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OSTEOPETROSIS AND BARTTER SYNDROME: STRUCTURAL-FUNCTIONAL INVESTIGATION OF MUTATIONS CAUSING DISEASES

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The gene family of chloride transporting proteins, CLC, includes plasma membrane chloride channels and endosomal/lysosomal Cl-/H+ exchangers. CLC proteins are involved in many physiological processes including renal Cl- transport, skeletal muscle excitability, cell volume regulation and acidification of intracellular compartments. Independently of the ion transport mechanism (at least) four of the human CLCs (CLC-Ka and Kb, CLC-7, CLC-2) form heteromultimeric complexes with auxiliary β-subunits (Barttin, OSTM1, GliaCAM). Association of CLCs with their specific auxiliary β-subunits ensures proper targeting and stability at the complex.
Defects in genes encoding CLC proteins or their auxiliary subunits are associated with hereditary diseases. Loss of function mutations in the renal CLC-Ks and their subunit Barttin are associated with type III and IV Bartter syndrome, while mutations in the lysosomal CLC-7/Ostm1 complex lead to osteopetrosis and lysosomal storage diseases.
We used a combination of electrophysiological, confocal and optical assay to study the functional properties of mutations causing osteopetrosis and Bartter syndrome type IV.

We investigated 14 missense mutations in CLC-7 protein causing different type of osteopetrosis: autosomal recessive, autosomal recessive with primary neurodegeneration, and autosomal dominant. We found that autosomal recessive mutations are not functional, and localize inside in the protein, while the autosomal dominant mutations maintain Cl-/H+ exchange, but with alternated kinetics of activation and/or de-activation and are at the interface between the transmembrane region and the cytosolic part.

We also investigated the functional properties of two new identified mutations in Barttin protein causing Bartter syndrome type IV. Preliminarily results suggest two different behaviors: one mutant show a trafficking defect, while the other shows partially reduced functionality.

Data emerging from these two projects will help to understand the pathophysiology of two different genetic diseases: Osteopetrosis and Batter syndrome type III. Moreover the fuctional-structural information could be useful for future drug discovery and development of therapeutic treatments.

Analisi struttura-funzione di singole mutazioni che causano Osteopetrosi e sindrome di Bartter

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Osteopetrosi e Sindrome di Bartter

Coordinator: Alessandra Picollo
Duration (N. Years): 5
Starting year: 2015

Telethon Project (nr):

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Disease Name:

Osteopetrosis and Bartter's Syndrome

Keywords:

CLC chloride channels, Bartter syndrome, Osteopetrosis