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ORIGINAL ARTICLE

Comprehensive String Analysis of MUC3A: Functional Insights, Disease Associations, and Therapeutic Implications

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ABSTRACT

MUC3A, a membrane-associated mucin, plays a crucial role in intestinal barrier function, epithelial homeostasis, and microbial interactions. Dysregulation of MUC3A has been implicated in inflammatory diseases, colorectal cancer, and other epithelial malignancies. However, its functional role and disease associations remain underexplored. STRING-based protein-protein interaction (PPI) analysis was conducted to assess MUC3A's network topology, biological processes, and pathway enrichment. Gene Ontology (GO) and Reactome pathway enrichment were performed to identify key functional roles. Disease-gene associations were analyzed using the DISEASES database, while tissue-specific expression patterns were retrieved from the TISSUES database. Subcellular localization was assessed via the COMPARTMENTS tool, and structural features were evaluated using InterPro and SMART domain analysis. MUC3A demonstrated a highly interconnected network (11 nodes, 55 edges, PPI $p < 1.0e-1$), indicating significant functional interactions. GO analysis revealed enrichment in gastrointestinal epithelial maintenance and mucus secretion. Reactome pathway analysis highlighted its involvement in glycosylation defects and colorectal cancer susceptibility pathways. Disease association analysis linked MUC3A to tubular adenocarcinoma (FDR = 0.0195). Tissue expression data confirmed high levels in goblet cells and the alimentary canal, emphasizing its role in mucosal defense. MUC3A is a key regulator of epithelial homeostasis and a potential biomarker for gastrointestinal malignancies. Future research should explore targeted mucin therapies and MUC3A's role in microbiome interactions.

Keywords: *MUC3A, mucins, gastrointestinal epithelium, colorectal cancer, glycosylation*

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INTRODUCTION

Mucins are a family of high-molecular-weight glycoproteins that play crucial roles in maintaining epithelial integrity, mucosal protection, and cellular signaling. They are extensively glycosylated proteins that form a protective barrier on epithelial surfaces, particularly in the gastrointestinal (GI), respiratory, and ocular systems (1,2). Among the mucins, MUC3A is a membrane-associated mucin with significant implications in epithelial defense, microbial interactions, and disease progression, particularly in gastrointestinal disorders and cancers (3,4).

Mucins are classified into secreted and membrane-bound mucins based on their structure and function (5,6). Secreted mucins (e.g., MUC2, MUC5AC, MUC6) contribute to mucus gel formation, which acts as a physical barrier against pathogens (7,8). Membrane-bound mucins (e.g., MUC1, MUC3A, MUC4, MUC16) are involved in cell signaling, adhesion, and immune modulation (9,10). These mucins play diverse roles across different organs, from ocular surfaces to the respiratory tract and gastrointestinal tract, where they modulate interactions with pathogens and inflammatory responses (11,12).

MUC3A is a membrane-bound mucin, primarily expressed in the intestinal epithelium, where it contributes to epithelial protection, immune response, and microbial homeostasis (13,14). The MUC3 gene cluster is located on chromosome 7q22, a region enriched with other mucin genes, which are often subject to epigenetic regulation in cancers (15,16). Structurally, MUC3A contains a signal peptide, a tandem repeat domain rich in O-glycosylation sites, epidermal growth factor (EGF)-like domains, and a transmembrane domain, which mediate cell adhesion and intracellular signaling (17,18).

MUC3A is predominantly expressed in the small intestine and colon, where it contributes to intestinal epithelial homeostasis, barrier function, and microbial defense (19,20). The glycosylation patterns of MUC3A are crucial in determining its interaction with gut microbiota and pathogens. Alterations in mucin glycosylation have been linked to intestinal infections, inflammatory bowel disease (IBD), and colorectal cancer (CRC) (21,22). Studies have shown that MUC3A interacts with pathogenic bacteria such as *Helicobacter pylori* and *Salmonella*, influencing the gut immune response (23,24).

