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National Centre For Cell Science
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(An Autonomous Institution of the Department of Biotechnology, Government of India)

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TO WHOM IT MAY CONCERN

Nucleoporins are proteins that form nuclear pore complexes (NPCs), which are molecular gates that regulate the transport of macromolecules between the nucleus and the cytoplasm. Around 30 different nucleoporins are present in NPCs. A subset of nucleoporins is present away from the NPCs on the ER subdomains called **annulate lamellae (AL)**. Although AL were discovered in the 1950s, **their functions are unclear**.

Misregulation of cellular processes like **nucleo-cytoplasmic transport (NCT), microRNA (miRNA)-mediated regulation of gene expression and ER-mitochondria contact sites (ERMCSs)** have been implicated in the pathogenesis of multiple diseases including neurodegenerative diseases and cancers. Whether these processes are interconnected and if any unified mechanism exists that explains the development of these diseases is currently unknown.

Dr. Jomon Joseph's lab is focused on understanding the role of AL, primarily through one of its constituents, Nup358. Joseph's lab is embarking on this to explore if the newly discovered functions may be compromised in the abovementioned diseases.

Studies from his lab have shed light on the specific role of Nup358 in the regulation of miRNA-mediated mRNA translation (**Sahoo et al., 2019; EMBO Reports**) and restricting ER-mitochondria connectivity (**Kalarikkal et al., 2024; EMBO Reports**). Preliminary results from his lab also implicate Nup358 in calcium (Ca^{2+}) homeostasis, particularly in maintaining the Ca^{2+} levels in the mitochondria and cytoplasm, a failure of which triggers Ca^{2+}-induced autophagy (**Saikia et al., manuscript in preparation**). Recent results also suggest that Processing bodies (PBs), mRNPs involved in the post-transcriptional gene regulation are also present at the ERMCSs and their maintenance requires ERMCSs (**More & Joseph, J Cell Sci., under revision**).

Given that the nucleoporin Nup358 is mutated in a class of neuronal disease called '**Acute Necrotizing Encephalopathy-1 (ANE-1)**' and that the NCT is impaired in a multitude of neurodegenerative diseases and cancers, the fundamental discoveries showing a new role for Nup358 in miRNA-mediated translational regulation and ERMCS functions provide newer avenues to explore the relevance of these discoveries in disease biology and therapeutic intervention strategies. In support of this, the work from Joseph's lab revealed that a mutation (T585M) in Nup358 that is prevalent in the ANE-1 patients compromised Nup358's function in the regulation of miRNA-mediated translation process (**Deshmukh et al., 2021; BBRC 2021**).

In summary, Joseph's lab has significantly contributed to the understanding of the functional relevance of AL, particularly of Nup358, which will provide molecular insights into the cellular processes that go awry in diseases and disease management.

With best regards,

Sabapat 13/08/2024

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