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Targeting apoptotic machinery as approach for anticancer therapy: Smac mimetics as anticancer agents

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ABSTRACT

Apoptosis is a chief regulator of cellular homeostasis. Impairment of apoptotic machinery is a main characteristic of several diseases such as cancer, where the evasion of apoptosis is a cardinal hallmark of cancer. Apoptosis is regulated by contribution of pro- and anti- apoptotic proteins, where caspases are the main executioners of the apoptotic machinery. IAP (inhibitors of apoptosis proteins) is a family of endogenous inhibitors of apoptosis, which perform their function through interference with the function of caspases. Smac (second mitochondria-derived activator of caspases) is endogenous inhibitor of IAPs, thus it is one of the major proapoptotic endogenous proteins. Thus, the development of Smac mimetics has evolved as an approach for anticancer therapy. Several Smac mimetic agents have been introduced to clinical trial such as birinapanet 12. Herein, the history of development of Smac mimetics along with the recent development in this field is briefly discussed.

1. Introduction

Apoptosis is a process of programmed cell death, that is involved in keeping homeostasis by maintaining cell populations in tissues. Physiologically, apoptosis is essential for embryonic development, cell turnover, proper development of the immune system and hormone-dependent atrophy [1]. It takes place through sequence of steps: disruption of cellular membranes, breakdown of cytoplasmic and nuclear skeleton, degradation of chromosomes, extrusion of cytosol and nuclear fragmentation [2]. Balance between cell proliferation and apoptosis is critical for normal development of organisms and it is kept under tight control of group of pro and antiapoptotic proteins [1]. Loss of this balance is a main characteristic of wide variety of diseases; excess apoptosis leads to Alzheimer's and Parkinson's diseases, AIDS and cardiovascular diseases, while loss of balance in favor of proliferation is common feature of various types of cancers [3,4]. Thus, apoptotic machinery pathways and the involved proteins have evaded as targets for rational therapeutic approaches against several diseases.

2. Theory

2.1. Machinery of apoptosis

Apoptotic cell death proceeds through the action of several proteins that can be classified according to their role into sensors and effectors. Sensors monitor the cellular environment to detect signals that trigger apoptosis -as DNA abnormalities- and subsequently activate the effectors of apoptotic cell death. Apoptosis is initiated via two different pathways: extrinsic and intrinsic pathways. Extrinsic pathway is stimulated by the activation of the death receptors on the cell surface as the FAS receptor activation by FAS and TNF-R1 activation by TNFa, while intrinsic pathway is initiated when intracellular sensors detect abnormalities as DNA damage and signaling imbalance [5–7]. Both pathways proceeds via activating caspaes, the main executioners of apoptosis. Initially, caspases are found in inactive form (procaspases) that activated by proteolytic cleavage. Caspases can be grouped into upstream initiator caspases (as caspases 8 and 9) and downstream effector caspases (as caspases 3, 6 and 7) [8,9].

2.2. Endogenous inhibitors of apoptosis

On the other side, several families of proteins are involved in apoptosis inhibition as ADEDs family of proteins that suppress initiator caspases, antiapoptotic members of Bcl-2 family of

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proteins (Bcl-xL, Bcl-2, KSHV-Bcl-2, Bcl-w) [10] and IAPs that suppress the down-stream effector caspases [9]. Diagrammatic representation of pro- and anti-apoptotic proteins involved in extrinsic and intrinsic pathways of apoptosis are shown in Fig. 1 [11]. The whole process is executed through sequence of protein–protein interactions [12].

2.3. Evading apoptosis in cancer

Apoptosis evasion is one of the main cancer hallmarks, where cancerous cells acquire the ability to overcome apoptotic signals. This hallmark is acquired through several mechanism such as: mutation of the p53 tumor suppressor gene and the resulting loss of function of the proapoptotic p53 protein -as observed in more than 50% of human cancers-up regulation of a nonsignaling decoy FAS receptor that competes with FAS receptor for cell death inducing signals [2], overexpression of Bcl-2 -as observed in several types of cancers as breast cancer, prostate cancer, B-cell lymphomas and colorectal adenocarcinomas [1,13]. Additionally, it was observed that Smac -an endogenous inhibitor of IAP- was found at low levels in several types of tumor cells [14] while high levels of XIAP -a cardinal inhibitor of apoptosis- is highly expressed in wide spectrum of tumors [15]. Thus, targeting inhibitors of apoptosis has evolved as rational for targeted anticancer therapy. This review attempts to cover the different anticancer therapeutic approaches that target antiapoptotic proteins [16]. Actually, there are two strategies for targeting apoptotic machinery: inhibiting cell death inhibitors that are upregulated in cancerous cells- mainly IAP family of proteins and antiapoptotic proteins of Bcl-2 family- and stimulation of extrinsic apoptotic pathway through applying death receptor agonist as TRAIL or agonistic antibodies targeting death receptors [17], where the first strategy is the focus of this review, as we describe the different approaches for development of Smac mimetics that inhibit IAP. The general idea of design of agents that target antiapoptotic proteins is development of molecules that target hot spots on the protein–protein interface at which PPI controlling the protein function occurs [12].

