Unraveling the Role of Oncofetal Proteins in Cancer Stem Cell Biology: A Comprehensive Analysis

Abstract:

Cancer poses a significant global health challenge, prompting ongoing efforts to unravel its complexities and devise effective treatment strategies. Central to cancer progression are cancer stem cells (CSCs), exhibiting stem-like characteristics akin to embryonic stem cells. The expression of oncofetal proteins lies at the crux of CSC pathology, orchestrating tumor initiation, advancement, and therapy resistance. This study embarked on a meticulous exploration of oncofetal proteins, focusing on their disorder characteristics and implications in cancer biology.

Our investigation began with compiling a comprehensive catalog of 100 oncofetal proteins sourced from the UniProt database, laying the groundwork for subsequent analyses. Through rigorous examination using the Ridao platform, we pinpointed a subset of 12 oncofetal proteins characterized by pronounced disorder, forming the focal point of our study. Employing advanced tools such as STRING for protein-protein interaction mapping, AlphaFold for precise structural predictions, and d2p2/Fuzdrop for assessing disorder and phase separation potential, we delved into the intricate landscape of oncofetal proteins in the context of CSC biology.

Our findings underscored the pivotal role of these proteins in governing CSC maintenance and function, shedding light on their involvement in critical cancer-related processes. Through elucidating protein-protein interaction networks and predicting three-dimensional structures, we gained invaluable insights into the intricate regulatory mechanisms driving cancer progression. Furthermore, the assessment of disorder characteristics and phase separation potential offered novel perspectives on oncofetal protein function in cellular signaling and organization.

The implications of our research extend far beyond elucidating molecular mechanisms; our findings hold profound promise for cancer therapy. By identifying potential therapeutic targets and unveiling novel treatment strategies, our study lays the groundwork for the development of more efficient, targeted therapies tailored to combat cancer. Ultimately, this research not only enhances our understanding of cancer biology but also heralds a new era in precision oncology, offering renewed hope in the relentless pursuit of effective cancer treatments.

Keywords: intrinsic disordered protein, oncofetal proteins, protein interactions.

1.Introduction:

Despite significant advancements in cancer research and treatment modalities, cancer remains a leading cause of mortality worldwide, inflicting immense suffering and loss. The understanding of cancer has evolved, encompassing insights into its molecular underpinnings, tumor heterogeneity, recurrence, metastasis, and innovative nanoplatforms for therapeutic interventions. Notably, this progress has unveiled the presence of cancer stem cells (CSCs), a subset of cells endowed with stem cell-like properties, capable of self-renewal and generating the bulk of tumor cells.

Similar to embryonic stem cells, CSCs express pluripotent transcription factors (TFs) and activate developmental signaling pathways termed 'Oncofetal Drivers'. These drivers play a pivotal role in maintaining the stem-like properties of CSCs and driving tumor progression. Therefore, targeting the oncofetal proteins associated with these drivers holds promise for identifying cancer types and devising effective therapeutic strategies to mitigate metastasis and enhance treatment efficacy.

The exploration of oncofetal proteins and their involvement in CSC biology presents a compelling avenue in the battle against cancer. Understanding their mechanisms underlying tumor initiation, progression, and therapy resistance can potentially revolutionize treatment approaches, offering more targeted and efficient therapies.

In this paper, we delve deeper into the realm of oncofetal proteins, with a specific focus on elucidating their disorder characteristics. Initially, we curated a comprehensive list of 100 oncofetal proteins, including their FASTA sequences and descriptions, utilizing the 'UniProt' database. Subsequently, employing the 'Ridao' platform, we conducted an in-depth analysis of the disorder within these proteins, identifying a subset of 12 highly disordered proteins for further investigation.

Our study centers on these 12 oncofetal proteins, aiming to unravel their disorder profiles and elucidate their significance in cancer biology. To comprehensively understand their role, we explore their protein-protein interactions using the 'STRING' database, predict their three-dimensional structures utilizing 'Alpha-Fold', and assess their disorder extent and liquid-liquid phase separation potential through 'd2p2' and 'Fuzdrop'.

By elucidating the disorder characteristics and functional implications of oncofetal proteins, our research aims to contribute to a deeper understanding of cancer biology and pave the way for the development of targeted and efficient therapeutic interventions against this formidable disease.

2.Materials and Methods:

2.1.Protein datasets:

The proteins analyzed in this study were obtained from research papers authored by Michael D. Lucroy, Benjamin Boyerinas, Sun-Mi Park, Noam Shomron, Mads M. Hedegaard, Jeppe Vinther, Jens S. Andersen, Christine Feig, Jinbo Xu, Christopher B. Burge, Marcus E. Peter, Qian Yan, Xiaona Fang, Chenxi Li, Ping Lan, and Xinyuan Guan. Specifically, we focused on oncofetal proteins mentioned in these papers, such as Carcinoembryonic Antigen and Alpha Fetoproteins, which served as the primary proteins for our bioinformatics analysis. Subsequently, an additional 100 oncofetal proteins were selected from the UniProt database for further analysis. The sequences of these proteins were gathered in FASTA format from the UniProt database for subsequent examination.

2.2. Evaluation of Intrinsic Disorder Predisposition

To assess the likelihood of intrinsic disorder in all proteins, we employed several commonly used per-residue disorder predictors, including PONDR® VLS2, PONDR® VL3, PONDR® VLXT, PONDR® FIT, IUPred-Long, and IUPred-Short. We utilized a web application called Rapid Intrinsic Disorder Analysis Online (RIDAO) to collect results from each predictor in bulk. The percent of predicted intrinsic disorder residues (PPIDR) for each protein served as the basis for classifying their levels of disorder. A residue was considered disordered if it had a value of 0.5 or higher.

Typically, proteins with a PPIDR value of less than 10% are considered highly ordered, those with PPIDR between 10% and 30% are moderately disordered, and those with PPIDR greater than 30% are highly disordered. Additionally, we calculated a mean disorder score (MDS) for each protein, which represents a protein length-normalized sum of all per-residue disorder scores. Based on their MDS values, proteins were categorized as highly ordered (MDS < 0.15), moderately disordered or flexible (MDS between 0.15 and 0.5), and highly disordered (MDS > 0.5). So, of all the 100 oncofetal proteins we found 12 highly disordered oncofetal proteins (AKAP8_HUMAN , CHERP_HUMAN, CREM_HUMAN, HMGA1_HUMAN, HMGA2_HUMAN,HMGA2_MOUSE,HNRPC_HUMAN,LN28A_HUMAN,LN28B_HUMAN, STAU1_HUMAN,YBOX1_HUMAN,ZSC10_HUMAN.)

2.3. PPI Networks

Protein-protein interaction (PPI) networks were constructed using the STRING (Search Tool for the Retrieval of Interacting Genes). In this study, we utilized STRING. Initially, we created a global interaction network encompassing all 100 proteins.

Subsequently, we generated networks specific to AKAP8_HUMAN , CHERP_HUMAN, CREM_HUMAN, HMGA1_HUMAN, HMGA2_HUMAN,HMGA2_MOUSE,HNRPC_HUMAN,LN28A_HUMAN,LN28B_HUMAN, STAU1_HUMAN,YBOX1_HUMAN,ZSC10_HUMAN.

2.4. Disorder-Based Functional Annotations

The utilization of the Database of Disordered Protein Predictions (D2P2) enabled the identification of binding sites via the ANCHOR algorithm and the detection of various post-translational modification (PTM) sites. Furthermore, D2P2 offers forecasts of Structural Classification of Proteins (SCOP) domains using the SUPERFAMILY predictor, along with predictions of disorder utilizing a range of predictors including PONDRVLXT, PONDRVSL2b, PrDOS, PV2, ESpritz-DisProt, Espritz-XRay, Espritz-NMR, IUPred-Long, and IUPred-Short.

2.5. 3D Model Structures of Main Proteins

Structural models in three dimensions for the main proteins (AKAP8_HUMAN , CHERP_HUMAN, CREM_HUMAN, HMGA1_HUMAN, HMGA2_HUMAN,HMGA2_MOUSE,HNRPC_HUMAN,LN28A_HUMAN,LN28B_HUMAN, STAU1_HUMAN,YBOX1_HUMAN,ZSC10_HUMAN.) were produced utilizing the AlphaFold tool.

2.6. Analysis of Liquid-Liquid Phase Separation Potential

To evaluate the likelihood of spontaneous liquid-liquid phase separation and to furnish a sequence-based score for pinpointing regions that promote this phenomenon within the 12 oncofetal proteins (AKAP8_HUMAN , CHERP_HUMAN, CREM_HUMAN,HMGA1_HUMAN,HMGA2_HUMAN,HMGA2_MOUSE,HNRPC_HUMAN, LN28A_HUMAN,LN28B_HUMAN,STAU1_HUMAN,YBOX1_HUMAN,ZSC10_HUMAN), we utilized a tool called FuzDrop. This involved analyzing the protein sequences to identify regions with characteristics conducive to liquid-liquid phase separation, aiding in the understanding of how these proteins may behave within cellular environments.

3.Results

3.1. Evaluating Intrinsic Disorder Functionality in Main Proteins

In the initial phase of our investigation, we delved into the intrinsic disorder tendencies of twelve primary proteins: AKAP8_HUMAN , CHERP_HUMAN, CREM_HUMAN,HMGA1_HUMAN,HMGA2_HUMAN,HMGA2_MOUSE,HNRPC_HUMAN, LN28A_HUMAN,LN28B_HUMAN,STAU1_HUMAN,YBOX1_HUMAN,ZSC10_HUMAN.

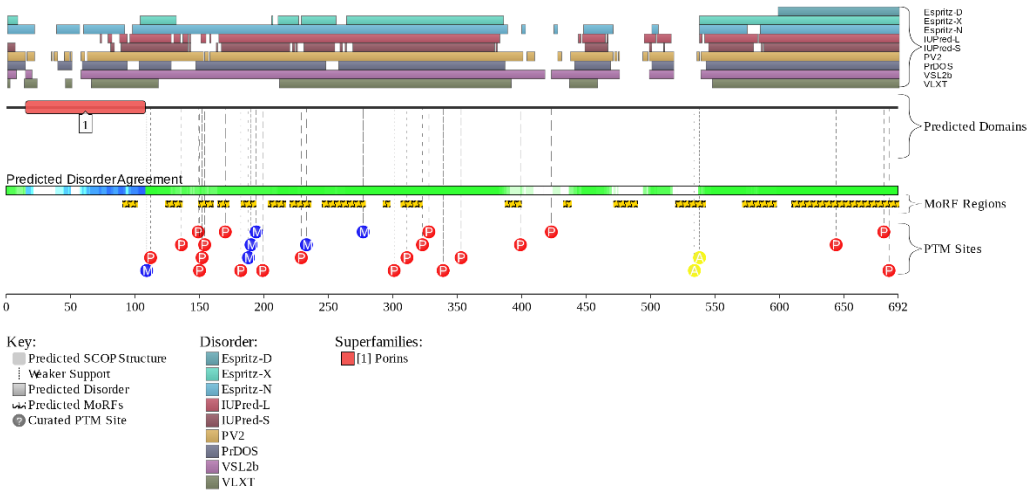
. The comprehensive disorder analysis results for these proteins are visually represented in Figures 1–12. Our examination of these primary proteins involved scrutinizing the per-residue disorder profiles generated by RIDAO, exploring functional disorder profiles through the D2P2 platform, studying protein-protein interaction networks via STRING, and examining 3D structural models created by AlphaFold.

3.1.1. AKAP8_HUMAN

Figure 1 depicts the outcomes of a functional disorder analysis conducted on human AKAP8, a protein comprising 1026 residues characterized by distinct structural domains: a head region spanning residues 1–200, an unstructured and flexible (UF) rod domain spanning residues 97–413, and a tail region spanning residues 414–1026. Notably, the tail region is significant for containing functional motifs crucial for protein-protein interactions and subcellular localization.

