SIGNALLING IN THE CENTRAL NERVOUS SYSTEM
JOSE RAMON BAYASCAS

PROFILE

Jose Ramon Bayascas was born and educated in Barcelona, were he graduated in Biological Sciences from the University of Barcelona in 1992 and received a Ph.D. in Biological Sciences in 1998 under the supervision of Professor Emili Saló, University of Barcelona. He then carried out postdoctoral research for nine years, first with Professor Joan Comella at the University of Lleida from 1998 to 2002, and then with Professor Dario Alessi at the University of Dundee, Scotland, from 2002 to 2007, were he became proficient in the analysis of cell signaling in metabolism, cancer and neurobiology. In 2007 he joined the Departament de Bioquímica i Biologia Molecular of the Universitat Autònoma de Barcelona, were he has leadershipping a new Institut de Neurociencies research team ever since, first as a Ramon y Cajal Fellow and from October 2014 as a Serra Húnter Associate Professor. His current research aims to define the neurodevelopmental functions of the PDK1 signaling network and its consequences to neurodegenerative and mental illness.

Neurons born from progenitor cells progress to their mature phenotype by means of intricate genetic programs which controls cell survival, growth, differentiation, migration and synapses formation. During this process, neurons encounter a great diversity of growth factors and hormones that activate different signal transduction pathways that ultimately control the physiology of the cell.

Among them, the PI3K-PKB pathway emerged during the last decade as a central mediator of neurotrophic factor-induced neuronal survival, and PKB is considered nowadays as a drug target to treat neurodegenerative disorders. However, most of the studies are based in the use of specific inhibitors of the phosphoinositide 3-kinase (PI3K) combined with overexpression experiments of dominant negative and constitutively active forms of the protein kinase B (PKB). Since specific PKB inhibitors are not available at present, genetic evidences demonstrating a role of PKB in regulating neuronal survival are needed.

The 3-phosphoinositide-dependent protein kinase 1 (PDK1) was originally discovered as the missing link in the PI3K/PKB signalling pathway. PDK1 acts as an upstream protein kinase phosphorylating and activating not only PKB isoforms, but also many other AGC kinases involved in the control of cell growth, proliferation, survival and metabolism regulation. Although it is been though that many if not all of the cellular effects of growth factors are mediated through activation of PKB/akt, the former and most popular substrate, PDK1 activates as well the p70S6K, SGK, p90rsk and PKC isoforms, among others. PKB activation by PDK1 relies on a phosphoinositide binding domain termed PH-domain. Both PDK1 and PKB contain PH-domains which mediate their co-localisation to the plasma membrane. On the contrary, the rest of PDK1 substrates lack PH-domains but contain a docking-site which is recognised by a small groove located in the catalytic domain of PDK1 named PIF-pocket. Two specific PDK1 point mutations which impair the function of either the PH-domain or the PIF-pocket motif were designed and used to generate two tissue specific conditional knock-in mice. These last generation rodent models have been proved instrumental in dissecting out the role of the two major branches of the PDK1 regulated signalling pathways in the control of glucose homeostasis, and I aim to use them to analyse the contribution of the PKB versus the non PKB signalling branches in promoting PI3K driven neuronal survival and differentiation.

RESEARCH

RESEARCH INTERESTS

Understand the importance that the dysfunction of the mechanisms of signal transduction might play in brain pathology. They focussed on the PI 3-kinase/Akt signaling pathway, which controls essential roles during neuronal development and is deregulated in different mental disorders. They generated brain-specific conditional knock-in mice expressing two distinct rationally designed, crystal structure-based, point mutant forms of the PDK1 kinase, a master hub on this signaling pathway. In the PDK1 K465E mice, activation of Akt is selectively impaired, whereas in the PDK1 L155E mice, activation of most of the effectors of this signaling axis including S6K, RSK, SGK, and PKC, but not Akt, is abolished**.**

STRATEGIC OBJECTIVES

The research activity of our group aims to define the neurodevelopmental functions of the PDK1 signalling network and its consequences to neurodegenerative and mental disease.

MAIN RESEARCH LINES

1) To investigate whether the PDK1 K465E mice is protected from Alzheimer Disease. In the PDK1 K465E knock-in mice, reduced activation of Akt caused subtle morphogenetic defects that did not lead however to adverse behavioral outputs. We learned that the hypomorphic reduction of the Akt axis protected these mice from a number of insults disrupting homeostasis, which might singularly be also protected from neurodegeneration.

2) To define the contribution of the PDK1 substrates different from Akt to mental disease. In the PDK1 L155E mice, the normal and exclusive activation of Akt among the different PDK1 substrates caused profound defects in the patterning of the central nervous system, leading to severe mental disorders reminiscent of human schizophrenia.

LAB FEATURED PUBLICATIONS

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