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Perspective

Biomolecular Condensates and its Pathological Functions in Cancer and Neurodegenerative diseases

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DESCRIPTION

Biomolecular condensates, or simply condensates, are a potent tool for the intracellular compartmentalization of both proteins and nucleic acids. Phase separation, a well-known phenomena in polymer chemistry, is how these structures are formed. Numerous macromolecules hundreds or perhaps thousands make up intracellular biomolecular condensates, which are very multicomponent systems with a strikingly varied composition. It has been demonstrated that many types of multivalent interactions, including weak, temporary, multivalent interactions typically between Intrinsically Disordered Regions (IDRs) and protein-protein, protein-RNA, and RNA-RNA interactions between ordered domains, contribute to phase separation. Cation-anion, π-π interactions, dipole-dipole, and cation-π interactions are included in the final category of interactions. Given that biomolecular condensates are involved in a variety of cellular functions, it is simple to assume that changes in a cell's ability to modulate phase separation are what lead to pathological conditions. This has received special attention in the context of crippling neurodegenerative diseases, where maturation of condensates to an irreversible solid state has been connected to the biogenesis of Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), and Alzheimer's disease. Recently, the development of aberrant condensates in additional disorders, including cancer and immunological signalling, has been investigated. Solid tumours such breast, prostate, colorectal, and stomach tumours have been linked to the Speckle-Type POZ Protein (SPOP). SPOP facilitates substrate ubiquitination by serving as a substrate adapter for the cullin3-RING ubiquitin ligase. Cancer-related mutations in SPOP, however, prevent SPOP-substrates from being assembled in nuclear speckles and from being recruited to the ligase. It has recently been demonstrated that SPOP experiences phase separation, which is caused by its dimerization and multivalent interactions with substrates in both cells and *in vitro*.

Proto-oncogenic proteins accumulate as a result of disease-associated SPOP mutations that prevent the protein's phase separation and co-localization in biomolecular condensates. Similar to this, SHP2, a non-receptor protein tyrosine phosphatase, can accumulate in condensates as a result of mutations. The RAS-Mitogen-Activated Protein Kinase (MAPK) signalling pathways are thereby hyperactivated, which promotes cancer. It's interesting to note that Src Homology Protein Tyrosine Phosphatase 2 (SHP2) allosteric inhibitors can specifically reduce the phase separation of cancer-related SHP2 mutations. Elvitegravir (EVG), an anti-HIV medication, may also specifically disrupt phase separation of cancer-associated Steroid Receptor Coactivator 1(SRC-1), a previously recognised transcriptional coactivator for nuclear hormone receptors, therefore reducing oncogenic transcription. Condensates are additionally produced by A-Kinase Anchoring Protein 95 (AKAP95), a nuclear protein involved in splicing regulation. Tumorigenesis may be dramatically impacted by modifications to the dynamics and fluidity of these condensates. Cancer is characterised by transcriptional dysregulation. It has been discovered that a number of transcriptional coactivators that are known to control carcinogenesis go through phase separation. The Hippo pathway's downstream effectors, transcriptional activators Yes-Associated Protein 1 (*YAP*) and Transcriptional Co-Activator with PDZ-Binding Motif (*TAZ*), can trigger the transcription of genes involved in a range of functions, including cell proliferation. *YAP* and *TAZ* condense in cancer cells, promoting carcinogenesis and anti- Programmed Cell Death Protein 1 (PD1) treatment resistance.

Transcriptional condensates are also recruited by tamoxifen, another Food and Drug Administration (FDA) approved anti-cancer drug used to treat Oestrogen Receptor (ER) positive breast cancer. However, the relocation of ER caused by tamoxifen recruitment to the condensates causes their disruption. As a result, breast cancer cells express less oncogenes. The tiny compounds and over-the-counter medications lipoamide and lipoic acid also preferentially dissolve SGs. As a potential new approach to treating ALS, the effect of lipoamide or lipoic acid-mediated SG disruption has been studied. Results indicate that it enhances the recovery of motor capabilities in

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Drosophila melanogaster and inhibits dieback of motor neurons generated from ALS patients. Another FDA-approved anti-cancer drug, tamoxifen, is drawn to transcriptional condensates to treat (ER) positive breast cancer. However, ER is displaced when tamoxifen is recruited to the condensates, leading to their disruption. Oncogene expression is decreased as a result in breast cancer cells. Since SGs have been demonstrated to influence various oncogenic processes, investigating the effect of lipoamide and lipoic acid in cancer cells should yield intriguing results. Together, these results demonstrate the significance of biomolecular condensates in tumour biology and show the possibility of using phase separation as a cancer treatment strategy.

Biomolecular condensates are kept in a liquid or gel-like form under physiological conditions, allowing for dynamic molecule exchange. However, it has been discovered that some condensates mature with time and create irreversible aggregates. This is a characteristic of a number of neurodegenerative illnesses, including Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), and Alzheimer's Disease (AD). For Fused in Sarcoma (FUS), DNA-Binding Protein 43 (TDP43), and-synuclein, progression from reversible dynamic condensate to irreversible pathological aggregation has been demonstrated. Post-Translational Modifications (PTMs) and mutations linked to illness can initiate and control the development of the condensate to aggregate.

CONCLUSION

Mutations in condensate components or altered regulation of the interactions causing molecular demixing are only a few examples of the many causes that might change a condensate's material properties. It is still of utmost importance to define on how living cells govern the physical characteristics of biomolecular condensates and how this regulation is changed in diseased situations.