Anna Margherita Corradi

Associate professor

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Education and training

2000
Phylosophy Doctor in Molecular and cellular biology
Ebf2 a new regulator of neuronal differentiation from gene identification to analysisof the Ebf2 -/- mouse
Dibit San Raffaele Scientific Institute Open University London - Milano - IT

1989
Master degree in Biology
110/110
Università di Genova - Genova - IT

Academic experience

2005 - ONGOING
Ricercatore Universitario
Dimes Fisiologia Università di Genova - genova - IT
Research activity on the molecular mechanisms of neurotransmitter release

2002 - 2005
Senior Post Doctoral fellow
Dimes Fisiologia Università di Genova - Genova - IT
Research activity on the mechanisms of neurotransmitter release and myelination

1994 - 2001
PhD student and postdoctoral fellow
Dibit San Raffaele Scientific Institute - Milano - IT
Research activity on genes regulating brain development

1998
Fellow
Max Planck Institute - Munich - DE
Generation of Ebf2-/- mouse knock out

1991 - 1993
Fellow
Istituto Nazionale per la Ricerca sul Cancro - Genova - IT

Research activity on protein secretion

Language skills

English
Independent

Research interests

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 fuction, 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 invoved in myelination defects (Moruzzo 2016, Giacomini 2011).

Grants

2016 - ONGOING

Prrt2 a novel synaptic gene causing epilepsy dyskinesia and migraine functional studies in KO mice and reprogrammed neurons

Compagnia di San Paolo - IT
Participant
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
Participant

2014 - 2016

Role of the novel presynaptic protein PRRT2 in neuronal physiology

Telethon - IT
Participant

2009 - 2012

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

Ministery of University and Research (MIUR) PRIN 2009 - IT
75.000 - Pricipal investigator
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. Affected individual of this family (males,
because SynI gene is on chromosome X) showed epilepsy alone or in combination with learning difficulties, behavioural disturbances and/or ASD. Since that time, a
genetic screening effort (in collaboration with CHUM, Université de Montreal) gave rise to the identification of 11 additional mutations involving the three Syn genes
associated with epilepsy, ASD or both, strengthening the link between these pathologies and Syn proteins. These finding may suggest that synaptic defects may exist in
both epilepsy and autism.
Most of the information about Syn functions and its regulation by phosphorylation and by interactions with other SH3 synaptic partner

2008 - 2011

Ebf2 role in peripheral nervous system development and myelination

Compagnia di San Paolo - IT
80.000 - Participant
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.