DOTTORATO IN MEDICINA MOLECOLARE E DELLO SVILUPPO

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CICLO DI DOTTORATO XXXII

Al collegio dei docenti del dipartimento di Medicina Molecolare e dello Sviluppo

The ankyrin protein family comprises three members: Ankyrin 1, Ankyrin 2, Ankyrin 3. They are ubiquitously expressed, although they are most abundant in erythrocytes, brain and in node of Ranvier and in epithelial cells, respectively. These proteins link integral membrane proteins with the cortical cytoskeleton.
In striated muscles, a group of small muscle specific isoforms of Ankyrin 1 have been identified. Their expression is driven by an alternative promoter located between the exon 39 and exon 40 of the Ank1 gene. These small isoforms (ank1.5, ank1.6, ank1.7 ank1.8 and ank1.9) are localized on the sarcoplasmic reticulum membrane. Among the small isoforms, Ank1.5 is the most abundant and it interacts with the COOH terminus of Obscurin, generating a molecular bridge between the sarcoplasmic reticulum and the myofibrils of the sarcomere.
Recent studies identified an association between an increase of the transcriptional activity of Ank1.5 promoter and the type two diabetes mellitus.
In order to understand whether the increase of Ank1.5 expression would lead to type two diabetes, transgenic animal models have been generated: in these mice the expression of small Ankyrin 1.5 is under the regulation of the myosin light chain promoter.
During the second year of PhD, I bred heterozygous transgenic mice in order to obtain animals with higher levels of sAnk1.5 protein. Wild type, heterozygous and homozygous animals were born with a correct mendelian relationship.
To characterize these animals, I performed Western Blot and quantitative PCR experiments on gastrocnemius muscles to compare sAnk1.5 protein and mRNA levels. The results of qPCR show that the levels of sAnk1.5 mRNA is above 15 and 37-fold higher, in the heterozygous and homozygous mice respectively, than those obtained in wild type. Surprisingly, the analysis of sAnk1.5 protein levels show that there is only an increment of above 60% than to wild type, both in heterozygous and homozygous transgenic mice.
At same time, I have induced the obesity model in mice by high fat diet. Five wild type and five homozygous transgenic mice were fed with high fat diet for 12 weeks; five wild type and three homozygous transgenic animals were fed with standard diet as control, for the same period. After this month of diet, I have performed a glucose tolerance test, to explore the role of sAnk1.5 in regulation of muscle glucose metabolism. The results show a slight but not significative increase in level of blood glucose in homozygous transgenic mice compared to wild type.
A second experiment on five animals per group is still ongoing.

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