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Review

Alarmins firing arthritis: Helpful diagnostic tools and promising therapeutic targets

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ABSTRACT

Alarmins are endogenous molecules with homeostatic roles that have reached the focus of research in inflammatory arthritis in the last two decades, mostly due to their ability to indicate tissue related damage after active or passive release from injured cells. From HMGB1, S100A8/A9 and S100A12 proteins, over heat-shock proteins (HSPs) and purine metabolites (e.g. uric acid, ATP) to altered matrix proteins and interleukin-33 (IL-33), a number of alarmins have been determined until now as having a role in rheumatoid arthritis, psoriatic and juvenile idiopathic arthritis, as well as spondyloarthritis and gout. Although formerly being linked to initiation and chronification of inflammatory arthritis, driving auto- and paracrine inflammatory loops, more recent research has also unraveled the alarmins' role in the crosstalk between innate and adaptive immunity and in resolution of inflammation.

Providing a state-of-the-art overview of known alarmins, this review lists the known modes of action and pathologic contribution of alarmins to inflammatory arthritis, as well as biomarker potential of alarmins in the clinical setting for tracking disease severity. Based upon research on animal experimental models (CIA, AIA) and clinical trials, a look is made into potentially viable strategies for modifying alarmin secretion and their target receptor (e.g. TLR, RAGE) interaction with the purpose of attenuating arthritic disease.

1. Introduction

During the last two decades, molecular targeted biological therapies have determined and partly overridden our clinical management of inflammatory arthritis. At the same time, our possibilities in precisely detecting local inflammatory processes by measuring endogenous signals reflecting tissue damage have emerged. While certain cytokines are the main targets of biological therapy, sensing them in patient material is ambitious and still not suitable for clinical routine. Measuring activation of innate immunity involved in inflammatory arthritis as important player of its pathogenesis by danger signals that confer inflammatory signaling via pattern recognition receptors (PRR) are promising alternatives [1].

These endogenous signals have been termed according to their ability to indicate tissue damage as alarmins or damage associated molecular pattern (DAMPs) molecules. Both concepts evolved almost in parallel, but the terms have been introduced for the same side of the coin, and are used as synonyms for them. Derived mainly from innate immune cells, these molecules unify intracellular functions related to cell homeostasis and extracellular cytokine capabilities leading to PRR involvement and triggering of inflammatory responses by recruitment of immune cells, activation of adaptive immunity and starting of multiple feedback loops to amplify inflammation [1].

Participation of alarmins in inflammatory arthritis was initially described for HMGB-1 and phagocyte-specific S100-proteins, due to elevated levels in inflamed joints and also in peripheral blood. Until now, a number of alarmins have been defined and include, but are likely not limited to high mobility group box 1 protein (HMGB-1), S100 proteins (most notably S100A8/A9 and S100A12), heat-shock proteins (HSPs), purine metabolites (e.g. uric acid and ATP), altered matrix proteins and, recently interleukin (IL)-33, an alarmin-type cytokine. Specific alarmins like HMGB1 can be recognized by various receptors (e.g. RAGE, TLRs), while on the other hand some receptors like TLR4 can recognize a broad range of different alarmins (e.g. HMGB1, HSPs, S100-proteins). Currently known alarmin-receptor pairs are listed in Tables 1 and 2.

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Table 1
Overview main alarmins.

