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Intrinsic Disorder in Autophagy-Related Proteins: Insights for Therapeutic Development

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INTRODUCTION

Autophagy is an essential cellular process responsible for degrading and recycling intracellular components, ensuring cellular homeostasis (Liang et al., 1999). The process is regulated by autophagy-related proteins, many of which lack a stable three-dimensional structure, classifying them as Intrinsically Disordered Proteins (IDPs) (Fernandez & Levine, 2016). IDPs enable dynamic interactions required for autophagy regulation [3]. However, mutations affecting IDPs may disrupt disorder-mediated interactions, leading to diseases such as neurodegeneration and cancer (Fecto et al., 2011; Nakamura et al., 2020).

This study aims to:

- Analyze the prevalence of IDPs in autophagy-related proteins.
- Examine the overlap between disease-linked mutations and intrinsically disordered regions (IDRs).
- Identify potential IDP-targeted therapeutic strategies.

METHOD

- **Proteins Analyzed**: In this study, we analyzed 95 autophagy-related proteins from the Human Autophagy Database (HADb) and UniProt using sets of bioinformatics tools like Espritz, leveraging by datasets trained on X-ray, NMR, and DisProt data (Rea et al., 2014). Then percentage of disorder per protein (Borden et al., 2021) was analyzed along with presence of long disordered segments (with >30 and/or >50 amino acids) (Dooley et al., 2014), and the functional classification of IDP-enriched proteins was also done (Morani et al., 2014).
- **Mutation Overlap Analysis:** Mapping of disease-associated mutations onto IDRs (Stadel et al., 2015) was done and the mutation-enriched IDRs in key autophagy proteins were identified (Waters et al., 2018).

RESULTS & DISCUSSION

Intrinsic Disorder in Autophagy Proteins

- Mean disorder content: 34.36% and 80.21% of autophagy-related proteins contain at least one disordered region longer than 30 amino acids, along with 65.97% contain at least one disordered region exceeding 50 amino acids.

Mutation Overlap in IDRs

- 37% of disease-associated mutations in autophagy proteins occur within IDRs and Proteins identified with the highest IDR-mutation overlap are :

  - ❑ SQSTM1 (p62) – Paget's Disease, ALS, FTD
  - ❑ Beclin-1 – Breast & Ovarian Cancer
  - ❑ ATG5 & ATG7 – Neurodegeneration & Cancer

- **Mutation Hotspots in Disordered Regions:** Proteins SPP01106, SPP01100, and SPO95817 contain mutation clusters in disordered domains.

Table 1: Overlap of Disease-Associated Mutations with IDRs in Autophagy Proteins

Protein Name	Mutation(s) Identified	Disease Association	Mutation Located in IDR?	IDR Position(s)
SQSTM1 (p62)	P392L, G425R, A381V, G411S	Paget's Disease, ALS, FTD	Yes	350-440
Beclin-1 (BECN1)	T119M, F359C, R388X	Breast Cancer, Ovarian Cancer	Yes	110-140, 340-400
ATG5	T181A, Y193C	Systemic Lupus Erythematosus, Cancer	Yes	170-210
ATG7	R421Q, D522N	Neurodevelopmental Disorders, Cancer	Yes	400-540
ATG12	R25Q, D49G	Ataxia-Telangiectasia, Neurodegeneration	Yes	20-60
ULK1	F983I, R1132H	Cancer, Metabolic Disorders	No	N/A
WIPI2	G80S, A147T	Neurodegenerative Disorders	Yes	70-160
NBR1	E452K, S304T	Cancer, Neurological Disorders	Yes	300-460

CONCLUSION

These results reinforce the critical role of IDPs in mediating transient and dynamic interactions that are essential for autophagy. This study advances our understanding of the molecular dynamics of autophagy-related proteins and provides a foundation for developing disorder-targeted therapeutic strategies. Such strategies hold potential for addressing neurodegenerative diseases, cancers, and other disorders linked to autophagic dysregulation.

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