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Therapeutic Opportunities in Disorder: Integrated Analysis of Cancer-Linked IDPs Reveals Druggable Motifs and Interaction Hubs

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INTRODUCTION & AIM

Intrinsically disordered proteins (IDPs) and intrinsically disordered regions (IDRs) lack stable tertiary structure yet remain fully functional, enabling flexibility, and rapid regulatory responses. These disordered regions participate in essential cellular processes including signal transduction, transcriptional regulation, and cell-cycle control. Due to their conformational plasticity, many IDPs function as hub proteins within protein-protein interaction networks. Cancer-associated proteins such as p53, BRCA1, and c-Myc are especially enriched in disordered regions, which enhance interaction promiscuity, PTM regulation, and adaptive stress responses, all of which are hallmarks of oncogenic transformation. However, most previous studies rely heavily on prediction-based disorder models, creating uncertainty due to false positives and low-resolution annotations. To overcome this limitation, this work exclusively analyzes experimentally validated IDPs from the DisProt database, which provides high-confidence, residue-level disorder data from NMR, X-ray crystallography, and biophysical experiments. Cancer-associated proteins in DisProt were categorized as Fully Disordered (FIDPs ≥90%), Moderately Disordered (MIDPs 30–90%), and Ordered Proteins (ODPs <30%) and further utilized for the MoRF profiling, PPI network mapping, Phosphorylation hotspot identification, and LLPS propensity and can serve as potential targets for therapeutic design, biomarker development, and precision-oncology applications.

METHOD

Experimentally validated cancer-associated intrinsically disordered proteins (IDPs) were retrieved from the DisProt database (version 2024_03), using functional and disease-related keywords to extract high-confidence, residue-level disorder annotations. Proteins were classified into Fully Disordered Proteins (FIDPs), Moderately Disordered Proteins (MIDPs), and Ordered Proteins (ODPs) following established disorder thresholds; only FIDPs and IDPs were analyzed further. Molecular Recognition Features (MoRFs) within intrinsically disordered regions were predicted using the deep learning–based tool fIDPnn, and mapped to the corresponding DisProt sequences. Protein–protein interaction (PPI) networks were generated using STRING (v12.0, confidence ≥0.7). Disorder coupled phosphorylation propensity was assessed using the PONDR-DEPP predictor to identify serine, threonine, and tyrosine phosphorylation hotspots enriched within IDRs. Liquid–liquid phase separation (LLPS) potential was computed using FuzDrop, with proteins scoring above 0.6 classified as LLPS-prone and further cross-validated using additional condensate predictors. This integrated workflow allowed functional interpretation of MoRFs, phosphorylation sites, LLPS signatures, and network connectivity within experimentally supported cancer-linked IDPs.

RESULTS & DISCUSSION

A total of 181 experimentally validated cancer-associated proteins were retrieved from the DisProt database and analyzed for disorder content. Based on residue-level disorder percentage, proteins were classified into:Fully Intrinsically Disordered Proteins (FIDPs): 11 proteins (6.1%), Moderately Intrinsically Disordered Proteins (MIDPs/IDPs): 28 proteins (15.5%), and Ordered Proteins (ODPs): 142 proteins (78.5%). The distribution is illustrated that although the majority of cancer-associated proteins remain ordered, a notable subset (~21.6%) possess substantial disorder, reinforcing the selective enrichment of IDRs in cancer biology. Only the highly disordered groups (11 FIDPs)were taken forward for functional analysis. These FIDPs displayed highly abundant IDRs, multiple MoRF-rich segments, and dense phosphorylation hotspots, strongly suggesting regulatory flexibility and interaction promiscuity.

