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Review

Skeletal muscle cells actively shape (auto)immune responses

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ABSTRACT

Histopathological analyses of muscle specimens from myositis patients indicate that skeletal muscle cells play an active role in the interaction with immune cells. Research over the last few decades has shown that skeletal muscle cells exhibit immunobiological properties that perfectly define them as non-professional antigen presenting cells. They are able to present antigens *via* major histocompatibility complex molecules, exhibit costimulatory molecules and secrete soluble molecules that actively shape the immune response in an either pro- or anti-inflammatory manner. Skeletal muscle cells regulate both innate and adaptive immune responses and are essentially involved in the pathophysiological processes of idiopathic inflammatory myopathies. Understanding the role of skeletal muscle cells might help to identify new therapeutic targets for these devastating diseases. This review summarizes the immunobiological features of skeletal muscle cells, especially in the context of idiopathic inflammatory myopathies, and discusses shortcomings and limitations in skeletal muscle related research providing potential perspectives to overcome them in the future.

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Abbreviations: ADAM, a disintegrin and metalloproteinase; APP, amyloid precursor protein; APC, antigen presenting cell; Aβ, β-amyloid; B7-H1, B7-homolog 1; CARD, caspase activation and recruitment domain; CCR, C-C chemokine receptor; CIM, C-protein induced myositis; Ca2+, calcium; CatS, cathepsin S; CK, creatine kinase; CTLA-4, cytotoxic T-lymphocyte-associated receptor 4; DAMP, damage-associated molecular pattern; DC, dendritic cell; DM, dermatomyositis; ER, endoplasmic reticulum; EAM, experimental autoimmune myositis; HD, healthy donor; HMGB1, high mobility group box protein 1; HRS, histidyl-tRNA synthetase; HLA, human leukocyte antigen; hBD, human β –defensin; MIF, migration inhibitory factor; ICOS, inducible T-cell costimulator; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IIM, Idiopathic inflammatory myopathies; IL, interleukin; IL-1R, interleukin 1 receptor; IHCS, Immunohistochemical staining; KIR, killer cell immunoglobulin like receptor; K2P, two pore domain potassium channel; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; MIF, macrophage migration inhibitory factor; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; NKG2DL, natural killer group 2D ligands; NLRP, NACHT, LRR and PYD domains-containing protein; NOD, nucleotide-binding oligomerization domain; PRR, pattern recognition receptor; PAMP, pattern-associated molecule pattern; PM, polymyositis; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PYD, pyrin domain; ROS, reactive oxygen species; SR, sarcoplasmatic reticulum; SkMC, skeletal muscle cell; sIBM, sporadic inclusion body myositis; TCR, T cell receptor; TLR, toll-like receptor; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

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1. Introduction

More than a century has passed since Wagner and Unverricht described the first cases of idiopathic inflammatory myopathy (IIM) [1,2]. However, research has neglected the participation of skeletal muscle cells (SkMC) in IMM-related immune reactions for a long time, focusing instead on invading immune cells. Recent studies rather emphasize an active than passive role of SkMCs in the interaction with immune cells, shaping (auto)immune responses in health and disease [3–6].

SkMCs exhibit certain immunobiological properties that perfectly define them as non-professional antigen presenting cells (APCs). They express major histocompatibility complexes (MHCs) I and II under inflammatory stimuli and are able to upregulate membrane bound molecules strictly necessary for their interaction with T cells [4,5,7–9]. These comprise adhesion molecules like intercellular adhesion molecule 1 (ICAM-1), selectins and T cell costimulatory molecules such as CD40, molecules of the B7 family or natural killer group 2D ligands (NKG2DL) [4,5,10,11]. Through secretion of cytokines, chemokines or endopeptidases, muscle cells regulate the immunological microenvironment of immune reactions [4,9,10,12,13]. Furthermore, receptors linked to innate immune responses have been found to be upregulated in SkMCs [5,10]. *In vitro* experiments and animal models have helped to gain further insights into the complex regulation of these immunologically relevant molecules and their role in the interaction with immune cells [14]. Immunohistochemical stainings (IHCSs) have been especially useful to characterize muscle tissues from IIM specimens [4]. However, many mechanisms of muscle cell– immune cell interactions remain poorly understood.

This review summarizes findings of the last few decades, emphasizing the immunobiological features of SkMCs actively shaping (auto)immune responses.

Further, we will discuss shortcomings and limitations in skeletal muscle related research and provide potential perspectives to overcome them in the future.

2. Innate immune response

Invading microorganisms are initially recognized by humoral or cellular factors of the innate immune system that make up the first line of defense. This response finally leads – in the best case – to the direct destruction of microbial pathogens by antimicrobial molecules such as defensins, aggregated complement factors or by attracted macrophages. If the infection is not resolved, foreign antigens are processed and presented to components of the adaptive immune system in order to activate the second line of host defense [15].

