Distinct Biological Profiles of Mucinous Carcinoma with a Solid Papillary Carcinoma Component Compared to Other Histological Types

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Abstract

Aim: To elucidate the biological and molecular differences among mucinous carcinomas (MCs) based on the presence or absence of solid papillary carcinoma (SPC)-like histological features
Materials & Methods: MCs from *The Cancer Genome Atlas Breast Invasive Carcinoma* (TCGA-BRCA) cohort were subclassified into two groups according to histopathological features: those with a SPC component (MC-SPC) and those without (MC-OTHER). Clinicopathological and transcriptomic data were statistically compared.
Results: Functional enrichment analysis revealed that the MC-OTHER group showed upregulation of pathways related to extracellular matrix (ECM) organization and cell adhesion, whereas the MC-SPC group was enriched for synaptic signaling and neurotransmitter transport pathways.
Conclusion: This study identifies two transcriptionally distinct subtypes of mucinous carcinoma based on histopathological features.

Introduction

Mucinous carcinoma (MC) of the breast is histologically classified into two types: type A, which is a hypocellular tumor with rich extracellular mucin, and type B, which is a hypercellular tumor with less abundant mucin. In addition, neuroendocrine differentiation is often observed in type B MCs [1].

Solid papillary carcinoma (SPC) is a variant of breast tumor characterized by a solid tumor nests containing fibrovascular cores. SPCs also frequently exhibit neuroendocrine differentiation and mucin production [1].

In clinical practice, some MCs display hypercellular solid nests with fibrovascular cores and neuroendocrine features, closely resembling SPC. Therefore, in this study, **we aimed to elucidate the biological and molecular differences among MCs based on the presence or absence of SPC-like histological features.**

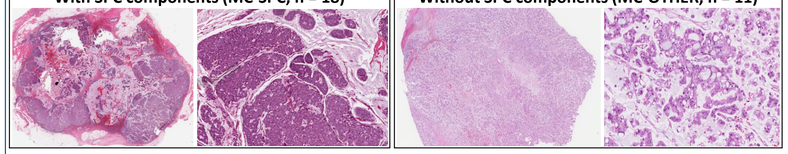
Methods and Materials

TCGA-BRCA cohort (n = 1084) — The data were obtained from *the Breast Invasive Carcinoma* (BRCA) dataset of *The Cancer Genome Atlas* (TCGA) Research Network [2].

Mucinous carcinoma (n = 29) — Clusters of neoplastic cells floating in abundant extracellular mucin.

SPC component: tumor nests with fibrovascular cores.

With SPC components (MC-SPC, n = 18) / **Without SPC components (MC-OTHER, n = 11)**



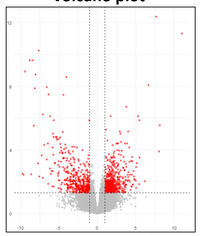
Differentially expressed genes (DEGs; FDR < 0.05, $|\log_2 FC| > 1$) were analyzed and visualized using clusterProfiler with Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment.

Results

Table 1. Clinicopathological characteristics of MC variants.

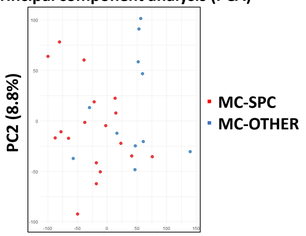
Characteristics	MC-SPC (n = 18)	MC-OTHER (n = 11)	p-value
Age (years, range)	67.5 (41–85)	55 (38–79)	0.163
Type of MC, n (%)			
Type A	1 (5.6)	7 (63.6)	**0.001**
Type B	**17 (94.4)**	4 (36.4)	
Subtype, n (%)			**0.014**
HR+/HER2-	**16 (100)**	6 (60)	
HER2+	0 (0)	**4 (40)**	
Triple-negative	0 (0)	0 (0)	
Stage, n (%)			0.46
Ⅰ	4 (22.2)	1 (9.1)	
Ⅱ	10 (55.6)	5 (45.5)	
Ⅲ	4 (22.2)	5 (45.5)	

