Proteomic analysis of residual disease identifies potential prognostic biomarkers of triple-negative breast cancer after neoadjuvant chemotherapy

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Introduction

- Triple negative breast cancer(TNBC) patients with residual disease after neoadjuvant chemotherapy have a poor prognosis.
- Residual cancer burden (RCB) can provide some prognostic information,but there is still a lack of effective molecular markers.
- The study is aimed at exploring the prognostic biomarkers in TNBC patients with residual disease post-neoadjuvant therapy via proteomics analysis.

Methods and Materials

- This retrospective study collected TNBC patients who received neoadjuvant therapy at Cancer Hospital, Chinese Academy of Medical Sciences, from February 2015 to December 2022.
- TNBC patients with residual disease after neoadjuvant chemotherapy were categorized into recurrence and non-recurrence groups, with balanced baseline characteristics.
- Sixty residual tumor samples from patients were selected for whole proteome analysis using Liquid Chromatography-Mass Spectrometry.
- Differential protein screening, pathway enrichment analysis, protein - protein interaction network analysis, and immune infiltration analysis were performed between the two groups. Finally, the expression of differential proteins was validated at the immunohistochemical(IHC) level.

Results

- Sixty postoperative residual tumor samples (30 each in recurrence and non-recurrence groups) were analyzed.
- Baseline characteristics were comparable between the two groups, with no significant differences in either pre-neoadjuvant T/N staging or postoperative T/N staging; However, patients who experienced recurrence exhibited a modestly higher tumor burden(Table 1).

Characteristics	Recurrence Group(N=30)	No Recurrence Group(N=30)	*P*
cT			0.934
0-2	21 (70.0)	22 (71.0)	
3-4	9 (30.0)	9 (29.0)	
cN			0.642
0	5 (16.7)	8 (26.7)	
1-2	18 (60.0)	16 (53.3)	
3	7 (23.3)	6 (20.0)	
ypT			0.374
ypT0-1	15 (50.0)	17 (56.7)	
ypT2	11 (36.7)	12 (40.0)	
ypT3-4	4 (13.3)	1 (3.3)	
ypN			0.817
ypN0	10 (33.3)	12 (40.0)	
ypN1	10 (33.3)	10 (33.3)	
ypN2-3	10 (33.3)	8 (26.7)	
ypTNM			0.833
I	7 (23.3)	7 (23.3)	
II	13 (43.3)	15 (50.0)	
III	10 (33.3)	8 (26.7)	

- Compared to the non-recurrence group, 49 up-regulated and 237 down-regulated proteins were found in the recurrence group.
- GO and KEGG analyses revealed that immune-related proteins, especially those in the T cell pathway, were significantly down-regulated in recurrence group compared to non-recurrence group(Figure 1 and Figure 2).
- Immune infiltration analysis revealed down-regulated immune cell-related expression in recurrence group, with decreased expression of CD4+ effector T cells, dendritic cells, macrophages, and so on.

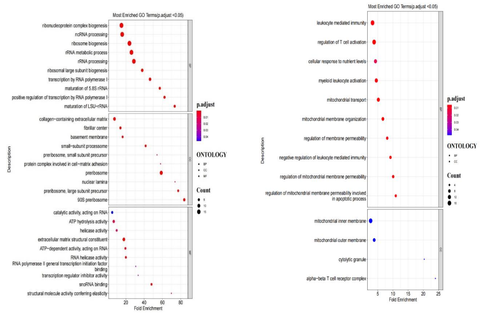


Figure 1. (A)Up-regulated protein GO enrichment analysis.
(B)Down-regulated protein GO enrichment analysis.

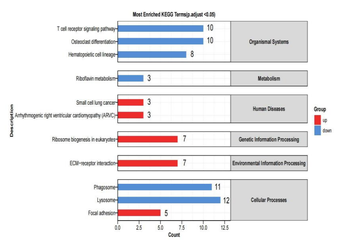


Figure 2.KEGG enrichment analysis

- IHC was used to verify the expression of CD4, CD40, and CD68. Results showed that the recurrence group had significantly lower expression levels. The tumor-infiltrating lymphocytes in the recurrence group were also significantly lower than in the non-recurrence group (median 10% vs. 20%, P<0.001).
- Protein-protein interaction network analysis identified 25 key proteins, most were immune–related, including CD1C, CD247, CD2, CD300A, CD3D, CD40, CD68, CD84, GZMB, CD20, and CD150. Survival analysis indicated CD68 and CD40 down-regulation most significantly affected patient survival(Figure3).

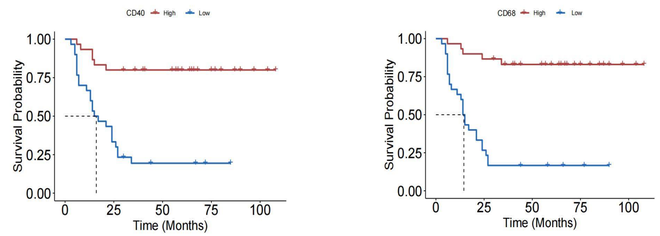


Figure3.(A) RFS in patients with high versus low CD40 expression. (B) RFS in patients with high versus low CD68 expression.

Conclusions

- The study found that in patients with residual disease after neoadjuvant therapy for TNBC, the downregulation of immune-related proteins, particularly in the T cell pathway, is closely associated with short term recurrence. Immunohistochemistry confirmed that CD4, CD40, and CD68 are downregulated in the recurrent group.
- Our study preliminarily confirms that the downregulation of immune-related proteins is an important prognostic factor for TNBC patients with residual disease, offering valuable insights for future research and clinical practice.

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