Ageing in Biomolecular Condensates

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Two lectures: 10am,16 & 18 May, TCM Seminar Room.

Liquid-liquid phase separation (LLPS) has emerged as an important organizing principle of the cell interior, where aggregation of proteins and nucleic acids into liquid condensates has been shown to underlie the formation of membraneless compartments [1,2]. However, some biomolecular condensates, which are liquid-like during health, can age over time becoming gel-like pathological systems [3]. This gradual rigidification has been postulated to represent one of the key pathological steps in the onset of several neurodegenerative disorders such as Alzheimer, Parkinson, or Amyotrophic Lateral Sclerosis [4,5]. During these two lectures of TCM Topics of Current Research, we will show how ageing of RNA-binding protein condensates can emerge from the progressive accumulation of inter-protein β-sheets. We shall employ a computational multiscale approach that integrates atomistic simulations, sequence-dependent coarse-grained simulations of condensates, and minimal models to uncover the molecular and kinetic factors explaining condensate ageing. We find that ageing notably increases condensate viscosity but does not transform the phase diagrams. Moreover, the network of molecular connections within condensates is drastically altered during ageing and culminates in gelation when the network of strong inter-protein β-sheets fully percolates. Our simulations predict that single-component condensates of *fused in sarcoma* (FUS) which are initially homogeneous and liquid-like can transform into gel-core/liquid-shell or liquid-core/gel-shell multiphase condensates as they age, due to gradual and limited enhancement of inter-protein interactions [6]. Furthermore, we will show how the type of multiphase architecture critically depends on the surface tension of the liquid and gel coexisting phases, which itself is determined by the ageing mechanism, the molecular organization of the gel and liquid phases, and the chemical make-up of the protein [7]. Moreover, we will explore potential routes to decelerate ageing in RNA-binding protein condensates. By adding relatively high concentrations of RNA, the accumulation of inter-protein β-sheets can be hindered, thus, abrogating the effects of ageing [8]. Overall, in these lectures we shall explore the molecular and kinetic factors explaining condensate ageing and suggest potential mechanisms to slow ageing down.

References:

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[2] Boeynaems *et al. Trends in Cell Biology*, **28**, 420-435 (2018).
[3] Feric *et al. Cell*, **165**, 1686-1697 (2016).
[4] Guillen-Boixet *et al. Cell*, **181**(2):346–361, (2020).
[5] Patel *et al. Cell*, **162**:1066–1077, (2015).
[6] Garaizar, Espinosa *et al. PNAS (in press) (2022) BioRxiv* 10.1101/2021.10.09.463670
[7] Wang *et al. Cell*, **174**, 688-699 (2018).
[8] Tejedor, Sanchez-Burgos *et al. Nat. Comm.* (*under review*) (2022) *BioRxiv* 10.1101/2022.03.30.486367