Volcano plot



▪ significant

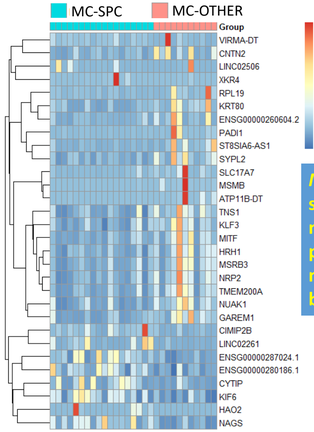
Principal component analysis (PCA)



(MC-SPC vs MC-OTHER)

Distinct DEGs — No clear separation (whole-transcriptome profiles)

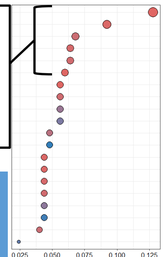
Heatmap of the top 30 DEGs



Distinct molecular expression profiles between the two groups

GO enrichment

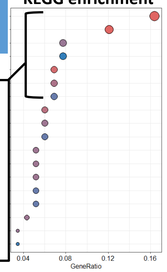
- Regulation of membrane potential
- Signal release
- cognition
- Synapse assembly
- Learning or memory
- Action potential



MC-SPC were **enriched** for **synaptic signaling** and **neurotransmitter transport pathways**, reflecting **neuroendocrine-associated biology**

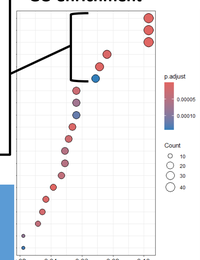
KEGG enrichment

- Neuroactive ligand-receptor interaction
- Neuroactive ligand signaling
- Hormone signaling
- Calcium signaling pathway
- Glutamatergic synapse
- Retrograde endocannabinoid signaling
- Motor proteins



GO enrichment

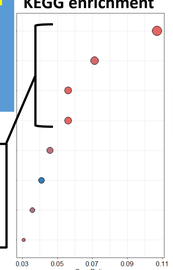
- ECM organization
- Extracellular structure organization
- External encapsulating structure organization
- Ossification
- Cell-substrate adhesion
- Axonogenesis



MC-OTHER showed **upregulation** of pathways related to **extracellular matrix (ECM) organization** and **cell adhesion**, suggesting a **mesenchymal-like phenotype**

KEGG enrichment

- Cytoskeleton in muscle cells
- Focal adhesion
- ECM-receptor interaction
- Protein digestion and absorption



Discussion

- Certain type B MCs exhibit neuroendocrine differentiation and are transcriptionally indistinguishable from neuroendocrine carcinoma of the breast [3].
- SPC may serve as a precursor lesion for MCs with neuroendocrine differentiation [4].

➤ In our study, **type B MC predominated among MC-SPC with upregulation of synaptic signaling and neurotransmitter transport pathways**, supporting the possibility that **a subset of MCs may originate from SPC**.

- Focal adhesion kinase (FAK) and ECM components are known to promote breast cancer invasion, metastasis, and epithelial–mesenchymal transition [5,6].

➤ Taken together, our findings and these prior reports suggest that **the mesenchymal-like transcriptional program observed in MC-OTHER reflects ECM-FAK signaling and microenvironmental remodeling**, which may contribute to its **more aggressive biological behavior** compared with MC-SPC.

Conclusions

This study identifies two transcriptionally distinct subtypes of MC based on histopathological features, with MC-OTHER showing mesenchymal-like characteristics and MC-SPC exhibiting neuroendocrine-associated molecular traits.

Acknowledgments

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References

1. WHO Classification of Tumours Editorial Board. Breast tumours. 5th ed. Lyon (France): International Agency for Research on Cancer; 2019.
2. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012 4;490(7418):61-70.
3. Weigelt B, et al. Mucinous and neuroendocrine breast carcinomas are transcriptionally distinct from invasive ductal carcinomas of no special type. Mod Pathol. 2009 22(11):1401-1414.
4. Otsuki Y, et al. A morphological and immunohistochemical study of ductal carcinoma in situ, invasive breast carcinoma of no special type, and mucinous carcinoma of the breast in comparison with solid papillary carcinoma regarding neuroendocrine marker expression. Virchow Archiv 2024 485:547-555.
5. Luo M and Guan JL. Focal adhesion kinase: a prominent determinant in breast cancer initiation, progression and metastasis. Cancer Lett. 2010 28;289(2):127-139.
6. Oskarsson T. Extracellular matrix components in breast cancer progression and metastasis. Breast. 2013 22:566-72.

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