Distinct Immune and Metabolic profiles in Latin American Breast Cancer Patients With Obesity Enrolled in FLEX

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Introduction

- Latin American (LA) women are more often diagnosed with aggressive early breast cancer (EBC) than Non-Hispanic White (NHW) women[1].
- Prior work showed elevated immune gene expression in BluePrint® (BP) Luminal B tumors from LA patients (pts) with obesity vs Black and NHW cohorts[2].
- Although high immune activation is characteristic of aggressive subtypes such as Basal breast cancer[2]—and can be associated with improved survival—its role in the distinct biology observed in LA women remains unclear
- In this study, we present:
  - i. updated clinical comparisons between LA, NHW, and Black pts with EBC.
  - ii. Whole transcriptome analysis (WTA) comparing BP Luminal B and Basal BC in pts with obesity.

Methods

Study Cohort

- 15,577 pts (Latin American, Black, NHW, Table 1) from the FLEX Study (NCT03053193).
- All received MammaPrint® (MP), BP, and consented to WTA.
- ImPrint® 53-gene immune signature classified HR+ EBC tumors as immune-positive (+) or immune-negative (–)
- WTA comparisons were performed within each BP Luminal B and BP Basal, matching BMI-obese LA pts to NHW and Black pts by age, T stage, and LN status (Table 2).

Statistics

- Chi-square and t-tests were conducted on clinical groups using arsenal R package.
- Differentially expressed genes (DEGs) were evaluated using limma, and pathway enrichment was performed using gene set enrichment analysis (GSEA) with Hallmark gene sets.
- P-values were adjusted for multiple testing using Benjamini–Hochberg. Significant results were reported with adjusted p < 0.05.

Results

Table 1. Clinical Characteristics Overall

Characteristic	LA (n=1446) (%)	Black (n=1656) (%)	NHW (n=12,475) (%)	p value Black vs LA	p value NHW vs LA
Age (Years)					
Median	57	59	63	<0.001	<0.001
Mean (SD)	56.6 (±12)	58.4 (±13)	61.5 (±12)		
Menopausal Status				<0.001	<0.001
Pre-/Peri-	434 (21.3)	390 (25.6)	2338 (20.0)		
Post-	931 (68.2)	1133 (74.4)	9375 (80.0)		
Type 2 Diabetes				0.274	<0.001
Yes	283 (26.9)	399 (28.9)	1452 (13.4)		
No	769 (73.1)	981 (71.1)	9369 (86.6)		
BMI				<0.001	<0.001
<18.5	17 (1.2)	13 (0.8)	199 (1.6)		
18.5-24.9	229 (16.2)	184 (11.6)	3141 (26.0)		
25-29.9	451 (31.9)	406 (25.6)	3665 (30.4)		
>30	718 (50.7)	984 (62.0)	5058 (41.9)		
T Stage				0.373	<0.001
T1	483 (57.5)	627 (55.0)	4911 (65.7)		
T2	274 (32.6)	406 (35.6)	2141 (28.6)		
T3	63 (7.5)	73 (6.4)	329 (4.4)		
T4	20 (2.4)	33 (2.9)	96 (1.3)		
N Stage				<0.001	0.001
LN-	640 (78.4)	784 (71.1)	5941 (83.0)		
LN+	176 (21.6)	310 (28.3)	1221 (17.0)		
Grade				<0.001	<0.001
G1	336 (25.3)	330 (22.0)	3389 (29.7)		
G2	652 (49.1)	672 (44.7)	5923 (51.8)		
G3	339 (25.5)	500 (33.3)	2113 (18.5)		
Ki67%				<0.001	<0.001
0-10	322 (29.2)	247 (22.4)	2718 (33.3)		
11-20	266 (24.1)	229 (20.7)	2125 (26.1)		
>20	514 (46.4)	629 (56.9)	3308 (40.6)		
MammaPrint				<0.001	<0.001
UltraLow Risk	225 (15.6)	151 (9.1)	1962 (15.7)		
Low Risk	465 (32.2)	410 (24.8)	4618 (37.0)		
High Risk 1	464 (32.1)	653 (39.4)	4351 (34.9)		
High Risk 2	292 (20.2)	442 (26.7)	1543 (12.4)		
BluePrint				<0.001	<0.001
Luminal A	667 (47.3)	545 (33.9)	6307 (52.6)		
Luminal B	506 (35.9)	694 (43.1)	4344 (36.2)		
HER2	65 (4.6)	74 (4.6)	411 (3.4)		
Basal	173 (12.3)	297 (18.4)	925 (7.7)		
ImPrint HR				0.049	<0.001
ImPrint-	870 (91.0)	1066 (88.4)	9418 (95.3)		
ImPrint+	86 (9.0)	140 (11.6)	460 (4.7)		

