

MOLECULAR MODELING ON HIF2A-ARNT DIMER DESTABILIZATION CAUSED BY HIF2A V192D AND/OR R171A MUTATIONS

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The hypoxia-inducible-factors (HIFs) are responsible for cellular adaptations to low oxygen stress by activating transcriptional programs such as erythropoiesis and angiogenesis. Because these programs are related to tumor growth and progression, HIFs have become attractive targets for cancer therapy. To function as oxygen-sensitive regulatory subunits, HIF2 α must form a heterodimer with the aryl hydrocarbon receptor nuclear translocator (ARNT). Both HIF and ARNT proteins have a basic-helix-loop-helix (bHLH) domain for DNA reading in their amino-termini, followed by two tandem Per-ARNT-Sim (PAS) domain, namely PAS-A and PAS-B, for HIF-ARNT dimerization, and transactivation domains (TAD) in their carboxyl-termini. According to the recently solved HIF2 α -ARNT dimer structure (not covering their TADs), there are six domain-domain interfaces including HIF2 α 's bHLH with ARNT's bHLH, HIF2 α 's PAS-A with ARNT's PAS-A, HIF2 α 's PAS-B with ARNT's PAS-A, HIF2 α 's PAS-B with ARNT's PAS-B, HIF2 α 's PAS-A with HIF2 α 's PAS-B, and HIF2 α 's bHLH with HIF2 α 's PAS-B. Structural comparison shows that HIF2 α 's bHLH, PAS-A, and PAS-B domains are compactly interconnected; whereas ARNT's bHLH, PAS-A, and PAS-B domains are linked by long flexible loops to grant structural adaptability to dimerize different bHLH-PAS proteins members. Lately, co-immunoprecipitation experiments have shown that R171A and/or V192D on HIF2 α 's PAS-A domain impair HIF2 α -ARNT dimerization. Herein we applied molecular dynamics simulations to investigate the structural and dynamic impact brought by these mutations. Our results conclude that these mutated amino residues, located in HIF2 α 's PAS-A with HIF2 α 's PAS-B interface, change the relative orientation and motion of PAS-A and PAS-B and therefore these two PAS domains are not recognizable by ARNT.