Cytokine 110 (2018) 222–225

Contents lists available at ScienceDirect

Cytokine

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

Short communication

Exercise alarms the immune system: A HMGB1 perspective

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ARTICLE INFO

Keywords:
Alarmins
Exercise
HMGB1
Immune

ABSTRACT

The "danger" model of immunology states that the immune system detects and responds to danger by releasing endogenous molecules called alarmins. Strenuous exercise perturbs physiological homeostasis, increasing circulating alarmins to drive the inflammatory response. We describe a working concept of exercise-induced High Mobility Group Box (HMGB)1, a prototypical alarmin, in modulating immune responses and adaptations.

1. Exercise training, inflammation and the immune system

While studies of the immune system have largely focused on its role in defence against pathogens, its role in homeostasis is becoming clear. In particular, the immune system is affected by and modulates metabolic states, including exercise. Indeed, a single bout of intense exercise can induce both pro- and anti-inflammatory cytokines and chemokines, as well as an increase in circulating leukocytes. Exercise-induced circulating cytokines and chemokines include interleukin (IL)-6, 8, 10 and monocyte chemotactic protein (MCP)-1. In the 1990s, the research groups led by Pedersen and Febbraio [1] demonstrated that skeletal muscle contraction directly induces IL-6 release from monocytes and redefined its novel role as an exercise-induced, anti-inflammatory cytokine, with the capability to upregulate substrate-relevant pathways *via* AMPK, PGC-1α [1]. Since the discovery of IL-6 as a muscle-derived factor, other cytokines and chemokines including IL-15 and brain-derived neurotrophic factor (BDNF) have been shown to be released upon skeletal muscle contraction, and collectively discussed as "myokines" in this context [2]. Such research developments demonstrated that exercise modulates inflammation, which can precede overt chronic diseases, such as diabetes mellitus, cancer and atherosclerosis. Furthermore, growing interest in myokines paved the way for current research to understand the systemic cross-talk between exercising skeletal muscles and other target organs. In this regard, one promising area of research lies in elucidating the role of alarmins and immune cross-talk, and how these interactions can be modulated by exercise training (See. Fig. 1).

2. Alarmins and the immune response

Alarmins are endogenous molecules that perform physiological functions at homeostasis but can be released rapidly from activated immune cells (leukocytes) or released from damaged cells after stress, infection or injury [3]. Alarmins differ from cytokines and chemokines in that during cellular homeostasis, they participate in antimicrobial, gene regulation or chromatin-binding functions. Alarmins are located in different cellular compartments; high mobility group box-1 (HMGB1) protein is an archetypal alarmin and typically sequestered in the nucleus, where it binds DNA, while others - S100 proteins or heat shock proteins (HSPs), reside in the cytoplasm [4]. Upon encountering danger, alarmins are released quickly from stressed or damaged cells and leave their physiological milieu, where they behave like cytokines and mediate a sterile, inflammatory response involving cytokines and chemokines. Oppenheim and colleagues have thus aptly coined alarmins as "first responders" to sterile injury or infections [4].

Circulating HMGB1 forms a heterocomplex with C-X-C motif chemokine 12 (CXCL12) and together, the complex binds surface receptors on leukocytes, including C-X-C motif chemokine receptor 4 (CXCR4), as well as pattern recognition receptors (PRRs) like toll-like receptor (TLR)-4 and receptor for advanced glycation end product (RAGE) [4]. The redox status of circulating HMGB1 regulates the downstream inflammatory response. When the C106 residue and the C23 and C45 residues are in reduced thiol form and disulphide bridge formation respectively, HMGB1 is activated and will bind PRRs on immune cells to induce cytokine (e.g. TNF-α) release and contribute to pro-in-

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https://doi.org/10.1016/j.cyto.2018.06.031
Received 4 April 2018; Received in revised form 14 June 2018; Accepted 28 June 2018