Table 2. Clinical characteristics of obese pts matched by age, T, and N stage

Basal Characteristics	LA (n=77) (%)	Black (n=77) (%)	NHW (n=77) (%)	p value
Age				0.698
Median	50	52	52	
Mean (SD)	52.45 (±14)	53.61 (±13)	51.73 (±14)	
Menopausal				0.234
Pre-/Peri	26 (36.6)	24 (33.3)	34 (46.6)	
Post	45 (63.4)	48 (66.7)	39 (53.4)	
Type 2 Diabetes				0.153
Yes	15 (27.3)	10 (14.9)	10 (15.4)	
No	40 (72.7)	57 (85.1)	55 (84.6)	
Tumor Stage				0.986
T1	16 (29.1)	17 (30.9)	16 (30.8)	
T2	26 (47.3)	24 (43.6)	26 (50.0)	
T3	10 (18.2)	10 (18.2)	8 (15.4)	
T4	3 (5.5)	4 (7.3)	2 (3.8)	
N Stage				0.697
LN-	35 (66.0)	38 (73.1)	36 (72.0)	
LN+	18 (34.0)	14 (26.9)	14 (28.0)	
Grade				0.43
G1	0 (0)	1 (1.4)	1 (1.4)	
G2	12 (17.6)	6 (8.3)	8 (11.0)	
G3	56 (82.4)	65 (90.3)	64 (87.7)	

Luminal B Characteristic	LA (n=215) (%)	Black (n=215) (%)	NHW (n=215) (%)	p value
Age				0.961
Median	56	56	56	
Mean (SD)	55.9 (±12)	56.18 (±11)	55.92 (±11)	
Menopausal				0.705
Pre-/Peri	65 (32.8)	58 (29.3)	65 (32.5)	
Post	133 (67.2)	140 (70.7)	135 (67.5)	
Type 2 Diabetes				0.002
Yes	56 (33.1)	59 (31.4)	35 (18.2)	
No	113 (66.9)	129 (68.6)	157 (81.8)	
Tumor Stage				0.582
T1	71 (53.0)	76 (56.3)	72 (55.0)	
T2	51 (38.1)	48 (35.6)	54 (41.2)	
T3	9 (6.7)	9 (6.7)	5 (3.8)	
T4	3 (2.2)	2 (1.5)	0 (0)	
N Stage				0.695
LN-	101 (74.8)	104 (76.5)	95 (72.0)	
LN+	34 (25.2)	32 (23.5)	37 (28.0)	
Grade				0.478
G1	23 (11.6)	25 (13.2)	28 (14.1)	
G2	119 (60.1)	106 (55.8)	124 (62.6)	
G3	56 (28.3)	59 (31.1)	46 (23.2)	

Data presents n (%) unless indicated otherwise. Unknowns not listed. p<0.05 indicates significance.

Fig.1 WT comparison in obese EBC across race/ethnicity. Volcano plots show DEGs between obese LA vs Black pt (A,B) or LA vs NHW pt (C,D) cohorts, matched by age, T, and N stage. Analyses were stratified by BP subtypes Basal (A,C) and Luminal B (B,D).