The innate immune system has been regarded for a long time as unspecific and, therefore, not as essential in the context of autoimmunity. However, there are close interactions between innate and adaptive immune responses and recent findings provide evidence that both components are essential for (auto)immune responses (Fig. 1).

2.1. Defensins and pathogen recognition receptors (PRRs)

Pathogens breaking through anatomic barriers into the body immediately face the biochemical first line of immune defense. Soluble molecules such as antimicrobial enzymes and peptides attack microbial cell wall components, destroying the undesired invaders. For the next line of defense, innate immune cells recognize certain microbial products, also referred to as pathogen-associated molecule patterns (PAMPs), by a variety of pattern recognition receptors (PRRs). These can be further classified by their cellular localization: either soluble, membrane bound or cytoplasmatic signaling PRRs recognize microbial cell-wall components, foreign RNA or DNA as well as endogenous molecules. Binding of innate sensors like toll-like receptors (TLRs) or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) initiates intracellular signaling pathways mediated by transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to production of cytokines and T cell costimulatory molecules [15] (Fig. 1).

Defensins play a crucial role in the defense against microbial pathogens by recognizing PAMPs and harming cell surface components of microbial cell membranes. Furthermore, they exhibit chemotactic properties mediated by C-C chemokine receptors (CCRs) type 2 and 6 [16]. The expression of human β-defensins (hBDs) was found to be upregulated in muscle specimens of polymyositis (PM) and sporadic inclusion body myositis (sIBM) patients [7,17–19]. In the case of sIBM, hBDs were found to be co-localized with TLR3, markers of autophagy and β-amyloid (Aβ) in IHCS [17,18]. These molecules might attract dendritic cells (DCs) and T cells to sites of Aβ expression in order to clear cells bearing Aβ [16,20].

Expression of various TLRs has been detected in myoblast cell cultures and in muscle tissue of IIM patients either constitutively or under inflammatory stimuli, hinting at properties of self-defense. *In vitro* experiments with cultured SkMCs have been helpful to investigate the PAMP/TLR-interaction in order to measure immune responses [17–19,21–24] (Fig. 1).

Among the PAMPs, lipopolysaccharides (LPS) are well characterized. LPS, a cell membrane component of gram-negative bacteria, is known to interact with the PRR TLR4, resulting in a strong immune response [25]. In SkMCs, the LPS-TLR4-interaction leads to secretion of cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6 and CC- and CXC-chemokines [21,22,26], inducing immune cell invasion into the muscle.

TLR3, an ancient receptor recognizing viral double stranded RNA, has been implicated in the interaction of innate and adaptive immune responses [27]. Studies from Tournadre et al. examined the expression, regulation and function of TLR3 in PM and dermatomyositis (DM) muscle tissue and cultured myoblasts. In their experiments, both Poly(I:C) synthetic double stranded RNA and the TH1 cytokine interferon (IFN) γ were found to induce TLR3 expression in human myoblasts. However, the TH17 cytokine IL-17A was shown to reduce TLR3 expression in general and to inhibit IFN-γ mediated effects on TLR3 expression. This indicates that TH1 or TH17 responses act to differentially regulate expression of TLR3 [19,24]. TLR3 expression leads to increased secretion of IL-8 and the type I IFN IFN-β, two cytokines sharing chemoattractant and immunomodulating properties [23,24]. Particularly, the IFN type I signature is considered to be of high pathogenic relevance in IIMs [28]. TLR3 expression was also associated with increased expression levels of NKG2DLs [23]. The NKG2DL-NKG2D-interaction offers an alternative cytotoxic effector pathway contributing to progressive muscle cell destruction in IIMs [11].

PRRs do not only recognize exogenous but also endogenous molecules. Intracellular molecules released into the extracellular space by damaged muscle cells contain so-called damage-associated molecular patterns (DAMPs) recognized by certain PRRs. In case of IIMs, histidyl-tRNA synthetase (HRS) has been considered as a potential antigen. Thus, recent research has focused on establishing a myositis model driven by HRS inoculation [14]. These models helped to characterize chemotactic and immunomodulating properties of HRS on T cells and DCs mediated by both TLR2 and TLR4. However, an immediate effect of HRS on SkMCs in the context of the observed reaction has not been considered yet [29–31].

Another well-characterized DAMP is HMGB1 (high mobility group box protein 1), a nuclear chromatin protein organizing DNA and regulating gene transcription. Its release to the extracellular space has been observed in myositis specimens [32]. *In vitro* experiments and animal models have implicated an essential role for HMGB1 in muscle dysfunction and inflammation upon TLR4-ligation in SkMCs [32–34]. Upon HMGB1-TLR4-interaction, calcium ($Ca2+$) re-uptake into sarcoplasmic reticulum (SR) is reduced [32,34] and proinflammatory responses like MHC-I-expression or TNF-α- and IL-6-secretion are initiated [33].

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