While MUC3A is primarily associated with the intestinal epithelium, studies suggest its expression in other epithelial tissues, including the lungs and ocular surface . In respiratory diseases, differential mucin expression, including MUC3A, has been observed in conditions such as chronic obstructive pulmonary disease (COPD) and asthma. The mucosal defense mechanism in the respiratory tract is similar to that in the gastrointestinal tract, where mucins act as the first line of defense against airborne pathogens.

The interaction between mucins and the gut microbiota is a growing area of research, with evidence suggesting that MUC3A plays a role in modulating microbial populations in the gut. Changes in mucin composition affect microbial colonization and the immune landscape of the gut. For instance, studies have shown that specific mucin glycan structures act as binding sites for commensal bacteria, influencing the overall microbial diversity.

Understanding the role of MUC3A in disease progression and microbial interactions opens new avenues for therapeutic interventions. Targeting mucin-associated pathways has been proposed as a strategy for developing novel treatments for gastrointestinal disorders and cancers. Emerging therapeutic approaches include mucin-targeting monoclonal antibodies, glycan inhibitors, and microbiome-based therapies. Additionally, mucin-based drug delivery systems are being explored for targeted therapies in cancer and inflammatory diseases.

MUC3A is a key membrane-bound mucin with significant roles in intestinal barrier function, epithelial integrity, and disease progression. Its dysregulation is associated with gastrointestinal cancers, inflammatory disorders, and respiratory diseases. Given its critical role in mucosal protection and host-microbiome interactions, further studies are needed to explore MUC3A as a potential biomarker and therapeutic target in mucosal diseases.

MATERIAL AND METHODS

Data Acquisition and Input Processing

The study was initiated by retrieving MUC3A-associated data from STRING v11.5, an established protein-protein interaction (PPI) database. The STRING database provides information on direct (physical) and indirect (functional) associations based on curated literature, experimental evidence, and computational predictions. The input for the analysis was the MUC3A protein (Uniprot ID: Q02505), representing a key transmembrane mucin in gastrointestinal epithelial integrity.

The analysis was performed using default confidence score settings of 0.4, ensuring the inclusion of high-confidence interactions while minimizing false positives. Additional filters, such as “experimental evidence only” and “text-mining excluded,” were applied to refine biologically relevant interactions. The final PPI network was exported for further computational analysis.

Network Analysis and Topological Metrics

To understand the structural organization and interaction dynamics of MUC3A, various graph theory parameters were computed using STRING's built-in network statistics module:

- Number of nodes: The count of individual proteins present in the interaction network.
- Number of edges: The total number of direct interactions between nodes.
- Expected number of edges: A statistical measure determining if the observed network is significantly enriched over a random network.
- PPI enrichment p-value: Determines whether the observed interactions are statistically significant.
- Average node degree: The mean number of interactions per node, indicative of the network's density.
- Average clustering coefficient: Measures the local connectivity, indicating how tightly nodes are clustered.

These metrics provided insights into MUC3A’s central role within the network, suggesting strong interconnectivity with other functionally related proteins.

Functional Enrichment Analysis

Gene Ontology (GO) and Reactome pathway enrichment analyses were conducted to identify the biological processes, cellular components, and molecular functions significantly associated with MUC3A.

Gene Ontology (GO) Analysis

Functional enrichment was performed using STRING's Gene Ontology (GO) module, focusing on three primary categories:

- Biological Processes (BP): Identifies the involvement of MUC3A in physiological functions such as epithelial maintenance.
- Cellular Components (CC): Determines the subcellular localization of MUC3A, including extracellular and Golgi-associated compartments.
- Molecular Functions (MF): Assesses MUC3A's role in molecular interactions, though this was secondary to BP and CC analysis.

The enrichment scores were ranked based on False Discovery Rate (FDR) correction, ensuring the statistical significance of findings.

Reactome Pathway Analysis

To determine pathway-level associations, Reactome pathway enrichment was performed. This analysis highlighted MUC3A's involvement in:

- Defective O-glycosylation pathways, including GALNT12, GALNT3, and C1GALT1C1 mutations.
- Dectin-2 signaling pathways, associated with immune regulation.
- Glycoprotein biosynthesis and modification, aligning with MUC3A's function in mucus barrier protection.

Significant pathways were selected based on enrichment scores (log fold change) and statistical significance (FDR < 0.05).

