O-21.2 Invited speaker

Biomolecular Condensates: Illuminating a Novel Source of Cellular Order Emerging from Molecular Disorder in Health and Disease

Irene Diaz-Moreno [1], Rafael L. Giner-Arroyo [1], Joaquín Tamargo-Azpilicueta [1], Alejandra Guerra-Castellano [1], Ana B. Uceda-Mayo [2], Pablo Rivero-García [1], Andrea Fernández-Veloso [1], Jaime Hiniesta-Valero [1], Miguel A. De La Rosa [1]

[1] University of Sevilla, Seville, Spain

[2] Universitat de les Illes Balears, Palma de Mallorca, Spain

Cells use compartmentalization by liquid-liquid phase separation (LLPS) to control reactions spatially and temporally. Among them, nucleolar trafficking and arrest of mRNA translation in cytoplasmic stress granules (SGs) occur by biomolecular condensation. Nucleophosmin (NPM1) is a histone chaperone involved in nucleolar ribosome synthesis, while T-cell intracellular antigen 1 (TIA-1) is the main SGs nucleator.In the nucleolus, NPM1 harbors cytochrome c (Cc)—which translocates from mitochondria upon DNA damage—in the cavity formed by its arms, the disordered acidic regions of NPM1. Cc does trigger an extended-to-compact conformational change in NPM1 drives the release of the ARF tumor suppressor from the condensate. Nuclear Cc emerges as a molecule with sequence-encoded heterotypic phase-separation properties, with its Lys-rich clusters being responsible for controlling the trafficking of nucleolar proteins. TIA-1 phosphorylation triggers the disorder-to-order transition resulting from the assembly of a α-hairpin at the intrinsically disordered domain, thereby facilitating self-association into SGs. Since several mutations in the unstructured domain of TIA-1 have been linked to aberrant SGs and neurodegenerative diseases, a better understanding of the mechanisms underlying the liquid de-mixing of TIA-1 provide valuable data for the development of therapeutic treatments.