Seminars in Cancer Biology 35 (2015) S78–S103

Contents lists available at ScienceDirect

Seminars in Cancer Biology

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

Review

Broad targeting of resistance to apoptosis in cancer

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ARTICLE INFO

Article history:
Available online 28 April 2015

Keywords:
Apoptosis
Necrosis

ABSTRACT

Apoptosis or programmed cell death is natural way of removing aged cells from the body. Most of the anti-cancer therapies trigger apoptosis induction and related cell death networks to eliminate malignant cells. However, in cancer, de-regulated apoptotic signaling, particularly the activation of an anti-apoptotic systems, allows cancer cells to escape this program leading to uncontrolled proliferation resulting in tumor survival, therapeutic resistance and recurrence of cancer. This resistance is a complicated phenomenon

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http://dx.doi.org/10.1016/j.semcancer.2015.03.001
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Autophagy
Apoptosis evasion
Nuclear transporters, natural chemopreventive agents

that emanates from the interactions of various molecules and signaling pathways. In this comprehensive review we discuss the various factors contributing to apoptosis resistance in cancers. The key resistance targets that are discussed include (1) Bcl-2 and Mcl-1 proteins; (2) autophagy processes; (3) necrosis and necroptosis; (4) heat shock protein signaling; (5) the proteasome pathway; (6) epigenetic mechanisms; and (7) aberrant nuclear export signaling. The shortcomings of current therapeutic modalities are highlighted and a broad spectrum strategy using approaches including (a) gossypol; (b) epigallocatechin-3-gallate; (c) UMI-77 (d) triptolide and (e) selinexor that can be used to overcome cell death resistance is presented. This review provides a roadmap for the design of successful anti-cancer strategies that overcome resistance to apoptosis for better therapeutic outcome in patients with cancer.

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1. Introduction

According to the GLOBOCAN factsheet (http://globocan.iarc.fr/), there were approximately 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in the year 2012 worldwide. Among these, 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less/under-developed regions of the world. Cancer treatment requires a careful selection of one or more interventions, such as surgery, radiotherapy, and chemotherapy. However, despite major advances in new targeted drug development and tailored clinical trial designs, therapy resistance is commonly observed in most cancers.

Most cancers harbor significant genetic heterogeneity [1], and patterns of relapse following many therapies are due to evolved resistance to treatment. While efforts have been made to combine targeted therapies, a lack of success, rising drug costs, and significant levels of toxicity have stymied efforts to effectively treat cancer with multi-drug combinations using currently approved therapeutics [2]. Therefore, overcoming therapy resistance mechanisms is one of the most sought-after goals in cancer research.

To accomplish this goal, a non-profit organization entitled Getting to Know Cancer launched an initiative called "The Halifax Project in 2011 with the aim of producing a series of overarching reviews in each of the areas that are widely considered to be cancer hallmarks [3]. This novel approach is premised on many of the insights of genomic sequencing in cancers and it aims to target many disease-specific pathways simultaneously. This is proposed to be done by using low-cost chemistry with little to no toxicity – to address this heterogeneity (in contrast to the limited number of actionable targets that have become the norm in combination chemotherapy).

Our task in the project was to assess the many target choices that exist for resistance to cell death, and to identify up to ten important targets as well as prospective non-toxic approaches that could potentially be combined to produce a low-toxicity therapeutic approach for this area of concern. So our intent here is to discuss the inter-relationship between major mechanisms driving resistance to apoptosis in cancer and then to define a broad-spectrum therapeutic approach aimed at reaching these important targets [3]. In theory, this approach would then be combined with similar approaches being recommended for the other hallmark areas under review in this special issue.

Apoptosis or programmed cell death is evolutionarily conserved process that plays an essential role in organism development and tissue homeostasis [4]. However, in pathological conditions, particularly cancer, cells lose their ability to undergo apoptosis induced death leading to uncontrolled proliferation. Cancer cells are often found to over express many of the proteins that play important roles in resisting the activation of apoptotic cascade. Several mechanisms allow cells to escape programmed cell death and among them is the over expression of the anti-apoptotic molecules. Originally most of the research on apoptosis signaling focused on BH3 pathway proteins leading to acceptance of the Korsmeyers [5] rheostat model. This model predicted a balance between pro-survival and pro-death BH3 members. When the balance shifts toward pro-death signaling, apoptosis occurs, and in instances when pro-survival molecules outnumber pro-death proteins, survival signaling is activated leading to pathological conditions such as cancer and other diseases. With this simplistic model, the drug discovery arena moved at a rapid pace developing small molecule inhibitors (SMI) that interfere with the anti-apoptotic pathways proteins such a B-Cell Lymphoma 2 (Bcl-2), B-Cell Lymphoma extra large (Bcl-xL, Induced myeloid leukemia cell differentiation protein (Mcl-1), Bcl-2-like-protein-2 (BCL2L2/Bcl-w) and Bcl-2 related protein A1 (A1/Bfl1). Nevertheless, most of these approaches have shown little success, and in almost all instances tumor cells become resistant to such apoptosis inducing drugs [6].

Emerging evidence shows that resistance to apoptosis is multifactorial and involves many secondary players that run either parallel to Bcl-2 signaling or function in complete independence [7]. Here we review the known and emerging pathways that modulate the apoptosis signaling and discuss strategies to overcome apoptosis resistance. We anticipate that a comprehensive understanding of the resistance molecules (and the strategies to target them) will help in the design of clinically successful strategies for cancer in general and specifically in patients who show disease relapse.

2. Role of Bcl-2 family proteins in resistance to apoptosis

One of the major hallmarks of human cancers is the intrinsic or acquired resistance to apoptosis [8,9]. Evasion of apoptosis may contribute to tumor development, progression, and also to treatment resistance, since most of the anticancer therapies that are currently available include chemotherapy, and radio- and immunotherapy (which primarily act by activating cell death pathways *i.e.*, apoptosis in cancer cells). Hence, a better understanding of the molecular mechanisms underlying tumor resistance to apoptotic cell death is expected to provide the basis for a rational approach for the development of molecular targeted therapies.

There are two types of apoptosis programs *i.e.*, intrinsic and extrinsic. The Bcl-2 protein functions through hetero-dimerization with pro-apoptotic members of the BH3 family to prevent mitochondrial pore formation and prevent cytochrome *c* release and initiation of apoptosis [10] (Fig. 1). However, there is evidence suggesting that Bcl-2 may play an oncogenic role through survival pathways other than its function at the mitochondrial membrane [11]. It has been reported that Bcl-2 activates nuclear factor-κB (NF-κB) by a signaling mechanism that involves Raf-1/MEKK-1-mediated activation of inhibitor of NF-κB kinase subunit beta (IKKβ) [12]. Mortenson and colleagues [13] have shown that overexpression of Bcl-2 increases the activity of AKT and IKK as well as NF-κB transcriptional activity in cancer. While Kumar and colleagues [14] found that Bcl-2-induced tumor cell proliferation and tumor cell invasion were significantly mediated by interleukin-8.

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