



Anna Margherita Corradi

Professoressa associata

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Istruzione e formazione

1989

Master Degree in Biology

110/110

University of Genova - Genova - IT

2000

Phylosophy Doctor in Molecular and Cellular Biology

Generation and characterization of Ebf2^{-/-} mouse

Dibit San Raffaele Scientific Institute Open University London - Milano - IT

Esperienza accademica

2005 - IN CORSO

Assistant Professor

University of Genova - Genova - IT

Research activity on Synaptic genes and teaching Human Physiology

2002 - 2005

Senior postdoctoral fellow

University of Genova - Genova - IT

Research activity on peripheral neuropathies

1994 - 2001

PhD student and postdoc

Dibit San Raffaele Scientific Institute - Milano - IT

Reserach activity on brain development and transcription factors

1998

Fellow

Max Planck Institute - Munich - DE

Generation of Ebf2 KO mouse

1991 - 1993

Fellow

Istituto Nazionale per la Ricerca sul Cancro - genova - IT

Research activity on protein secretion

Competenze linguistiche

English

Buono

Attività didattica e di ricerca nell'alta formazione

Supervisione di dottorandi, specializzandi, assegnisti

I have been supervisor of several master degree and PhD students (Caterina Giacomini, Veronica Lapadula, Diego Moruzzo), postdoctoral fellows (Pia Rossi, Bruno Sterlini, Simona Gasparini).

Partecipazione al collegio dei docenti nell'ambito di dottorati di ricerca accreditati dal Ministero

Since 2005 Lecturer and member of the board for the PhD course in Neuroscience, School of Medicine, University of Genoa

Interessi di ricerca

My research activity is focused in understanding the mechanisms of neurotransmitter release by studying the genes involved in synaptic physiology and their mutations leading to pathologies such as epilepsy and movement disorders. In the last years, I concentrated on PRRT2 (Proline Rich Transmembrane protein 2) a causative gene for epilepsy and paroxysmal disorders. To get insight into its function, I developed, in collaboration with Gaslini Institute, the generation of Induced Pluripotent Stem Cells by genetic reprogramming of the fibroblasts of patients carrying mutation in PRRT2, followed by their differentiation to human excitatory neurons (Fruscione 2018, Valente 2018, Michetti 2017, Rossi 2016, Valente 2016).

Previously I was involved in the study of the role of Synapsin genes in epilepsy and autism (Fassio 2011, Corradi 2014, Giovedì 2014, Tagliatti 2014) and in the continuing my former research on the characterization of the peripheral neuropathy of Ebf2 KO mice and on the identification of Ebf2 target genes involved in myelination defects (Moruzzo 2016, Giacomini 2011).

Progetti di ricerca

2016 - IN CORSO

PRRT2 A NOVEL SYNAPTIC GENE CAUSING EPILEPSY AND DYSKINESIA FUNCTIONAL STUDIES IN MUTANT MICE AND IPSC DERIVED NEURONS

Compagnia di San Paolo - IT

Partecipante

Objectives and specific aims. Epilepsy, paroxysmal dyskinesia and

hemiplegic migraine have a strong genetic component and a number of associated genes are likely to be uncovered. A large number of recent reports identified the Proline-Rich Transmembrane protein 2 (PRRT2) as the single causative gene for this group of paroxysmal syndromes of infancy that combine infantile epilepsy, paroxysmal movement disorders and migraine. The variable phenotypic spectrum of PRRT2 mutations ranges from mild forms that improve with age to severe phenotypes. The latter ones need new and specific therapeutic approaches. At present, the function of PRRT2 is completely unknown. The goal of the project is to assess the impact of PRRT2 in neuronal physiology and in the pathogenesis of these pleiotropic diseases. The specific aims are to:

- (i) investigate the functional role of PRRT2 at the synapse in knocked down primary neurons and knock out mice.
- (ii) characterize the phenotype of human neurons reprogrammed from fibroblasts of a subset of patients with distinct PRRT2 mutations;
- (iii) elucidate specific synaptic interactors of PRRT2 to identify new potential therapeutic targets for the diseases.

2014 - 2017

Role of the novel presynaptic protein PRRT2 in neuronal physiology and in the pathogenesis of paroxysmal neurological disorders.

