

Skeletal Muscle Ageing; implications for the immune response

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Skeletal muscle is the largest organ system within the human body, comprising 40% of total weight and 50% of total protein. Typically its primary function as motor for daily-life is well characterised, however, recent studies have identified an alternate role in immunity.

Skeletal Muscle and Ageing

Ageing can be defined as “the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age”(1). In terms of skeletal muscle, ageing is characterised by a progressive decline in muscle mass, force and condition, termed sarcopenia. Sarcopenia is associated with impaired mobility (2) and increased frailty. The loss of strength (30-40%) by the age of 70 years in skeletal muscle is believed to be as a result of muscle fibre atrophy, with reduction in cross sectional area (25-30%) (3). Furthermore, reduction in total fibre number has been associated with the specific loss of type II (fast, glycolytic) over type I (slow, oxidative). This loss of type II fibres leaving a predominant type I population is exhibited in the slow contraction and decreased limb mobility in the aged individuals. Moreover the loss of skeletal muscle has been correlated with replacement by adipose and connective tissue (4). Skeletal muscle does however have a capacity to regenerate and repair following damage via the presence of satellite cells that function as myogenic stem cells – regenerating muscle fibres (5). This regenerative capacity is attenuated in the aged individual (6). Overall, the loss of skeletal muscle mass and function has a significant effect upon the aged individual. Research has focused on methods of protecting against this loss of muscle mass and function.

Defence of Skeletal Muscle

Skeletal muscle is a very plastic organ, with the capability to adapt and protect during instances of stress and infection; heat shock proteins (HSPs) have been found to play a significant role in this stress response. HSPs are a highly conserved family of proteins, characterised by their molecular weight. They function as chaperones by binding to and stabilising nascent peptides, assisting in protein folding and transportation. Under conditions of stress (i.e. exposure to heat, pH, heavy metals, infection, inflammation) HSP expression is up-regulated in an effort to stabilise proteins within the cell and to promote cell survival (7). HSP up-regulation in skeletal muscle has been shown to be associated with significant remodelling alongside up-regulation of antioxidant enzymes (8). In the normal aged individual the ability to instigate a stress response is attenuated (9). *In vivo* studies using aged HSP70 overexpressor (in skeletal muscle) mice showed protection and the capability of recovery following a damaging (lengthening) contraction protocol, in comparison with aged wild-type mice (10). Thus, HSPs play a critical role as means of defence and cytoprotection, an importance that is further reinforced in the aged individual. Data suggest that an attenuated heat shock response plays a role in the atrophy and reduction in skeletal muscle mass presented in the aged individual.

Skeletal Muscle; impact of HSP production on immunity

It is clear that HSPs play a pivotal intracellular role in maintaining cell survival under instances of stress, particularly in the aged individual. However recent evidence has indicated HSPs that can also be detected in the extracellular environment, whereby their role alters. From chaperone functions to a more immuno-modulatory roles, extracellular Heat Shock Proteins (eHSPs) have been described as having cytokine-like properties (11).

Extracellular HSPs have been widely characterized as “danger-signals” for the immune system during the early-stages of trauma/infection. A wide variety of research has implicated the capacity of eHSP60 and 70 to interact with T-cells. Extracellular HSP72 (eHSP72) has been shown to have a direct inflammatory capacity when exposed to airway epithelium, whereby, eHSP72 result in the up-regulation of several inflammatory cytokines in the airway such IL-8 and TNF- α (12). Furthermore, the up-regulation of inflammatory cytokines was mediated by NF κ B, a key cytokine transcription factor. It was found that the interaction between HSP72 and epithelial cells of the airway occurred exclusively via Toll like receptor 4 (TLR4). This indicates the potency that eHSPs harbour, and the significant role they can play in instigating an immune response; such importance cannot be understated since the aged individuals ability to produce HSPs is attenuated and their susceptibility to infection/insult is far greater.

The notion of HSPs being acutely involved in signalling pathways as part of the immune response provides a new perspective to the role of skeletal muscle during inflammation. Typically under conditions of stress skeletal muscle exhibits a significant up-regulation of HSPs, therefore it could be hypothesized that they may play roles in the extracellular environment alongside their intracellular chaperone function.

Research has also demonstrated the release of cytokines from skeletal muscle, termed myokines. This suggests that skeletal muscle is not simply a mechanical organ, a bystander in immunity, but instead has a more specific role. Release of IL-6 from contracting skeletal muscle is particularly well described, alongside IL-8 and IL-15.

IL-6 release was exponential in response to exercise and independent of muscle damage (13). The function of the released IL-6 is not widely known. IL-6 has been defined as anti-inflammatory (14) with suppression of TNF- α levels (13). However these results seem paradoxical as elevated systemic levels of IL-6 have been associated with morbidity and loss of muscle mass in the aged individual(15).

What is clear however is that myokines play an important role, however the processes which determine whether they are detrimental or not, are yet to be determined.

The potential for skeletal muscle to provide a source of eHSPs and cytokines adds to the possible function of muscle as an immunogenic organ in an autocrine or paracrine manner to itself or neighbouring cells; interactions which may have a role in the ability of skeletal muscle to adapt. Interaction of muscle derived HSPs and myokines primarily with immune cells indicates the ability of cross-talk to occur between skeletal muscle and the immune system in a paracrine or endocrine manner.

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