Pharmacology & Therapeutics 143 (2014) 24–33

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: B. Teicher

Inflammasome: Cancer's friend or foe?☆

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ARTICLE INFO

Available online 8 February 2014

Keywords:
Inflammasome
Chronic inflammation
Carcinogenesis
Tumor progression
Tumor immunology

ABSTRACT

High serum concentrations of IL-1β and IL-18 are correlated to malignancies with low-rate survival from the time of diagnosis. The multimeric complex of the inflammasome is responsible for IL-1β/IL-18 synthesis/release. A number of endogenous (damage-associated molecular patterns) and exogenous (pathogen-associated molecular patterns) stimuli can provide signals for inflammasome activation in cancer. These stimuli can behave as tumor promoters via inducing chronic inflammation that, rather than providing a protective response to loss of tissue homeostasis, aberrantly facilitates tumor development. This view is contrasted in animal models of colon cancer in which the activation of some inflammasome complexes is associated with tumor protection. More studies are needed to understand the biology of the inflammasome in cancer and explore its therapeutic potential.

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1. Introduction

Inflammation is the seventh hallmark for cancer establishment and progression and represents the link between intrinsic (oncogenes, genome instability) and extrinsic (immune and stromal components) factors (Zitvogel et al., 2012). Essential to the development of cancer is the accumulation of genetic lesions in cells (Hanahan & Weinberg, 2011). However, while these autonomous cell properties are necessary for tumorigenesis, they are not sufficient. Research over the last two decades has solidified the concept that tumor development and malignancy is the result of processes involving both the cancer cells themselves and non-cancer cells, many of which compose the heterocellular tumor compartment (Hanahan & Weinberg, 2011; Zitvogel et al., 2012; Elinav et al., 2013). Many tumors are associated with the infiltration of inflammatory cells that in most cases, due to their immune-suppressive nature, are related to a bad prognosis (Pinto et al., 2011; Balkwill & Mantovani, 2012). Of note, pro-inflammatory cytokines, such as IL-1β and IL-18, are detected at high levels in cancer patients, and while their pathophysiological role is still elusive, a number of studies document their ability to promote an immune-suppressive tumor microenvironment (Dinarello, 2009a; Zitvogel et al., 2012; Novick et al., 2013). Chronic inflammation allows malignant cells to escape from or suppress anti-tumor immunosurveillance mechanisms (Hanahan & Weinberg, 2011; Balkwill & Mantovani, 2012; Zitvogel et al., 2012; Coussens et al., 2013). In fact, carcinogenesis and tumor progression are either stimulated or restrained by inflammatory and immune processes. The main goal of cancer immunotherapy is to induce tumor cell death via the activation of cytotoxic T lymphocytes (CTLs) and to subvert concurrent immune-suppressive mechanisms (Coussens et al., 2013).

Abbreviations: NLR, NOD-like receptors; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TLR, Toll-like receptors; IFN I, type I interferon; HMGB1, high-mobility group box 1.

☆ RS was supported by a fellowship from the Programma Operativo Regionale (POR) Campania 'Model Organism' (MODO) FSE 2007–2013; MT was supported by a fellowship from Programma Operativo Regionale (POR) FSE 2007–2013 Research in Experimental Medicine (CREME).

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0163-7258/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2014.02.002

The incidence of tumors is associated to chronic infections, dietary factors, obesity, inhaled pollutants, tobacco and autoimmunity (Jemal et al., 2010; Siegel et al., 2012; Elinav et al., 2013). A higher incidence of tumor development is reported in tissues/organs which are most exposed to both external and commensal pathogens, such as the lung, the intestine and, to a lower extent, the liver (Elinav et al., 2013; Kamada et al., 2013). In addition, according to the sterile inflammation theory, noninfectious insults, such as reactive oxygen species (ROS), oxidized and/or methylated DNA, high-mobility group box 1 (HMGB1), heat-shock proteins, and ATP, generally identified as damage-associated molecular patterns (DAMPs), can independently induce chronic inflammation (Rider et al., 2011; Drexler & Yazdi, 2013). Such endogenous and exogenous stimuli can behave as tumor promoters via the induction of chronic inflammation that, rather than providing a protective response to loss of tissue homeostasis, can aberrantly facilitate tumor development. All these insults are sensed by the multimeric complex called inflammasome (Gross et al., 2011).

The inflammasome is a multicomplex system composed of several proteins that promote caspase-1 activation (Fig. 1). Its activation follows engagement of Toll-like receptors (TLRs) and NOD-like receptors (NLRs), two classes of sentinel receptors that are pivotal in the detection of pathogen-associated molecular patterns (PAMPs and DAMPs) (Table 1) (Gross et al., 2011). The cooperation between these two systems allows to 'sense', and respond to a large number of infectious and sterile insults. While most TLRs, except for TLR3, TLR7 and TLR9, are membrane receptors, NLRs are intracellular and, together with the adapter protein, apoptosis-associated speck-like protein containing a CARD (ASC), can assemble to form the active components of the inflammasome complexes. The recognition of PAMPs or DAMPs by TLRs can accompany or strengthen the activation of inflammasome complexes composed of specific NLRs, depending on the stimulus, leading to the activation of caspase-1 (Stutz et al., 2013) (Fig. 1). Initially, NLRs were proposed to regulate inflammation through apoptosis, but nowadays this concept has been modified in that, while NLRs may serve as sentinels for cellular distress, their activity in the inflammasome complex is not necessarily conducive to cell death (Gross et al., 2011; Rathinam et al., 2012). Several NLR have so far been identified in both humans and mice, i.e., NLRP1, NLRP3, NLRP6, NLRC4, and the HIN200 protein AIM2 (Schroder & Tschopp, 2010). These proteins recognize distinct signals (Table 1) and, most importantly, are expressed at different levels in hematopoietic and stromal cell lineages. The expression of some NLRs is induced after the recognition of an insult (e.g. LPS) that triggers NF-κB-dependent gene expression. In contrast, NLRC4 and AIM2 are constitutively expressed in hematopoietic cells and are directly activated by flagellin-like molecules and dsDNA, respectively (Schroder & Tschopp, 2010).