Ministero della Salute Bando Ricerca Finalizzata - IT
Partecipante

2014 - 2016

Role of the novel presynaptic protein PRRT2 in neuronal physiology

Telethon - IT
Partecipante

2009 - 2012

Role of Synapsins in control of synaptic transmission and plasticity implications in the pathogenesis of epilepsy and autism

Ministry of University and Research (MIUR) PRIN 2009 - IT
75.000 - Responsabile scientifico

Mutations in over 70 genes now define biological pathways leading to Epilepsy, including a number of genes involved in neural development, synaptogenesis and synaptic transmission.

Autism-spectrum disorders (ASD) are a heterogeneous group of disorders characterized by behavioural abnormalities. Mutations in genes encoding for synaptic proteins have been found in autistic patients, leading to the hypothesis that ASD is due to abnormal synaptic function and/or neural connectivity. Epilepsy and autism frequently associate, as shown by the presence of epileptic seizures in one third of ASD cases and the observation of autistic features in several forms of severe epilepsy associated with mental retardation. These findings suggest that these diseases may share common genes and mechanisms. Synapsins (Syns) are a family of neuron specific phosphoproteins, that, by a dynamical association with synaptic vesicles (SV) and actin cytoskeleton, regulate SV trafficking and neurotransmitter release. They have been also implicated in neuronal development and in the synapse formation. The Syns are highly conserved evolutionarily, and orthologues have been found in invertebrates and lower vertebrates. In mammals, they are encoded by three distinct genes (SynI, SynII and SynIII), which by alternative splicing generates distinct isoforms. Single and multiple knock-out (KO) mice for either Syns isoforms, with the exception of single SynIII KO, exhibit early onset spontaneous epileptic seizures. Although the generation of Syn KO mice and the analysis of their phenotype strongly suggested a correlation between Syn dysfunction and epilepsy, the first direct link between SYN genes and human epilepsy appeared in 2004 through the identification of a nonsense mutation in SynI gene in a family with X linked epilepsy. The aim of this project is to understand the molecular mechanisms by which SynII and SynIII mutations lead to epileptic and/or autistic phenotype. To underscore the molecular pathways leading to these pathologies we will analyze different properties of the mutated isoforms. Firstly, we will analyze their effect on neuronal development and on establishment of synaptic connections, due to the crucial importance of these events in the pathogenesis of both epilepsy and autism. Secondly, we will analyze the biochemical properties of the mutated proteins, that may lead to synaptic dysfunctions. Due to the poor available information about these two isoforms we need first to characterize SynII

2008 - 2011

Ebf2 role in peripheral nervous system development and myelination

Compagnia di San Paolo - IT
80.000 - Responsabile scientifico

Nervous system development and myelination are complex events regulated by action of several molecules acting at different times. Ebf2 is a transcription factor with potential role in this field as suggested by preliminar analysis of Ebf2^{-/-} mice, that present a peripheral motor neuropathy.

Objective and rationale:

The objective of this project is three-fold:

- Characterization of Ebf2^{-/-} mice peripheral nerve phenotype.
- Study on the molecular basis of mouse phenotype and the different contribution of Motorneurons (MN) and Schwann cells (SC) to generation of mouse pathology.
- Mutations screening in human EBF2 gene in a selected cohort of patients affected by distal hereditary peripheral neuropathy (dHMN), characterized by an involvement of the motor part of the peripheral nervous system (PNS).

Experimental plan:

First, we will perform morphological characterization of myelin, axon, MNs, dorsal and

ventral roots during development to define the mouse phenotype.

Second, we will study SCs and MNs with different approaches. We will establish

Dorsal Root Ganglia (DRG) organotypic cultures to follow myelination in vitro and MN

cultures to study development in vitro.

Third, we will screen the EBF gene for mutations in 60 dHMN patients

Expected results and their relevance:

Ebf2 is a new molecule with putative role in PNS development and myelination. The

clarification of its function in development and differentiation of SCs and MNs may

help in understanding the molecular mechanisms of these events.

Moreover, we expect to verify a possible involvement of EBF2 gene in human

hereditary peripheral neuropathies.