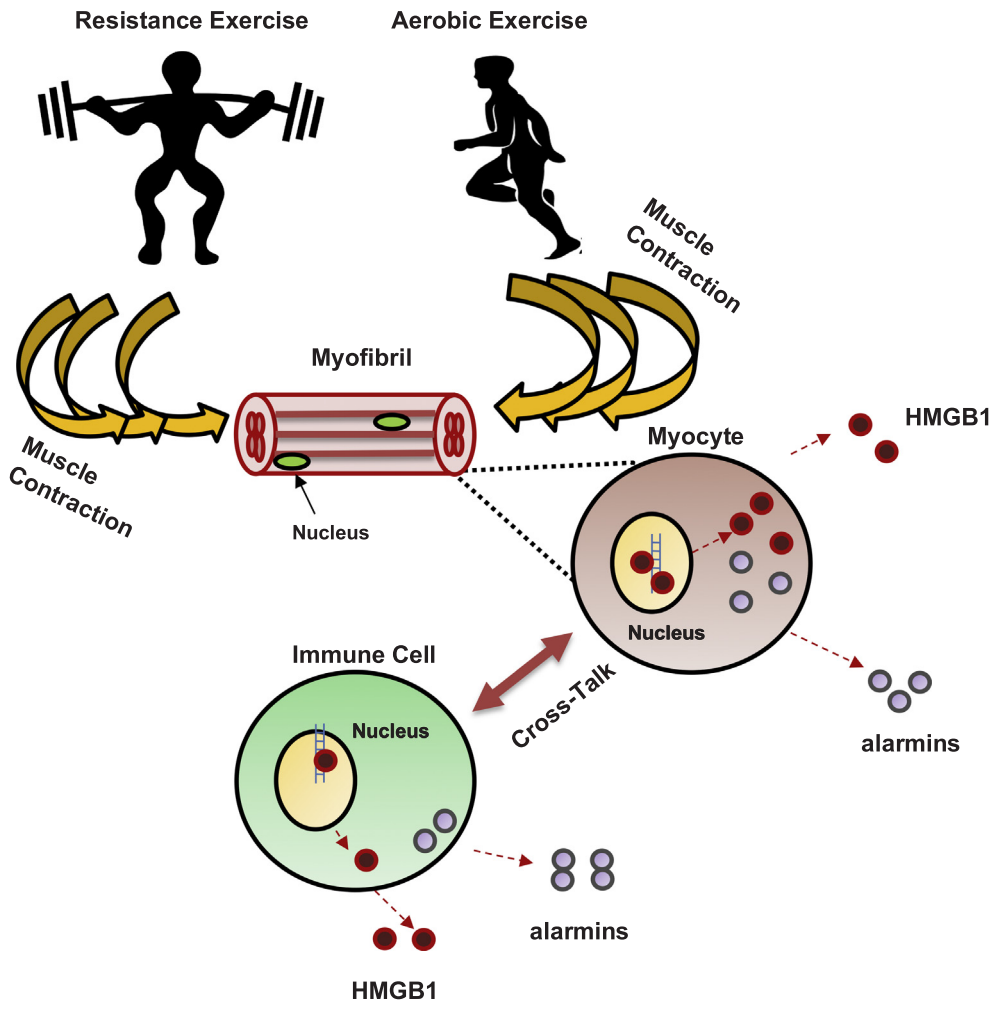

Fig. 1. Working model of exercise-induced alarmin response. Aerobic and resistance exercises involve skeletal muscle contraction, which may induce some alarmins (HMGB1) to be released from either skeletal muscle cells (myocytes) or other immune cells. The ensuing molecular cross-talk between myocytes and immune cells can then activate other components of the immune response, including activation of specific immune subsets, chemotaxis and adherence of immune cells to skeletal muscle.

flammatory signalling [5]. Thereafter, immune cells get activated and migrate to damaged tissue, such as skeletal muscle for repair and removal of necrotic cells [6,7]. Conversely, oxidization of cysteine residues results in an inactive form of HMGB1, coinciding with a dampening of the inflammatory response [5].

The role for HMGB1 in mediating the systemic response to injury has often been reported in clinical studies. Patients sustaining multiple traumatic injuries [8] or exercise-induced heat stroke [9] presented with systemic HMGB1 that were 30- and 25-fold higher than healthy controls respectively. The augmented HMGB1 response to trauma was observed an hour after injury- an early response, compared with the late response (days) typically observed in sepsis [8]. This phenomenon suggests that the kinetics of HMGB1 in sterile injury are different from pathogenic infections. Interestingly, HMGB1 released from monocytes after exertional heat stroke peaked at 48 h post-injury and was several-fold higher than at 3 h post-injury [9], implying that monocytes are not major contributors of HMGB1 during the early phase of the injury. Instead, damaged or necrotic cells consequent to heat injury may be the main source of HMGB1.

3. HMGB1 is a "Danger" molecule induced by exercise

Strenuous exercise is similar to mild trauma [10], as the physiological state during exercise (e.g. lactate acidosis, tissue ischemia, oxidative stress, cytokinemia, inflammation and skeletal muscle trauma) are reminiscent of injuries to soft tissues, while the ensuing cytokine "storm" and leucocytosis are remarkably similar to that observed in polytrauma. When individuals perform strenuous exercises they are unaccustomed with, they may experience skeletal muscle breakdown- a rare, but life-threatening condition known as rhabdomyolysis [11]. Under such circumstances, HMGB1 released from damaged skeletal muscle cells may function as a "danger" signal to activate and mobilize immune cells.

In the first publication of exercise and HMGB1, the authors reported a 5- to 6-fold increase from ~1 ng/mL at rest, to ~6 ng/mL immediately after healthy men completed a strenuous run on a treadmill [12]. Circulating HMGB1 returned to pre-exercise concentrations after 30 min of rest. In another exercise study [13], 34 and 36 non-professional male and female marathoners and half-marathoners completed their respective races, with blood specimens collected 1–2 days prior to, immediately and 2–7 days after the races. Serum concentrations of HMGB1 increased significantly by ~1.5-fold (half-marathon; 3.13 ± 1.63 ng/mL to 4.78 ± 2.1 ng/mL) and ~2.3-fold (marathon; 2.58 ± 1.58 ng/mL to 6.02 ± 2.18 ng/mL) after the races, with concomitant increase in circulating sRAGE for the half- but not the full-marathon. Elevated HMGB1 and sRAGE concentrations returned to pre-exercise levels during the recovery period.

Not all exercise studies reported a positive response of systemic HMGB1 to a single bout of exercise. In a recent study, plasma HMGB1 remained below the detection limits (78 pg/mL) of the assay kit after