MHC Class I Expression and Outcomes in Breast Cancer in the Real-World Clinico-Genomic Data and the FinXX Trial

Abstract#

Yi Liu[1], Sachin Kumar Deshmukh[2], Yaohua Ma[1], Jodi M. Carter[3], Sharon Wu[2], Joanne Xiu[2], Nadine Norton[4], Kathryn J. Ruddy[5], Edith A. Perez[6], Shipra Gandhi[7], Priscila Barreto Coelho[8], Maryam Lustberg[9], Matthew P. Goetz[5], Heikki Joensuu[10], George W. Sledge[2], E. Aubrey Thompson[4], Keith L. Knutson[11], Saranya Chumsri[6]

[1]Department of Quantitative Health Sciences, Mayo Clinic, FL; [2]Caris Life Sciences, Phoenix, Arizona; [3]Laboratory Medicine and Pathology, University of Alberta, Edmonton, Canada;[4]Department of Cancer Biology, Mayo Clinic, FL; [5]Department of Oncology, Mayo Clinic, MN; [6]Jacoby Center for Breast Health, Mayo Clinic, FL; [7]Deparment of Hematology/Oncology, Rosswell Park, NY; [8]Deparment of Oncology, University of Miami, FL; [9]Center for Breast Cancer, Yale School of Medicine, CT; [10]Department of Oncology, Helsinki University Hospital and University of Helsinki; Helsinki, Finland; [11]Department of Immunology, Mayo Clinic, FL, USA

Abstract

Background: Major histocompatibility complex class I (MHC I) plays a critical role in immune surveillance by binding peptides derived from intracellular proteins and presenting them on the cell surface for recognition by CD8+ T cells. Loss or downregulation of MHC I expression has been identified as a key mechanism of immune evasion in cancers. Here, we evaluated MHC I expression and outcomes in all subtypes of breast cancer (BC).

Methods: 9,038 BC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ), including triple-negative BC (TNBC) 3,038, HER2-positive (HER2+) 1,082, and hormone receptor-positive (HR+HER2-) 4,918. Immune cell fractions were estimated using WTS deconvolution (Quantiseq). MHC I (*HLA-A/HLA-B/HLA-C*)-high (H) and -low (L) were classified by RNA expression above or below the 25th percentile. Real-world overall survival (OS) was derived from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier. NanoString IO360 was performed in 114 samples from the FinXX trial (NCT00114816). Statistical significance was assessed using chi-square, Mann-Whitney U, ANOVA, and Cox regression with multiple comparison adjustments (q<.05).

Results: TNBC had higher expression of *HLA-A* and *HLA-B* (median TPM: 169 and 191) compared to HER2+ (146.6 and 170, q<0.05) and HR+HER2- (141.7 and 157.5, q<0.05). However, there was no significant difference in *HLA-C* expression across 3 BC subtypes. In TNBC, MHC I-H tumors had higher frequencies of PD-L1 positivity (66.2% vs. 13.1%) as well as higher infiltration of B cells (4.5% vs. 3.2%), M1 macrophages (5% vs. 1.5%), M2 macrophages (4% vs. 2.1%), Tregs (2.8% vs. 0.8%), $CD8^+$ T cells (1.8% vs. 0%), dendritic cells (3.2% vs. 2.8%), higher T-cell inflamed score (137 vs. -144), and IFNγ score (0.02 vs. -0.49) compared to MHC I-L TNBC (all q<.05). MHC I-H TNBC was associated with significant improvement in median OS (30.1 vs. 15.2 months, HR 0.55, 95% CI 0.46-0.65, p<0.0001). However, this survival difference was not observed in patients with MHC I-H vs. MHC I-L in HER2+ (HR 1.04, 95% CI 0.74-1.47, p = 0.81) and HR+HER2- (HR 0.87, 95% CI 0.75-1.02, p= 0.09) BC subtypes. We further validated the MHC I expression in the FinXX trial. Similarly, patients with MHC I-H had significant improvement in recurrence-free survival (HR 0.27, 95%CI 0.11-0.66, p = 0.002) and OS (HR 0.23, 95% CI 0.09-0.57, p = 0.0005) compared to MHC I-L.

Conclusions: Our findings demonstrate that higher MHC I expression is associated with higher immune infiltration and improved outcomes in TNBC but not in HER2+ or HR+HER2- BC subtypes. These results suggest that MHC I expression plays a critical role in the tumor microenvironment of TNBC. Future studies are needed to evaluate the prognostic value and potential therapeutic target of MHC I in TNBC.

