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The role of epigenetics in the regulation of apoptosis in myelodysplastic syndromes and acute myeloid leukemia☆

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Contents

Abstract

Disordered stem cell epigenetics and apoptosis-regulating mechanisms contribute essentially to the pathogenesis of myelodysplastic syndromes (MDS) and may trigger disease-progression to secondary acute myeloid leukemia (AML).

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Expression of apoptosis-mediators FAS (CD95) and DAPK1 the latter being also known for its association with autophagy are upregulated in neoplastic cells in patients with low-risk MDS and epigenetically silenced and downregulated in high-risk MDS and AML as confirmed by a study 50 MDS and 30 AMLs complementing this review. 5-Azacytidine (AZA) and 5-aza-2′deoxycytidine (DAC), promoted FAS and DAPK1 gene demethylation and their (re)expression as well as apoptosis in leukemic cell lines (HL-60, KG1) which can be reversed by siRNA against FAS. Thus, promoter-demethylation of FAS and DAPK1 represents a critical mechanism of drug-induced apoptosis in neoplastic cells in MDS and AML which underscores the clinical implication of epigenetically active therapies.

Keywords: Epigenetics; Apoptosis; Autophagy; Demethylating drugs

1. Background

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders primarily occurring in the elderly. Hematopoietic stem cells are the disease-initiating cells in MDS [1].

Clinically, MDS are characterized by ineffective hematopoiesis associated with morphological evidence of bone marrow (BM) dysplasia, resulting in refractory peripheral cytopenias despite normal or increased BM cellularity [2,3].

Although MDS is known for its heterogeneous physiology, subsets of this disease can be largely explained by disordered stem cell epigenetics [4].

There is an abundance of data demonstrating that disturbed apoptosis is a decisive factor in the pathogenesis of MDS [3,5–17].

In line with the heterogeneity of the disease, MDS subtypes are differently affected by apoptosis. Whereas increased apoptosis is observed in patients with low risk MDS, the contrary is seen in high-risk MDS patients.

1.1. Epigenetic regulation of apoptosis in low risk MDS

An increased apoptosis resulting from both intrinsic and extrinsic pathways is documented in low risk subtypes of MDS, such as refractory cytopenia with multilineage dysplasia (RCMD) or refractory anemia with ring sideroblasts (RARS) [6,18,19].

It has been suggested, that stem cells from MDS compete with normal hematopoietic stem cells in the patients by increasing their frequency at the expense of normal hematopoiesis, that the loss of MDS myeloid progenitors by programmed cell death and programmed cell removal are, in part, responsible for the cytopenias in addition to key mediators from apoptosis that are upregulated in low risk subtypes of MDS [1,6,8].

One mechanism contributing to the constellation of hypercellular marrow and peripheral blood cytopenia is a significant increase in programmed cell death (apoptosis) in hematopoietic cells. Tumor necrosis factor (TNF)-α, Fas-ligand, TNF-related apoptosis inducing ligand (TRAIL) and other pro-apoptotic cytokines are upregulated in early stage/low-risk MDS, and neutralization of these signals may improve hematopoiesis. TRAIL induces apoptosis preferentially in clonal cells, which may contribute to containment of the clone [20]. FAS, which is not expressed in normal bone marrows, is overexpressed and functional in about 40% of early MDS marrows [21].

Considering the microenvironment which is also known to play a critical role in epigenetic regulation at least when a functional extracellular matrix is provided [22], fibroblasts and macrophages from low risk MDS marrow presented an increased apoptotic index and produced higher levels of IL-6 and tumor necrosis factor-α (TNF-α) than their normal counterparts [23].

Another study has revealed that TNF may mediate some of its effects on the dysplastic clone through contact-dependent signals derived from stroma cells which are provided with TNF receptors [24].

A recurrent loss of granulocyte-macrophage progenitors (GMPs) in the bone marrow was postulated as a typical feature of low risk MDS. The loss of GMPs appears as a consequence of increased apoptosis and increased phagocytosis, the latter due to the up-regulation of cell surface calreticulin, a prophagocytic marker. Blocking of calreticulin (which plays a role in folding of glycoproteins in the lumen of the endoplasmic reticulum) on MDS myeloid progenitors was shown to rescue these cells from phagocytosis in vitro [1].

However, the exact nature of these apoptosis-regulators and how they may trigger disease progression or drug resistance is still a subject of discussion and a challenge to clarify the epigenetic background.

In addition, a determination of mechanisms from normal aging is important to understand the molecular pathology of age associated diseases such as initiation of MDS.

Like apoptosis, aging is a progressive biological process regulated by complex genetic interactions and influenced by environmental factors. It is difficult to study molecular events of this process because of its slow progressive nature.

During aging, modulation of hematopoiesis becomes disordered, impairing the ability of older people to respond appropriately to the physiological demand for blood cell replacement. This may contribute to the increase in anemia observed during aging. In addition, genomic mutations secondary to oxidative stress or impaired regulation of cytokine production, may contribute to the emergence of abnormal clones of hematopoietic cells. Currently, there is neither a