Título del Proyecto	**Linking the actin-binding protein cofilin and calcium deregulation: a precision approach for the treatment of Friedreich's ataxia.**
Nº de expediente asignado	PID2020-115190RB-100
Abstract	Friedreich's ataxia (FRDA) is a rare disease characterized by the degeneration of the large sensory neurons at the dorsal root ganglia (DRG), in charge of proprioception and sense of positioning. The cause of this disease is the lack of frataxin, a mitochondrial protein that has been frequently associated with an increase in reactive oxygen species (ROS) and has an important role in proper calcium (Ca^{2+}) handling. The imbalance of this ion has a direct effect in neurons, such as in the formation of multiple axonal spheroids. Concretely, frataxin-silenced cells showed an impairment in Ca^{2+} buffering, as a consequence of reduced mitochondrial Ca^{2+} uptake capacity due to an impairment of the interactions between endoplasmic reticulum (ER) and mitochondria (MAMs). In previous projects we have describe the presence of frataxin also in MAMs, in addition to a clear and robust direct relation of this protein with GRP75 and IP3R, proteins with an important role in ER-mitochondrial interactions. These results suggest a pivotal role of frataxin in the regulation and maintenance of this protein network. Improvement of mitochondrial Ca^{2+} uptake in frataxin-deficient cells after antioxidant treatment (Trolox and NAC) matches with the ER-mitochondrial contacts interactions recovery. Because of that, any compound with a specific mechanism of action in the MAMs' domain could be interesting as a therapeutical approach for FRDA. This is the case of Fluvoxamine (Flv), a selective serotonin reuptake inhibitor with high affinity for Sigma-1R. Flv treatment rescue the impaired mitochondrial Ca^{2+} buffering in our cellular model of FRDA. Abnormalities in actin cytoskeleton have been linked to FRDA, and Ca^{2+} imbalance can trigger the cytoskeletal disorganization. We have demonstrated that cofilin dysregulation, an actin-binding protein, affects the dynamics of growth cones and neurite growth. Thus, cofilin emerges, for the first time, as a link between frataxin deficiency and actin cytoskeleton alterations. In healthy cells, actin polymerization is important to maintain the ER-mitochondria contact sites and trafficking, leading to a vicious circle when alteration appears. Recent findings describe a novel role of actin dynamics in the regulation of mitochondrial morphology and function. Here cofilin acquires an important role because of its capacity of altering actin turnover, especially under cellular stress situations. So, we will study whether cofilin is able to affect ER-mitochondrial contacts and thereby controlling ER-mitochondrial Ca^{2+} transfer, acquiring a direct role in the mitochondrial dysfunction described in the FRDA cells. Moreover, cofilin dysregulation also triggers cofilin-actin rods formation, which contribute to the degenerative processes. Our hypothesis is that the critical event in the progression of FRDA pathology is the reduction of the interactions between mitochondria and ER. The restoration of these interactions offers a new research field regarding MAMs as therapeutic targets. We propose cofilin, cofilin modulators and Ca^{2+} flux stimulators as good targets, whose modulation could improve cellular pathophysiology. To confirm this, we propose to perform three pre-clinical trial in a mouse model of FRDA, in addition to different assays using cellular models of the disease.
Entidad Financiadora	Ministerio de Ciencia e Innovación (MCIN) / Agencia Estatal de Investigación (AEI)

Convocatoria:	Convocatoria de Proyectos de I+D+i», en el marco del Programa Estatal de Generación de Conocimiento y Fortalecimiento Científico y Tecnológico del Sistema de I+D+i y del Programa Estatal de I+D+i Orientada a los Retos de la Sociedad, del Plan Estatal de Investigación Científica y Técnica y de Innovación 2017-2020.
Importe de la ayuda	193.600,00 €
Fechas de ejecución del proyecto	01/09/2021-31/08/2024
	Proyecto **PID2020-115190RB-100** financiado por:
	
Enlaces:	Grupo CIBER: https://www.ciberisciii.es/areas-tematicas/grupo-de-investigacion?id=17121