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SMAC Mimetics: Promising Therapeutic Agents in Cancer and other Diseases

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Abstract

Smac mimetics are a very promising new class of anticancer agents demonstrating an acceptable safety profile and efficacy in some preclinical models of cancers when used as a single agent or in combination with conventional or nonconventional therapies. Future preclinical and clinical trials could enlarge their spectral of action in inflammatory, fibrotic and infectious diseases.

Keywords: Smac mimetics; Nonconventional therapies; Apoptosis; Inflammasome

Abbreviations:

cIAPs: Cellular IAPs; IL: Interleukin; MAPK: Mitogen-activated Protein Kinase; NF-κB: Nuclear Factor kappa-light-chain-enhancer of Activated B Cells; NODs: Nucleotide-binding Oligomerization Domain-containing Proteins; PAMPs: Pathogen-associated Molecular Pat-terns; PRRs: Pattern-recognition Receptors; RIG I: Retinoic Acid-inducible Gene I; Smac: Second Mitochondria-derived Activator of Caspases; SMs: Smac Mimetics; TLRs: Toll-like Receptors; TNFR: Tumor Necrosis Factor Receptor; XIAP: X-chromosome Linked IAP.

Introduction

The inhibitor of apoptosis proteins (IAPs) were initially discovered in baculovirus in a genetic screen aiming to identify viral proteins able to block the death of infected cells [1]. IAP homologs were then described in yeasts, nematode, insects, fishes and mammals based on structural feature. The IAP family is defined by the presence of at least one specific domain named Baculovirus IAP Repeat (BIR) located at the N-terminal end of the protein. Some IAPs also harbor a C-terminal RING domain that confers an E3-ubiquitine ligase activity (For review, see [2,3]). Mammalian cells contain 8 IAP members including the X-chromosome linked IAP (XIAP), the cellular IAP 1 and 2 (cIAP1 and cIAP2) and the melanoma apoptosis inhibitory protein (ML-IAP) that exert an anti-apoptotic activity. Among them, XIAP can directly block the activity of initiator caspase-9 and executor caspases-3 and -7, thereby inhibiting both intrinsic and extrinsic pathways of apoptosis [4]. Upon activation of intrinsic pathway, XIAP is neutralized by the second mitochondria-derived activator of caspases (Smac) that is released from the mitochondria as a result of the mitochondria outer membrane permeabilization (MOMP). As an additional checkpoint preventing unforeseen caspase activation, cIAP1, cIAP2 and ML-IAP can bind, sequester and target Smac for ubiquitin proteasome system (UPS)-mediated degradation, thus favoring XIAP in caspase inhibition [5]. The structural characterization of the interaction of XIAP with caspases or Smac demonstrated that they bind at the same binding interface e.i. a surface hydrophobic groove located within some BIR domains. Thus, Smac acts as a competitive inhibitor of XIAP-caspase interaction. These results led to the design of synthetic IAP antagonist compounds mimicking the activity of Smac and named Smac mimetics (SMs) [6,7]. This brief review will summarize advances on the use of SMs in cancer therapy and will present recent preclinical studies highlighting the therapeutic potential of SMs in inflammatory, fibrotic and infectious diseases (Figure 1).

SMs in Cancer Therapy

Because (i) IAPs display potent anti-apoptotic properties, (ii) their expression were showed to be upregulated in number of human tumor samples and correlated with advanced progressive disease, aggressiveness, and poor prognosis and (iii) they constitute a resistance factor to anticancer therapy, SMs have been developed for the purpose of anti-cancer treatments. Number of preclinical studies showed their capacity to inhibit tumor growth in multiple solid tumors, acute lymphocytic leukemia (ALL) and multiple myeloma xenograft models and demonstrated a synergic activity of SMs with conventional therapeutic agents and with novel therapy e.g. tumor necrosis factor (TNF) related apoptosis-inducing ligand (TRAIL), proteasome inhibitors, BH3-mimetics or immune checkpoint inhibitors [6,8-11]. Importantly, these compounds were well tolerated by animals and did not display toxicity against normal lymphocytes, bone marrow stromal cells or normal mammary epithelial cells [12]. SMs have entered into active human clinical trials for review, see [6,13]. They are being evaluated as a single agent or in combination with an anticancer drug in both solid tumors and hematological malignancies. The first clinical trials results demonstrated a good tolerance and target inhibition [14,15].

