The hyperactivity of Estrogen Receptor fusion proteins in breast cancer

SpT-06-2

A. Gherghelas[I], C. Toseland[I]

[I]University of Sheffield, Sheffield, United Kingdom

Estrogen Receptor-positive (ER+) cancers represent 70% of all breast cancer cases. Despite their initial response to anti-hormonal treatments, acquired resistance eventually arises, allowing the disease to progress into an aggressive, metastatic form. An emerging mechanism of therapeutic resistance is through chromosomal translocations that fuse a diverse set of genes with the *ESR1* gene in a way that eliminates the ligand-binding domain of the ER. These chimeric proteins possess constitutive, ligand-independent activity that leads to increased cell growth, proliferation and initiation of the metastatic cascade.

A growing body of research suggests that liquid-liquid phase separation (LLPS) may be a mechanism driving aberrant gene transcription and genome organisation. Research in the Toseland Lab has revealed that *ESR1* fusion proteins recurrently form nuclear condensates in various breast cancer cell lines. Considering the transcriptional role of ER, we hypothesise that *ESR1* fusion condensates represent transcriptional hubs that drive gene expression programmes associated with breast cancer. To test this, the ER+ epithelial cell line MCF7 was transiently transfected with the patient-derived fusions *ESR1-DAB2* and *ESR1-SOX9* to test their LLPS capacity and contribution to the cancer phenotype.

We have thus far demonstrated that *ESR1* fusion condensates display various LLPS characteristics including spherical morphology, reversibility, and fusion upon contact. Furthermore, these hubs are associated with elevated levels of RNA Polymerase II, indicating enhanced transcriptional activity. Additionally, their localisation in areas of active transcription and the altered levels of chromatin condensation provide evidence for chromatin re-organisation. Unravelling condensate formation, dynamics, and their functional relevance should provide new insights on oncofusion-driven cancers and may open new therapeutic avenues for treating advanced, therapy-resistant breast cancers.