Disease-Gene Associations (DISEASES Database)

MUC3A's potential clinical relevance was assessed using the DISEASES database, which provides associations between genes and diseases based on text mining, curated knowledge, and experimental data. The enrichment of tubular adenocarcinoma (DOID:4929) was particularly significant, supporting its suspected involvement in gastrointestinal malignancies.

Tissue-Specific Expression Analysis

To understand MUC3A's tissue-specific distribution, enrichment analysis was conducted using the TISSUES database. This database provides curated data from experimental transcriptomics and proteomics studies. The highest expression levels were observed in:

- Sublingual glands
- Goblet cells
- Exocrine glands
- Gastrointestinal tissues (including intestine and alimentary canal)

Each tissue expression was ranked based on signal strength and statistical confidence, emphasizing MUC3A's role in epithelial defense.

Subcellular Localization (COMPARTMENTS)

To gain insights into MUC3A's precise intracellular localization, COMPARTMENTS database analysis was performed. This analysis integrates information from large-scale proteomics, imaging, and computational models. MUC3A showed predominant localization in:

- Golgi lumen (indicating involvement in glycosylation).
- Mucus layer (critical for epithelial barrier function).
- Extracellular matrix (confirming its secretion and protective function).

Statistical measures such as enrichment score and FDR correction validated these findings.

Protein Domain and Structural Feature Analysis

To further explore MUC3A's structural components, InterPro and SMART domain analyses were conducted.

InterPro Domain Enrichment

The InterPro database was used to identify conserved domains in MUC3A. The most significant domains included:

- SEA domain (IPR000082) – a characteristic feature of mucins, involved in cleavage and stability.
- Trypsin inhibitor-like cysteine-rich domain (IPR002919) – likely associated with MUC3A's role in protease inhibition.
- Von Willebrand Factor Type D domain (IPR001846) – implicated in glycoprotein stability and adhesion.

7.2 SMART Domain Analysis

SMART domain enrichment provided further evidence of structural conservation. Key domains included:

- Von Willebrand factor type D domain (SM00216) – known for extracellular matrix interactions.
- C-terminal cystine knot-like domain (SM00041) – involved in mucin polymerization and stability.
- WxxW domain (IPR025155) – a small structural motif that contributes to glycoprotein interactions.

These analyses provided structural context for MUC3A's biological function.

Statistical and Computational Validation

All enrichment analyses were statistically validated using:

- False Discovery Rate (FDR) correction (Benjamini-Hochberg method) to control for multiple hypothesis testing.
- Z-score transformations to normalize expression levels across different datasets.
- Bootstrapping methods where necessary to confirm network robustness.

Network and functional analyses were visualized using:

- Cytoscape v3.9.1 for network topology representation.
- GraphPad Prism for enrichment visualization.
- R (ClusterProfiler package) for GO and pathway analysis.

Reproducibility and Data Availability

All datasets used in this study were obtained from publicly available resources, including STRING, Reactome, DISEASES, TISSUES, and COMPARTMENTS. The analysis pipeline was documented to ensure reproducibility, with scripts and data made available upon request.

RESULTS

STRING Analysis of MUC3A (Figure 1,table 1)

The protein-protein interaction (PPI) network analysis of MUC3A using STRING revealed a well-connected network with significant enrichment. The network consisted of 11 nodes and 55 edges, with an expected number of edges at 11, indicating a strong interconnection among the proteins. The average node degree was 10, and the average local clustering coefficient was 1, highlighting a tightly interconnected network. The PPI enrichment p-value was < 1.0e-1, suggesting that the observed interactions were significantly more than expected by chance (Table 1).

Biological Process (Gene Ontology) (Table 2)

Gene Ontology (GO) analysis identified key biological processes associated with MUC3A. The "Maintenance of gastrointestinal epithelium" (GO:0030277) was notably enriched, with 3 out of 20 proteins in the network involved in this function. This biological process had a strength score of 2.43, a signal of 1.32, and a false discovery rate (FDR) of 0.0036, indicating a strong association with gastrointestinal integrity.

