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The persisting puzzle of racial disparity in triple negative breast cancer: looking through a new lens

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1. ABSTRACT

Triple-negative breast cancer (TNBC) is characterized by the absence of estrogen and progesterone receptors and absence of amplification of human epidermal growth factor receptor (HER2). This disease has no approved treatment with a poor prognosis particularly in African-American (AA) as compared to European-American (EA) patients. Gene ontology analysis showed specific gene pathways that are differentially regulated and gene signatures that are differentially expressed in AA as compared to EA. Such differences might underlie the basis for the aggressive nature and poor prognosis of TNBC in AA patients. In-depth studies of these pathways and differential genetic signature might give significant clues to improve our understanding of tumor biology associated with AA TNBC to advance the prognosis and survival rates. Along with gene ontology analysis, we suggest that post-translational modifications (PTM) could also play a crucial role in the dismal survival rate of AA TNBC patients. Further investigations are necessary to explore this terrain of PTMs to identify the racially disparate burden in TNBC.

2. INTRODUCTION

Triple-negative breast cancer (TNBC), a subtype of breast cancer (BC), accounts for 15-20% of all BC diagnoses in the US. It has been recognized that women of African descent are twice as likely to develop TNBC than women of European descent (1). As the name foretells, TNBCs lack estrogen, progesterone, and human epidermal growth factor receptors. Unfortunately, TNBCs are defined by what they "lack" rather than what they "have" and thus this negative nomenclature provides no actionable information on "druggable" targets. Aptly, this particular BC subtype has no FDA-approved targeted therapies thus far, and the survival rate is dismal (2-5).

Primarily, TNBC patients exhibit higher resistance to chemotherapy than hormone receptor (HR) positive BCs (6). TNBC patients, whose tumors metastasize to visceral organs, survive only for a year. Thus, diagnosis of metastatic TNBC is necessarily a death sentence for patients (6). The heterogeneous tumor biology, aggressive clinical course, and higher metastatic potential underscore an unmet need to understand the molecular

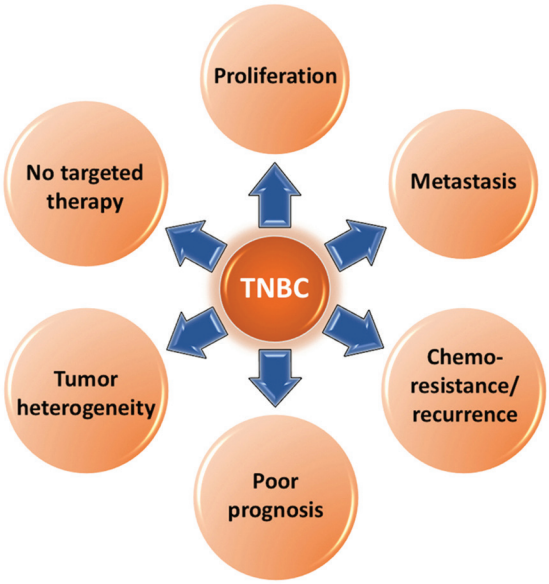

Figure 1. Variety of critical aspects attributed to TNBC aggressiveness.

pathways and signaling circuitries that could be targeted in TNBC to develop effective novel molecules to ultimately improve its prognosis (7) (Figure 1). Literature reports several targeted molecular therapies for TNBC that have shown promising results. These novel agents include small molecule inhibitors that specifically target poly-ADP-ribose-polymerase (PARP-1) (8, 9), epidermal growth factor receptor (EGFR) (10, 11), multi-tyrosine kinases (12, 13), as well as anti-angiogenic agents (14, 15). A study by Sparano JA *et al.*, pointed out a distinct molecular signature; ~70% of genes related to kinase activity, cell division, proliferation, DNA repair, anti-apoptosis, and transcriptional regulation are differentially expressed in TNBC vs. non-TNBC subtype (16). This review focuses on racially-distinct differential gene expression signatures in TNBC and how these distinct features may provide insights into the mechanistic basis for aggressive TNBC and offer cues about druggable target space in racially diverse TNBC patients. More importantly, we offer a new perspective to look at racial disparities through the lens of post-translational modifications of key molecules.

3. DISSECTING THE TNBC RACIALLY DISPARATE BURDEN

3.1. Does race influence TNBC onset and progression?

TNBC in AA women present higher mortality rates compared to women of European descent. The major contributing factors for such disparity are barriers to early screening, advanced disease stage at diagnosis, socio-demographic factors, socio-economic status, and lack of access to the healthcare treatment (17). AA premenopausal women exhibit a higher incidence and mortality rate compared to EA counterparts. However, postmenopausal women, do not show such a racial disparity (4, 18), suggesting that TNBC is significantly associated with younger age women of African descent (5).

