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Selective Activation of Necroptosis could it be a Therapeutic Target in AML in the Future?

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Abstract

The strong relationships between the elevated expression of multiple HOX genes in AML and patient survival support the possibility that HOX proteins could be therapeutic targets in this malignancy. HXR9 is a short cell penetrating peptide that inhibits HOX proteins interaction with the PBX cofactor. The mechanism of HXR9-mediated cell death does not depend on apoptosis, but instead on necroptosis.

Abbreviations: AML: Acute Myeloid Leukemia; NPMc+: Cytoplasmic Nucleophosmin; MLL: Mixed Lineage Leukemia; DNMT3A: DNA Methyltranferase 3A; PBX: Pre B-cell Leukemia Transcription Factors; HSCs: Hematopoietic Stem Cells

Introduction

AML is a genetically diverse disease as there are many pathways and mutations that can cause leukemic transformation [1]. The molecular mechanisms underlying the pathogenesis of AML are known to involve members of the HOX family of transcription factors, both as partners in chimeric fusion proteins and also in their wild form [2]. Multiple HOX genes are over expressed in cases with poor prognosis AML, whereas the expression of these genes is characteristically low in cases with prognostically favorable cytogenetics, for example in APL [3].

Many HOX genes including HOXA9 are strongly expressed in HSCs and early progenitors, but the expression is down regulated in more differentiated cells suggesting a role in differentiation as well as in proliferation. HOXA9 over expression induces a partial block in B lymphopoiesis as well as enhancing myelopoiesis resulting in an increased number of mature granulocytes. It has also been shown that switching certain HOX proteins on or off can change the phenotype of blood cells [1]. HOX proteins are expressed in a higher rate in leukemic cells than in normal hematopoietic cells. Evidence suggests that the posterior HOXA genes, among them HOXA9, are important in leukemogenesis [1].

Common Mutations in AML and their Association with HOX Genes

Deregulation of HOX genes are involved in leukemogenesis in myeloid and lymphoid cells. For example, the homeobox gene PBX1 is translocated to the E2A gene in precursor B - cell ALL with t(1;19), and the HOX11 gene is involved in the translocation t(10;14) in precursor T – cell ALL(3). The chromosomal translocation (7;11)(p15,p15) appears in 1% of AML patients and is associated with very poor prognosis and short overall survival [4]. The chromosomal translocation t(7;11)(p15, p15), encode the fusion protein NUP98-HOXA9 (NHA9). NHA9 brings the FG repeat-rich portion of the nucleoporin NUP98 upstream of the homeodomain and PBX heterodimerization domains of HOXA9, and acts as oncogenic transcription factor. The pathogenic events underlying NHA9 remain poorly understood [5].

FLT3-ITD and mutations in NPM1 and DNMT3A are more common in HOXhigh patients [6]. The mechanism by which NPMc+ up-regulated several HOX genes and cofactors, including HOXA9 and PBX3 is not known. AML cells expressing a mutated form of DNMT3A exhibit statistically significant hypomethylation of HOX genes, implicating an increased expression of these HOX genes. MLL-rearranged AML cells express high levels of HOX genes. There is no known association between Myc mutations and HOXA9 over expression [1].

HOX Proteins

The strong relationships between the elevated expression of multiple HOX genes in AML and patient survival support the possibility that HOX proteins could be therapeutic targets in this

malignancy [7]. The HOX proteins contain a highly conserved peptide sequence, called the homeodomain that allows for DNA binding. All HOX proteins contain the same homeodomain structure. In addition, HOX proteins contain sequences that are distinctive for each HOX protein and allow binding to protein partners. Such partners, called cofactors e.g. PBX, increase the precision of DNA binding as well as determine whether the activity at the binding site will cause activation or repression [1].

In AML cells, HOX/PBX dimers inhibit necroptosis and block p21 expression at both the RNA and protein level. The relationship between p21 and apoptosis is complex and varies between cell types: p21 can promote apoptosis in some contexts but prevent apoptosis in others [7]. An alternative strategy to targeting HOX proteins is to inhibit their interaction with the PBX cofactor which can be achieved using HXR9 [2].

HXR9 in AML

HXR9 is a short cell penetrating peptide that mimics the conserved hexapeptide of HOX proteins responsible for PBX binding. It consists of 18 amino acids and contains a hexapeptide sequence (YPWM) and a polyarginine sequence (R9). The YPWM hexapeptide is present in many HOXproteins from group 1-9 and is required for their ability to bind to PBX. The polyarginine sequence is a cell-penetrating peptide that allows delivery into mammalian cells without the need for any specific receptors [1]. HXR9 have a cytotoxic effect on several different types of cancer cells, among them melanoma, meningioma, prostate cancer and breast cancer [1].

Does HXR9 Stimulation of AML Cells Induce Apoptosis?

The mechanism of HXR9-mediated cell death depends on necroptosis [7]. Necroptosis is considered a regulated form of necrosis that in some respects parallels apoptosis, as it can be triggered by the same external stimuli [7]. Accumulating evidence indicates that necroptosis functions as a safeguard mechanism for killing cancer cells that fail to die by apoptosis, suggesting a pivotal role in cancer biology and therapy [8]. In contrast to apoptosis, which seems to be immunologically quiescent, necroptosis is often a more potent inducer of immune response by activating CD8+ T cells or NKT cells [8]. The more robust immune response elicited by necroptosis may function as a defensive mechanism by eliminating tumor-causing mutations and viruses [8].

The lack of apoptosis after HXR9 treatment might be a result of increased p21 expression, although further dissection of this complex molecular pathway is needed in order to confirm this [7]. The synergistic interaction between HXR9 and PKC-mediated signaling points to possible combinatorial approaches when targeting AML using HOX/PBX inhibitors. This was supported by results obtained using a murine model. Further work will help to refine this approach to establish the selective activation of necroptosis as a therapeutic target in AML [7].

Is there is difference in the effect of the HOX inhibitor HXR9 on AML cells with different mutations?.

In AML cells, HXR9 exerts cytotoxic and possibly pro-maturating effects, but the effect may be unspecific [1].

Is the effect of HXR9 dependent on HOXA9 expression level?

The effect of the HOX inhibitor HXR9 on AML cells is independent of HOXA9 expression level [1].

Conclusion

HOX-inhibition could be a potential future treatment option for certain group of bad prognostic AML patients with more extensive studies concerning mechanism of action of HXR9 are needed to be performed to refine this approach and establish the selective activation of necroptosis as a therapeutic target in AML.

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