Cytokine & Growth Factor Reviews 33 (2017) 35–39

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

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

Mini review

DNA damage talks to inflammation

Idan Cohen*

Galilee Medical Center, Nahariya Hospital, 22100, Israel

ARTICLE INFO

Article history:
Received 25 October 2016
Accepted 14 November 2016
Available online 18 November 2016

Keywords:
Alarmin
Sterile inflammation
Interlukin-1
Danger model
DNA damage
Chromatin

ABSTRACT

Interleukin-1 alpha (IL-1α) and beta (IL-1β) are pleiotropic cytokines affecting multiple cells and regulating many immune and inflammatory responses. The recent finding that nuclear IL-1α is recruited to sites of DNA damage, and its ability to actively sense and report genotoxic stress to the surrounding tissue, dramatically alters the way we view IL-1 biology. This discovery add a new face to the classical "danger theory" and show that danger signaling is not strictly limited to passive release or dying cells. Most importantly, as now physiological stresses are linked to the release or secretion of IL-1α, chronic danger signaling and the alarmin inhibition should be considered as a new therapeutic approach for many diseases that are characterized by ongoing DNA damage, stress signaling and inflammation.

© 2016 Published by Elsevier Ltd.

Interleukin-1 alpha (IL-1α) and Interleukin-1 beta (IL-1β) are classical cytokines that are mostly known for their extracellular activity following their binding the IL-1 receptor (IL-1R), and for their biological role as pro-inflammatory agents. Despite the fact that both proteins have been intensively studied, the fundamental differences between the two molecules and their effects on non-conventional inflammatory processes, aside from their role in acute inflammation, are often disregarded. For instance, the two IL-1 proteins (solely or synergistically) were shown to play distinct roles in numerous physiological processes not typically associated with inflammation, including pregnancy maintenance [1], spontaneous abortions [2], headaches, migraines [3] and depression [4], appetite control [5,6], insulin secretion [7], insulin-derived growth factor/growth hormone (IGF/GH) physiology [8,9], and even tissue repair and wound healing [10,11]. Thus, it appears that both IL-1 forms play different roles during sterile inflammatory processes, whereby the recruitment of different myeloid cells and the promotion of different stages of inflammation are regulated by their timely and specific activity [12]. While IL-1α release initiates the recruitment of neutrophils [13], IL-1β was shown to promote the recruitment and retention of macrophages [12]. Thus, the recent finding of IL-1α activity as a sensor of DNA damage that can actively detect genotoxic stress and intracellular danger [11], exemplifies the different roles played by the two IL-1 related proteins, and provides another link between the unusual and enigmatic nuclear localization of IL-1α, and its extracellular activity as a cytokine.

Initially, IL-1α and IL-1β are synthesized as precursor proteins (pro-IL-1α and proIL-1β) of 31–33 kDa. Although pro-IL-1α is already active in its precursor form [14], in contrast to pro-IL-1β, both proteins can be further proteolytically processed by several proteases forming a number of different active cytokines, including proIL-1α, several forms of mature IL-1α (mIL-1α), and mature IL-1β (mIL-1β) [15]. Thus, the question of why IL-1 exists in so many different biologically active forms is often raised, and this issue is even more puzzling when one considers that upon binding to the IL-1R, all these forms activate the same downstream signaling pathway. If so, how can we explain these various biological activities? Indeed, it seems that this diversity in function could be mainly attributed to the major differences of these two separate genes in their specific transcriptional and intracellular regulatory mechanisms in different cell types and tissues.

