Cancer Letters 332 (2013) 325–334

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Targeting apoptosis proteins in hematological malignancies

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ARTICLE INFO

Keywords:
Apoptosis
Hematological diseases
Drugs
TRAIL
IAPs
Bcl-2

ABSTRACT

The apoptotic machinery plays a key role in hematopoietic cell homeostasis. Terminally differentiated cells are eliminated, at least in part, by apoptosis, whereas part of the apoptotic machinery, including one or several caspases, is required to go through very specific steps of the differentiation pathways. A number of hematological diseases involve a deregulation of this machinery, which in most cases is a decrease in cell sensitivity to pro-apoptotic signals through over-expression of anti-apoptotic molecules. In some situations however, *e.g.* in the erythroid lineage of low grade myelodysplastic syndromes, cell sensitivity to apoptosis is increased in a death receptor-dependent manner and cell death pathways are inhibited only when these diseases progress into high grade and acute leukemia. Therapeutic strategies targeting the apoptotic machinery specifically block cell death inhibitors that are over-expressed in transformed cells, mainly Bcl-2-related proteins and Inhibitor of Apoptosis Proteins (IAPs). Another strategy is the activation of the extrinsic pathway to apoptosis, mainly through the death receptor agonist Tumor necrosis factor-Related Apoptosis Inducing Ligand (TRAIL) or agonistic antibodies targeting TRAIL receptors. The use of inhibitors of death receptors could make sense when these receptors are involved in excessive cell death or activation of survival pathways. Most of the drugs targeting apoptotic pathways introduced in clinics have demonstrated their tolerability. Their efficacy, either alone or in combination with other drugs such as demethylating agents and histone deacetylase inhibitors, is currently tested in both myeloid and lymphoid hematological diseases.

1. Introduction

A tight regulation of the apoptotic machinery is required for appropriate differentiation of hematopoietic cells. Pro-apoptotic molecules are activated in specific differentiation pathways in the absence of cell death, *e.g.* caspase-3 activation is required for erythropoietin (Epo)-induced erythroblast maturation [1], caspase-3, -8 and -9 are involved in CSF-1-driven differentiation of monocytes into macrophages [2], and the localized release of cytochrome c leading to spatially restricted maturation of caspase-3 participates in the formation of pro-platelets [3,4] (Fig. 1). Activation of caspases in these differentiation settings does not lead to death. One of the reasons is that caspase activity in differentiating cells might be lower than that measured in cells undergoing apoptosis [5]. Also, key targets could be protected from proteolysis by chaperones, *e.g.* in the red cell lineage, caspase-3 activated upon Epo stimulation does not kill the cells because of the chaperoning of GATA-1 by the stress protein HSP70 [1]. On the other hand, death by apoptosis can be required for hematopoietic tissue homeostasis, *e.g.* for the appropriate maturation of the lymphocyte repertoire, and the elimination of terminally differentiated cells such as activated lymphocytes [6] and mature granulocytes [7].

Deregulated expression of apoptosis-related molecules was identified in most hematologic malignancies. The

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doi:10.1016/j.canlet.2011.06.016

