Seminars in Cell & Developmental Biology 39 (2015) 132–138

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

Smac mimetics as IAP antagonists

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ARTICLE INFO

Article history:
Available online 27 December 2014

Keywords:
Smac mimetic
IAP proteins
Cell death
Cancer

ABSTRACT

As the Inhibitor of Apoptosis (IAP) proteins are expressed at high levels in human cancers, they represent promising targets for therapeutic intervention. Small-molecule inhibitors of IAP proteins mimicking the endogenous IAP antagonist Smac, called Smac mimetics, neutralize IAP proteins and thereby promote the induction of cell death. Smac mimetics have been shown in preclinical models of human cancer to directly trigger cancer cell death or to sensitize for cancer cell death induced by a variety of cytotoxic stimuli. Smac mimetics are currently undergoing clinical evaluation in phase I/II trials, demonstrating that therapeutic targeting of IAP proteins has reached the clinical stage.

Contents

1. Introduction

High expression levels of Inhibitor of Apoptosis (IAP) proteins have been encountered in various human cancers [1]. Since overexpression of IAP proteins is related to tumorigenesis, progression of cancer, resistance to treatment approaches and unfavorable prognosis, IAP proteins are considered as promising targets for therapeutic intervention [1]. This has led to the development of several approaches to antagonize IAP proteins in cancer cells. These efforts include the design of small-molecule inhibitors as well as antisense oligonucleotides. The current review focuses on discussing Second mitochondrial activator of caspases (Smac) mimetics, *i.e.* small-molecule inhibitors that mimic the endogenous IAP antagonist Smac and neutralize X-linked IAP (XIAP), cellular IAP 1 (cIAP1) and cIAP2.

2. Mechanisms of action of Smac mimetics

Most Smac mimetics bind to several IAP proteins and antagonize XIAP, cIAP1 and cIAP2 [1]. This leads to the release of XIAP from its

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http://dx.doi.org/10.1016/j.semcdb.2014.12.005
1084-9521/

Table 1
Combination treatments with Smac mimetics.

Compound	Stimulus	Cancer type	Reference
Chemotherapeutics			
Smac mimetic BV6	Temozolimide, BCNU, VP16	Glioblastoma	[26]
Smac mimetic BV6	Glucocorticoids	ALL	[28]
Smac mimetic BV6	Cytarabine	AML	[27]
Smac mimetic JP1400	Gemcitabine, cisplatin, SN38, paclitaxel, 5-fluorouracil (5-FU) and etoposide	Breast, colon, lung, pancreatic prostate and skin carcinoma	[17]
Smac mimetic JP1201	Gemcitabine	Pancreatic carcinoma	[24]
IAP inhibitors IDN	AraC, gemcitabine, cyclophosphamide, doxorubicin, VP16, vincristine, taxol	ALL	[14]
Death receptor agonists			
IAP inhibitor IDN	TRAIL	Pancreatic carcinoma	[30]
IAP inhibitor IDN	TRAIL-R1 Ab, TRAIL-R2 Ab	Pancreatic carcinoma	[29]
IAP inhibitor IDN	TRAIL	CLL	[31]
IAP inhibitor IDN	TRAIL	ALL	[32]
Smac mimetic JP1584	TRAIL	Cholangiocarcinoma	[33]
Smac mimetic compound A	CD95L	Squamous cell carcinoma	[35]
IAP inhibitor IDN	MegaFasL	ALL	[34]
Smac mimetic compound 3	TNFα	Solid cancers (pancreatic, lung carcinoma, glioblastoma, osteosarcoma), ALL	[36]
IAP inhibitor IDN	MegaFasL	ALL	[34]
Radiation			
Smac mimetic BV6	γ-Irradiation	Glioblastoma	[39]
Smac mimetic LBW242	γ-Irradiation	Glioblastoma	[22]
IAP inhibitor IDN	γ-Irradiation	Glioblastoma	[37]
IAP inhibitor IDN	γ-Irradiation	Pancreatic carcinoma	[38]
Signal transduction inhibitors			
Smac mimetic BV6	5-Aza, DAC	AML	[41]
Smac mimetic Birinapant	5-Aza, DAC	AML	[42]
Smac mimetic LCL161	PKC412, nilotinib	AML	[43]
Smac mimetic LBW242	PKC412, chemotherapy (doxorubicin, AraC)	AML	[44]
Smac mimetic LBW242	Imatinib, nilotinib, NVP-AEW541, PKI 166	Glioblastoma	[45]
Smac mimetic compounds 67, 74, 75, 76	Bortezomib	Melanoma	[46]
Smac mimetic compound 3	Trastuzumab, lapatinib, gefitinib	Breast carcinoma	[47]
Immune stimuli			
Smac mimetic LCL161	Oncolytic virus, poly(I:C), CpG oligonucleotides	Solid cancers	[48]
Smac mimetic BV6	IFNα	AML	[49]
Smac mimetic compound C	BCG	Bladder carcinoma	[50]