Within the tail region of AKAP8, conserved sequences known as AKAP motifs facilitate its interaction with PKA and other signaling molecules. Additionally, AKAP8 harbors multiple phosphorylation sites, including serine residues within specific motifs. Phosphorylation events on AKAP8 modulate its subcellular localization and protein-protein interactions, thereby regulating cellular signaling pathways. For instance, phosphorylation within specific regions may enhance AKAP8's binding affinity for PKA, facilitating localized PKA signaling. Conversely, phosphorylation within other regions may disrupt protein-protein interactions, thereby influencing downstream signaling events.

In essence, AKAP8 plays a critical role in coordinating cellular signaling cascades through its dynamic interactions and phosphorylation-mediated regulation, underscoring its importance in cellular physiology and maintenance of homeostasis.



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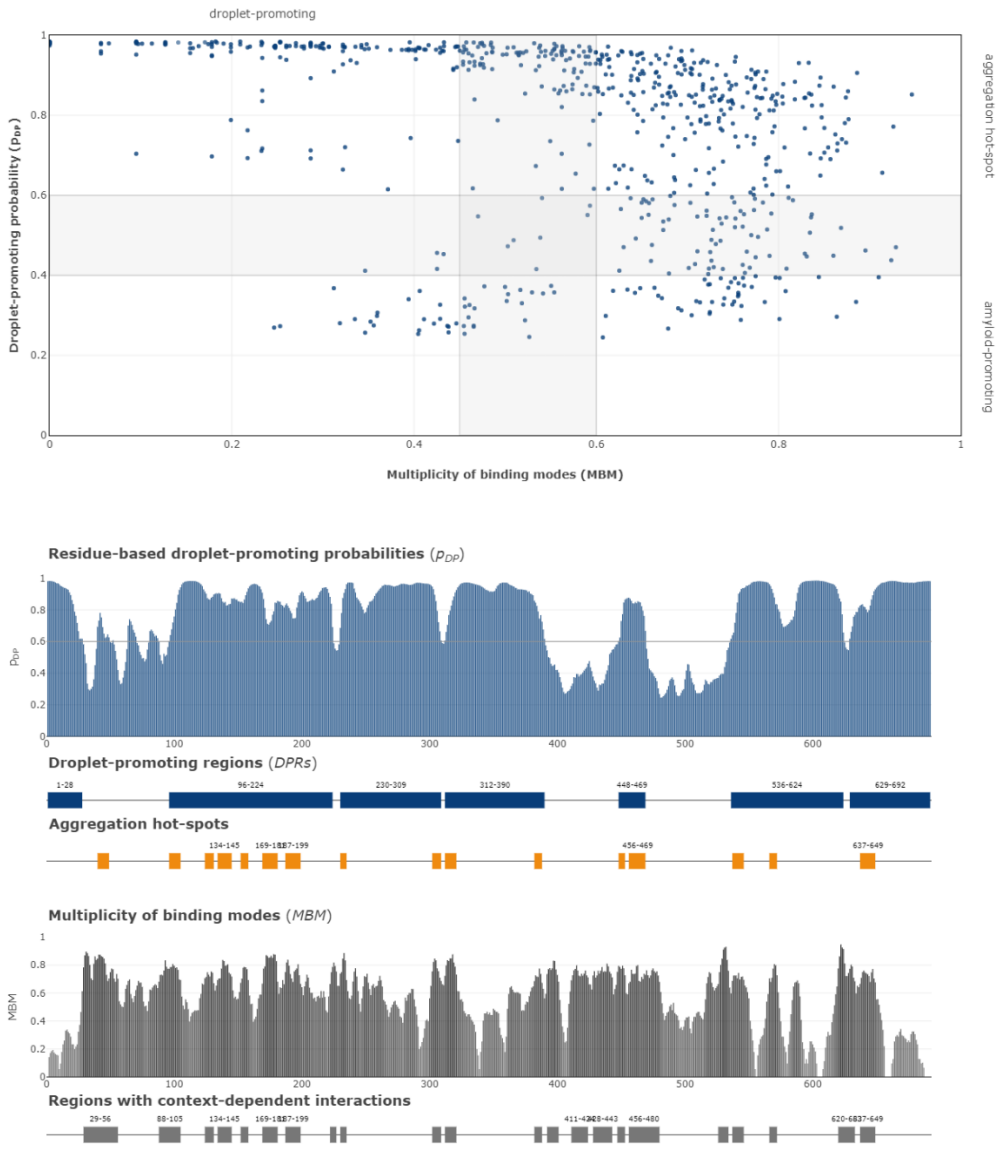
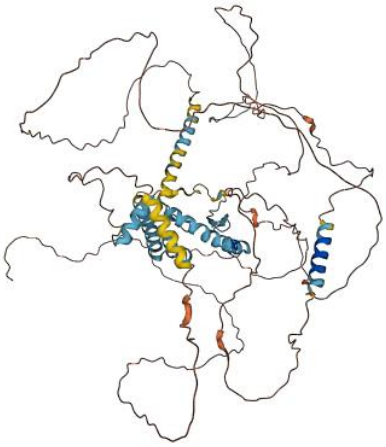

droplet-promoting
Droplet-promoting probability (p_{DP})
Multiplicity of binding modes (MBM)
aggregation hot-spot
amyloid-promoting
Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
1-28
96-224
230-309
312-390
448-469
536-624
629-692
Aggregation hot-spots
134-145
456-469
637-649
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions
29-56
88-105
134-145
456-480
620-649

B



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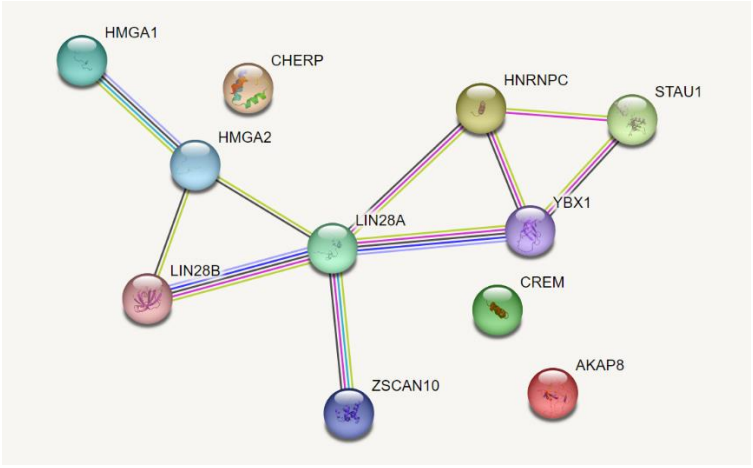
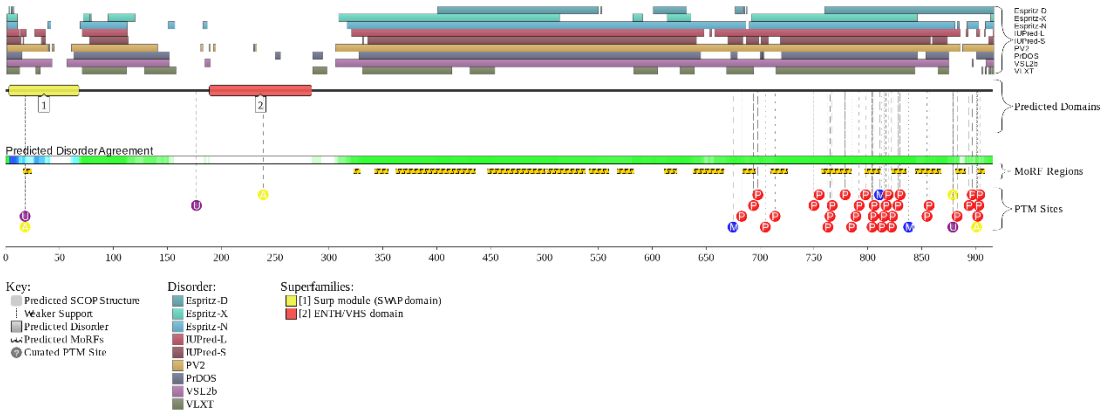


D

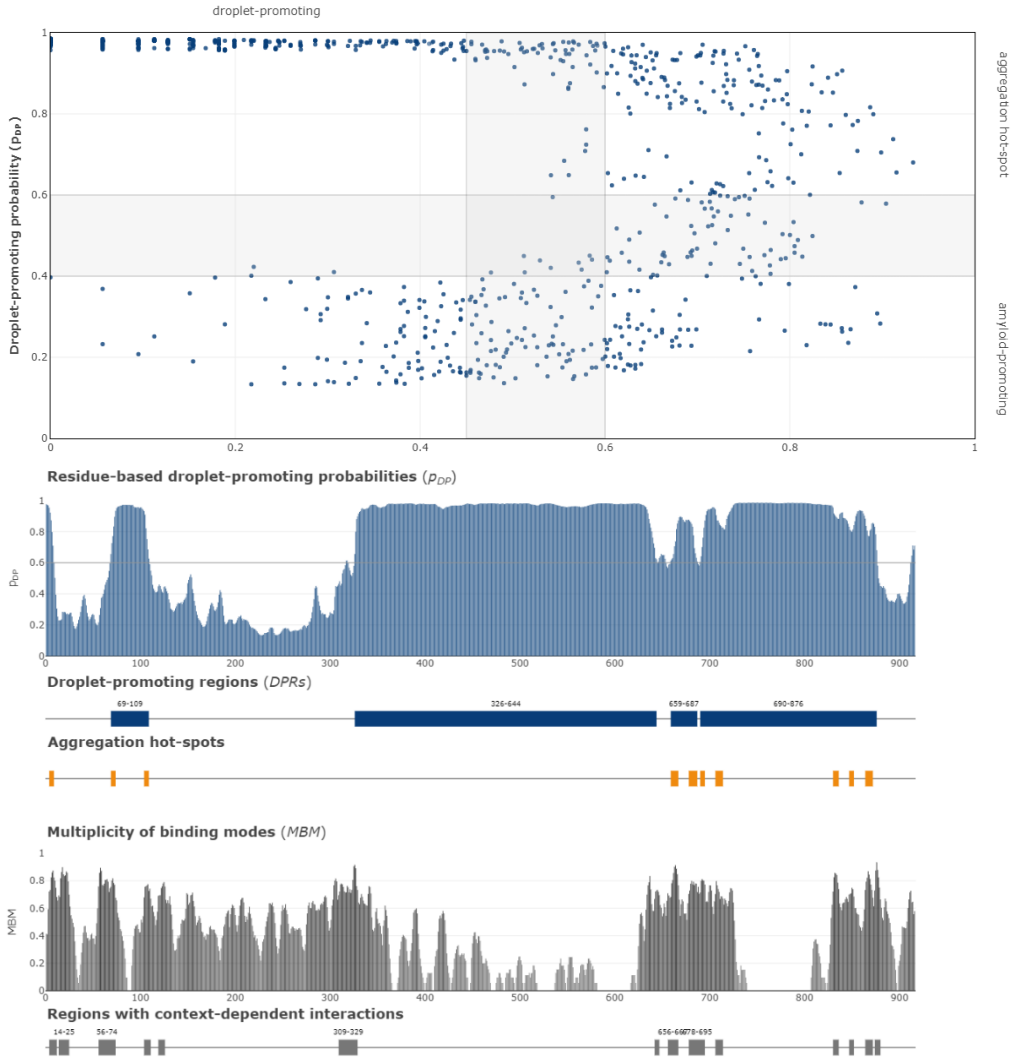
Figure 1. Functional Disorder analysis of AKAP8_HUMAN **A** The functional disorder profile of AKAP8_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. These predictions are represented by nine differently colored bars at the top of the plot. The blue-green-white bar in the middle reflects the consensus among these predictors, highlighting disordered regions in blue and green Above the consensus bar, two lines with colored and numbered bars indicate the positions of functional SCOP domains predicted by the SUPERFAMILY predictor. Predicted disorder-based binding sites, known as MoRF regions, identified by the ANCHOR algorithm, are represented by yellow zigzagged bars. At the bottom of the plot, sites of various posttranslational modifications (PTMs), are depicted by differently colored circles. **B** Liquid Phase separation analysis for AKAP8_HUMAN **C** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of AKAP8_HUMAN. It helps distinguish between regions with high-confidence predictions, which are likely structurally well-defined, and those with lower confidence, where caution may be warranted regarding their structural interpretation. **D** String generated PPI network

3.1.2. CHERP_HUMAN

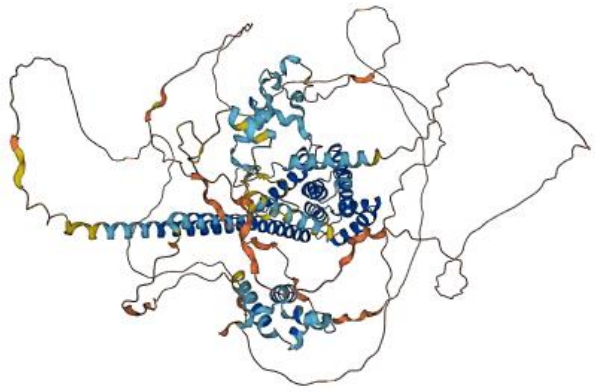
CHERP_HUMAN, also known as Chromatin Enriched RNA Binding Protein, is a protein in humans with UniProt ID Q96GS4. It consists of 570 amino acids and is involved in RNA binding and chromatin organization. The protein features various structural domains, including regions involved in RNA binding and chromatin interaction. Disorder prediction analysis suggests that CHERP_HUMAN contains disordered regions, which may confer flexibility and enable interactions with multiple binding partners.