Differences in survival outcomes among racially diverse TNBC patients remains controversial. Studies led by various groups such as Lund *et al.*, (19) Bauer *et al.*, (5) Carey *et al.*, (20) and Sachdev *et al.*, (21) have reported worse survival outcomes for women of African origin, after adjusting for socioeconomic factors, treatment delay, and tumor characteristics. Sachdev *et al.*, showed that both unadjusted and stage-adjusted survival outcomes were better in EA over AA TNBC patients (21). On the other hand, other groups like Dawood *et al.*, (22) O' Brien *et al.*, (23) and Sparano *et al.*, (24) found no significant difference in survival outcomes between racially-distinct TNBC patients (4). Underlying these inconsistent results could be the nonuniformity of the biomarkers tested, lack of certainty of pathological parameters, lack of availability of treatment information to deduce the survival outcomes, and failure to consider multiple factors such as stage, grade, poverty index, and other treatment related factors (19).

Recently, Ademuyiwa *et al.*, reported a detailed mutational analysis of AA and EA TNBC patients comparing the mutational landscape between the racially-distinct patient populations. Interestingly, they found no compelling

differences in the panorama of mutated genes between AA and EA TNBC patients. Also, they found no racial differences between AA and EA TNBC patients in high prevalence genes (TP53, PI3CA, MLL3), attributed to the fact that there is no significant difference in somatic mutations of these genes (25). Collectively, these findings suggest that the aggressive disease course seen among AA TNBC patients may be independent of the dysregulation in common tumor growth promoting pathways. It is likely that there may be hitherto unknown biomarkers that offer an enhanced understanding of the racial divide in TNBC outcomes.

Studies above suggest that the TNBC incidence and mortality rates are higher in AA compared to EA, even after adjusting for clinical and socioeconomic variables that might explain the differential outcome among the races (17). Thus, it is tempting to speculate that intrinsic biological factors might be responsible for the racially disparate burden of TNBC. In this lieu, it has been shown that TNBC patients of African descent harbor a higher prevalence of the basal-like-1 tumor phenotype which is characterized by enhanced proliferation and sensitivity to chemotherapy (17). AA women with TNBC tumors demonstrate a higher rate of invasion, distant metastasis (7.37% vs. 4.67%, p=0.05), angiogenesis and cell growth compared to their EA counterparts (26). Thus, proteins/biomarkers that are differentially expressed among the races and are involved in pathways associated with cell cycle regulation, epithelial-mesenchymal transition (EMT), and angiogenesis may hold the key to understanding therapeutically druggable targets to minimize the disparity gap. Indeed, selective inhibitors for specific pathways, which are in overdrive or underdrive, merit exploration to delineate a precise molecular mechanism of aggressiveness that is significantly associated with AA TNBC patients.

3.2. Tumor microenvironment in TNBC and racial disparity

Tumor cells do not live in isolation, rather they create a favorable niche known as tumor microenvironment (TME) to enhance the crosstalk with various other cells. Apart from tumor cells, TME is comprised of immune cells, fibroblasts, lymphocytes, signaling molecules, and tumor vasculature proteins. TME supports the growth, angiogenesis and metastasis of tumor cells (54). It has been reported that TME significantly influences the malignant behavior and is crucial for reprogramming the surrounding cells in TNBC. Myriad of available literature suggest that tumor infiltrating lymphocytes (TILs) are critical in regulating TNBC microenvironment. Elevated number of T regulatory cells (Tregs) in TME has been correlated with poor prognosis in many types of cancers including TNB (55, 56). Our unpublished data demonstrate a higher fraction of TILs in AA over EA TNBCs, suggesting that TME plays an essential role in racially disparate TNBC population. Moreover, vast majority of literature shed light on various TME related molecules (CXCL12, CXCR4, VEGF, Resistin, MCP1, MMP2, MMP-9, SOS1, PSPHL, uPA, IL6, RASSF1A, etc.) that are significantly up-regulated in AA over EA BC (57). These molecules along with their precise molecular action warrants further investigations to delineate the aggressive tumor biology associated with AA TNBC. Previously, various groups have reported that tougher extracellular matrix (ECM) was efficient in blocking the crosstalk between the cells. However, the recent data have suggested that stiffer the tumor stroma, more aggressive the breast cancer subtype is likely to be (55, 58). Thus, increased ECM rigidity might contribute in altering the mechano-signaling, tumor vasculature and pro-tumorigenic infiltration and thereby provide clues about highly invasive AA tumor phenotype over EA in TNBC. A detailed study characterizing the differential TME associated with AA and EA TNBC might give further insights into the TNBC racial disparity and could improve the prognosis of AA TNBC patients.