Abbreviations: Ab, antibody; ALL, acute lymphoblastic leukemia; AML; acute myeloid leukemia; αCD95, anti-CD95; CLL, Chronic lymphocytic leukemia; IDN, IDUN; MegaFasL, MegaFas ligand; TNFα, tumor necrosis factor α; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R2 Ab, TRAIL receptor 2 antibody.

inhibitory function against caspase-3, 7 and -9, thereby promoting caspase activation and cell death [1]. In addition, Smac mimetics trigger degradation of cIAP1 and cIAP2 *via* the proteasome, by stimulating the E3 ubiquitin ligase activity of cIAP proteins [1]. The Smac mimetic-imposed change in conformation of IAP proteins triggers their autoubiquitination and is followed by their proteasomal degradation. Smac mimetic-mediated depletion of cIAP proteins leads in turn to activation of the non-canonical nuclear factor-kappa B (NF-κB) signaling pathway [1]. Under resting conditions, cIAP proteins are responsible for constitutive ubiquitination of NF-κB-inducing kinase (NIK) and its subsequent proteasomal degradation [2,3]. As a result, protein expression of NIK is usually very low in resting conditions and non-canonical NF-κB signaling is consequently shut off.

Smac mimetic-imposed proteasomal degradation of cIAP proteins causes accumulation of NIK, which in turn phosphorylates and activates the IkappaB kinase complex (IKK). Once activated, IKK engages processing of the NF-κB precursor protein p100 *via* phosphorylation, which produces p52 that subsequently translocates to the nucleus to stimulate transcription of NF-κB target genes [3,4]. Tumor necrosis factor (TNF)α is one of the typical NF-κB target genes that are upregulated *via* NF-κB activation upon treatment with Smac mimetics. While on one side this cytokine has been implicated as an important mediator of inflammation and associated survival signaling, TNFα has also been shown to be a key mediator of Smac mimetic-mediated cell death in cancer cells *via* an autocrine/paracrine loop [5,6]. Accordingly, Smac mimetic-stimulated production of TNFα results in its secretion into the extracellular space, where it engages TNF receptors in an autocrine or paracrine manner [5,6]. Since cIAP proteins are depleted upon treatment with Smac mimetics, the survival branch of TNF receptor signaling is ablated upon Smac mimetic treatment. This unleashes the TNF receptor-induced path to cell death. One critical regulator in this context is Receptor-Interacting Protein (RIP)1 which is no longer ubiquitinated in the absence of the cIAP proteins. Deubiquitination of RIP1 favors its association with cell death signaling components, including Fas-Associated protein with Death Domain (FADD) and caspase-8, to form a multiprotein complex that leads to cell death.

3. Structural composition of Smac mimetics

Smac mimetics mimic the N-terminal portion of the endogenous protein Smac that encompasses a 4-amino acid stretch, Ala-Val-Pro-Ile. This peptide motif is critical for the binding of Smac to the Baculovirus IAP Repeat domain (BIR)3 and BIR2 domains of