ABSTRACT

Matrix metalloproteinases (MMPs) are best known to have their function in the extracellular environment through the degradation of a large number of extracellular matrix proteins and cell surface components. Unexpectedly, MMPs also have been found inside the cells: in the nucleus, cytosol and organelles, where they are involved in the cleavage of many intracellular proteins. Matrix metalloproteines-2 and -9 are considered to play a major role in exercise-induced extracellular matrix (ECM) remodeling. It is, however, unknown, what are the cellular sources of gelatinases in the muscle tissue upon exercise, and what their subcellular distribution is.

In control Soleus (Sol) and Extensor Digitorum Longus (EDL) muscles, the activity of the gelatinases was barely detectable. In contrast, after 5 days of intense exercise, in Sol significant upregulation of gelatinolytic activity in myofibers was observed mainly in the nuclei, as assessed by high resolution *in situ* zymography. The nuclei of quiescent satellite cells did not contain the activity. Within the myonuclei, the gelatinolytic activity colocalized with an activated RNA Polymerase II. There were few foci of mononuclear cells in Sol with strongly positive cytoplasm, associated with apparent necrotic myofibers. These cells were identified as activated satellite cells/myoblasts. No extracellular gelatinase activity was observed. Gel zymography combined with subcellular fractionation revealed training-related upregulation of active MMP-2 in the nuclear fraction, and increase of active MMP-9 in the cytoplasmic fraction of Sol. Using RT-PCR, selective increase in MMP-9 mRNA was observed. Although the overall changes of enzymatic activity in trained EDL muscle were statistically unsignificant, the precise analysis of activity and protein level of MMP-9 showed the upregulation in the area of synaptic cleft and postsynaptic part of neuromuscular junction.

In conclusion, the results of this thesis demonstrate that training activates nuclear MMP-2 in Sol, and increases expression and activity of MMP-9 at the neuromuscular junction of EDL. The findings suggest that the gelatinases are involved in muscle adaptation to training, and that MMP-2 may play a novel role in myonuclear functions, and MMP-9 may be involved in activity-dependent synaptic changes.