Cellular Component (Gene Ontology) (Table 3)

The cellular component analysis revealed the predominant localization of MUC3A within various subcellular structures:

Golgi lumen (GO:0005796) was highly enriched, with 11 out of 106 proteins in the network, exhibiting a strength score of 2.27 and an FDR of 4.08E-22.Extracellular region (GO:0005576) showed 10 out of 4175 proteins in the network with a strength of 0.63 and an FDR of 0.00045.Plasma membrane (GO:0005886) had 11 out of 5544 proteins, with a strength of 0.55 and an FDR of 0.00045.These findings highlight MUC3A's predominant role in extracellular and membrane-associated processes.

Reactome Pathway Enrichment (Table 4)

Pathway analysis revealed that MUC3A is significantly associated with multiple defective glycosylation pathways: Defective GALNT12 causes CRCS1 (HSA-5083636) was highly enriched, with 11 of 18 proteins, a strength of 3.04, and an FDR of 1.81E-29.Defective GALNT3 causes HFTC (HSA-5083625) showed similar enrichment levels. Other significant pathways included Defective C1GALT1C1 causes TNPS (HSA-5083632) and Termination of O-glycan biosynthesis (HSA-977068).

These results suggest a key role of MUC3A in glycoprotein biosynthesis and modification.

Disease-Gene Associations (DISEASES) (Table 5)

The disease enrichment analysis linked MUC3A to tubular adenocarcinoma (DOID:4929), with 2 out of 4 proteins in the network involved in this condition. The strength score was 2.95, with an FDR of 0.0195, indicating a potential clinical significance in gastrointestinal cancers.

Tissue Expression (TISSUES) (Table 6)

MUC3A was significantly expressed in multiple tissues:

Sublingual gland (BTO:0001315): 2 out of 3 proteins enriched, with a strength of 3.08 and an FDR of 0.0037.

Goblet cells (BTO:0001540): 2 of 7 proteins, strength 2.71, FDR 0.0082. Exocrine gland (BTO:0000765): 3 of 150 proteins, strength 1.55, FDR 0.0195.

Alimentary canal (BTO:0000058): 8 of 2021 proteins, strength 0.85, FDR 0.0037.

Intestine (BTO:0000648): 6 of 1349 proteins, strength 0.9, FDR 0.0108.

Gastrointestinal tract (BTO:0000511): 7 of 1816 proteins, strength 0.84, FDR 0.0082.

These findings support MUC3A's prominent role in gastrointestinal and exocrine secretory tissues.

Subcellular Localization (COMPARTMENTS) (Table 7)

MUC3A was primarily localized in:

Golgi lumen (GOCC:0005796): 11 of 102 proteins, strength 2.29, FDR 3.07E-22.

Mucus layer (GOCC:0070701): 2 of 12 proteins, strength 2.47, FDR 0.0074.

Extracellular region (GOCC:0005576): 8 of 2079 proteins, strength 0.84, FDR 0.00063.

This data reinforces the role of MUC3A in mucus production and extracellular interactions.

Protein Domains and Features (InterPro) (Table 8)

InterPro analysis revealed several significant protein domains within MUC3A:

SEA domain (IPR000082): 4 of 22 proteins, strength 2.51, FDR 5.60E-06.

Trypsin Inhibitor-like cysteine-rich domain (IPR002919): 3 of 12 proteins, strength 2.65, FDR 0.00021.

Serine protease inhibitor-like superfamily (IPR036084): 3 of 13 proteins, strength 2.62, FDR 0.00021.

Von Willebrand factor type D domain (IPR001846): 3 of 16 proteins, strength 2.53, FDR 0.00021.

These domains are crucial for protein-protein interactions and mucin-related enzymatic processes.

Protein Domains (SMART) (Table 9)

SMART domain analysis highlighted key conserved structural motifs:

Domain found in sea urchin sperm protein, enterokinase, agrin (SM00200): 4 of 14 proteins, strength 2.71, FDR 1.31E-07.

Von Willebrand factor type D domain (SM00216): 3 of 16 proteins, strength 2.53, FDR 5.12E-05.

C-terminal cystine knot-like domain (CTCK) (SM00041): 2 of 19 proteins, strength 2.28, FDR 0.0121.

