Cofinanciado por:

Projecto nº: 031773

Referência do Projecto: PTDC/BIA-BFS/31173/2017 (POCI-01-0145-FEDER-031173)

Título: Molecular tools for Machado-Joseph disease: chaperoning toxic protein conformers in polyglutamine-containing proteins.

Montante envolvidos:

Investimento total: 239.560,42€

IBMC-Instituto de Biologia Molecular e Celular - 200.960,42€

Apoio FEDER: 170.816,36 €

Apoio OE: 30.144,06

Localização do projecto: Porto, Portugal

CNC - Centro De Neurociências e Biologia Celular - 38.600,00€

Apoio FEDER: 32.810,00€

Apoio OE: 5.790,00€

Localização do projecto: Coimbra, Portugal

Sintese do projecto:

Machado-Joseph disease (MJD) is a rare neurodegenerative disorder highly prevalent in patients of Portuguese descent, caused by abnormal expansion of a continuous glutamine tract (polyQ) in the multidomain protein Ataxin-3 (Atx3). Expansion of the polyQ segment triggers a pathogenic cascade culminating on the appearance of cellular inclusions enriched in the mutant proteins. Despite their controversial roles in disease pathogenesis, these insoluble aggregates with amyloid-like properties represent a typical late-stage fingerprint of all polyQ-related diseases. Multiple mechanisms, likely acting in concert, have been proposed to contribute to initial pathogenesis elicited by polyQ expansion. Alterations in functional inter-molecular protein interactions, and self-assembly into toxic (soluble) oligomers, are emerging as central culprits of downstream neurotoxicity.

Although the fine molecular details underlying neuronal dysfunction are still unclear, multiple regions contribute to Atx3 self-assembly in vitro. While the aggregation-prone sequences in the catalytic Josephin domain (JD) initiate Atx3 oligomerization in both normal and pathogenic Atx3, a later step leading to the formation of mature fibrils is strictly dependent on polyQ expansion. Increased PolyQ length enhances the frequency of long-range conformational fluctuations that expose aggregation hot spots in the distal JD, thereby accelerating Atx3 aggregation. With its modular multidomain architecture, Atx3 is known to engage in complex intermolecular interaction networks, and to be associated with multiple pathways linked to cell quality control, transcriptional regulation, and genome integrity. Hence, to prevent deleterious effects, discrimination between normal and pathogenic forms is critical for therapeutic design.

By gathering a team with combined expertise in protein aggregation and structural biology (SMR and PJBP, IBMC/i3S), chemical kinetics modeling (PM, IBMC/i3S) and synapse biology (ALC, CNC/IBILI), supported by a network of external collaborators with expertise in proteinopathies (GB, UCLA, USA), advanced mass spectrometry (JL, UCLA, USA), supramolecular chemistry (TS, Duisburg-Essen, DE) and biophysics (MB, FCUP, PT), we designed a multidimensional approach to tackle a multifaceted disease with complex neuropathogenic mechanisms. We aim to target early modifications associated with MJD, by exploring the ability of synthetic and highly versatile molecules (molecular tweezers, peptides and nanobodies) to recognize structural features/conformers

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preferentially found in pathogenic Atx3. These modular molecules and the profiling of their binding mechanism(s) will allow us to build a molecular toolbox, which we expect to iteratively optimize to explore their potential as lead molecules in therapy (toxic oligomerization inhibitors) or diagnostic (conformation-sensitive biosensors) applications for these highly incapacitating and ultimately fatal diseases.