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Perspective

The Role of Transcription Factor HIF2α in the Acute Myeloid Leukemia

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DESCRIPTION

The aggressive disease known as Acute Myeloid Leukemia (AML) is typified by unchecked proliferation and myeloid differentiation arrest. AML is a genetically heterogeneous disease that defines disease subgroups and clonal or functional populations within individual individuals due to a variety of karyotypic abnormalities, mutations, gene expression, and epigenetic profiles. Intense chemotherapy and allogeneic hematopoietic cell transplantation, for qualified individuals, are the primary therapeutic options available to AML patients. New targeted medicines have recently been introduced for certain patient populations. However, younger patients who have remission after standard therapies frequently relapse because of the genetic flexibility of clonal AML populations and therapy-resistant leukemia stem cells. Additionally, older people are unable to tolerate extremely toxic treatments. These factors contribute to the depressingly poor AML survival rate, making the need for new treatment alternatives urgent.

One typical characteristic of AML is the blockade of myeloid differentiation, which can happen at various phases of development and produce morphological subsets that are only partially determined by genetic characteristics. APL's PML-RARα fusion protein is one example of how oncogenic drivers in certain subgroups of AML impose a block of differentiation by directly disrupting the expression of genes related to lineage commitment. In other cases, oncogenic transcriptional regulators (such IDH or TET mutants) use epigenetic processes to influence the expression of differentiation genes. The molecular foundations of the differentiation block are often still unclear, and it's unclear if AML subtypes share any similar regulatory pathways.

In addition to providing valuable information about the pathophysiology of AML, defining the specifics of stopped differentiation is essential for turning this trait into a fixable vulnerability. This is why the discovery that All-Trans Retinoic Acid (ATRA) stimulates terminal differentiation to cause an APL exhaustion has been a game-changer for AML therapy and has generated a great deal of interest in applying this strategy to other AML subtypes. The success of ATRA is still restricted to APL and a small number of other AML subtypes, nevertheless. Due to epigenetic suppression of differentiation genes, this prevents transcriptional activation by ATRA-dependent transcription factors, the majority of non-APL AMLs are resistant to ATRA-induced differentiation. Because of this, more effective differentiation therapies now include ATRA together with epigenetic medications to enable the de-repression of differentiation genes. Our research reveals the transcription factor HIF2α as a novel regulator of the AML differentiation block within this system. Hypoxia Inducible Factors (HIFs) are transcription factors that are heterodimeric, consisting of a constitutive β subunit and an inducible α subunit. HIF1α and HIF2α, the two primary α subunits, regulate distinct target genes that are specific to different cell types and carry out non-redundant tasks. Numerous studies have examined the role of HIF factors in solid tumors, where they are known to facilitate the growth of tumors by controlling stem cell characteristics, metastasis, neo-angiogenesis, and cell metabolism. HIF1α and HIF2α have recently been identified in AML research as either tumor promoters or tumor suppressor genes, underscoring the need for more studies to fully understand their roles. Recent investigations using various experimental techniques in different AML subsets have linked HIF transcription factors as either tumor promoters or tumor suppressors in AML. In an attempt to resolve this seeming paradox, we have conjectured that HIFα factors might have distinct roles in pre-leukemic hematopoiesis as opposed to overt leukemia, or in particular subgroups of AML. In order to verify this theory, we examined the roles played by HIF1α and HIF2α in well-established leukemia models (such as cell lines and PDX) representing several AML subtypes. Parallel knockdown tests revealed a distinct role for HIF2α in preventing AML differentiation and demonstrated that both factors had leukemia-promoting effects in the AML models we have used.

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