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Skeletal muscle matrix metalloproteinase and exercise in humans

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Abstract

Skeletal muscle is a highly plastic tissue; it has a great capacity to adapt to environmental demands throughout life. The structural and functional changes that occur in response to exercise training are well characterized whereas much less is known about these adaptive processes at the cellular and molecular levels. A possibly underestimated aspect of skeletal muscle adaptation to exercise is the remodeling of the extracellular matrix (ECM). Degradation and processing of the extracellular matrix are carried out by a specific category of proteases, especially the matrix metalloproteinase family (MMPs). Such remodeling is of crucial importance for successful extravasation of circulating cells and for the migration of cells between the compartments of the tissue. Furthermore, degradation products of ECM components are not always mere debris; several fragments of structural proteins have biological activity after proteolytic processing, and MMP activity may also release growth factors stored in the ECM. Little is known about these enzymes in skeletal muscle of humans and how physiological stimuli such as exercise and exercise training affect their expression and activity.

Therefore, the aim of this thesis was to characterize: 1. skeletal muscle MMP activation in response to a single bout of exercise and exercise training with regard to gene expression and enzyme activity, 2. exchange of factors associated with MMP activity between exercising leg and the circulation during exercise, 3. possible cellular sources of MMP in skeletal muscle tissue and blood, 4. the effects of restricted leg blood flow, and thereby reduced oxygen delivery, to the exercising leg on skeletal muscle and circulating levels of MMP and 5. the effects of the myokine interleukin-6 on MMP levels in skeletal muscle and in the circulation.

MMP-9 is activated and transcriptionally upregulated in human skeletal muscle after a single bout of exercise. In contrast, MMP-2 is activated and transcriptionally upregulated in human skeletal muscle by exercise training but not after a single bout of exercise. Factors possibly linked to proteolytic processing of MMP-9, such as collagen IV and VEGF-A, are released from the leg to the circulation during a single bout of exercise in humans. Circulating levels of MMP-9 increase during and after a single bout of exercise in humans but do not seem to originate from the skeletal muscle. The myokine interleukin-6 induces an increase in circulating MMP-9 in parity with what is seen after a single bout of exercise in humans, interleukin-6 also induces gene-expression and release of MMP-9 from the human moncyte cell-line THP-1, but not from human myoblasts, myotubes or endothelial cells indicating that monocytes could be the source of the interleukin-6 induced increase in circulating MMP-9.

The results from this thesis show that both MMP-2 and MMP-9 are expressed in skeletal muscle and upregulated by a physiological stimulus such as exercise but probably through different mechanisms. Furthermore, it indicates that remodeling of extracellular matrix and release of growth factors in the skeletal muscle occur after only a few minutes of exercise. Overall, the results support MMPs to play a role in the adaptation of the skeletal muscle to physical activity in humans.

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