Role of transsulfuration pathway in skeletal muscle physiopathology

The reverse transsulfuration pathway (TSP) is a complex multi-step reaction system deputed to the generation of several sulfur metabolites, including L-cysteine, glutathione, taurine and the gasotransmitter hydrogen sulfide (H_2S). It is well established that the tight control of TSP is critical for the healthy cellular redox state. Indeed, disruption of TSP has been linked to aberrant redox homeostasis, which affects both central nervous system and peripheral organs and tissues. However, the involvement of TSP and its by-end products in skeletal muscle (SKM) physiopathology remains largely unknown. Recently, our research group has demonstrated the involvement of TSP in SKM function. Indeed, we have shown that H_2S biosynthesis is increased in Malignant Hyperthermia, a human syndrome characterized by an anomalous SKM hypercontractility following exposure to volatile anesthetics. Conversely, in Duchenne's muscular dystrophy, a genetic myopathy characterized by muscle atrophy, TSP results largely downregulated. This evidences strongly suggest a pivotal role for TSP, and in particular of H_2S, in SKM contractility. Our hypothesis is confirmed by the finding that mice lacking cystathionine γ-Lyase (CSE), one of the TSP main enzymes, fed with a diet poor in L-cysteine develop lethal myopathy and oxidative injury. Therefore, this proposal project aims to study the role of the TSP in SKM function in health and disease. To do so, the expression of genes and enzymes regulating the TSP in both cellular and animal models of different myopathies will be performed by using transcriptomic, proteomic and post-translational modification analysis. When available, human samples of SKM of patients affected by different myopathies/atrophies will be also analyzed. By targeting gene silencing strategy and/or selective pharmacological tools the altered genes and/or proteins regulating TSP, the project also aims to identify novel therapeutic targets to treat myopathies for which there is not yet an effective treatment.