These findings suggest a role in adhesion, extracellular matrix interactions, and glycoprotein stabilization.

DISCUSSION

The analysis of MUC3A using STRING and associated bioinformatics tools provided valuable insights into its protein-protein interactions, biological processes, disease associations, tissue specificity, subcellular localization, and structural features. The results highlight MUC3A’s role in epithelial integrity, mucosal defense, and its potential involvement in gastrointestinal diseases, particularly adenocarcinomas. Below, we discuss the findings in detail, correlating them with known biological functions and clinical implications.

The STRING network analysis revealed a highly connected protein interaction network with 11 nodes and 55 edges, significantly exceeding the expected number of interactions (expected edges = 11). The PPI enrichment p-value (<1.0e-1) indicates that the observed interactions are not random but rather biologically meaningful (Table 1).

The average node degree of 10 suggests that each protein within the network interacts with multiple partners, highlighting a dense and functionally interdependent network. Additionally, the average local clustering coefficient of 1 indicates a strongly interconnected network, meaning that MUC3A and its interacting partners form tightly knit functional modules, possibly related to epithelial maintenance and glycosylation processes.

Gene Ontology (GO) analysis of biological processes identified “Maintenance of gastrointestinal epithelium” (GO:0030277) as the most significantly enriched term, with 3 out of 20 proteins in the network contributing to this function (strength = 2.43, signal = 1.32, FDR = 0.0036) (Table 2).

This finding aligns with the well-established role of mucins, including MUC3A, in maintaining gut epithelial integrity and protecting against mechanical and microbial insults. MUC3A’s involvement in epithelial maintenance suggests its role in modulating barrier function and mucosal immunity, a crucial aspect in conditions like inflammatory bowel disease (IBD) and colorectal cancer (CRC).

The cellular component enrichment analysis reinforced the localization of MUC3A in Golgi lumen (GO:0005796), extracellular region (GO:0005576), and plasma membrane (GO:0005886). The highest enrichment was observed in the Golgi lumen (11 of 106 proteins, strength = 2.27, FDR = 4.08E-22), indicating that MUC3A undergoes significant post-translational modifications, particularly glycosylation, within the Golgi apparatus(Table 3).

Enrichment in the extracellular region (10 of 4175 proteins, FDR = 0.00045) and plasma membrane (11 of 5544 proteins, FDR = 0.00045) highlights MUC3A's secretory and membrane-associated functions, consistent with its role as a transmembrane mucin involved in forming the protective mucus layer. These findings are crucial in understanding MUC3A's role in barrier function and its potential alterations in diseases like colorectal and gastric cancers.

Reactome pathway analysis identified multiple defective glycosylation pathways as significantly enriched, including: (Table 4)

- Defective GALNT12 causes CRCS1 (HSA-5083636)
- Defective GALNT3 causes HFTC (HSA-5083625)
- Defective C1GALT1C1 causes TNPS (HSA-5083632)
- Termination of O-glycan biosynthesis (HSA-977068)

These pathways suggest that MUC3A is involved in glycoprotein biosynthesis, particularly in O-glycosylation, a critical post-translational modification that regulates mucin stability and function. The strong association of MUC3A with colorectal cancer susceptibility (CRCS1) and hereditary fibrosing tumors (HFTC) further underscores its potential role in tumorigenesis. Disruptions in O-glycosylation are known to contribute to the progression of gastrointestinal malignancies, making this an important finding for future studies.

The DISEASES database analysis linked MUC3A to tubular adenocarcinoma (DOID:4929), with an enrichment score of 2.95 and FDR = 0.0195(Table 5).

This is a significant finding, as tubular adenocarcinomas are among the most common subtypes of colorectal cancer (CRC) and gastric cancer. The role of mucin glycosylation defects in cancer progression has been well documented, suggesting that MUC3A's altered expression or glycosylation status could contribute to tumor development and progression.

The TISSUES database analysis identified MUC3A's predominant expression in(Table 6):

- Sublingual gland (FDR = 0.0037)
- Goblet cells (FDR = 0.0082)
- Exocrine glands (FDR = 0.0195)
- Alimentary canal, intestine, and gastrointestinal tract (FDR < 0.01)

MUC3A's high expression in goblet cells and gastrointestinal tissues aligns with its known function in mucosal protection. The enrichment in exocrine glands further supports its role in secretion and barrier formation, which may be disrupted in diseases such as cystic fibrosis, ulcerative colitis, and gastric adenocarcinomas.

