Liver-muscle crosstalk in sarcopenic obesity?

J.G. Okun,[1] J. Schumacher,[2] A. Zota,[2] M. Blüher,[3] M. Heikenwalder[4] and A.J. Rose ,[2,5] [1]Division of Inherited Metabolic Diseases, University Children's Hospital, 69120 Heidelberg, Germany, [2]Molecular Metabolic Control, German Cancer Research Center, 69120 Heidelberg, Germany, [3]Department of Medicine, University of Leipzig, 04103 Leipzig, Germany, [4]Chronic Inflammation and Cancer, German Cancer Research Center, 69120 Heidelberg, Germany and [5]Nutrient Signalling and Metabolism Lab, Metabolism, Diabetes and Obesity Program, Monash Biomedicine Discovery Institute, Clayton, VIC 3800, Australia.

Both obesity and sarcopenia are frequently associated in ageing, and together may promote the progression of related conditions such as diabetes and frailty. However, little is known about the pathophysiological mechanisms underpinning this association. By conducting serum amino acid profiling of obese/diabetic mouse models as well as matched controls in fed and fasted states, we uncovered a unique amino acid signature which had previously been observed in obese and diabetic humans. Furthermore, we could show that certain liver amino acid catabolic enzymes were differentially expressed in in the liver of obese/diabetic mice and humans. To test the hypothesis that the upregulation of such enzymes in the liver is causally related to systemic metabolic dysfunction, we then conducted experiments whereby we silenced such enzymes in an hepatocyte-selective manner by administration of adeno-associated viruses to drive the expression, via an hepatocyte-specific promoter, of a pre-selected synthetic short-hairpin RNAs designed to specifically silence the gene transcripts of interest. The silencing of the expression and activity of these enzymes within the liver revealed a clear role in systemic amino acid clearance which related to glycaemic control under acute and chronic metabolic challenges in wildtype mice. Interestingly, in obese/diabetic mice, not only did silencing the amino acid metabolic enzymes retard hyperglycaemia, but also reversed the reduced forelimb grip strength, which coincided with improved skeletal muscle size and muscle fiber cross-sectional area. Furthermore, these changes were independent of food intake as well as total body mass and fatness. Taken together, our preliminary studies reveal the existence of a hepato-muscular crosstalk potentially linking hyperglyceamia and sarcopenia in obesity.