A


droplet-promoting
Droplet-promoting probability (p_{DP})
aggregation hot-spot
amyloid-promoting
Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (*DPRs*)
69-109
326-644
659-687
690-876
Aggregation hot-spots
Multiplicity of binding modes (*MBM*)
Regions with context-dependent interactions
14-25
56-74
309-329
656-66678-695

B



C

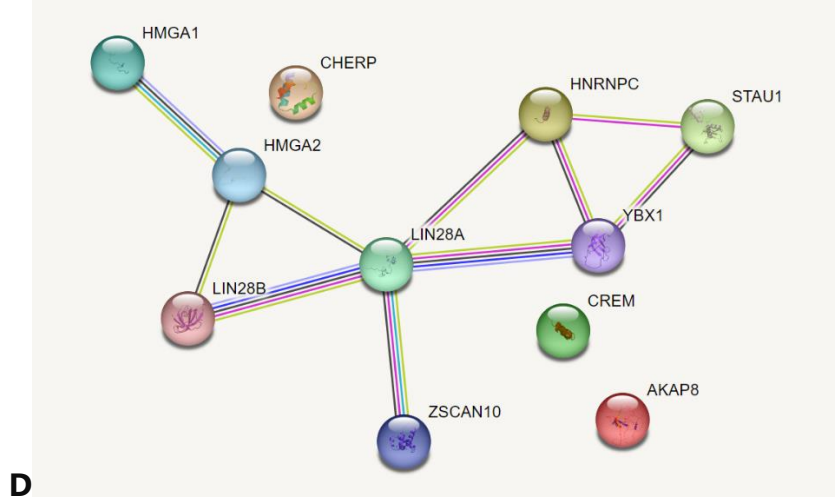
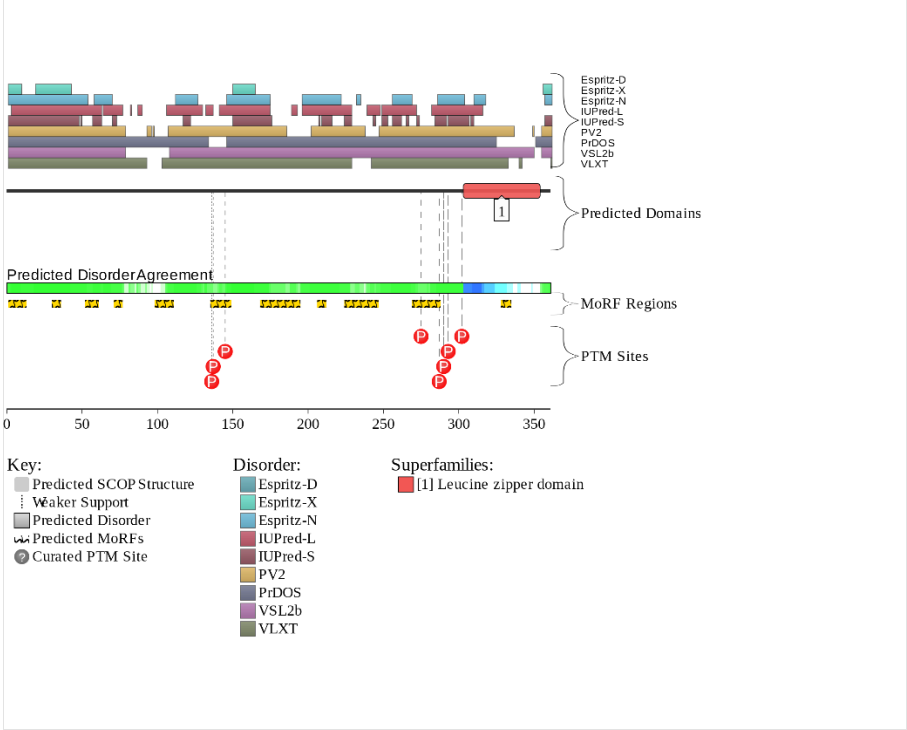
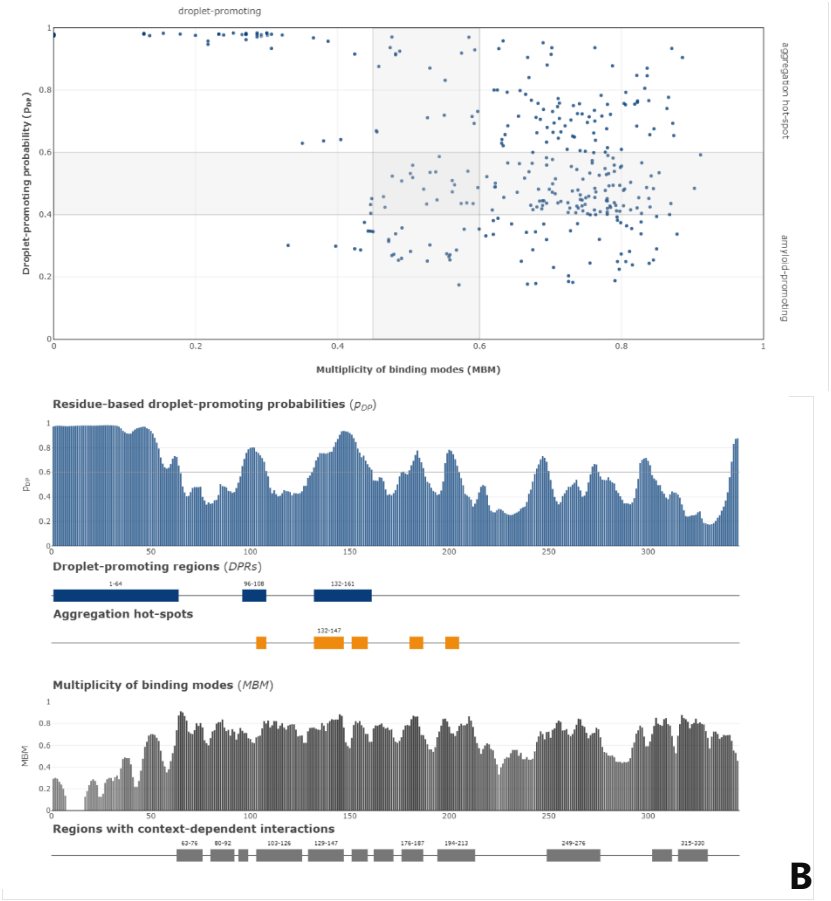


Figure 2. Functional Disorder Analysis of CHERP_HUMAN **A** The functional disorder profile of CHERP_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** Liquid-Liquid Phase separation analysis of CHERP_HUMAN **C** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of CHERP_HUMAN **D** String generated PPI network

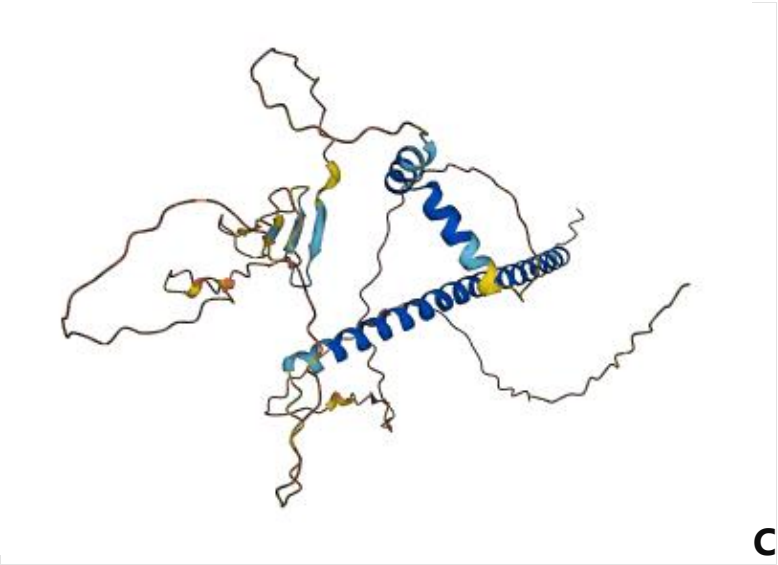
3.1.3 CREM_HUMAN

CREM_HUMAN, also known as cAMP-responsive element modulator, is a protein in humans with UniProt ID P16220. It consists of 341 amino acids and is involved in transcriptional regulation and gene expression modulation




droplet-promoting
aggregation hot-spot
amyloid-promoting
Droplet-promoting probability (p_{DP})
Multiplicity of binding modes (MBM)
Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
1-64
96-108
132-161
Aggregation hot-spots
132-147
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions
62-76
80-92
103-126
129-147
176-187
194-212
249-276
315-330