Canonical activation of the inflammasome responds to a two-signal model: the first signal induces the expression of NLRs, e.g. NLRP3, along with the synthesis of pro-IL-1β/IL-18 (Schroder & Tschopp, 2010; Gross et al., 2011; Rathinam et al., 2012). The first signal, defined as priming, mediates NF-κB activation in a TLR-dependent, but also TNF receptor (TNFR)-, IL-1 receptor (IL-1R)-, and P_2X_7-dependent manner upon PAMPs or DAMPs sensing. The second signal involves the intracellular recognition of PAMPs or DAMPs by NLRs themselves, and their

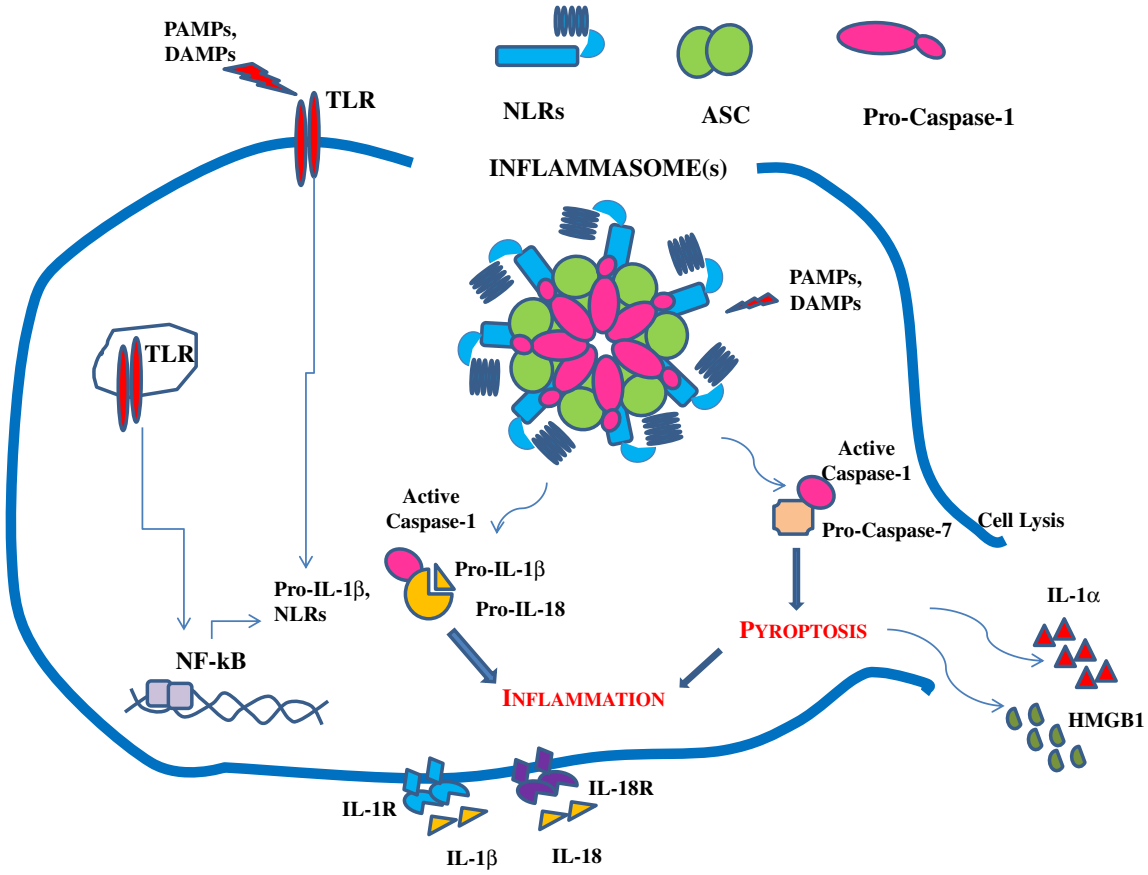

Fig. 1. The inflammasome is a multicomplex system whose activation is induced either directly by specific PAMPs and/or DAMPs or by the two-signal model as in the case of NLRP3. The recognition of PAMPs and/or DAMPs by extracellular or cytoplasmic TLRs leads to the activation of NF-κB (first signal), which in turn promotes the transcription of pro-IL-1β/IL-18 or some NLRs (e.g. NLRP3). NLRs assemble into the inflammasome complex which via the CARD domain can recruit pro-caspase-1 and promote its autocatalytic cleavage (second signal). Caspase-1 can lead to a cascade of pro-inflammatory events via the activation of pro-IL-1β and pro-IL-18, which then interact with their own membrane receptors amplifying the inflammatory response. On the other hand, active caspase-1 can lead to cell pyroptosis with the consequence of membrane rupture and release of such alarmins as IL-1α and HMGB1.