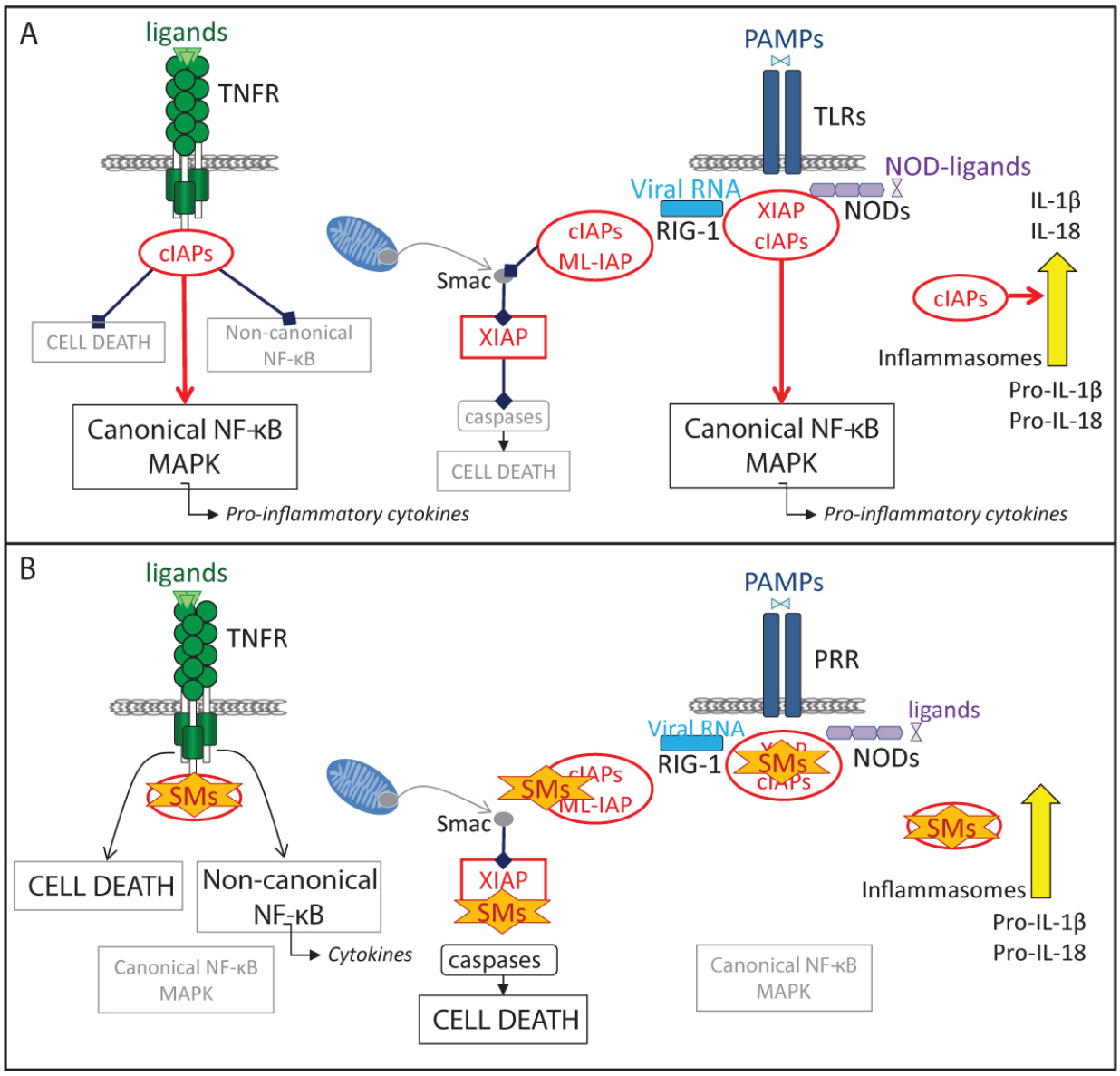

Figure 1: A- Cell signaling activity of IAPs. IAPs are important cell signaling regulators of TNFR signaling pathways. They are required for the canonical NF-κB activation, MAPK activation and pro-inflammatory cytokine production and they inhibit cell death and the non-canonical NF-κB activation. IAPs can also control the canonical NF-κB activation in response to PRRs. XIAP blocks apoptosis by inhibiting caspases and cIAPs and ML-IAP prevent Smac from neutralizing XIAP. Moreover, cIAPs have been involved in inflammasome activation. B- Mechanisms of action of Smac mimetics. Smac mimetics can bind XIAP, cIAPs and ML-IAP. They favor apoptosis by blocking XIAP-caspase interaction. They induce the ubiquitin-proteasome system-mediated degradation of cIAP1 and in some situation cIAP2 and XIAP, inhibiting canonical activation of NF-κB in response to TNFR and PRR engagement, inhibiting inflammasome activation, promoting the non-canonical NF-κB activation and priming cells to TNF-induced cell death.