B



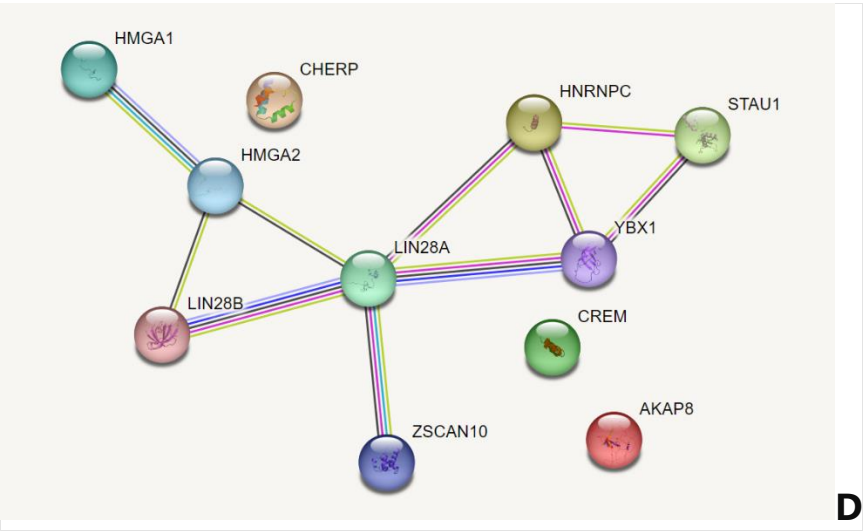
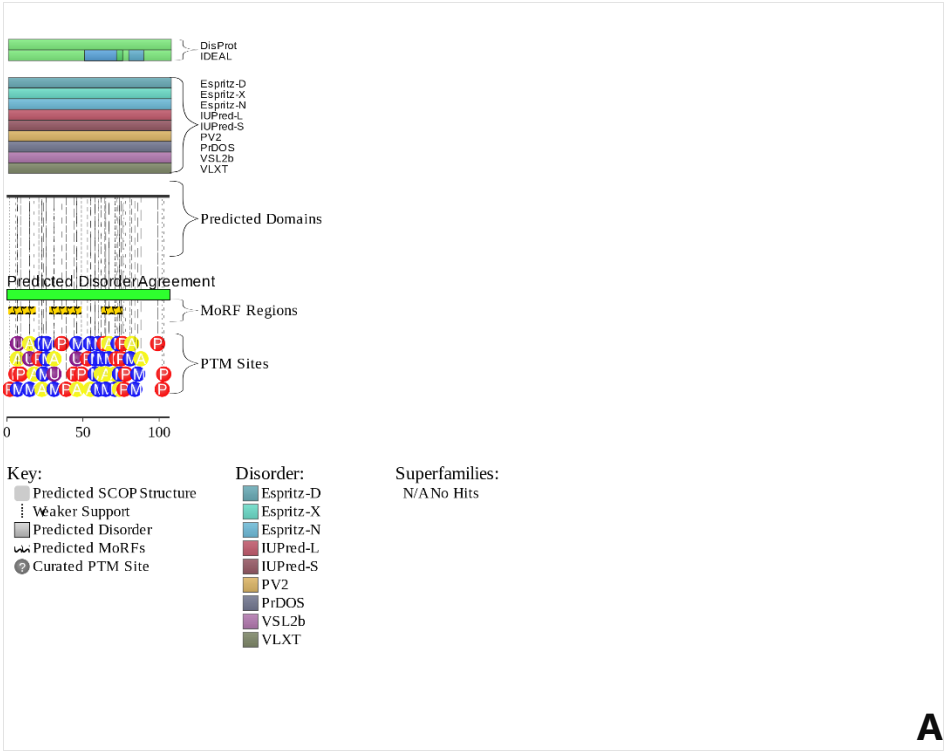
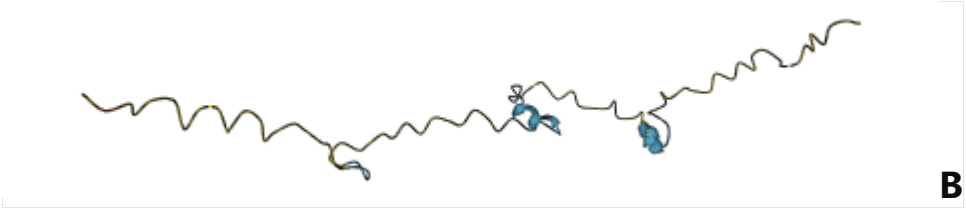


Figure 3. Functional disorder analysis of CREM_HUMAN **A**The functional disorder profile of CREM_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** Liquid-Liquid Phase separation analysis of CREM_HUMAN **C** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of CREM_HUMAN **D** String generated PPI network

3.1.4. HMGA1_HUMAN

HMGA1_HUMAN, also known as High Mobility Group Protein A1, is a protein found in humans with the UniProt ID P17096. It is a member of the high mobility group (HMG) family of proteins. HMGA1 plays crucial roles in diverse cellular processes such as embryonic development, cell growth, and differentiation, as well as in the pathogenesis of various diseases including cancer.





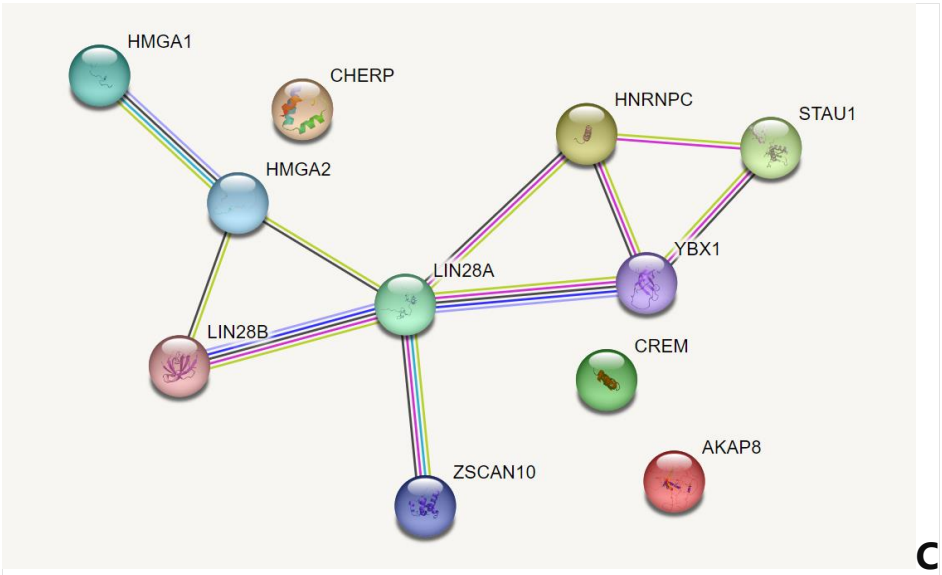


Figure 4. Functional disorder analysis of HMGA1_HUMAN **A**The functional disorder profile of HMGA1_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and

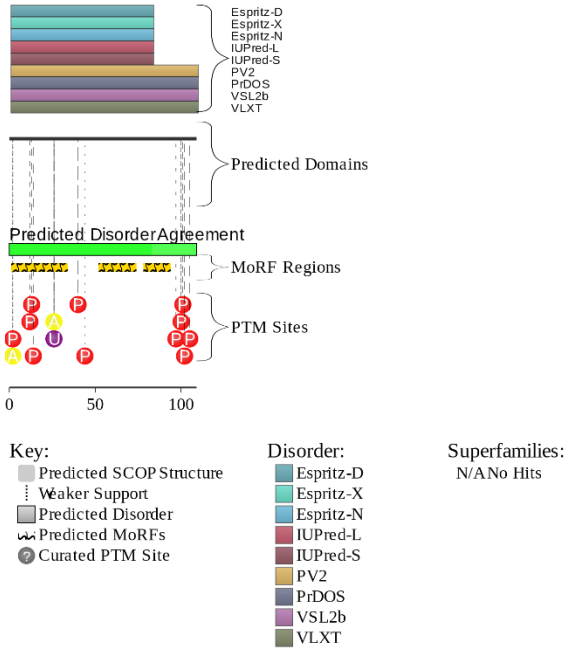
confidence level of the predicted 3D structure of HMGA1_HUMAN **D** String generated PPI network

3.1.5 HMGA2_HUMAN

HMGA2_HUMAN, also known as High Mobility Group Protein A2, is a protein found in humans with the UniProt ID P52926. Like HMGA1, it belongs to the high mobility group (HMG) family of proteins, which are involved in chromatin structure regulation and gene expression modulation. In terms of function, HMGA2 is implicated in a wide range of biological processes, including embryonic development, cell proliferation, and differentiation. Its dysregulation has been associated with tumorigenesis, particularly in various cancers, where HMGA2 can act as an oncogene promoting tumor progression.

Furthermore, HMGA2 undergoes post-translational modifications such as phosphorylation, acetylation, and methylation, which regulate its activity, stability, and subcellular localization.

In summary, HMGA2_HUMAN is a multifaceted protein with crucial roles in chromatin remodeling, gene regulation, and cancer progression, highlighting its significance in both normal physiological processes and disease pathology.



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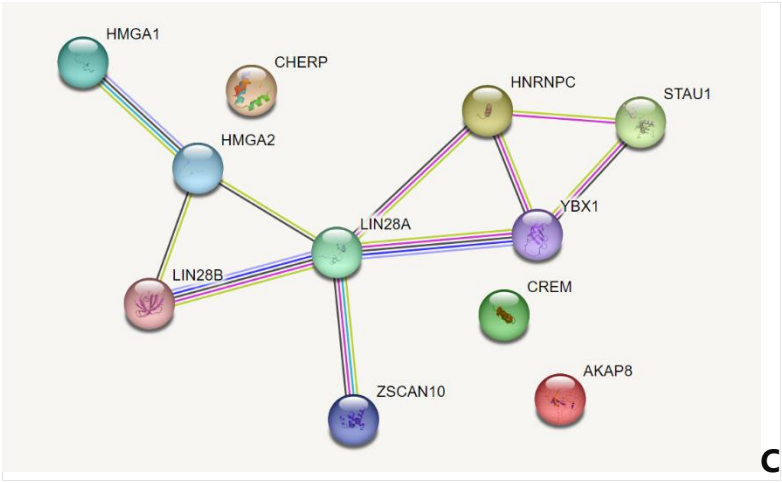

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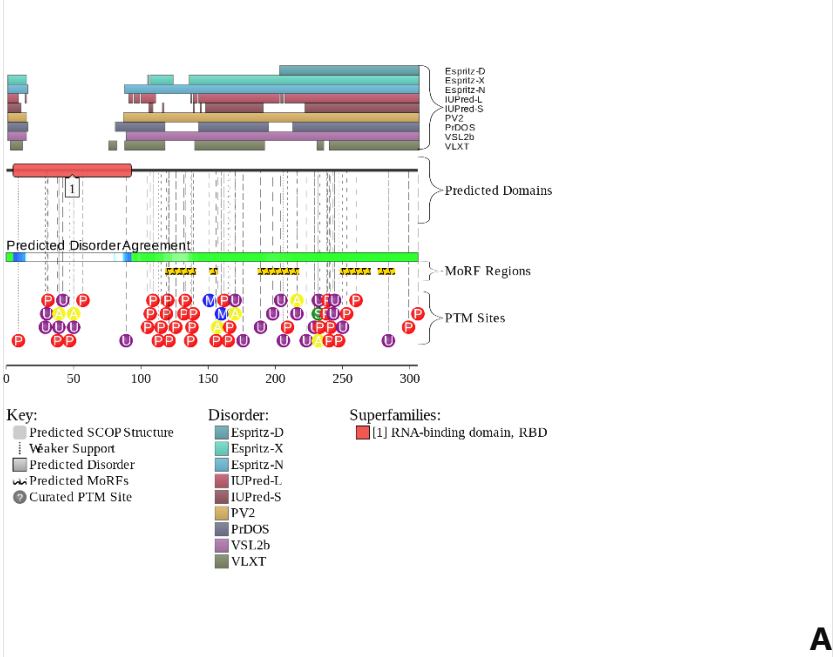
Figure 5 . . Functional disorder analysis of HMGA2_HUMAN **A**The functional disorder profile of HMGA2_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of HMGA2_HUMAN **D** String generated PPI network

3.1.6 HNRPC_HUMAN

HNRPC_HUMAN, also known as Heterogeneous Nuclear Ribonucleoprotein C, is a protein found in humans with the UniProt ID P07910. It is a member of the heterogeneous nuclear ribonucleoprotein (hnRNP) family, which plays crucial roles in RNA processing and gene expression regulation. HNRPC_HUMAN has been implicated in various cellular processes such as cell cycle progression, DNA repair, and apoptosis, highlighting its versatility and importance in cellular physiology.

Post-translational modifications such as phosphorylation and methylation regulate the activity, localization, and interactions of HNRPC_HUMAN, further modulating its function in RNA processing and gene expression regulation.

In summary, HNRPC_HUMAN is a multifunctional RNA-binding protein essential for the coordination of RNA metabolism and gene expression, with implications in diverse cellular processes and disease pathogenesis.



