Deciphering the tumor microenvironment related to immune regulation in triple-negative breast cancer

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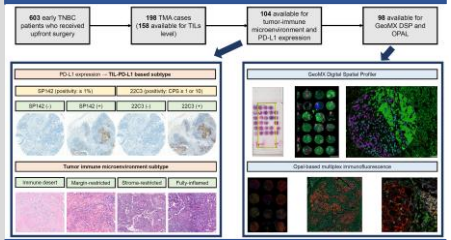
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Introduction

Triple-negative breast cancer (TNBC) is a highly heterogeneous and aggressive subtype of breast cancer, with the features of tumor microenvironment and the underlying molecular mechanisms of immune-regulation remaining largely elusive. This study aimed to explore the immune landscape of TNBC by assessing tumor-infiltrating lymphocytes (TILs) level, programmed cell death ligand 1 (PD-L1) expression, and the degree of TIL infiltration within the tumor. Utilizing the GeoMX Digital Spatial Profiler platform, we also performed spatially resolved transcriptomic profiling of tumor, immune, and stromal cells, focusing on the distinctions between immune-activated and immune-suppressed phenotypes.

Materials and Methods



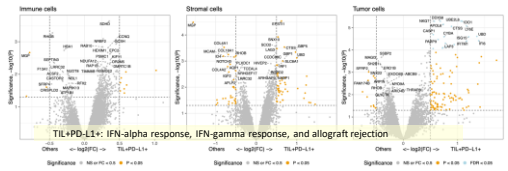
Results

Baseline characteristics according to TIL-PD-L1-based subtypes.

Variables	TIL+PD-L1+	TIL+PD-L1-	TIL-PD-L1+	TIL-PD-L1-	P-value
Age					0.285
< 50	14 (51.9)	6 (54.5)	8 (66.7)	21 (38.9)	
≥ 50	13 (48.1)	5 (45.5)	4 (33.3)	33 (61.1)	
Tumor grade*					0.132†
1 or 2	4 (15.4)	3 (27.3)	0	15 (27.8)	
3	22 (84.6)	8 (72.7)	12 (100)	39 (72.2)	
Ki-67					0.261†
< 20%	1 (3.7)	1 (9.1)	1 (8.3)	10 (18.6)	
≥ 20%	26 (96.3)	10 (90.9)	11 (91.7)	44 (81.5)	
Tumor stage					0.780
1	14 (51.9)	6 (54.5)	7 (58.3)	24 (44.4)	
≥ 2	13 (48.1)	5 (45.5)	5 (41.7)	30 (55.6)	
Nodal status					0.918†
Negative	20 (74.1)	7 (63.6)	9 (75.0)	40 (74.1)	
Positive	7 (25.9)	4 (36.4)	3 (25.0)	14 (25.9)	
Chemotherapy					0.953†
Yes	2 (7.4)	1 (9.1)	1(8.3)	6 (11.1)	
No	25 (92.6)	10 (90.0)	11 (91.7)	48 (88.9)	
Radiotherapy					0.471†
Yes	9 (33.3)	2 (18.2)	6 (50.0)	18 (33.3)	
No	18 (66.7)	9 (81.8)	6 (50.0)	36 (66.7)	

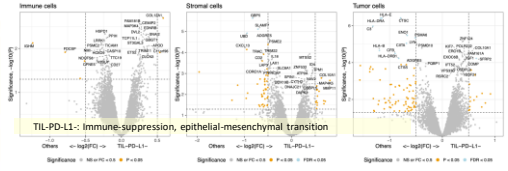
Results

Transcriptomic features of the TIL+PD-L1+ subtype in TNBC



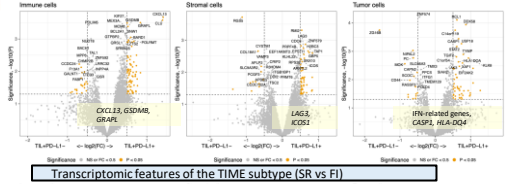
TIL+PD-L1+: IFN-alpha response, IFN-gamma response, and allograft rejection

Transcriptomic features of the TIL-PD-L1- subtype in TNBC

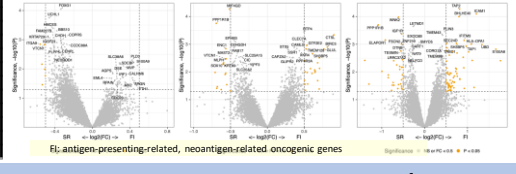


TIL-PD-L1-: Immune-suppression, epithelial-mesenchymal transition

Comparison of transcriptomic features between the TIL+PD-L1+ and TIL+PD-L1-

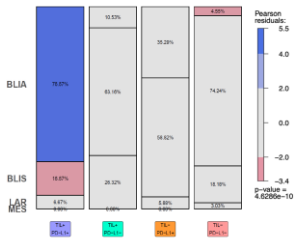


Transcriptomic features of the TIME subtype (SR vs FI)

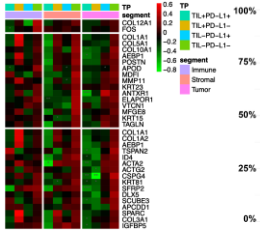


FI: antigen-presenting-related, neoantigen-related oncogenic genes

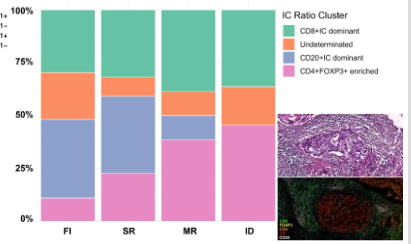
Distribution of Burstein molecular subtypes inferred from tumor cell transcriptomes



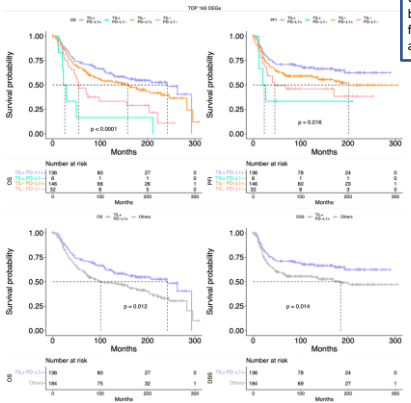
ECM remodeling and fibrosis-related genes enriched in TIL-PD-L1- tumors



Relative proportions of immune cell subsets by TIL–PD-L1-based subtypes

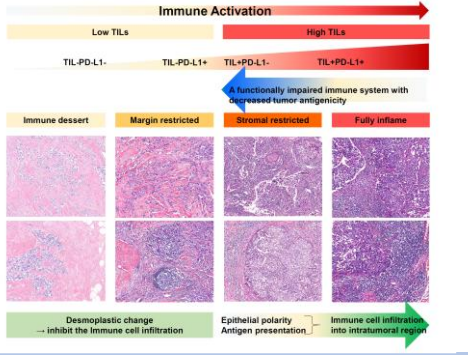


External validation of the TIL+PD-L1+ tumor gene signature using the METABRIC-TNBC cohort



Discussion & Conclusion

Our findings underscore the potential clinical utility of TILs and PD-L1 as integrated biomarkers for predicting clinical outcomes and guiding systemic treatment strategies for early-stage TNBC. Moreover, we identified the key mechanisms and biomarkers associated with variations in immune-related microenvironments



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