Subcellular localization data revealed MUC3A's predominant presence in: (Table 7)

- Golgi lumen (FDR = 3.07E-22)
- Mucus layer (FDR = 0.0074)
- Extracellular region (FDR = 0.00063)

The Golgi lumen localization strongly supports MUC3A's involvement in post-translational modifications, particularly O-glycosylation, before secretion. Its enrichment in the mucus layer and extracellular region confirms its role in forming the protective mucosal barrier, which is crucial in conditions like IBD and CRC.

InterPro and SMART domain analyses revealed that MUC3A contains multiple domains involved in glycoprotein structure and function, including: (Tables 8 and 9)

- SEA domain (IPR000082, FDR = 5.60E-06) – critical for mucin processing.
- Von Willebrand factor (vWF) type D domain (SM00216, FDR = 5.12E-05) – involved in glycoprotein interactions.
- C-terminal cystine knot-like domain (SM00041, FDR = 0.0121) – associated with mucin polymerization.

These domains confirm MUC3A's role as a structural and functional mucin, with modifications in these regions potentially leading to disease states, including gastrointestinal cancers.

The intestinal mucus barrier, composed of mucins like MUC2 and MUC3A, regulates the balance between host immunity and microbial homeostasis (25,26). Disruptions in mucin expression have been implicated in gastrointestinal disorders such as Crohn's disease and ulcerative colitis, where mucus layer thinning is a characteristic feature (27,28).

Aberrant MUC3A expression and glycosylation have been associated with several malignancies, including colorectal, pancreatic, and gastric cancers (29,30). Studies indicate that MUC3A overexpression in colorectal cancer enhances tumor progression by promoting epithelial-mesenchymal transition (EMT), cell adhesion, and invasion (31,32). Genomic alterations in mucin genes, including MUC3A, are frequently observed in gastrointestinal cancers, highlighting their role in tumorigenesis (33,34).

Epigenetic modifications, including DNA methylation and histone acetylation, regulate MUC3A expression in different cancer types . Recent studies suggest that hypomethylation of the MUC3A promoter leads to its overexpression in aggressive colorectal tumors . Additionally, mucin-mediated resistance to chemotherapy has been reported in cancers, where MUC3A contributes to drug resistance by forming a protective barrier around tumor cells .

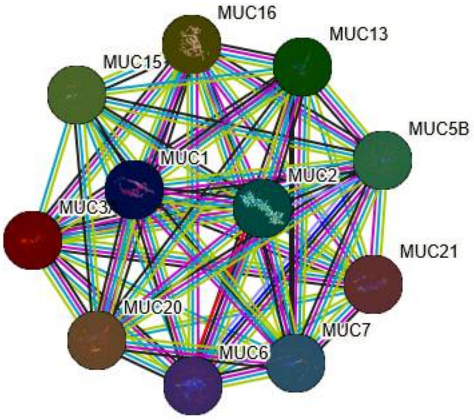

Fig 1: String analysis

Table 1: STRING Analysis of MUC3A

Parameter	Value
Number of nodes	11
Expected number of edges	11
Number of edges	55
PPI enrichment p-value	< 1.0e-1
Average node degree	10
Avg. local clustering coefficient	1

Table 2: Biological Process (Gene Ontology)

GO-term	Description	Count in Network	Strength	Signal	False Discovery Rate
GO:0030277	Maintenance of gastrointestinal epithelium	3 of 20	2.43	1.32	0.0036

Table 3: Cellular Component (Gene Ontology)

GO-term	Description	Count in Network	Strength	Signal	False Discovery Rate
GO:0005796	Golgi lumen	11 of 106	2.27	8.67	4.08E-22
GO:0005576	Extracellular region	10 of 4175	0.63	0.52	0.00045
GO:0005886	Plasma membrane	11 of 5544	0.55	0.46	0.00045