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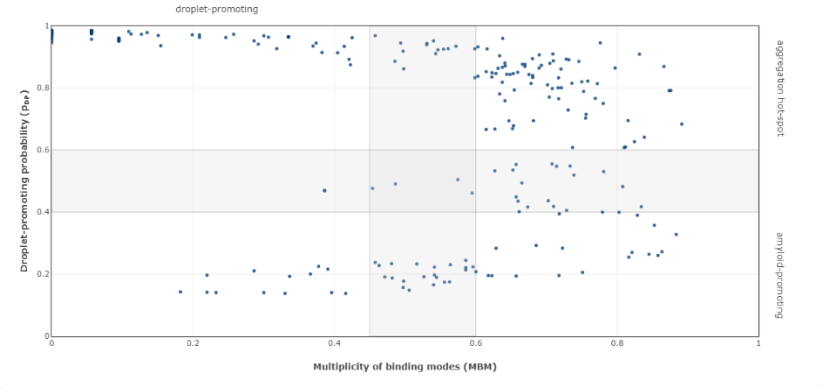
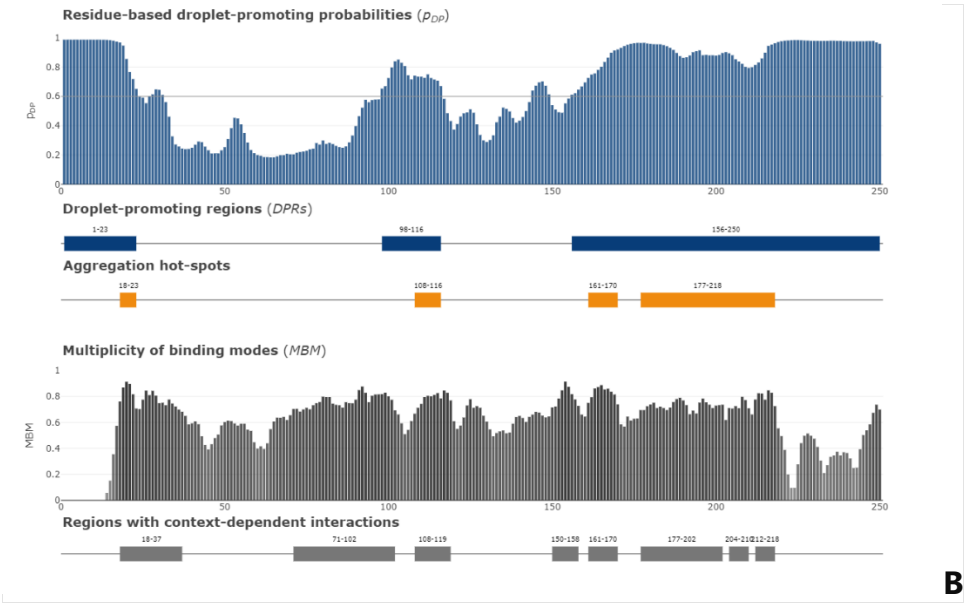
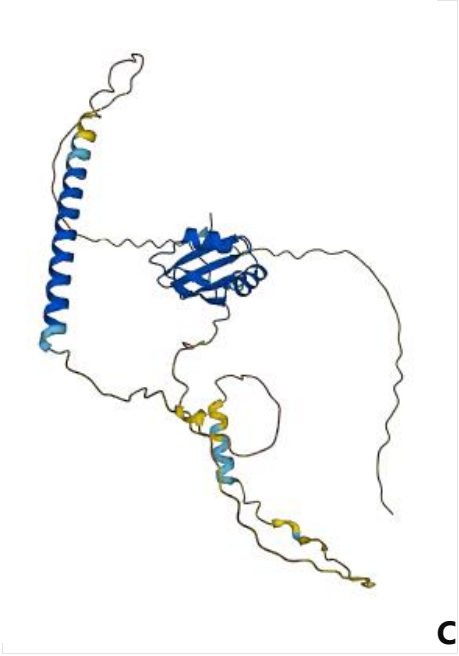



Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
1-23
98-116
156-250
Aggregation hot-spots
18-23
108-116
161-170
177-218
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions
18-37
71-102
108-119
150-158
161-170
177-202

B



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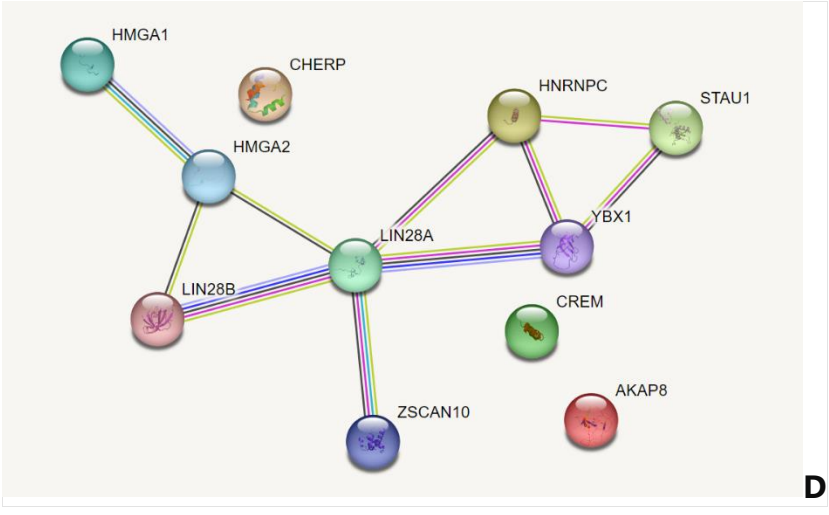
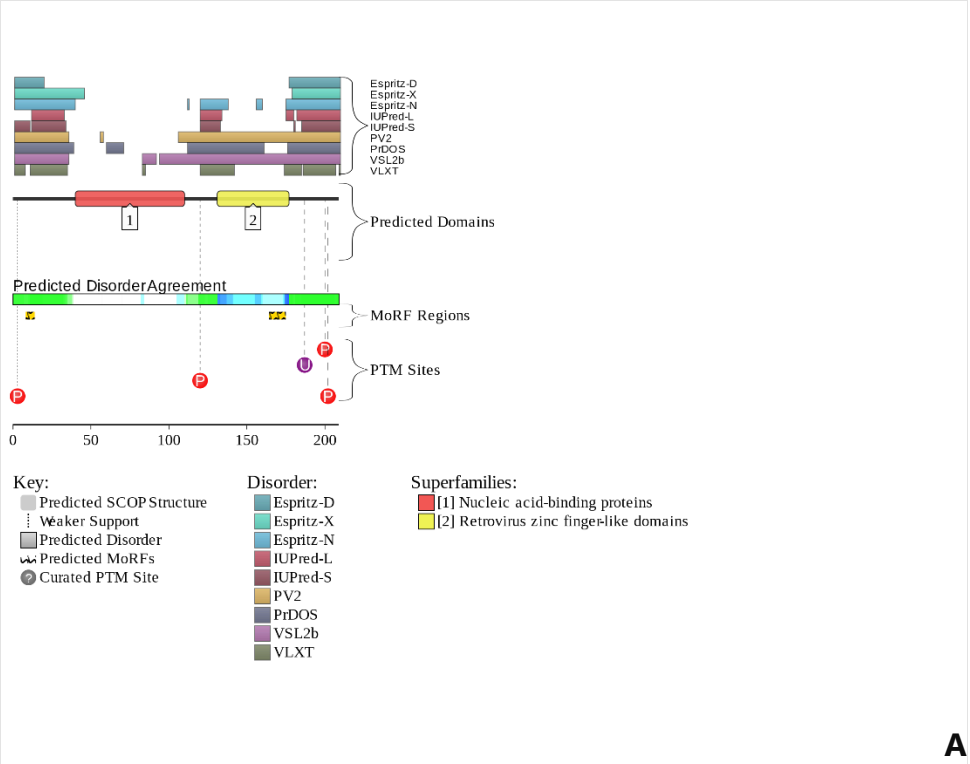

HMGA1
CHERP
HNRNPC
STAU1
HMGA2
YBX1
LIN28A
LIN28B
CREM
AKAP8
ZSCAN10

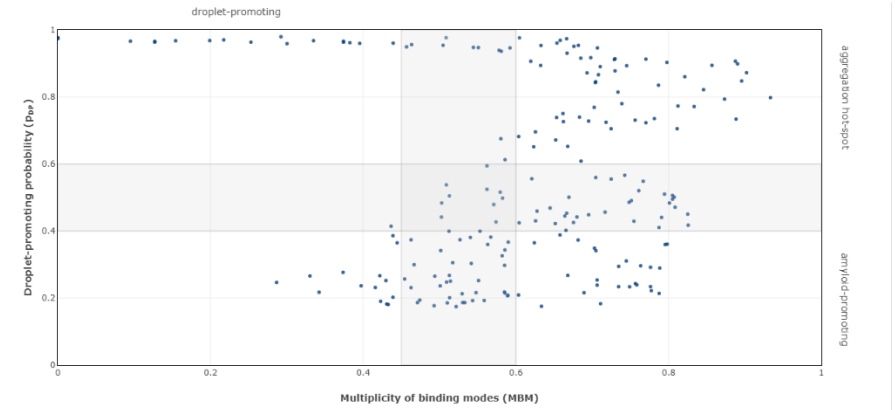
D

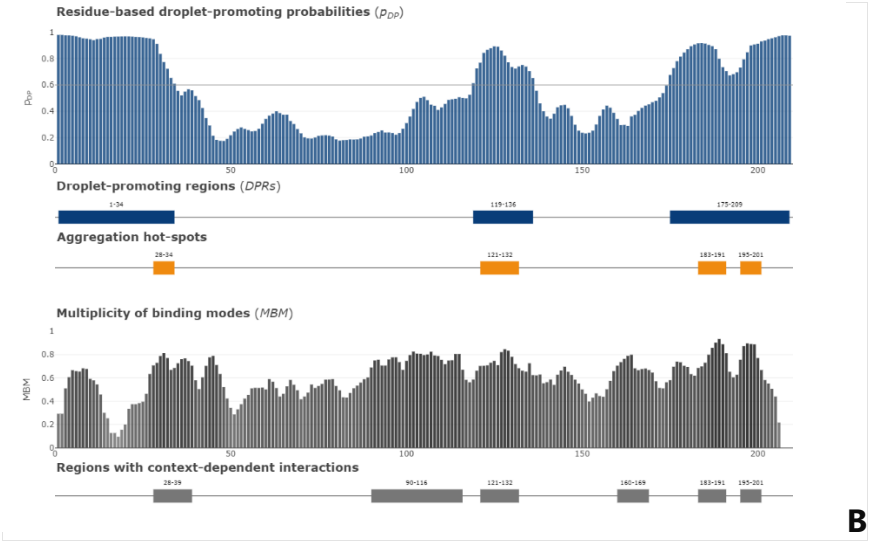
Figure 6. . Functional disorder analysis of HNRPC_HUMAN **A**The functional disorder profile of HNRPC_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of HNRPC_HUMAN **D** String generated PPI network

3.1.7 LN28A_HUMAN

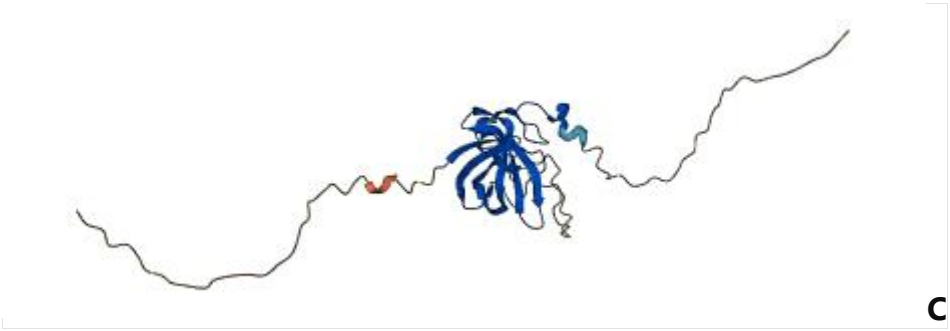
Lin-28 homolog A (LIN28A) is a highly conserved RNA-binding protein that plays crucial roles in various biological processes, including embryonic development, stem cell pluripotency, and metabolism regulation. LIN28A is involved in post-transcriptional regulation of gene expression through its interaction with microRNAs (miRNAs) and messenger RNAs (mRNAs). LIN28A is a multifunctional protein with diverse roles in development, metabolism, and disease, making it an important target for research in various fields, including cancer biology and regenerative medicine.




