Epigenetic mechanisms underlying predisposition to metabolic syndrome-associated diseases

Project abstract:

Metabolic diseases such as Type-II Diabetes are among the leading causes of disability in developed countries and constantly increase their contribution to the global burden of disease. They have multiple origins from genetic, epigenetic to environmental factors. Human studies identified loci containing T2D susceptibility genetic variants. However, it has so far not been translated into mechanistic insights that might in turn lead to clinical benefits. Indeed, many variants do not alter protein coding sequences and are therefore difficult to explore functionally in biologically meaningful context. It was hypothesized that many of these variants actually act on epigenomic regulatory elements. The understanding of their functional implications is currently one of the major challenges in metabolic diseases genetics and pathophysiology.

We propose to address this gap in knowledge through an integrated approach using two models: i) an animal model known to display epigenetic modifications in response to perinatal undernutrition and linked to metabolic diseases ii) genetic analyses in human. Our goal is to identify sequences that are subject to long-lasting epigenetic modifications, associated with maternal nutritional stress and that contains T2D susceptibility variants. By merging large-scale scans data from our laboratories we will define specific candidate sequences that will be studied to identify molecular mechanisms for both environmentallyand genetically-induced factors. The results obtained will be then put into perspective for building models and networks of the gene regulation in the context of intracellular signal transduction. Comparison of the identified sequences in both experimental approaches will allow to identify epigenetic marks associated with T2D risks. Thus, this innovative project will pave the way to new preventive and therapeutic approaches at the individual level and for ameliorating the quality of life at the general population level.

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