3.3. Differential gene signatures and pathways in racially distinct TNBC

Although various research groups have developed several small molecule

inhibitors and antibodies against cell cycle pathway components, none to date have shown full clinical translation (27). It is imperative to understand the intrinsic tumor biology, heterogeneity and molecular basis of TNBC in AA women to improve their prognosis and identify novel therapeutic targets. Thus, investigating tumor suppressor proteins and oncogenes having differential expression profile between AA and EA TNBC patients represents an advantageous strategy, as explored in this section.

Various studies have demonstrated that the breast tumor microenvironment varies between AA and EA TNBC patients (25, 28, 29). Recently, published data from our laboratory, Ogden A *et al.*, have demonstrated that nuclear (n) KIFC1 is a poor prognosis marker in AA TNBC compared to EA TNBC. In this multi-institutional study, we evaluated the expression of nKIFC1 in 163 AA and 144 EA TNBC patients using immunohistochemistry. Our data suggest that KIFC1 is an essential biomarker required for migration of AA TNBC tumor. High nKIFC1 weighed index (WI) was significantly related to worse overall survival (OS), progression-free survival (PFS) and high distant metastasis-free survival (DMFS) in AA but not EA TNBC (30). Using microarray analysis, Ademuyiwa *et al.*, identified the top twenty upregulated genes in AA TNBC patients, including CRYBB2, FAM3A, CROCCL1, SCXB, PIF1, TRABD, TSPO, C6orf108, MIIP, C21orf70, TOP1MT, NACA2, PWP2, and BAX compared to EA TNBC patients. AA women have higher p53 gene mutations and lower PI3CA mutations over EA patients (25). Using laser capture microdissection, Martin *et al.*, (28) analyzed genome-wide mRNA expression specific to tumor epithelium and stroma in AA and EA BC patients. Theirs and other related studies demonstrated upregulation of a panel of genes including CDKN2A, CCNA2, CCNB1, CCNE2, TMPO, AFMR, PSPHL, CXCL10, CXCL11, VEGF, syndecan-1, AURKB, CDCA5, CENPM, DDX11, and MK767 in AA TNBC patients compared to EA patients (28, 31, 32). It may be worthwhile to conduct validation studies to confirm the battery of genes or a "gene signature" that can stratify racially-distinct tumors and predict their risk of metastasis. Indeed, additional *in vitro* and *in vivo* experiments are warranted to reconcile the gene expression-based findings.

Even though TNBC incidence is higher in AA, several reports pinpoint significantly lower incidence of BRCA1 germline mutations in AA over EA TNBC, suggesting that other genetic mechanisms beyond germline BRCA1 mutation may explain the aggressive disease course in AA TNBC patients (33, 34). Genome-wide association studies (GWAS) showed that AA women have a higher frequency of risk variant at telomerase reverse transcriptase (TERT)-CLPTM1-like locus on chromosome 5p15 (odds ratio (OR)=1.25, $p=1.1*10^{-9}$) (35). A genetic variant in the LOC643714 gene is associated with 23% increased risk for TNBC in AA but not in EA TNBC (OR=1.23, 95% confidence interval) (36). Gene expression profiles revealed higher expression of IGF1R, VEGF, and nuclear EZH2 in women with AA decent than in women with EA decent (17). Recent genomic and transcriptomic analyses revealed a loss of RB1 expression in ~20% TNBC patients. This RB1 loss is significantly related to higher sensitivity towards gamma irradiation, doxorubicin, and methotrexate therapy (37). Thus, RB1 status, and the molecular network upstream and downstream of RB1 in AA and EA TNBC separately are pivotal to gain insights into pathways that confer chemo resistance in racially diverse TNBC population. While LOXL2 and SNCG are novel prognostic markers studied in TNBC EMT, invasion and metastasis (38, 39), these markers merit an in-depth investigation in the context of racial disparity in TNBC to obtain essential clues about metastasis and poor survival in AA TNBC. A prostaglandin is producing the enzyme, Cox-2, is involved in cancer cell proliferation, anti-apoptosis, angiogenesis and invasion (40, 41). Dhakal *et al*., (41) found that Cox-2 expression is positively correlated with poor prognosis in TNBC than in non-TNBC patients. This study suggests a prognostic value of Cox-2 in TNBC,

and thus, it is of significance to evaluate and validate its role within the racially diverse TNBC population.

