Title: Factors regulating VCP/p97 nucleocytoplasmic shuttling.

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Project description:

Maintenance of cellular protein homeostasis (proteostasis) requires temporally and spatially controlled protein quality control and degradation of regulatory proteins, as well as the continuous removal of erroneous proteins. The removal of proteins is mainly mediated by the ubiquitin-proteasome system (UPS), with a help of the major protein unfoldase VCP (also called p97), which both reside in the cytosol and nucleus. Our preliminary data suggest that VCP nucleocytoplasmic shuttling is a very dynamic process, however it is unclear how it is regulated. Recent studies demonstrated that the ability of VCP to properly shuttle between the cytosol and nucleus is disrupted by the mutations in VCP causing multisystem proteinopathy (also called IBMPFD) and frontotemporal dementia (FTD). As differential localisation of VCP modulates a local UPS-mediated degradation of variety of VCP substrates, its precise nucleocytoplasmic transport is crucial for the functional protein degradation and cell health.

Aim:

We aim to identify factors and pathways regulating nucleocytoplasmic VCP shuttling, expanding our understating of VCP biology and how this process is fine-tuned in response to internal and external cellular stressors. With the use of a CRISPR/Cas9-based high-throughput screening, state-of-the-art microscopy and biochemical methods, we aim to identify, characterise and define novel factors and pathways key for VCP shuttling between cytosol and nucleus. By using a variety of cellular models, from established cell lines to human induced pluripotent stem cell (iPSC)-derived neurons, we aim to broaden our understanding of the VCP function and provide possible therapeutic solutions to correct insufficient VCP nuclear localisation observed in cells carrying a disease-causing mutation in VCP.

Requirements:

- MSc degree in biology, biochemistry or related field
- Solid knowledge in at least one of the following disciplines: molecular biology, biochemistry, cell biology, neuroscience
- Understanding of mechanisms important for cellular proteostasis
- Basic hands-on experience in one of the fields: molecular biology, cell biology, fluorescent microscopy
- Prior experience in working with human induced pluripotent stem cell (iPSC)-derived neurons would be an advantage but not essential
- Interest in cellular proteostasis and neurodegeneration
- Written and spoken fluency in English
- Willingness to learn and take new challenges, ability to work independently, analytical thinking
- Good interpersonal skills and a collaborative attitude

Number of positions available: 1

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