Alarmin (Synonym)	Expression, intracellular localization	Homeostatic function	Receptors	Alarmin effects	Ref.
HMGB-1 (high-mobility group box-1)	Ubiquitously expressed in all mammalian cells Nucleus of all eukaryotic cells Cytoplasm, including mitochondria and lysosome	DNA binding events (replication, remodeling and recombination). Regulates physical interactions between DNA and transcription factors	RAGE, TLR2, TLR4, TLR9, β2 integrin, Mac-1, TIM-3	Joint destruction. Upregulates TNF expression in osteoclasts. Co-activator for the transcription of IL-1. Increase in the synovia of patients with RA	[2]
S100A8 (myeloid-related Protein (MRP)-8, Calgranulin A)	Monocytes granulocytes (ca. 40% of cytosolic protein content) Keratinocytes Cytoplasm	Calcium – homeostasis, interaction with microtubules, vimentin, keratin and actin filaments propagating transendothelial migration	RAGE, Heparan sulfate, *N*-glycans, TLR4	Activation of endothelial cells (apoptosis, upregulation of thrombogenic factors, increase of junctional permeability), activation of leukocytes, chemotaxis, antimicrobial activity, downstream signaling with NF-κB-activation	[3]
S100A9 (myeloid-related Protein (MRP)-14, Calgranulin B)	Monocytes granulocytes (ca. 40% of cytosolic protein content) Keratinocytes Cytoplasm	Calcium-homeostasis, interaction with microtubules, vimentin, keratin and actin filaments propagating transendothelial migration involved in myeloid differentiation stabilization of S100A8 and heterocomplex	RAGE, Heparan sulfate, *N*-glycans, TLR4	Activation of endothelial cells (apoptosis, upregulation of thrombogenic factors, increase of junctional permeability), activation of leukocytes, chemotaxis, antimicrobial activity, downstream signaling with NF-κB-activation	[3]
S100A12 (myeloid-related Protein (MRP)-6, Calgranulin C)	Granulocytes (<5% of cytosolic protein content), monocytes Cytoplasm	Zink-homeostasis	RAGE, N-glycans, TLR4	Activation of leukocytes, chemotaxis, antimicrobial activity, downstream signaling with NF-κB-activation	[3]
HSP10 family	Mitochondria and cytoplasm	Co-chaperone for HSP60 Essential for mitochondrial protein biogenesis	Various, e.g. CD14, CD91, CD40, LOX-1, CD36, TLR2, TLR4, SR-A	Inhibition of proinflammatory cytokines	[4,5]
HSP40 family	Constitutively present in the cytoplasm, translocates to the nucleus upon heat shock Cytosol Nucleus Nucleoli	Co-chaperone for HSP70 Regulation of HSP70 ATPase activity Associates with unfolded polypeptide chains and prevents their aggregation	See HSP10	Increased humoral response to HSP40 in RA, anti-inflammatory action – reduction of T cell proliferation, IL-10 stimulation	[6]
HSP60 family	Constitutively present, induced upon cell stress (heat, cold, oxidative stress, hypoxia, UV light, tissue remodeling wound healing) Cytoplasm and mitochondria	Mitochondrial protein import and macromolecular assembly Facilitates the correct folding of imported proteins, prevents misfolding and promotes refolding and proper assembly of unfolded polypeptides generated under stress conditions in the mitochondrial matrix	See HSP10	Proinflammatory mediator induction Anti-inflammatory mediator induction Treg proliferation Peptide (self) and antigenic (non-self) fingerprinting, eliciting anti-tumor, anti-viral, antiparasitic effects	[5,7]
HSP70 family	Constitutively present, induced upon cell stress (heat, cold, oxidative stress, hypoxia, UV light, tissue remodeling wound healing) Cytoplasm, mitochondria and endoplasmic reticulum	Stabilizes proteins against aggregation, mediates folding of polypeptides in cytosol and within organelles	See HSP10	Proinflammatory mediator induction Anti-inflammatory mediator induction Treg proliferation Peptide (self) and antigenic (non-self) fingerprinting, eliciting anti-tumor, anti-viral, antiparasitic effects	[5]
IL-33	*mRNA*: Multiple organs and cell types following pro-inflammatory stimulation *Protein*: Mainly in fibroblasts, epithelial and endothelial cells, most prominently in high endothelial venules	Chromatin-associated nuclear factor; Transcriptional repressor; Nuclear NF-κB/RELA sequestration	IL1RL1/ST2	Induction of Th2-associated cytokine secretion Th2 cells maturation Chemoattractant for Th2 cells Activation of mast cells, basophils, eosinophils and natural killer cells Alarmin – immune response amplification during tissue injury	[8,9]