# Hypoxia-Inducible Factor-1 activated by PIM1 assembles a non-canonical transcription complex and resultant regulon that drives progression of JAK2V617F myeloproliferative neoplasms

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Hypoxia-inducible factors (HIFs) are master transcriptional regulators, central to physiological oxygen homeostasis and cellular survival under limiting oxygen conditions (hypoxia), and frequently activated within malignancy. The context within which HIFs are activated significantly impacts their role within oncogenesis; this is particularly evident within acute myeloid leukaemia (AML), where HIF-1 has been characterised as both oncogenic and tumour suppressive. The mechanisms that regulate these disparities are not well understood. We therefore sought to determine whether the modality of HIF-1 activation determines its function, applying the JAK2V617F (JVF) model of myeloproliferative neoplasms (MPNs) in which HIF-1 is stabilised under normal oxygen (normoxic) conditions and is oncogenic. First, we identify that HIF-1 is stabilised in JVF cells downstream of disproportionate STAT1/5 signalling and increased PIM1 activity. Inhibition of PIM1 kinase activity eradicates HIF-1 from normoxic JVF cells. We identify a novel phosphorylation couplet (T498/S500) within the oxygen dependent degradation (ODD) domain of HIF-1 phosphorylated in JVF cells that inhibits normoxic proteasomal degradation. Applying a single-input dual-omics output chromatin interactome methodology (RIMESeq) in matched isogenic cell lines, we identify distinct transcriptional cofactors for HIF-1 in JVF cells and redistribution of HIF-1 across the genome. JVF-HIF-1 produces a non-canonical target gene signature that is differentially expressed in primary mouse and human JVF haematopoietic stem and progenitor cells (HPSCs). Analysing a cohort of 298 JVF-positive MPN patients, we observe significant association of the JVF-HIF signature-- but strikingly not the hypoxia-induced HIF-1 signature- with disease severity, progression, and survival of these patients. Finally, we identify a core set of 13 genes within the JVF-HIF-1 signature whose differential expression is significantly associated with spontaneous transformation of MPNs to acute myeloid leukaemia (AML). These findings demonstrate that the context and modality of HIF-1 activation can substantially alter its transcriptional function, and restore the potential for targeted HIF therapies that can delineate its activity co-opted by malignancy from its essential roles within physiological oxygen homeostasis.