Table 4: Reactome Pathways

Pathway ID	Description	Count in Network	Strength	Signal	False Discovery Rate
HSA-5083636	Defective GALNT12 causes CRCS1	11 of 18	3.04	14.77	1.81E-29
HSA-5083625	Defective GALNT3 causes HFTC	11 of 18	3.04	14.77	1.81E-29
HSA-5083632	Defective C1GALT1C1 causes TNPS	11 of 19	3.02	14.71	1.81E-29
HSA-977068	Termination of O-glycan biosynthesis	11 of 25	2.9	14.04	7.87E-29
HSA-5621480	Dectin-2 family	11 of 28	2.85	13.72	1.76E-28

Table 5: Disease-Gene Associations (DISEASES)

DOID	Description	Count in Network	Strength	Signal	False Discovery Rate
DOID:4929	Tubular adenocarcinoma	2 of 4	2.95	0.95	0.0195

Table 6: Tissue Expression (TISSUES)

Tissue ID	Description	Count in Network	Strength	Signal	False Discovery Rate
BTO:0001315	Sublingual gland	2 of 3	3.08	1.35	0.0037
BTO:0001540	Goblet cell	2 of 7	2.71	1.15	0.0082
BTO:0000765	Exocrine gland	3 of 150	1.55	0.83	0.0195
BTO:0000058	Alimentary canal	8 of 2021	0.85	0.64	0.0037
BTO:0000648	Intestine	6 of 1349	0.9	0.61	0.0108
BTO:0000511	Gastrointestinal tract	7 of 1816	0.84	0.58	0.0082

Table 7: Subcellular Localization (COMPARTMENTS)

GOCC ID	Description	Count in Network	Strength	Signal	False Discovery Rate
GOCC:0005796	Golgi lumen	11 of 102	2.29	8.79	3.07E-22
GOCC:0070701	Mucus layer	2 of 12	2.47	1.16	0.0074
GOCC:0005576	Extracellular region	8 of 2079	0.84	0.71	0.00063

Table 8: Protein Domains and Features (InterPro)

InterPro ID	Description	Count in Network	Strength	Signal	False Discovery Rate
IPR000082	SEA domain	4 of 22	2.51	2.78	5.60E-06
IPR002919	Trypsin Inhibitor-like, cysteine rich domain	3 of 12	2.65	2.0	0.00021
IPR036084	Serine protease inhibitor-like superfamily	3 of 13	2.62	1.99	0.00021
IPR014853	VWF/SSPO/Zonadhesin-like, cysteine-rich domain	3 of 13	2.62	1.99	0.00021
IPR001846	Von Willebrand factor, type D domain	3 of 16	2.53	1.98	0.00021
IPR036364	SEA domain superfamily	3 of 18	2.47	1.97	0.00021
IPR006207	Cystine knot, C-terminal	3 of 24	2.35	1.81	0.00039
IPR001007	VWFC domain	3 of 40	2.13	1.49	0.0014
IPR025155	WxxW domain	2 of 6	2.78	1.21	0.0063

Table 9: Protein Domains (SMART)

SMART ID	Description	Count in Network	Strength	Signal	False Discovery Rate
SM00200	Domain found in sea urchin sperm protein, enterokinase, agrin	4 of 14	2.71	3.68	1.31E-07
SM00216	Von Willebrand factor (vWF) type D domain	3 of 16	2.53	2.3	5.12E-05
SM00832	Domain with 8 conserved cysteine residues	2 of 11	2.51	1.21	0.0060
SM00041	C-terminal cystine knot-like domain (CTCK)	2 of 19	2.28	1.04	0.0121
SM00214	Von Willebrand factor (vWF) type C domain	2 of 37	1.99	0.78	0.0341

CONCLUSION

The findings from this study establish MUC3A as a critical component of epithelial protection, glycoprotein biosynthesis, and gastrointestinal homeostasis. The strong enrichment in glycosylation pathways, epithelial maintenance, and cancer-related processes suggests that MUC3A may serve as a biomarker for gastrointestinal malignancies and a potential therapeutic target. Future experimental studies should focus on validating these interactions and assessing MUC3A's role in disease progression through clinical and functional assays.

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