droplet-promoting
Droplet-promoting probability (p_{DP})
Multiplicity of binding modes (MBM)
aggregation hot-spot
amyloid-promoting


Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
Aggregation hot-spots
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions

B



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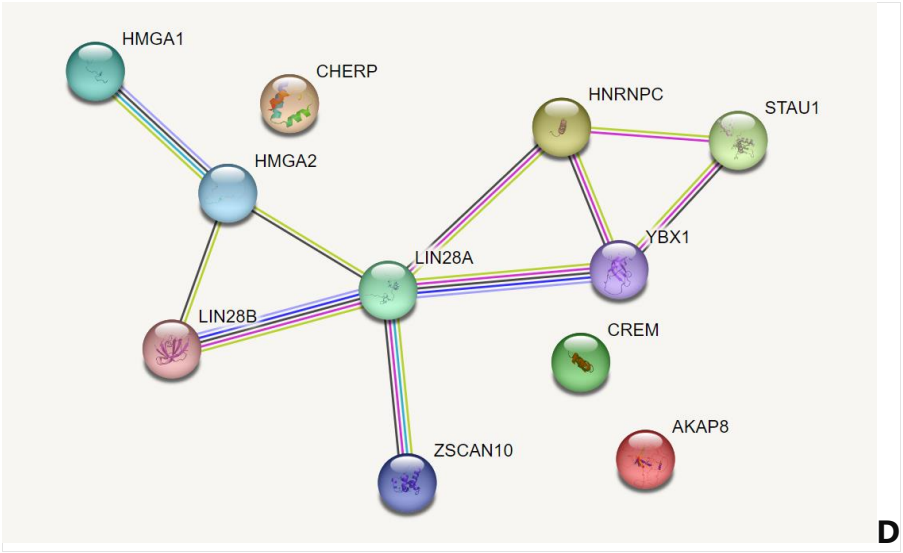
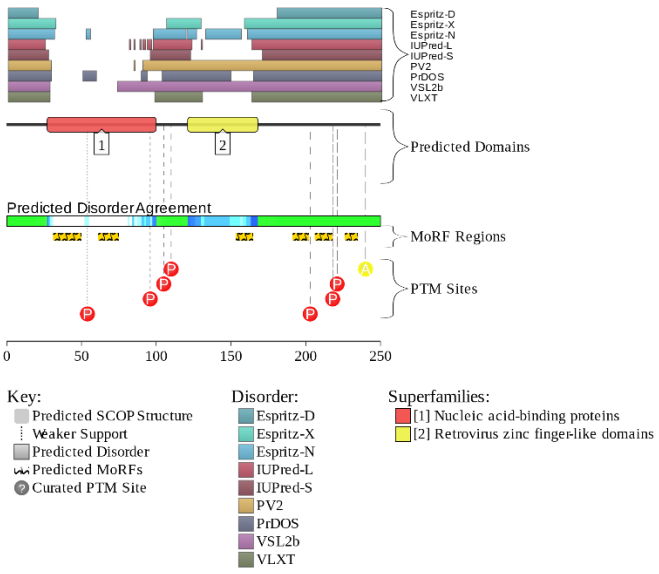

HMGA1
CHERP
HNRNPC
STAU1
HMGA2
YBX1
LIN28A
LIN28B
CREM
AKAP8
ZSCAN10

D

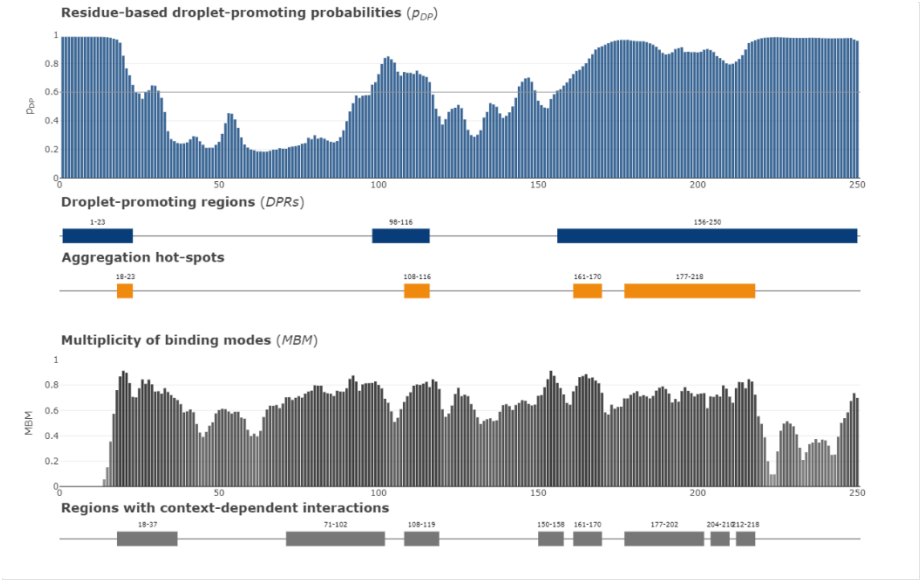
Figure 7. Functional disorder analysis of LN28A_HUMAN **A**The functional disorder profile of LN28A_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of LN28A_HUMAN **D** String generated PPI network

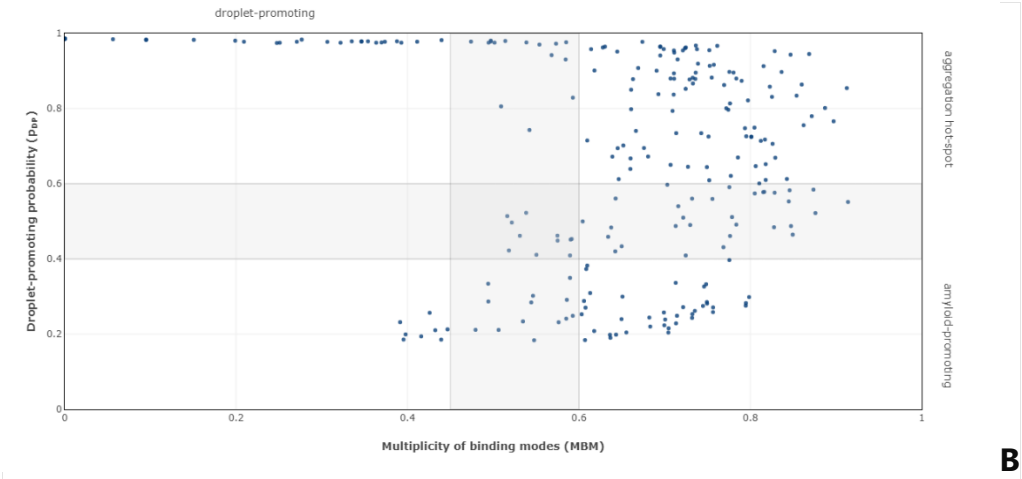
3.1.8 LN28B_HUMAN

LIN28 is an evolutionarily conserved RNA-binding protein with crucial roles in post-transcriptional gene regulation, stem cell biology, and metabolism. It regulates gene expression by modulating the biogenesis of let-7 family microRNAs, impacting various cellular processes. LIN28's involvement in stem cell pluripotency maintenance and metabolic regulation underscores its significance in development and disease. Dysregulation of LIN28 has been linked to cancer and metabolic disorders, highlighting its potential as a therapeutic target. Overall, LIN28 serves as a key player in cellular homeostasis and offers promising avenues for therapeutic intervention

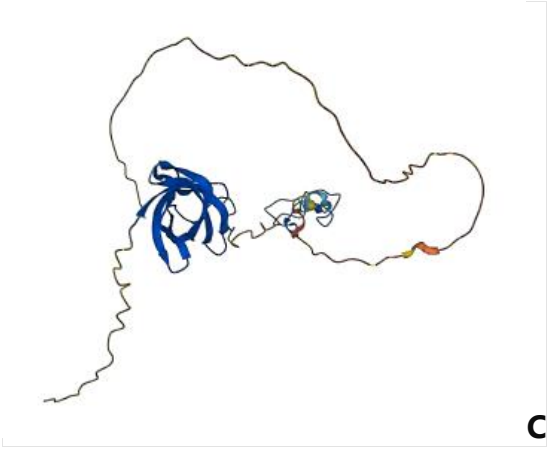


A


Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
1-23
98-116
156-250
Aggregation hot-spots
18-23
108-116
161-170
177-218
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions
18-37
71-102
108-119
150-158
161-170
177-202
204-212
212-218


droplet-promoting
Droplet-promoting probability (p_{DP})
aggregation hot-spot
amyloid-promoting
Multiplicity of binding modes (MBM)

B



C

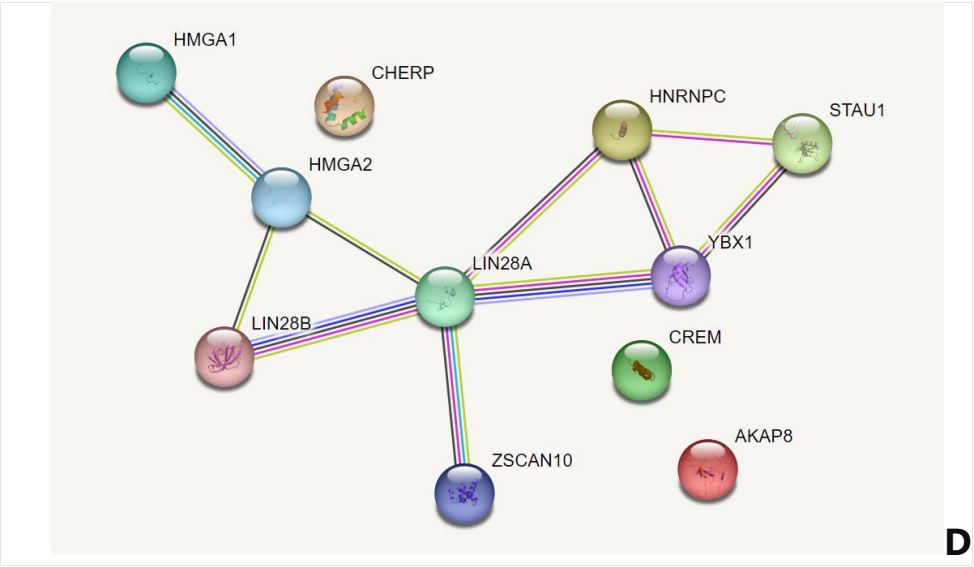
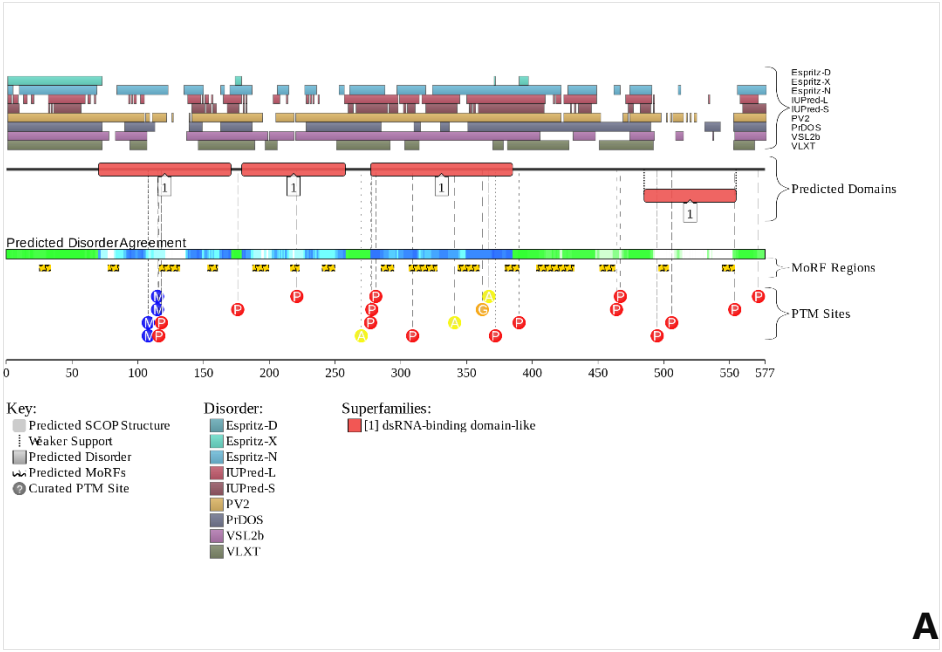


