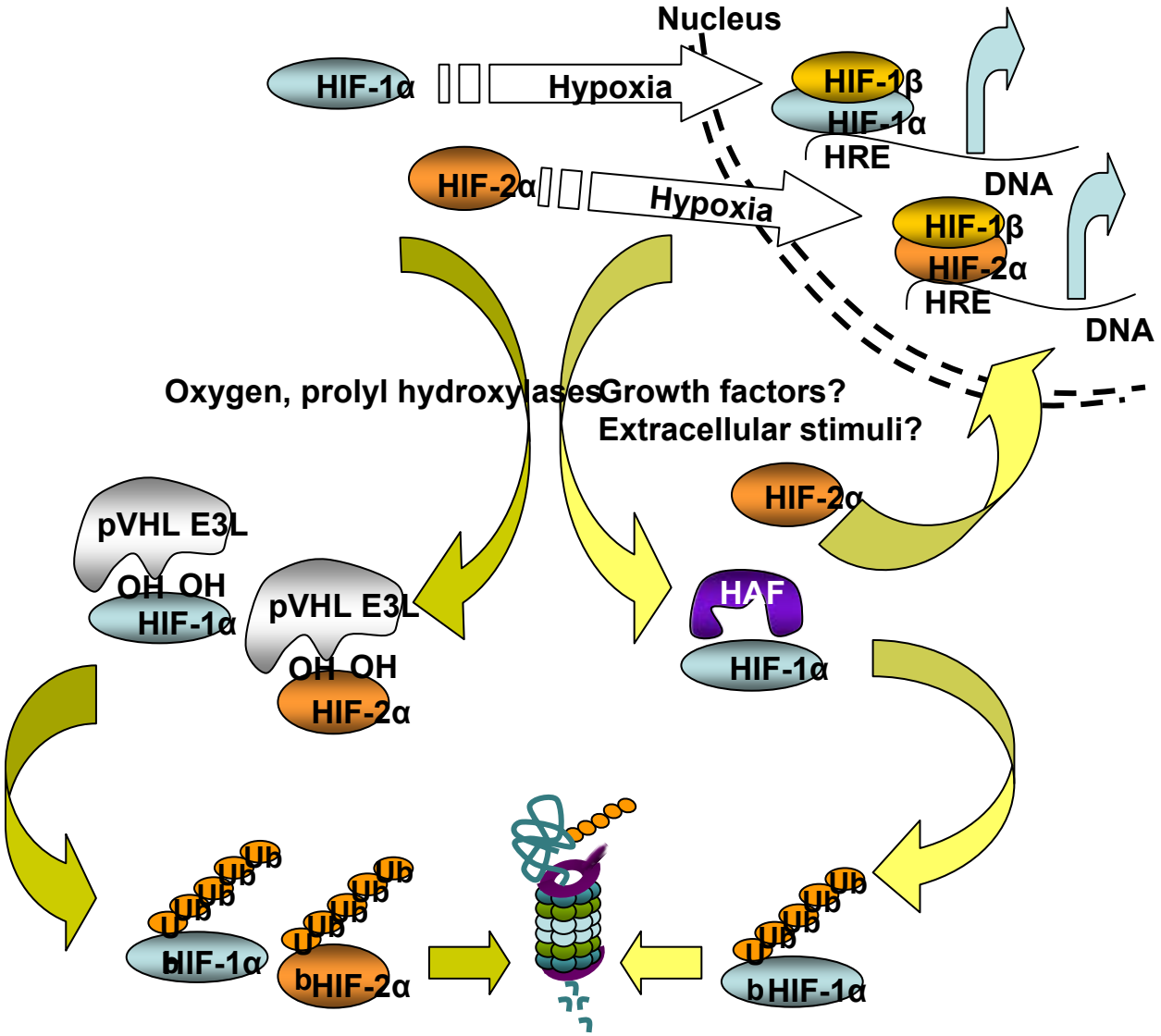
HAF, the new player in HIF-1α degradation.



Under aerobic conditions, the hydroxylation of both HIF-1α and HIF-2α by prolyl hydroxylases facilitates the binding of the pVHL E3 ligase complex (pVHL E3L) to HIF-1α and HIF-2α. This results in the poly-ubiquitination of HIF-1α and HIF-2α and their proteasomal degradation. Under hypoxic conditions, HIF-1α and HIF-2α are stabilized and they enter the nucleus where they heterodimerize with HIF-1β and initiate downstream transcription. The presence of growth factors or specific extracellular stimuli promote the binding of HAF to HIF-1α by a new oxygen-independent mechanism recently described in our laboratory. This promotes the poly-ubiquitination and degradation of HIF-1α while HIF-2α is allowed remain to activate downstream transcription.