Table 1. Summary of Intrinsically Disordered Regions (IDRs) and MoRF Distributions in 11 FIDPs

DisProt IDs	*UniProt IDs*	*IDR location*	*MoRF Count*
DP00016	P38936	1-8, 9-84, 85-164	63-82, 98-102, 136-164
DP00040	P17096	1-50, 51-75, 76-79, 80-89, 90-107	10-101
DP01128	O43806	1-24, 25-93, 94-158	13-23, 57-107, 112-119, 140-158
DP01876	P52926	1-109	12-98
DP00287	P40337	1-213	2-27, 32, 41-56, 107-113
DP01115	Q16236	1-16, 17-46, 47-605	6, 15-25, 569-572, 582-585, 592-599
DP01425	Q15004	1-111	7-111
DP04244	P40205	1-109	11-19, 23-32, 53-107
DP00018	P46527	1-21, 22-97, 98-180, 181-190, 191-198	13-23, 71-96, 149-156, 184-198
DP01102	P35637	1-284, 285-370, 371-420, 421-455, 456-507	12-23, 50-58, 65-66, 73-79, 90-104, 132-136, 147-161, 177-185, 203-223, 462-526
DP00333	P27797	18-417	200-205, 218-222, 271-276, 286-295, 304-309

Table 2. LLPS Scores and Droplet-Promoting Regions (DPRs) of 11 FIDPs

DisProt IDs	*UniProt IDs*	*LLPS Score (FuzDrop)*	*Droplet-Promoting Regions(DPR)*
DP00016	P38936	0.9341	1-15, 77-109, 113-148
DP00040	P17096	-	-
DP01128	O43806	0.972	1-27, 92-144
DP01876	P52926	0.6579	1-73, 94-104
DP00287	P40337	0.6579	1-73, 94-105
DP01115	Q16236	0.8701	1-15, 86-112, 293-321, 325-452, 536-550
DP01425	Q15004	0.9925	1-12, 24-52, 73-111
DP04244	P40205	0.1969	-
DP00018	P46527	0.9947	1-27, 90-198
DP01102	P35637	0.9999	1-294, 360-437, 443-526
DP00333	P27797	0.8045	188-304, 348-417

Their IDR boundaries correspond well with both MoRF and phosphorylation-dense regions, indicating structural–functional coupling typical of cancer-associated IDPs. The MoRF analysis revealed that each FIDP contained 4–15 MoRF clusters, with particularly dense MoRF distributions in DP00333 (P27797), DP01012 (P35637), and DP00040 (P17096)(Table 1). Such MoRF abundance reflects high interaction plasticity, a hallmark of oncogenic scaffolding proteins. MoRFs located within long IDRs serve as transient binding modules, enabling rapid rewiring of cancer pathways such as DNA repair, apoptosis regulation, transcriptional activation, and cell-cycle progression.

LLPS analysis revealed that 9 out of 11 FIDPs exceeded the LLPS threshold (>0.6), with proteins such as DP00018, DP01425, DP00333, DP00016, and DP01115 showing extremely high scores (0.93–0.99)(Table2). These proteins also contained multiple droplet-promoting segments, often overlapping MoRF and phosphorylation dense regions. This alignment suggests that dynamic condensate formation in cancer is cooperatively driven by disorder, MoRF flexibility, and PTM-rich hotspots. Together, the IDR mapping, MoRF architecture, phosphorylation density, and LLPS potential highlight a coherent functional signature of FIDPs: Extensive IDRs provide conformational freedom for multiple interaction modes. High MoRF density enables rapid, condition-dependent interactions in cancer signaling. Dense phosphorylation sites confer tight regulation via PTMs. High LLPS propensity suggests involvement in oncogenic biomolecular condensates. These properties indicate that cancer-associated FIDPs act as interaction hubs, regulatory switches, and phase-separated organizers within malignant cells.

CONCLUSION

This study provides a comprehensive functional characterization of 181 experimentally validated cancer-associated proteins, revealing that intrinsic disorder is a major structural and regulatory feature in oncogenic proteins. Although only 11 proteins qualified as Fully Intrinsically Disordered Proteins (FIDPs ≥90% disorder), these proteins displayed the highest concentration of functionally significant motifs, including long and continuous IDRs, abundant MoRF regions, dense phosphorylation hotspots, and strong LLPS propensity. Future studies will experimentally validate the predicted MoRFs, phosphorylation hotspots, and LLPS-prone regions to confirm their regulatory roles in cancer. Integrating these validated motifs with structural, mutational, and interactome data will enable the design of targeted therapeutics and biosensors that exploit IDR-mediated signaling vulnerabilities. Expanding this analysis across cancer subtypes will further refine IDP-based biomarkers and therapeutic strategies.

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