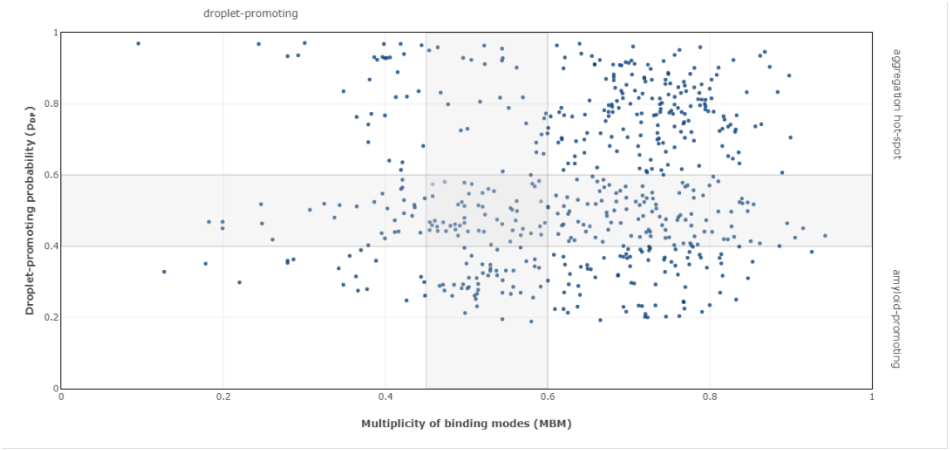
Figure 8. Functional disorder analysis of LN28B_HUMAN **A**The functional disorder profile of LN28B_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of LN28B_HUMAN **D** String generated PPI network

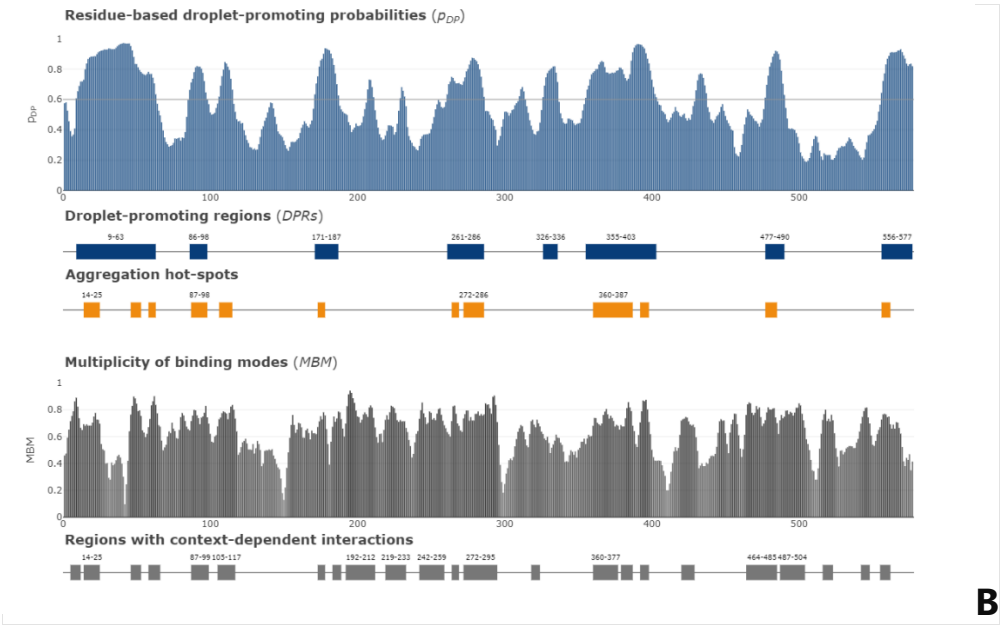
3.1.9 STAU1_HUMAN

STAU1_HUMAN, also known as Staufen homolog 1, is a conserved RNA-binding protein found in humans. It plays crucial roles in RNA metabolism, including mRNA localization, translation regulation, and mRNA decay. STAU1 is particularly important in neuronal development and synaptic plasticity due to its involvement in mRNA localization to dendrites. Dysregulation of STAU1 is associated with neurological disorders and cancer, making it a potential therapeutic target. Overall, STAU1_HUMAN is a key player in RNA regulation with implications in various cellular processes and diseases.


Espritz-D
Espritz-X
Espritz-N
IUPred-L
IUPred-S
PV2
PrDOS
VSL2b
VLXT
Predicted Domains
Predicted Disorder Agreement
MoRF Regions
PTM Sites
0 50 100 150 200 250 300 350 400 450 500 550 577
Key:
Predicted SCOP Structure
Weaker Support
Predicted Disorder
Predicted MoRFs
Curated PTM Site
Disorder:
Espritz-D
Espritz-X
Espritz-N
IUPred-L
IUPred-S
PV2
PrDOS
VSL2b
VLXT
Superfamilies:
[1] dsRNA-binding domain-like

A


droplet-promoting
Droplet-promoting probability (p_{DP})
Multiplicity of binding modes (MBM)
aggregation hot-spot
amyloid-promoting


Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
Aggregation hot-spots
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions

B

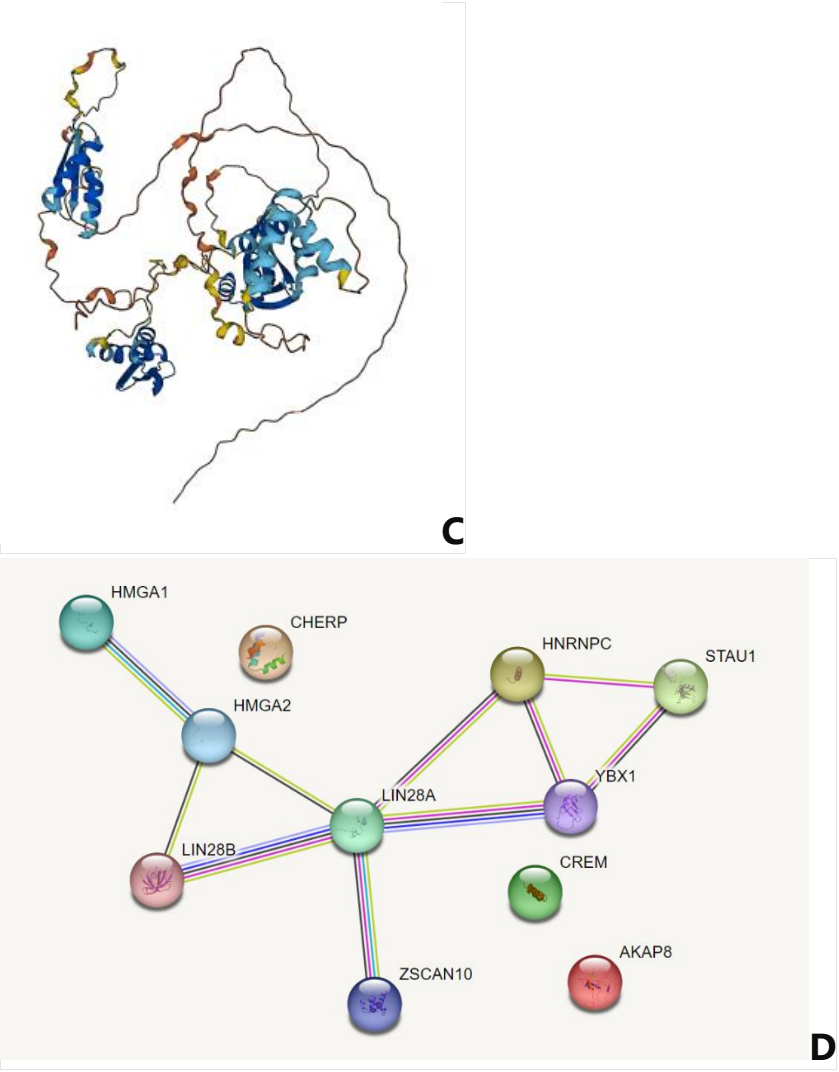
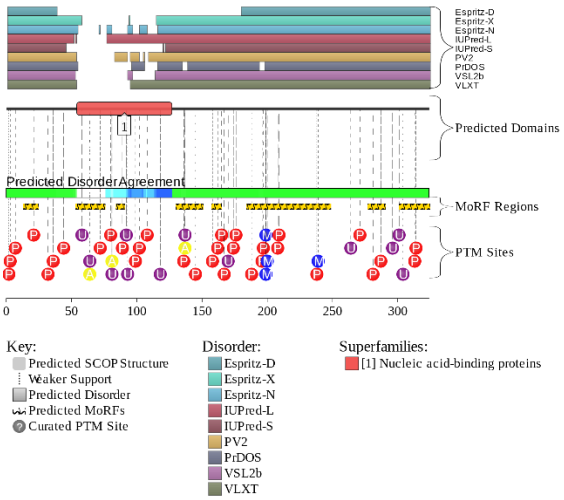


Figure 9. Functional disorder analysis of STAU1_HUMAN **A**The functional disorder profile of STAU1_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of STAU1_HUMAN **D** String generated PPI network

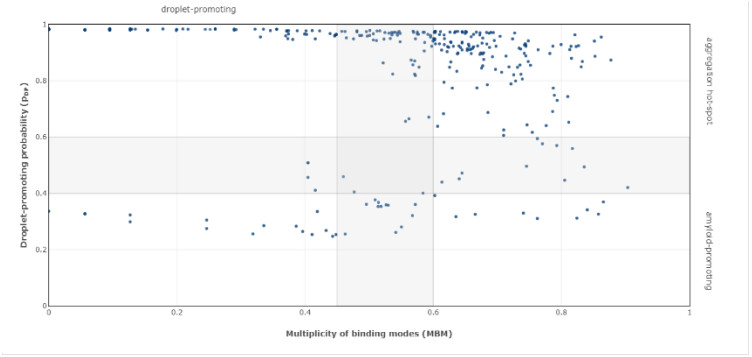
3.1.10 YBOX1_HUMAN

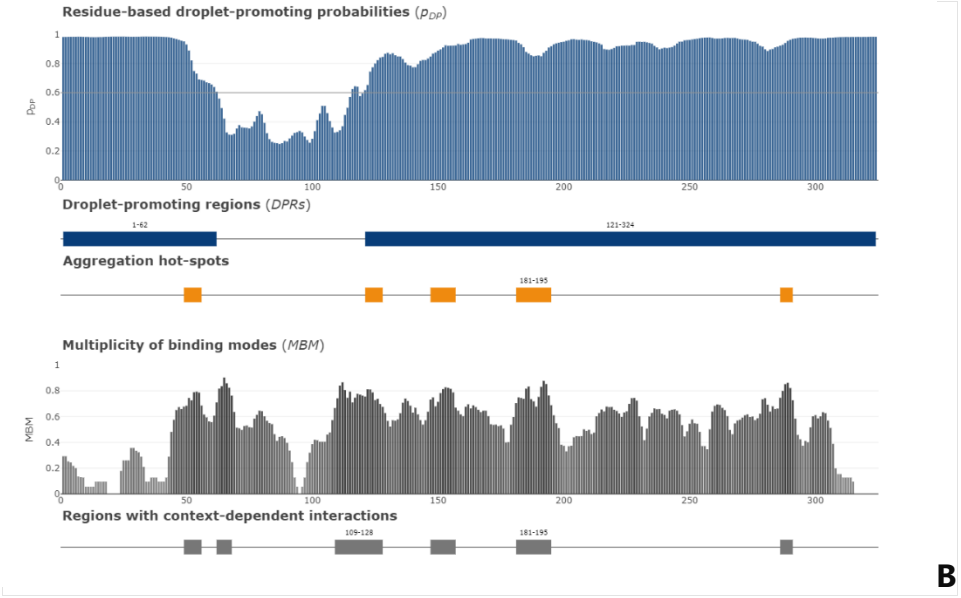
YBOX1_HUMAN, or Y-box-binding protein 1, is a protein in humans with the UniProt ID P16989. It binds to specific DNA and RNA sequences through its cold shock domain, regulating gene expression at transcriptional and post-transcriptional levels. YBOX1_HUMAN is involved in diverse cellular processes such as DNA repair, stress response, and embryonic development. Dysregulation of YBOX1_HUMAN has

been linked to diseases including cancer, inflammatory disorders, and neurodegenerative diseases, making it a potential therapeutic target.