While human IL-1α/β cytokines appear to be very similar biologically, they share only 20% amino acid sequence identity along their entire precursor proteins (i.e. pro-IL-1α and pro-IL-1β), and roughly 28% identity over the receptor interacting domains (i.e. mIL-1α and mIL-1β). Although both precursor proteins can be processed and cleaved by proteases to form the mature proteins (reviewed in [15]) they exhibit different affinities to IL-1R1 and to the decoy soluble receptor, IL-1R2 [14]. Another major difference between the two IL-1 gene products is their intracellular regulatory mechanisms, which seem to be cell-type dependent. For example, in cells of the immune system, both IL-1 proteins are expressed only after stimulation of Toll-like receptors (TLRs) or induction by other cytokines (such as TNF-α and IL-1, itself) [16]. In

* Corresponding author.
E-mail addresses: IdanC@gmc.gov.il, Idan5161@gmail.com (I. Cohen).

http://dx.doi.org/10.1016/j.cytogfr.2016.11.002
1359-6101/© 2016 Published by Elsevier Ltd.

contrast, IL-1α is constitutively expressed in many cell types, such as epithelial layers of the entire gastrointestinal tract, lung, liver, kidney, astrocytes or endothelial cells [17]. In addition, the intracellular processing, maturation and secretion mechanisms of the two proteins dramatically differ. While the active mIL-1β cytokine is produced via cleavage of pro-IL-1β by caspase-1, which is activated by the multi-protein inflammasome complex [18], and typically occurs after recognition of molecular patterns expressed by invading pathogens during infection [19], little is known about how IL-1α secretion is regulated. Accordingly, several lines of evidence show either inflammasome dependent or independent release of IL-1α [20–22] in its mature [20] or precursor form [23], depending on cell type or activation mode; while active caspase-1 may be needed for IL-1α secretion, [24] it is not proteolytically cleaved by this protease [24,25]. Pro-IL-1α is already fully active in its unprocessed form [26] and can initiate inflammation upon immediate release from cells; as it is rarely actively secreted by cells, it has been suggested to function as an "alarmin" or danger signal, released upon traumatic cell death, when cells lose their membrane integrity, and immediately able to initiate sterile inflammatory responses.

In addition, IL-1 proteins dramatically differ in their sub-cellular localization and compartmentalization. While IL-β is strictly localized to the cytoplasm, IL-1α is predominantly nuclear, and was previously associated with several nuclear processes. Thus, pro-IL-1α belongs to a class of intracellular proteins collectively termed 'dual-function' proteins, which in addition to their extracellular effects, also act as nuclear factors [27]. Although no specific or unique function was as yet attributed to nuclear IL-1α, the intracellular cytokine contains a strong nuclear localization signal (NLS) within its N-terminal domain [28], and exhibits robust nuclear localization [29].

Over the years, many studies have attempted to decipher why such cytokines would constitutively localize to the nucleus. It was suggested that dual function proteins evolved to form the first line of communication molecules in multi-cellular organisms, when their initial function was to serve as intracellular nuclear factors; only later did these molecules gain the ability to signal to other nearby cells following extracellular release. Nevertheless, to date, the constitutive expression of IL-1α in many cell types and its nuclear function remains a long-standing enigma. Initially, studies suggested that IL-1α is an intracellular regulator of cell proliferation, with conflicting reports of pro- or anti-proliferative effect depending on the cell type tested [30–34]. Additional reports suggested that intracellular overexpression of IL-1α nuclear forms is able to trigger malignant transformation or cell survival [33,35], or –in contrast- that they function as pro-apoptotic factors in malignant cells [36]. Further studies of the nuclear function of IL-1α demonstrated several non-related nuclear functions including co-localization with the splicosomal components [36], or alternatively, strong transactivation potential when IL-1α was fused to the Gal4p DNA-binding domain or in the UAS/GAL4 system [37,38]. Nevertheless, all these putative functions were detected either following strong ectopic expression or through non-physiological in vitro methods. Nonetheless, like the other dual function proteins, HMGB1 [39] and IL-33 [40], IL-1α was found to form a tight association with chromatin, based on biochemical evidence [11,29,41]. Despite the fact that its nuclear function is still an open question, it seems that the chromatin binding and nuclear localization activities of IL-1α are also linked to its immunological function as a cytokine regulating its release [11,29]. Moreover, the recent finding that IL-1α is dynamically recruited to DNA lesions or to cross-linked DNA [11] and can actively sense DNA damage constitutes a major change in the understanding of alarmin function.