3.4. Our perspective: looking racial disparity through a new lens

Using Next-Generation Sequencing (NGS) data from The Cancer Genome Atlas (TCGA), we analyzed several gene signatures in AA and EA TNBC. Surprisingly, we only found a few genes that showed a considerable difference in expression at the mRNA or protein level in AA and EA TNBC. These data indicated that the molecular basis of disparity might not be restricted to just the gene/protein expression based intrinsic tumor biology. It is well appreciated that protein diversity stemming due to alternative mRNA splicing or post-translational modifications (PTM) play vital roles in the modulation of cellular functions and protein-protein/protein-lipids crosstalks (42). PTMs are linked with a myriad of biological processes such as cell proliferation (43), differentiation (43), organismal development (44) and in the progression of human diseases including cancer (45). Advances in proteomics have critically fueled investigations into PTMs to reveal that these generate a complex combinatorial code regulating gene expression and protein functions, and whose deregulation has been documented in various types of cancers (46). PTMs at the molecular level amounts to altering the physical and chemical properties of proteins—in most cases reversibly—and in turn dictate their interaction with other cellular components such as protein, cell membranes, and DNA. Examples of PTMs, highly relevant in the context of cancer, include phosphorylation, acetylation, lipidation, sumoylation, methylation, and glycosylation which rewire the oncogenic signaling pathways in response to various stimuli surprisingly including tumor microenvironment, nutrient status, and hypoxia (47). The current status on the role of PTMs states that the pattern of post-translational modifications is a better predictive biomarker than the changes in total protein level and gives an additional layer of complexity by fine-tuning downstream signaling events (48). Thus, it is highly tempting to speculate that mapping of the PTMs patterns with the genomic and proteomic profile is likely to serve as a next-generation biomarker for improved prognosis of the disease, simultaneously providing a protein network framework amenable for therapeutic targeting in a spatiotemporal fashion.

Befittingly, a tantalizing possibility that may explain the TNBC disparity beyond differences at the gene and protein expression level is a differential profile of PTMs. Recent data by Golavilli PN *et al.*, have shown that in TNBC, AMP-activated protein kinases (AMPK) activates glycogen synthase kinase 3 beta (GSK3β) and Sirtuin 1(SIRT1) by inhibiting phosphorylation at Ser9 and Ser47, respectively. This activation of GSK3β and SIRT1, in turn, inhibit the upregulation of metadherin (MTDH) and suppresses TNBC cell proliferation (49). Hanigan TW *et al.*, have evidenced that c-Jun N-terminal kinase (JNK) mediated histone deacetylase 3 (HDAC3) phosphorylation in TNBC cells is essential for HDAC inhibitor binding and selectivity (50). These studies collectively suggest a non-trivial role of PTMs in TNBC. However, to the best of our knowledge, there is no study showing that PTMs might be one of the factors responsible for the underlying TNBC racial disparity. Our unpublished data suggest that PTMs (phosphorylation, acetylation, and sumoylation) may account for the disproportionately higher burden of TNBC in AA population and concomitantly may shed light on the aggressive nature of AA TNBC compared with EAs. This space of post-translational regulation is an uncharted terrain and presents an attractive avenue that merits extensive and intensive exploration to address racial disparity in TNBC.

Indeed, the cumulative effect of multiple genes and their underlying molecular pathways define the tumor phenotype. However, to date, there are very limited therapeutic options, mainly because of the paucity of in-depth knowledge about the intrinsic tumor biology of AA and EA TNBC. Identifying enrichment of biological networks in the tumor epithelium

Table 1. Significantly up and down-regulated genes in AA compared to EA TNBC analyzed using TCGA breast cancer dataset, p value less than 0.01 and log2fold change greater than 1.0 (upregulated) and less than -1.0. (downregulated)

