H.F.R.I.
Hellenic Foundation for Research & Innovation

Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project:

MOLECULAR AND FUNCTIONAL ANALYSIS OF in vivo MODELS OF DECREASED INHIBITION IN THE MOUSE CEREBRAL CORTEX

Principal Investigator:

Domna Karagogeos

Reader-friendly title:

INTER_RAC

Scientific Area:

LIFE SIENCES

Institution and Country:

IMBB-FORTH, GREECE

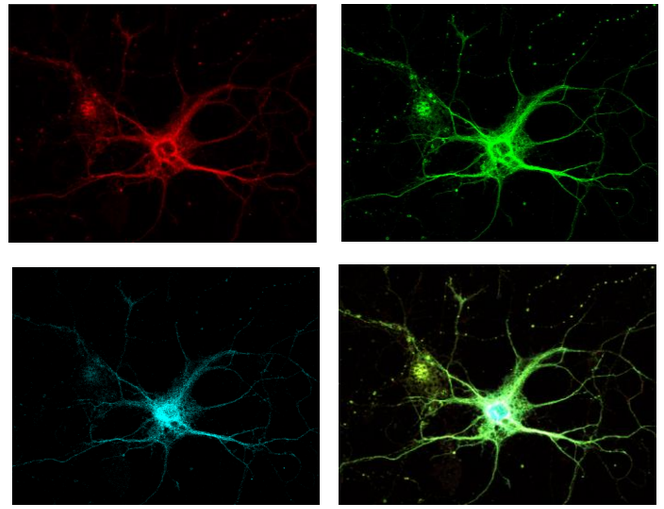
Host Institution:

FORTH

Collaborating Institution(s):

BSRC Alexander Fleming

Project webpage (if applicable):



Interneurons in culture: pan-neuronal marker (red), a marker for interneurons (green) and the inhibitory neurotransmitter GABA (cyan)

Budget: 179.859,60 Euros

Duration: 24 months

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Research Project Synopsis

GABAergic interneurons, although comprising ~20% of all cortical neurons, play important roles in cortical function and their loss or dysfunction has been implicated in severe disorders such as schizophrenia and epilepsy. Despite the progress in unraveling aspects of cortical interneuron (CIN) development, their exact contribution to cerebral function remains elusive. Some of the molecular components underlying the generation of extraordinary diversity in CINs have been uncovered recently. Also, the mechanisms guiding interneurons to the cortex have just started to be elucidated. In contrast to the multiplicity of extracellular signals, the intracellular proteins mediating the response to these cues are mostly unknown. We have demonstrated the unique and diverse roles of the RhoGTPases Rac1 and 3 in interneuron progenitors (cell cycle) and morphology (cytoskeletal defects) in transgenic animals where Rac1 and Rac1/3 were ablated specifically in CINs. In the Rac1 mutant, progenitors delay their cell cycle exit resulting in a 50% decrease in CINs and an imbalance of excitation/inhibition in cortical circuits. In the double mutant, there are additional severe cytoskeletal defects resulting in an 80% decrease in CINs. Both mice die from epileptic seizures postnatally. In this proposal we will attempt to characterize the molecular nature of the defects via novel, state-of-the-art approaches. First, we will define how Rac1 affects the cell cycle of CIN progenitors during embryogenesis. Second, we will determine whether Rac1 single and Rac1/3 double mutant CINs are integrated properly in cortical circuits by analyzing their electrophysiological profile and morphological/synaptic characteristics. Third we will focus on the identification of the molecular mechanisms by which these Racs exert their actions in CIN development by proteomic and signaling analysis of mutant and control cells. We hope our data will contribute to the understanding of CIN function, especially since several preclinical models of CIN-based cell therapies are being established.

Project originality

GABAergic interneurons are inhibitory neurons and protect neural tissue from excessive excitation. Cortical GABAergic neurons play a pivotal role for the generation of synchronized cortical network oscillations. Imbalance between excitatory and inhibitory mechanisms underlies many neuropsychiatric disorders including autism spectrum disorders, schizophrenia, bipolar disorder and depression and is correlated with abnormalities in oscillatory activity. One of our two mouse models, the one displaying ~50% fewer cortical interneurons, has been used to examine how this developmental decrease in the number of cortical interneurons results in neural circuit alterations. We showed that disruption in GABAergic inhibition alters synaptic properties and plasticity, while additionally disrupting the cortical neuronal synchronization in the adult barrel cortex (Kalemaki et al., 2018), thus contributing to the understanding of synaptic physiology of local cortical circuits. We plan to uncover the molecular mechanism via which these alterations may occur by utilizing this Rac1 single mutant line as well as the Rac1/3 double mutant line we have generated. Therefore, we anticipate that data stemming from this project may enhance the understanding of interneuron dysfunction often observed in animal models and clinical studies. In addition to the innovative methodology we will use (viral injections, *in utero* and *ex vivo* electroporation, electrophysiological experiments) an important novel aspect of the work will be the unraveling of protein networks mediating the effects of Racs as these are intercellular mediators found to be important in CIN development. In conclusion, these data, will not only contribute with novel information about the development of cortical assemblies but, in combination, will provide insight for unique neuron-type defects to specific neurodevelopmental diseases.

Expected results & Research Project Impact

“Brain disorders” encompass a wide variety of diseases, among which epilepsy, schizophrenia, autism spectrum disorders, Alzheimer’s, Parkinson’s disease and others, are of prime interest for two reasons: Firstly, there is a dramatic increase in the number of affected individuals during recent years. Secondly, there is a limited understanding of the underlying pathophysiology and as a result, a lack of definitive treatment. For these reasons, neurological and neuropsychiatric disorders are considered an immense threat to public health and tackling them is crucial for the society and the economy.

In the last decade, the significance of a specific neuronal population in normal brain function, namely the GABA-expressing inhibitory neurons, has been appreciated. Accumulating evidence links several diseases, such as the ones mentioned above, with deficits in the inhibitory system, and as a result we often refer to these diseases as “Interneuropathies” All these disorders are characterized, even during preclinical stages, by alterations in network activities, and GABAergic interneurons are considered to be the master regulators of the balance in brain network activities. Therefore, it is of high importance to produce a mechanistic understanding of the contribution of interneurons to each unique pathophysiology. Our primary aim should therefore be to expand our current understanding into how specific interneuron deficits contribute to the pathophysiology of each of these conditions. Our genetic mouse models involve strong phenotypes of interneuron deficiencies thus, we are able to contribute to the interneuron field by studying cortical development in a state of interneuron deficiency. Our data show that a decrease of GABAergic inhibition alters synaptic properties and plasticity, while it additionally disrupts the cortical neuronal synchronization in the adult cortex. Our aim is to clarify the pathophysiological mechanisms involved in developmental diseases of neuronal dysfunction, a field in which the emergence of new therapeutic goals is necessary and urgent.

The importance of this funding

My team has been honored to receive a substantial grant from the H.F.R.I. for our proposal on interneurons. This award is important not only as a recognition of merit of our research but also as it came after a long financial crisis that left basic research practically unfunded in Greece. It is important to note that H.F.R.I. pledges for the first time to provide funding in a continuous manner with regular calls for proposals that will continue to be open, curiosity-driven and not thematic.

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