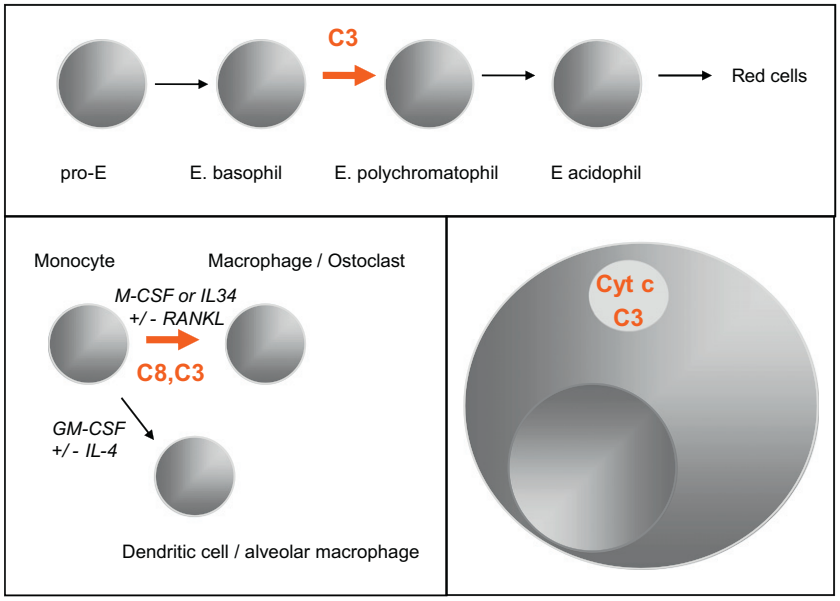

Fig. 1. Role of caspases in hematopoietic cell differentiation. Caspases (C, red arrows) are involved in specific pathways of hematopoetic cell differentiation that include the maturation of basophil into polychromatophil erythroblasts (C3, caspase-3; E, erythroblast), the M-CSF-driven differentiation of monocytes (caspase-8 and 3), and the formation of proplatelets (localized activation of caspase-3 by cytochrome c [Cyt c]). Deregulation of these pathways can lead to abnormal differentiation and death. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

defective erythropoiesis that characterizes low grade myelodysplastic syndromes and accounts for the anemia is related to a death receptor-mediated caspase-dependent apoptosis of erythroid progenitors [8]. Acute transformation of these myelodysplastic syndromes involves inhibition of cell death through the constitutive activation of NF-κB [9]. Accumulation of the anti-apoptotic protein Bcl-2 in B cells as a consequence of a *t*(14; 18) translocation is mandatory in the development of follicular lymphomas. Experiments in *bcl-2* transgenic mice reinforced the concept that ectopic expression of Bcl-2 could promote neoplastic transformation of hematopoietic cells [10] and Bcl-2 expression is deregulated in a number of haematological malignancies through various mechanisms, *e.g.* deletion in a critical region of 13q14 that eliminates miR-15A and miR-16-1, two negative regulators of Bcl-2 expression, is responsible for Bcl-2 overexpression in some chronic lymphocytic leukemias [11]. A caspase inhibitor of the Inhibitor of Apoptosis Proteins (IAP) family is deregulated in a subgroup of Mucosa-Associated Lymphoid Tissue (MALT) lymphomas through the *t*(11; 18) (q21; q21) that fuses *cIAP2* gene to the so-called *MALT1* gene [12]. The expression of surviving, another IAP, is a poor prognostic factor in several haematological malignancies [13]. An altered expression of death receptors at the plasma membrane level, the alternative splicing of *caspase-8* gene to generate a dominant-negative isoform, the expression of death inhibitory molecules in the tumor cell microenvironment, and the expression of anti-apoptotic viral proteins in tumor cells can also account for cell death inhibition (for review, see [14]).

Overexpression of molecules that inhibit apoptosis is one of the mechanisms that decreases the efficacy of therapeutic molecules, as clearly demonstrated in a mouse lymphoma model [15]. Strategies to overcome this resistance include inhibition of survival pathway by specifically targeting cell death inhibitors that are over-expressed in transformed cells, mainly Bcl-2, XIAP, and the other inhibitory proteins of these families (Fig. 2), or by blocking death-receptor-mediated survival pathway that operate in some tumor types. Another strategy is the activation of the extrinsic pathway to apoptosis, mainly through Tumor necrosis factor-Related Apoptosis Inducing Ligand (TRAIL) receptors.

2. TRAIL agonistic receptor activation

TRAIL is a membrane-linked or soluble ligand that plays a physiological role in tumor immune surveillance, *e.g.* the deletion of *TRAIL* gene in mice favors the occurrence of lymphoid malignancies [16]. This ligand interacts with five distinct receptors, two of which (TRAIL-R1/DR4 and TRAIL-R2/DR5) belong to the death receptor subgroup in the tumor necrosis factor (TNF) receptor superfamily. TRAIL interaction with DR4 or DR5 usually initiates a caspase-driven apoptotic pathway upon formation of a Death-Inducing Signaling Complex (DISC) [17] similar to that induced by Fas-Ligand/Fas interaction [18]. The three antagonistic receptors of TRAIL act through distinct mechanisms [14,19]. In accordance with its function in the host immune system and contrary to other death receptor ligands, TRAIL appears to spare normal cells while killing some malignant cells [20,21]. Strategies to therapeutically target this pathway include the use of a recombinant soluble trimeric ligand that binds all TRAIL receptors [22–24],