2.4. IAP antagonists

IAP is a family of proteins that act as key inhibitors of apoptosis. The family comprises eight members: cIAP1, cIAP2, XIAP, survivin, NAIP, livin, ILP2, and apollon. All family members share the presence of one or more Baculovirus IAP Repeat (BIR) domains that execute interactions with caspases. XIAP is the chief antiapoptotic member of the family, it posses RING zinc finger domain, that is responsible for ubiquitin ligase activity that mediate proteosomal degradation of caspases. Additionally, it contains three BIR regions, each performing different function; BIR2 region is a potent inhibitor for caspase-3 and 7, while BIR3 domain of XIAP primarily targets caspase-9 where it sequesters it in monomeric state preventing its catalytic activity [18]. Function of BIR1 has been recently identified to be binding to TAK1 (TGFβ-activated kinase) and TAB1 (TAK1 binding protein 1) [11,19].

Normally, several endogenous inhibitors of XIAP are found, the most important of which is smac. Smac binds to XIAP through its four N-terminal residues (Ala-Val-Pro-Ile, AVPI) that bind to BIR3 domain on the XIAP surface [17]. Smac binds competitively with XIAP preventing its binding to caspases and promoting apoptosis. Fig. 2 shows the binding of BIR3 of XIAP to the Smac protein with the AVPI residues lying in the BIR3 region (PDB: 1G73) [19] (see Fig. 3).

Attempting to inhibit IAP, mainly XIAP, smac mimetics were designed to competitively bind to XIAP and prevent its inhibitory action on caspases and promote apoptosis. Two main approaches were adopted: developing peptidomimetic inhibitors and small molecule inhibitor that are smac mimetics. Developing small molecule smac mimetics is based upon the presence of hot spots on the interaction surface between BIR3 domain and smac peptide [12].

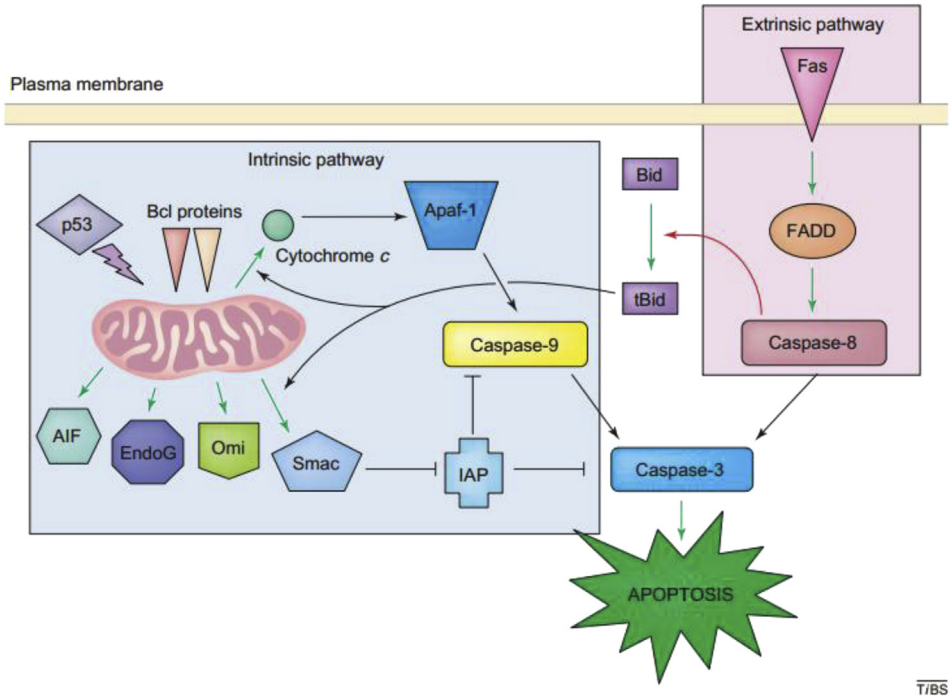

Fig. 1. Intrinsic and extrinsic apoptosis pathways activation [11].