Department of Biochemistry and Molecular Biology

PhD Oration

Friday 7th of December
3:30-4:30pm
Bio21 Institute Auditorium
30 Flemington Road, Parkville

Mona Radwan

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The role of dipeptide repeat proteins in C9ORF72-associated motor neuron disease and frontotemporal dementia

Mutations that expand a hexanucleotide (GGGGCC) tandem repeat sequence in intron 1 of the *C9ORF72* gene from tens of copies to hundreds is the major cause of familial Motor neuron disease (MND) and frontotemporal dementia (FTD) (C9-MND/FTD). The expanded repeat sequence invokes an unconventional ATG-independent translation in six reading frames that generate five different dipeptide repeat (DPR) proteins that accumulate in disease brain including poly-glycine-alanine (polyGA), poly-glycine-proline (polyGP), and poly-glycine-arginine (polyGR), poly-proline-arginine (polyPR), and poly-proline-alanine (polyPA). Of these, the R-rich peptides invoke potent toxicity through mechanisms that remain incompletely understood but include a purported poisoning of ribosome biogenesis. In my PhD project, I sought to better clarify the mechanisms involved by determining the interactors of these DPR proteins (as 100x repeats) in a neuronal cell culture model using quantitative proteomics. The PR and GR interactomes selectively included ribosomal proteins, translation initiation factors and translation elongation factors. Of note, the ribosome stalling factor ABCE1, was uniquely identified in the interactome of the PR_{100}, suggesting that translation of this protein induces ribosome stalling, rather than impairing ribosome biogenesis as previously reported. To test this hypothesis, I employed an assay of ribosome stalling, which involved monitoring the expression of two fluorescent proteins from a single mRNA sequence separated by the DPR sequences. The PR_{100} and GR_{100} were found to selectively and robustly stall the ribosome. I therefore conclude that the predominant effect of Arg-rich DPRs is the stalling of ribosome synthesis rather than poisoning of ribosome biogenesis. I propose that the long stretch of positive charges of arginine electrostatically interact with negatively charged residues of the ribosomal exit tunnel and hence provide a mechanism to broadly collapse ribosome activity.

ALL WELCOME. Please join us for Pizza to celebrate this PhD Oration!
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