Gene symbol	Gene name	Gene symbol	Gene name
KLK14	kallikrein-related peptidase 14	STON1-GTF2A1L	STON1-GTF2A1L readthrough
RETN	resistin	FAM83A	family with sequence similarity 83 member A
TREML4	triggering receptor expressed on myeloid cells like 4	NEFH	neurofilament heavy polypeptide
NACA2	nascent polypeptide-associated complex alpha subunit 2	DEFB1	defensin beta 1
UPK3B	uroplakin 3B	GNG4	G protein subunit gamma 4
KRT8P41	keratin 8 pseudogene 41	MUCL1	mucin like 1
HAPLN1	hyaluronan and proteoglycan link protein 1	NPTX2	neuronal pentraxin 2
TCTE1	t-complex-associated-testis-expressed 1	ADGRL3	adhesion G protein-coupled receptor L3
JSRP1	junctional sarcoplasmic reticulum protein 1	ENDOU	endonuclease, poly (U) specific
CCL3L1	C-C motif chemokine ligand 3 like 1	GPAT2	glycerol-3-phosphate acyltransferase 2, mitochondrial
KLK10	kallikrein-related peptidase 10	CAMP	cathelicidin antimicrobial peptide
MYEOV	myeloma overexpressed	FAIM2	Fas apoptotic inhibitory molecule 2
PPP1R14A	protein phosphatase 1 regulatory inhibitor subunit 14A	EYA1	EYA transcriptional coactivator and phosphatase 1
ACOXL	acyl-CoA oxidase-like	SYTL5	synaptotagmin like 5
LEFTY1	left-right determination factor 1	CYP2B7P	cytochrome P450 family 2 subfamily B member 7, pseudogene
SYCE1	synaptonemal complex central element protein 1	FGL1	fibrinogen like 1
CCDC154	coiled-coil domain containing 154	EPGN	epithelial mitogen
LAIR2	leukocyte-associated immunoglobulin-like receptor 2	ST8SIA2	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2
CSDC2	cold shock domain containing C2	FREM2	FRAS1 related extracellular matrix protein 2
DHDH	dihydrodiol dehydrogenase	AKR1B15	aldo-keto reductase family 1 member B15
AZU1	azurocidin 1	FABP6	fatty acid binding protein 6
FGF17	fibroblast growth factor 17	IGF2	insulin like growth factor 2
WNT6	Wnt family member 6	PRLR	prolactin receptor
BMP2	bone morphogenetic protein 2	TUBA3D	tubulin alpha 3d
FBXO2	F-box protein 2	FIGN	fidgetin, microtubule severing factor
MEF2B	myocyte enhancer factor 2B	NA	NA
C1QL2	complement C1q like 2	CLCA2	chloride channel accessory 2
MZB1	marginal zone B and B1 cell specific protein	AR	androgen receptor

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Table 1. Contd...

Gene symbol	Gene name	Gene symbol	Gene name
LRRC14B	leucine rich repeat containing 14B	RERGL	RERG like
TSGA10IP	testis specific 10 interacting protein	PHEX	phosphate regulating endopeptidase homolog, X-linked
PRKY	protein kinase, Y-linked, pseudogene	HTR1B	5-hydroxytryptamine receptor 1B
DCST2	DC-STAMP domain containing 2	NCAM2	neural cell adhesion molecule 2
CLIC3	chloride intracellular channel 3	NLGN1	neuroligin 1
ART3	ADP-ribosyltransferase 3	SLC7A2	solute carrier family 7 member 2
RNF112	ring finger protein 112	HOXA11	homeobox A11
MAPK15	mitogen-activated protein kinase 15	BEX1	brain expressed X-linked 1
AARD	alanine and arginine rich domain containing protein	ENPP3	ectonucleotide pyrophosphatase/ phosphodiesterase 3
FOXF2	forkhead box F2	FUT6	fucosyltransferase 6
ACTN3	actinin alpha 3 (gene/pseudogene)	NA	NA
CDHR1	cadherin related family member 1	ATP2B2	ATPase plasma membrane Ca2+transporting 2
SP7	Sp7 transcription factor	CLLU1OS	chronic lymphocytic leukemia up-regulated 1 opposite strand
KLK11	kallikrein related peptidase 11	DCX	doublecortin
FOXH1	forkhead box H1	NRG3	neuregulin 3
NKX2-3	NK2 homeobox 3	TENM2	teneurin transmembrane protein 2
FAM222A-AS1	FAM222A antisense RNA 1	NRXN3	neurexin 3
KRT3	keratin 3	TNR	tenascin R
P2RX1	purinergic receptor P2X 1	NKAIN1	Na+/K+transporting ATPase interacting 1
TSPAN32	tetraspanin 32	CLGN	calmegin
TUBB8	tubulin beta 8 class VIII	CYP4F22	cytochrome P450 family 4 subfamily F member 22
WNT2B	Wnt family member 2B	TMEM246	transmembrane protein 246
CAMKV	CaM kinase like vesicle associated	RIMKLA	ribosomal modification protein rimK like family member A
CALML6	calmodulin like 6	PKIB	protein kinase (cAMP-dependent, catalytic) inhibitor beta
LGR6	leucine rich repeat containing G protein-coupled receptor 6	DSG1	desmoglein 1
KISS1	KiSS-1 metastasis-suppressor	ZMAT4	zinc finger matrin-type 4
FOXQ1	forkhead box Q1	TRPA1	transient receptor potential cation channel subfamily A member 1
CNBD2	cyclic nucleotide binding domain containing 2	SH3GL2	SH3 domain containing GRB2 like 2, endophilin A1

