Universität Basel

Research Project

Statin-induced skeletal muscle toxicity: role of statin transport into myocytes and ofthe IGF-1R signaling pathway

Third-party funded project

Project title Statin-induced skeletal muscle toxicity: role of statin transport into myocytes and ofthe IGF-1R signaling pathway
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Statins, hydroxyl-methyl-glutaryl-coenzyme A reductase inhibitors, are among the most prescribed drugs in Western countries. They reduce morbidity and mortality in patients with cardiovascular disease and are generally well tolerated. However, myopathy is the major side effect occurring in approximately 0.1% of patients who receive statin monotherapy. The mechanisms of statin-induced myopathy are not fully elucidated.

Using Affymetrix expression arrays we found that genes regulated by Igf-1/PI3K/Akt and Ras/Raf/MEK/Erk signalling are dysregulated in simvastatin treated C2C12 myotubes. Specifically, atrogin-1 (ubiquitin E3 ligase) is upregulated. Atrogin-1 has been reported as a central factor driving muscle atrophy and recent work suggests a role of atrogin-1 also in statin induced myopathy. The effect of atrogin-1 is reversed as soon as cholesterol precursors, which are inhibited by statins (such as GGOH or mevalonate), are added. However, the precise mechanism, of how statins interfere with Igf-1R signalling hence leading to the induction of atrogin-1 and the detrimental effects in muscle cells is unclear. In our research project we aim to elucidate these interactions by investigating the following three important aspects:

First, we will investigate whether inhibition of the mevalonate pathway by statins leading to a decrease in dolichol intermediates results in a decline in N-linked glycosylation of Igf-1R, thereby impairing signal transduction of Igf-1. Second, we will study the impact of insulin on Igf-1R signalling. The protective effect of insulin in statin treated myotubes has never been investigated so far. Third, we will explore the function of geranylated small GTPases in Igf-1R signalling.

The studies will possibly explain the mechanisms responsible for statin-associated atrogin-1 overexpression and underscore the importance of atrogin-1 and Igf-1R signalling in statin-associated myopathies. They may foster new research projects in this field and provide a drug target for preventing this adverse reaction of statins.

Keywords Statins, hydroxyl-methyl-glutaryl-coenzyme A reductase, myopathy, atrogin-1, IgF-1
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