As expected, SMs abrogate XIAP-mediated caspases inhibition and restore apoptotic response in cancer cells. In addition to target XIAP, SMs also bind the BIR domains of ML-IAP, cIAP1 and cIAP2. SMs appeared to stimulate the E3-ubiquitine ligase activity of cIAP1, which results in the auto-ubiquitination and very fast degradation of cIAP1 and in some situation cIAP2 and XIAP. As a consequences, SM cause the production of TNF-α which can trigger cell death by an autocrine pathway [3]. These unexpected results highlighted the critical role of cIAPs as cell signaling regulators. Because of their capacity to bind and ubiquitinylate important signaling intermediates, they control the activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and MAPK (Mitogen-activated protein kinase) signaling pathways downstream of some members of the TNF receptor (TNFR) superfamily including TNFR1, TNFR2, CD30 (Cluster of

differentiation 30), CD40 and TWEAK (TNF-like weak inducer of apoptosis). They are required for the canonical activation of NF-κB and MAPK while they block the non-canonical NF-κB activating pathway and cytoplasmic caspase-activation platform assembly. By neutralizing XIAP and degrading cIAPs, SMs simultaneously stimulated NF-κB-mediated pro-inflammatory cytokines production and prime tumor cells for death receptor-mediated cell death [3]. Thus, tumor cells become highly sensitive to TNF-α produced by tumoral cells themselves or by CD8+ lymphocytes and NK (Natural Killer) cells within the tumor (9). Moreover, the boosted production of pro-inflammatory signals including IFNγ (Interferon gamma) and IL-2 (Interleukin-2) can elicit antitumoral immune response by promoting maturation of antigen-presenting cells and enhancing T-cell response [8,9,16-21].

SMs in Preventing PRR-Dependent Inflammatory Diseases

More recent studies enlarged the signaling function of IAPs in antimicrobial innate immunity by demonstrating their role in signaling pathways initiated by pattern-recognition receptors (PRRs) [22]. These include cytosolic nucleotide-binding oligomerization domain-containing proteins (NODs) activated in response to intracellular bacterial infection, membrane-bound Toll-like receptors (TLRs) that sensing pathogen-associated molecular patterns (PAMPs) originating from bacteria, viruses, fungi, parasites and cytosolic retinoic acid-inducible gene I (RIG I) that recognizes viral RNA. IAPs are recruited on the receptor-associated intracellular signaling complex upon receptor engagement and participate to the signal transduction inducing NF-κB and MAPK activation and the expression of pro-inflammatory genes [23]. Moreover, cIAPs have been in involved in the maturation of IL-1β and IL-18 by controlling the assembly of inflammasome (for review, see [22]). Thus, inhibiting IAPs with SMs could ultimately decrease the production of inflammatory cytokines, reduce the recruitment of immune cells at the site of inflammation and therefore could potentially prevent tissue damage caused by sepsis and chronic inflammatory conditions. A recent in vivo investigation demonstrated a benefic effect of the SM birinapant on liver injury and survival in endotoxemic mice [24].

SMs in Fibrotic Diseases

In 2016, Ashley et al. highlighted the therapeutic potential of SMs in fibrotic diseases [25]. Pulmonary fibrosis is a progressive disease with a high mortality rate and the therapeutic options available to patients are limited. Fibrosis can be triggered by exposure to various injuries such as infection, allergens, drugs, toxins or it occurs for unknown reasons (case of the idiopathic pulmonary fibrosis: IPF). Fibrosis is characterized by the differentiation of fibroblasts into myofibroblast-like cells producing extracellular matrix. The accumulation of extracellular matrix in the alveolar space causes irreversible damage affecting vital function of lung. An upregulation of XIAP- encoding gene has been reported in patient-derived IPF fibroblasts [26]. The role of a chronic inflammation and specially IL-1β has been demonstrated in a mice model of bleomycin-induced lung fibrosis [27]. Treatment of fibrotic mice with the SM AT-406 significantly decreases the expression of pro-inflammatory cytokines and reduced collagen accumulation. Interestingly, AT-406 has also an antifibrotic activity when administrated latter, after the early inflammatory phase of the disease [25].

SMs in Clearing Virus-infected Cells

IAPs were initially discovery for their properties to block apoptosis of viral infected insect cells, allowing viral propagation [1]. In mammals, cIAPs are a survival factors in HBV (hepatite V virus) infected hepatocytes, allowing viral persistence [28]. Therefore, SMs could be a good option to selectively clear latently infected cells. The efficiency of Smac mimetics in treating HBV infection has been evaluated in an immunocompetent mouse model of chronic HBV. SMs treatment significantly decreases the serum HBV DNA and serum HBV surface antigen level, reduces the amount of HB core antigen (HBcAG)-positives hepatocytes and decrease the content of HBV genome in infected livers. Moreover, SMs improve the efficiency of the antiviral nucleoside analog entecavir in clearing infection [29].

Conclusion

SMs are very promising novel class of therapeutic agents for treating cancer. Ongoing and future clinical trials will determine the efficiency, safety and drugs combinations. The ongoing investigations of mechanistic effects of SMs and the analysis of the genetic and environmental tumors profile should make possible to define hallmarks for predicting the response to SM treatment and for determining the appropriate indications. More work is required to decipher the relationship between IAPs and several cell signaling pathways, to determine the importance of this class of proteins in the physiopathology of inflammatory, fibrotic and infectious diseases and to analysis the potential therapeutic of IAP antagonists in these diseases. SMs are non-specific compounds targeting several IAPs. Ongoing work will determine whether more selective antagonists to one member of the family or to one specific IAP function could be relevant in a particular pathological context.

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