Contd...

Table 1. Contd...

Gene symbol	Gene name	Gene symbol	Gene name
ICAM5	intercellular adhesion molecule 5	PCP4	Purkinje cell protein 4
KRT38	keratin 38	STC1	stanniocalcin 1
TMPRSS5	transmembrane protease, serine 5	HCRTR2	hypocretin receptor 2
SLC22A20	solute carrier family 22 member 20	ELAVL3	ELAV like RNA binding protein 3
RADIL	Rap associating with DIL domain	AFF3	AF4/FMR2 family member 3
FOLR3	folate receptor 3	CA3	carbonic anhydrase 3

and tumor stroma might help to stratify the AA and EA TNBC patients and improve treatment regimen. Gene expression profiles suggested that tumor angiogenesis and chemotaxis pathway are functionally different between AA and EA BC patients (51-53). These pathways and underlying genes associated with these need to be evaluated in detail to understand the racial disparity in TNBC. We have performed a gene ontology (GO) analysis to trace out the genes and gene pathways that might be differentially regulated in AA and EA TNBC. Our analysis revealed the top ten gene pathways that are significantly up and down-regulated in AA and EA TNBC. The top five pathways that are up-regulated in AA TNBC include, i. Hematopoietic or lymphoid organ development (GO:0048534, p=0.0004), ii. Leukocyte differentiation (GO:0002521, p=0.00046), iii. Hemopoiesis (GO:0030097, p=0.0005), iv. Immune effector process (GO:0002252, p=0.00060), v. Lymphocyte differentiation (GO:0030098, p=0.00066). The top five pathways that are downregulated in AA TNBC over EA are i. Post-translational protein modification (GO:0043687, p=0.000494), ii. Homophilic cell adhesion (GO:0007156, p=0.00089), iii. Glycosylation (GO:0070085, p=0.00192), iv. Protein glycosylation (GO:0006486, p=0.0020), v. Macromolecule Glycosylation (GO:0043413, p=0.0020). The gene signatures associated with these up and down-regulated pathways must be studied to evaluate the precise molecular mechanism of action that can improve the trajectory of AA TNBC tumor biology and may give pointers on the aggressive disease course in AA TNBC over EA. Differentially expressed genes in AA TNBC can be found in Table 1. Future in-depth studies would be decisive in addressing the precise molecular regulation associated with the genes and pathways mentioned above to delineate the disparate tumor burden in AA TNBC. The landscape of molecular players that are differentially regulated at the transcriptional, post-transcriptional, translational or post-translational level may be the “next thing” to investigate to deconvolve the complexities surrounding TNBC racial disparity and might offer mechanistic cues that can directly translate to improve the prognosis and survival of AA TNBC patients.

4. CONCLUSION

A multitude of genes and their underlying molecular pathways define the tumor phenotype. Within the TNBC subtype, tumor phenotype is distinct among the women from African decent vs. the one with European descent, and thus AA women exhibit poor survival and prognosis. To date, there are very limited therapeutic options, mainly because of the intrinsic tumor biology of AA and EA TNBC is not clear. Thus, a landscape of molecular players that are differentially regulated at transcription, post-transcription, translation or post-translation level may be beneficial to investigate the TNBC racial disparity and might help to improve the prognosis and survival of AA TNBC patients. Identifying enrichment of biological networks in the tumor epithelium and tumor stroma might help to stratify the AA and EA TNBC patients and improve treatment

regimen. Gene expression profiles suggested that tumor angiogenesis and chemotaxis pathway are functionally different between AA and EA TNBC patients. These pathways and underlying genes associated with these need to be evaluated in detail to understand the racial disparity in TNBC. Thus, there is an unmet need to determine the molecular players and their underlying mechanism of action to improve the AA TNBC prognosis and survival.

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