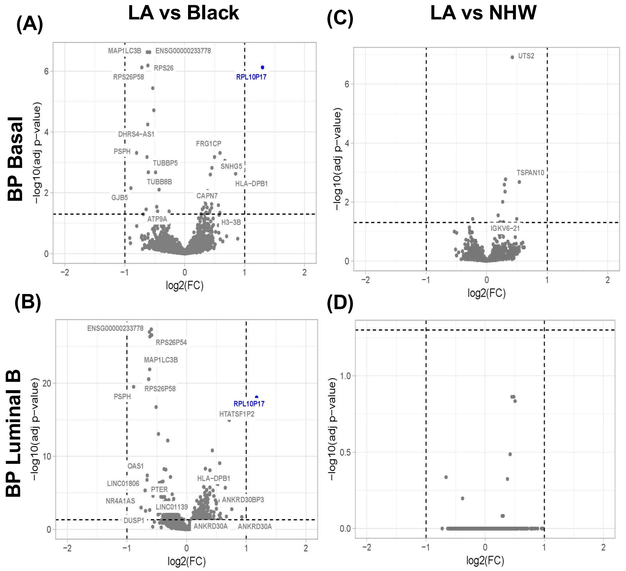
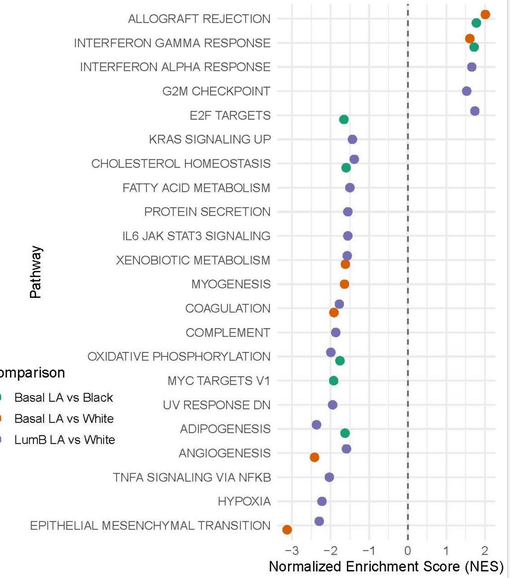


Fig.2 Pathway enrichment analysis of obese EBC across racial/ethnic groups. GSEA of obese EBC comparing LA vs Black and NHW patients by BP Basal and Luminal B subtypes. NES indicates pathway regulation direction and magnitude; pathways with adjusted p value < 0.05 are shown.



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- Latin American (LA) patients were younger and more frequently premenopausal compared with Black and NHW pts (Table 1).
  - Both LA and Black pts exhibited significantly higher rates of obesity compared with NHW pts (Table 1).
  - MP High Risk 2, BP Basal, and ImPrint+ tumor subtypes were significantly more common in LA and Black pts than in NHW patients (Table 1).
- LA pts had a higher prevalence of type 2 diabetes compared to NHW pts within both matched cohorts (BP Luminal B cohort: p = 0.002) (Table 2).
- Among obese EBC pts, metabolic pathways (adipogenesis, angiogenesis, epithelial–mesenchymal transition, oxidative phosphorylation) were significantly downregulated in LA pts relative to NHW and Black cohorts (Fig.3).
- Immune-related pathways (including allograft rejection and interferon gamma response) were enriched in LA pts with Basal cancers compared to NHW and Black pts (Fig.3).

Conclusions

- Obese LA EBC pts show significant suppression of metabolic pathways compared with NHW and Black cohorts, suggesting distinct metabolic vulnerabilities.
- Basal tumors in obese LA pts display enriched immune activation, indicating a unique inflammatory profile that may have potential implications for immune checkpoint therapy.
- These findings highlight potential therapeutic targets and underscore the need for racially and ethnically diverse representation in clinical trials to better define population-specific drivers of EBC outcomes.

References: [1] Fejerman L, et al; *Breast Cancer Risk and Mortality in Women of Latin American Origin*. Chapter 4. 2019. [2]Canola MM, et al; SABCS *2023*.

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