Support: Breast Cancer Research Foundation, Bankhead Coley, W81XWH-18-1-0564

Breast Cancer Patient Demographic

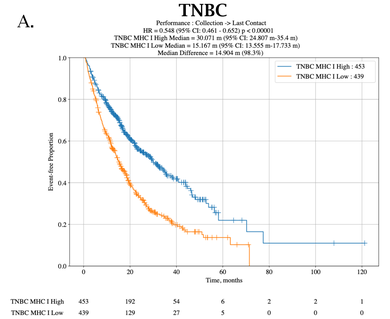
		TNBC	HER2+	HR+HER2-
Count (N)		3038	1082	4918
Median age [range]		61 [22 -> 89]	58 [19 -> 89]	62 [24 - > 89]
Race	**White**	61% (1412/2315)	66.59% (548/823)	73.75% (2866/3886)
	Black	28.94% (670/2315)	20.78% (171/823)	16.65% (647/3886)
	Asian/Pacific Islander	3.97% (92/2315)	4.74% (39/823)	4.07% (158/3886)
	Other	6.09% (141/2315)	7.9% (65/823)	5.53% (215/3886)
Ethnicity	**Not Hispanic or Latino**	83.14% (1825/2195)	83.04% (671/808)	85.96% (3264/3797)
	Hispanic or Latino	16.86% (370/2195)	16.965 (137/808)	14.04% (533/3797)
Tumor site	**Primary**	48.52% (1483/3038)	39.93% (432/1082)	35.18% (1730/4918)
	Metastatic	51.18% (1555/3038)	60.07% (650/1082)	64.82% (3188/4918)

HLA Gene Expression Across Breast Cancer Subtypes

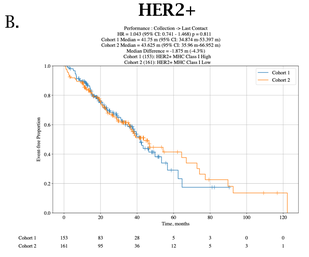
	Median (TPM)			TNBC vs HER2+		TNBC vs HR+HER2-	
	TNBC	**HER2+**	**HR+HER2-**	**p-value**	**q-value**	**p-value**	**q-value**
HLA-A	169	146.64	141.77	<0.0001	<0.0001	<0.0001	<0.0001
HLA-B	191	170.16	157.52	0.0001	0.0002	<0.0001	<0.0001
HLA-C	156.5	159.12	161.62	0.55	0.65	0.14	0.2
HLA-E	87.87	80.09	78.61	0.008	0.02	<0.0001	<0.0001
HLA-F	33.32	24.64	25.77	<0.0001	<0.0001	<0.0001	<0.0001
HLA-G	0.06	0.04	0.04	<0.0001	<0.0001	<0.0001	<0.0001
HLA-H	0.74	0.71	0.98	0.09	0.15	<0.0001	<0.0001
HLA-J	0.2	0.21	0.29	0.24	0.34	<0.0001	<0.0001
HLA-K	0.23	0.20	0.27	0.0004	0.001	<0.0001	<0.0001
HLA-L	0.42	0.37	0.44	<0.0001	<0.0001	0.07	0.11
HLA-DPA1	153.8	144.80	157.85	0.23	0.33	0.12	0.17
HLA-DPB1	79.84	74.87	82.76	0.24	0.34	0.006	0.01
HLA-DMA	38.21	36.46	38.99	0.11	0.17	0.26	0.34
HLA-DMB	38.36	36.88	38	0.66	0.74	0.54	0.63
HLA-DOA	8.29	7.98	8.76	0.15	0.23	0.01	0.02
HLA-DOB	2.34	1.27	1.2	<0.0001	<0.0001	<0.0001	<0.0001
HLA-DQA1	32.98	29.83	29.57	0.002	0.0052	0.0004	0.0008
HLA-DQB1	39.7	37.32	37.37	0.20	0.30	0.07	0.11
HLA-DRA	216.6	198.64	206.64	0.03	0.06	0.01	0.02
HLA-DRB1	114.6	105.70	106.92	0.09	0.16	0.06	0.1
HLA-DRB3	8.36	9.04	8.9	0.86	0.90	0.52	0.61
HLA-DRB5	0.89	0.79	0.83	0.64	0.72	0.88	0.91

MHC Class I and Outcomes

A.



B.



C.

Figure 2: A. The Kaplan-Meier curve of patients with TNBC in the Caris clinico-genomic database. High MHC class I expression was associated with a significant improvement in the event-free survival (EFS) with an HR of 0.548 (95% CI 0.461-0.652, P < 0.0001) corresponding to the median difference of 14.9 months. In contrast, there was no significant improvement in outcomes associated with MHC class 1 expression in **B.** patients with HER2+ and **C.** Hormone receptor-positive HER2-negative breast cancer.

Conclusions

- Higher MHC I expression is associated with higher immune infiltration and improved outcomes in TNBC but not in HER2+ or HR+HER2- BC subtypes.
- These results suggest that MHC I expression plays a critical role in the tumor microenvironment of TNBC.