Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
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Project Nº 12 (ASIGNADO)
Title: The zebrafish homologs of PP2A regulatory subunits: expression patterns and insights into their physiological roles during development
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Summary Protein phosphatase 2A (PP2A) accounts for the majority of serine-threonine phosphatase activity in mammalian cells and has been implicated in the regulation of a wide diversity of signaling pathways. PP2A complexes contain an active core dimer composed of a catalytic C subunit and a scaffolding A subunit. The AC dimer recruits a third regulatory B subunit that dictates the substrate specificity and localization of the PP2A heterotrimeric complex. At least 100 different PP2A heterotrimeric complexes are formed through combinatorial association of these subunits. Previous results from our group showed that inactivation of PP2A is a recurrent event in acute myeloid leukemia, and that the pharmacological activators of PP2A have additive effect with other drugs used in AML. The diversity of PP2A complexes suggests that dysfunction of several distinct PP2A complexes may affect specific pathways and, in turn, contribute independently to transformation. Therefore, the actual challenge is to identify the particular PP2A complexes affected in each disease, in order to develop more efficient therapeutic strategies. Several structural studies have provided insights into the mechanisms by which the regulatory B-type subunits act to regulate PP2A substrate specificity and activity; however, most of these functional data originate from cellular models, and the true biological functions of the B-type subunits remain underexplored owing to a lack of appropriate in vivo knockout models. Our aim is to explore the role of the PP2A regulatory subunits in zebrafish in vivo models by using antisense morpholino oligonucleotides and genome-editing technologies (CRISPR/Cas9) for the generation of mutant genetic disease models.