Summary

Obesity is a steadily increasing global pandemic of western societies. The development of type 2 diabetes mellitus is accompanied with obesity that is manifested by resistance of metabolic tissues to insulin, thus impairing glucose homeostasis. Moreover, obesity correlates with a low-grade chronic inflammation accompanied with macrophage infiltration into metabolic tissues and increased levels of circulating cytokines such as IL-6. Exercise has a strong potential to ameliorate obesity, allowing for skeletal muscle to clear blood glucose independent of insulin. Furthermore, skeletal muscle-derived IL-6 has been demonstrated to exert beneficial effects in the periphery by modulating glucose and fatty acid metabolism during exercise, but also contributing to the development of insulin resistance when chronically elevated.

While metabolic tissues respond to IL-6 in lean mice, this effect was diminished in obese mice due to the development of IL-6 resistance. Moreover, fasting increases IL-6 secretion by the skeletal muscle, whereas this effect is blunted in obese mice. Since skeletal muscle metabolism contributes to glucose homeostasis and is a major target of IL-6, we decided to ablate IL-6Rα specifically in skeletal muscle of mice (IL-6Rα^{MuKO} mice) to investigate the role of skeletal muscle IL-6 signalling in obesity-induced insulin resistance and glucose homeostasis. While IL-6Rα^{MuKO} mice exhibit unaltered body composition, HFD accelerates body weight gain due to lean mass increase in IL-6Rα^{MuKO} mice as a consequence of muscle insulin sensitivity. However, IL-6Rα^{MuKO} mice exposed to HFD show a slightly impaired glucose metabolism as a result of reduced IL-10 secretion, hepatic inflammation and steatosis. Moreover, the insulin-sensitive muscle of HFD-fed IL-6Rα^{MuKO} mice reveals altered mRNA expression of markers for protein degradation, energy utilisation and fatty acid metabolism, which results in reduced respiration efficiency in *quadriceps* muscle fibres and presumably alters fibre type composition due to insufficient substrate supply. Furthermore, HFD-fed IL-6Rα^{MuKO} mice show decreased skeletal muscle expression of SIRT-1, a potent activator of mitochondrial biogenesis underlying the role of skeletal muscle IL-6 action in mitochondrial homeostasis. Surprisingly, the altered fiber type composition in HFD-fed IL-6Rα^{MuKO} mice leads to a better training adaptation in treadmill experiments that is reduced in NCD-fed IL-6Rα^{MuKO} mice. Finally, the obesity-induced impairments of glucose homeostasis observed in IL-6Rα^{MuKO} mice might be a consequence of decreased fatty acid uptake and β-oxidation through the insulin-sensitive skeletal muscle thereby leading to hepatic lipid accumulation accompanied with infiltration of macrophages. Collectively, these data demonstrate that IL-6 exerts beneficial effects to maintain glucose homeostasis, although chronically elevated IL-6 under obese conditions is unable to exert these effects due to the development of IL-6 resistance.