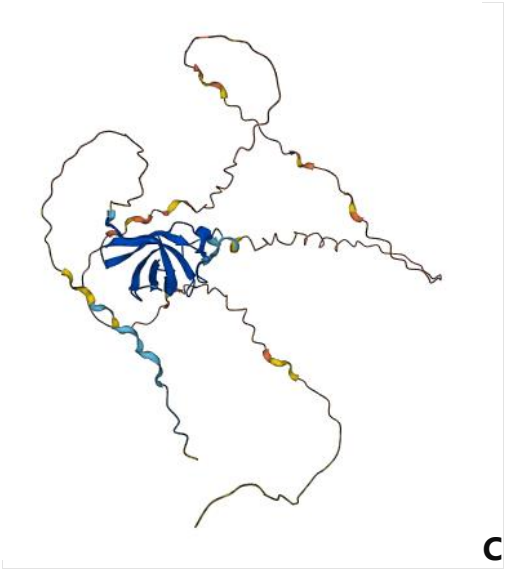


A





B



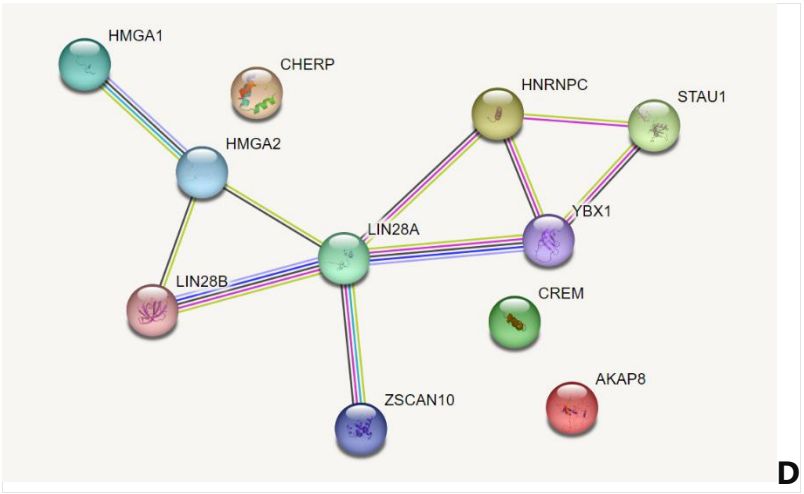


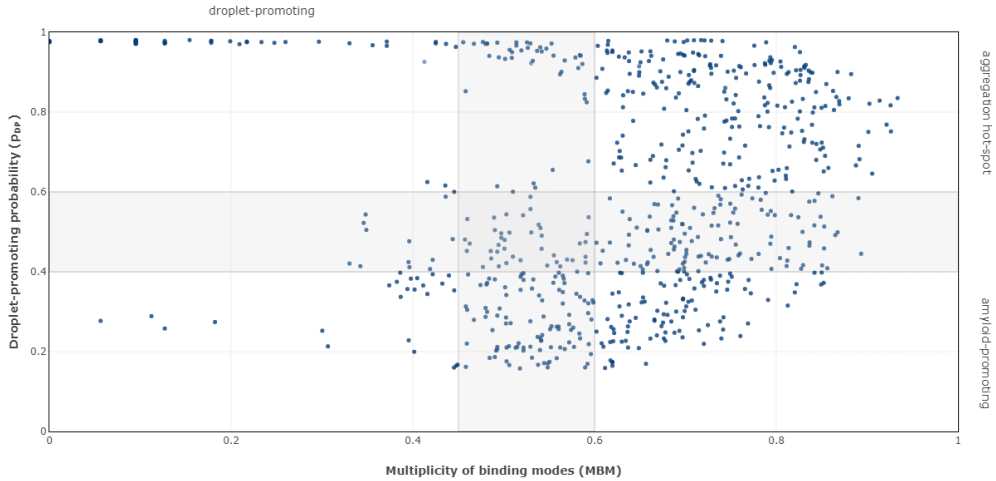
Figure 10. Functional disorder analysis of YBOX1_HUMAN **A**The functional disorder profile of YBOX1_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of YBOX1_HUMAN **D** String generated PPI network

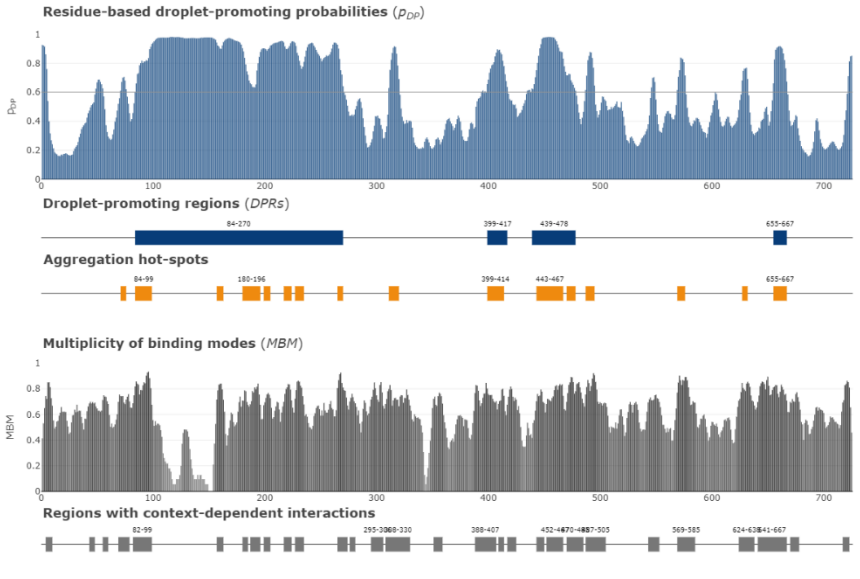
3.1.11 ZSC10_HUMAN

Embryonic stem (ES) cell-specific transcription factor required to maintain ES cell pluripotency. Can both activate and /or repress expression of target genes, depending on the context. Specifically binds the 5'-[GA]CGCNNGCG[CT]-3' DNA consensus sequence. Regulates expression of POU5F1/OCT4, ZSCAN4 and ALYREF/THOC4 (By similarity).

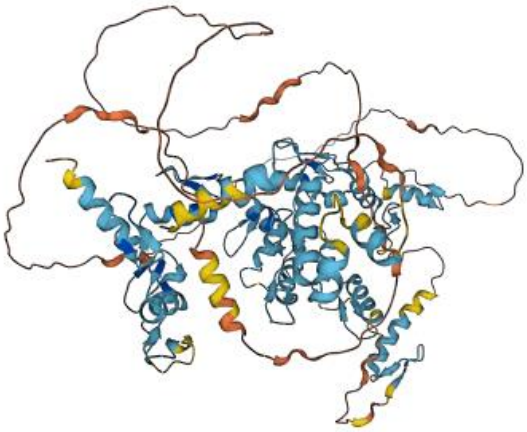

Predicted Domains
Predicted Disorder Agreement
MoRF Regions
PTM Sites
Key:
Predicted SCOP Structure
Weaker Support
Predicted Disorder
Predicted MoRFs
Curated PTM Site
Disorder:
Espritz-D
Espritz-X
Espritz-N
IUPred-L
IUPred-S
PV2
PrDOS
VSL2b
VLXT
Superfamilies:
[1] beta-beta-alpha zinc fingers
[2] Retrovirus capsid dimerization domain-like

A

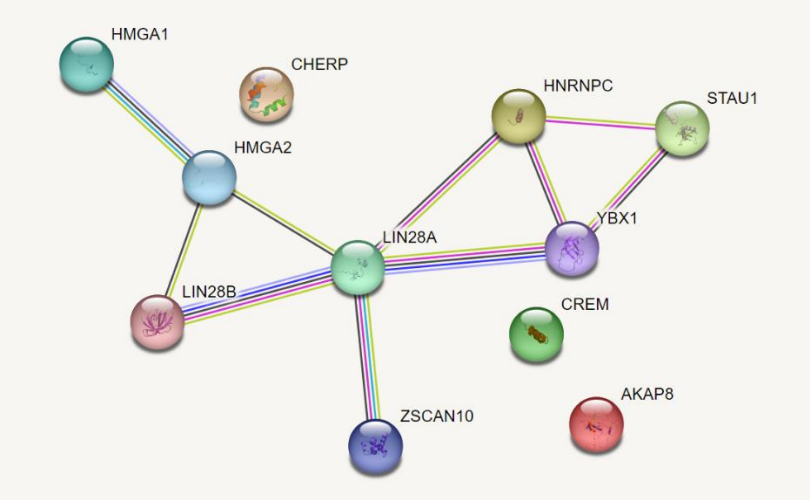

droplet-promoting
Droplet-promoting probability (p_{DP})
Multiplicity of binding modes (MBM)
aggregation hot-spot
amyloid-promoting


Residue-based droplet-promoting probabilities (p_{DP})
Droplet-promoting regions (DPRs)
Aggregation hot-spots
Multiplicity of binding modes (MBM)
Regions with context-dependent interactions

B



C



D

Figure 11. Functional disorder analysis of ZSC10_HUMAN **A**The functional disorder profile of ZSC10_HUMAN, generated by the D2P2 platform, depicts the localization of intrinsically disordered regions (IDRs) predicted by various algorithms, including IUPred, PONDR® VLXT, PONDR® VSL2, PrDOS, PV2, and ESpritz. **B** This color-coded visualization given by Alphafold offers insights into the reliability and confidence level of the predicted 3D structure of ZSC10_HUMAN **D** String generated PPI network

Conclusion:

Our research unveils a significant role for oncofetal proteins characterized by their high disorder in the regulation and maintenance of cancer stem cells (CSCs). Through our investigations, we have identified a complex interplay of protein-protein interactions among these oncofetal proteins, suggesting a sophisticated regulatory network at play. This network likely contributes to the observed tumor heterogeneity, metastatic potential, and resistance to therapeutic interventions observed in various cancers.

Furthermore, our study sheds light on the intriguing behavior of these proteins, indicating a propensity for phase separation. This phenomenon adds another layer of complexity to their regulatory mechanisms and underscores their multifaceted roles in cancer biology.

By unraveling the significance of oncofetal proteins and their involvement in CSC regulation, our findings provide valuable insights into the underlying mechanisms driving cancer progression. Moreover, they underscore the potential of targeting these proteins as a promising avenue for therapeutic intervention in cancer treatment strategies. Ultimately, our research contributes to a deeper understanding of cancer biology and highlights new directions for the development of more effective anticancer therapies.

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[1] PubMed Database: This entry would typically reference specific articles obtained from PubMed, formatted individually according to their respective authors, titles, journal names, and publication years.

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