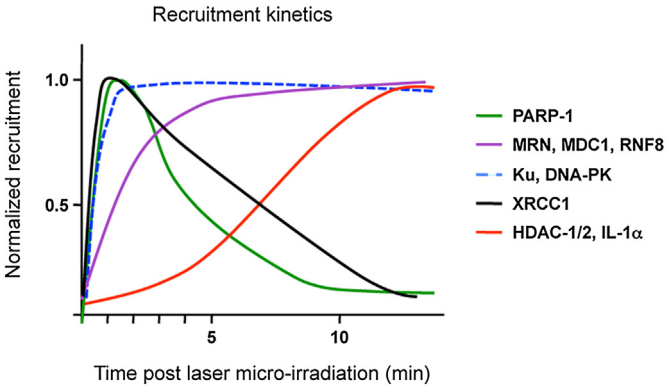

Fig. 1. Dynamics of protein recruitment and accumulation at DNA breaks. Recruitment dynamics of DNA damage recognition and signaling factors including PARP-1, MRN, MDC-1, RNF8, Ku proteins, DNA-PK and XRCC1 (data were adapted from Polo et al. [42]) and the late sequential recruitment dynamics of HDAC1/2 (taken from Miller et al. [44]) and IL-1α (taken from Cohen et al. [11]) to DNA lesions after DNA damage generated by laser micro-irradiation.

To date, the classical perception of the "Danger model" posited passive release of structural cell components, including DNA, RNA, histones or dual function proteins, during cell necrosis in order to initiate sterile inflammation. Under homeostatic conditions, those molecules are hidden from the immune system; when cells lose their membrane integrity, they release their intracellular contents and alert the immune system. In contrast, IL-1α acts as an active DNA damage sensor that is released from live cells upon non-lethal stress responses. Its ability to sense DNA damage adds a novel layer to the danger concept, by showing that alarmins can actively sense, report and communicate danger signaling to the surrounding tissue. Additionally, this activity also establishes a novel signaling cascade from the DNA damage response and injured cells, towards their microenvironment via alarmin signaling; such a response may help in the prevention of neoplastic transformation and ensure the removal of severely damaged cells.

Interestingly, the slow and late recruitment of IL-1α to DNA damage lesions (10–15 min after DNA damage is induced) resembles the recruitment of DNA repair factors like HDAC-1 or HDAC-2 (Fig. 1), but not the highly dynamic recruitment of DNA damage checkpoint signaling factors (which are recruited to the site of damage within a time frame of seconds to 1–2 min) that are responsible for initial sensing and detection of DNA damage sites, such as Ku-proteins, DNA-PK, MRN, ATM, XRCC-1 and PARP-1 (reviewed in [42]) (Fig. 1). HDAC1/2 are known to hypo-acetylate histone H3 lysine 56 (H3K56) during DNA damage repair. When HDAC1/2 are depleted, cells become hypersensitive to DNA-damaging agents and exhibit sustained DNA-damage signaling, or fail to complete DNA repair of specific types of DNA lesions [43], demonstrating the importance of H3K56 deacetylation during repair, and its role in promotion of DNA nonhomologous end-joining during chromatin reassembly [44]. Thus, aligning IL-1α recruitment to damaged DNA together with that of HDAC1/2, which deacetylate the IL-1α protein only at DNA damage sites and lead to its cytoplasmic shuttling, insures that only cells that can recover and initiate DNA damage recession, and are unlikely to undergo apoptosis, will release the cytokine (Fig. 2). Such signaling, which initiates inflammation, may help nearby undamaged cells reinforce selected stress-related signaling pathways, or can feed back to injured cells to promote DNA damage repair, which can be modulated by cytokines [45–47].

The use of dual function proteins brings immense advantage over structural cell components such as passive release of DNA, RNA, histones, or chemicals in stress signaling, leading to sterile

Download English Version:

https://daneshyari.com/en/article/5531204

Download Persian Version:

https://daneshyari.com/article/5531204

Daneshyari.com