

Escalation of Actions of Endocrine Networks for Treating Triple Negative Breast Cancer with Greater Efficacy: A Narrative Review

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Abstract

Earlier we had reviewed the detailed etiopathogenesis, treatment of BC, besides update on management of triple negative breast cancer (TNBC) along with how dysregulated cholesterol metabolism including oxysterols were implicated in the pathophysiology of breast cancer along with use that pathway for treating it, apart from 'using tocopherols/ phytosterols derived from *Pequi* (*Caryocar brasiliensis* Camb.) for complementing chemotherapy for BC treatment/alone or as new herbal therapy for improving 5 year survival, and part of syndecans in pathogenesis & detailed Selective estrogen receptors modulators (SERM) & Selective estrogen receptors degraders (SERD's) in avoiding post menopausal fractures & for BC therapy. As per the immunohistochemical categorized estrogen/ progesterone (P4) receptors decide the endocrine plausibility of the course of treatment of breast cancer. Possessing the properties of deficiency of estrogen receptor α , ER α negative breast cancer become detached from any kinds of endocrine regimens as far as the clinical scenario is concerned in routine specifically in case of TNBC. Nevertheless, this paradigm got challenges by the fact that triple negative breast cancers continued to possess retention of sensitivity along with susceptibility to endocrine substances. The crosstalking of hormone effects program earlier unappreciated was over time realized in addition to carcinogenic signaling, which were escalatingly examined. Correspondingly, the previously ignored endocrine reactivity in ER α negative breast cancers garnered interest providing innovative therapeutic approach in an ER α independent manner. Here we summarize the genomic in addition to non genomic steroid hormone effects along with endocrine correlated signals in TNBC, accompanied by the tag of hormone insensitivity. Moreover, insight is provided over non classical mechanistic modes determined in usual hormone substances for illustrating their pleiotropic actions. Further we highlighted how modulating gut microbiota (GM) might enhance these actions.

Keywords: Triple negative breast cancer; endocrine approach; steroid hormone; steroid hormone receptors; endocrine reactivity

INTRODUCTION

Breast cancer (BC) usually occurs in female patients and the hormonal environment works as the basic cause having remarkable influence on its etiopathogenesis. Acknowledged the genetic heterogeneity and the abnormalities in BC, clinically acceptable established molecular classification of breast cancer is canonically dependent on the expression of estrogen receptor ER α

(ER α), progesterone receptors (PRs), and overexpression of the human epidermal growth factor receptor 2 (HER2/ [EGFR]);

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These molecular biomarkers further work as a yardstick for evaluation of therapeutic reaction status like i) ER is a pointer to predilection for estrogen blockade and ii) overexpression of HER2 points to use of target immunotherapy.

Triple negative breast cancer (TNBC), entailing the problem of practically over 50% of morbidities in approximately 15-20% of all BC patients have the maximum depressing survival rates, where resistance might be partially **observed** in any targeted therapy with lack of target receptors [1]. The mortality rates in an epidemiological survey went to as high as 40%, in the cohorts having chemotherapy, and premenopausal women having hormonal enrichment portrayed the predisposed population [2]. Apart from lack of ER α , PR, HER2 in view of which endocrine treatment was not a probability and restricted the reactions to chemotherapy with cytotoxicity and 5yr survival rates were not enough for sustenance of combative adjuvant chemotherapy [3]. Therefore the docking based treatment format that depends on expression of hormone target receptors is pragmatically jeopardized leading to arrest of attractive applications [4].

Canonical applications of utilizing endocrine agents is made in ER α positive BC constituted of selective estrogen receptor modulators (SERM) selective estrogen receptor degraders (SERD), and aromatase Inhibitors (AI), whose working is for the repression of recurrence and long term survival advantages. The way corroborated by ER α negative shielded earlier from endocrine therapy attainment instigated sensitivity to tamoxifen [5], which pointed that endocrine reactions represented innovative manner of treatment of TNBC, that lack of target hormone receptors did not possess the capability of overpowering. Therefore the endocrine approaches attained rewiring and worked to trigger downstream signaling cascades **observed** to be significant.

The considerable escalation of hormone receptors for instance - glucocorticoid receptors (GR), androgen receptors (AR), and truncated isoforms of ER modulate key aid to endocrine reactions in TNBC, which licenses the alternate endocrine approaches with the idea of extending further than the canonical ER α blockade trajectory. Other than the acknowledged mechanistic modes regarding the estradiol-ER complex translocation to the nucleus pacey hormone actions modulated by membrane receptors have attained considerable interest that were implicated

in non genomic changes and are possessing the probability of being endocrine correlated targets [6].

One can commence by recalling the hormone correlated mechanistic modes and pathways for optimizing the endocrine management of ER α negative BC, specifically TNBC. Earlier we had reviewed the detailed etiopathogenesis, treatment of BC, besides update on management of triple negative breast cancer and how dysregulated cholesterol metabolism including oxysterols were implicated in the pathophysiology of BC and use that pathway for treating it, apart from 'using tocopherols/phytosterols derived from *Pequi* (*Caryocar brasiliensis* Camb.) for complementing chemotherapy for BC treatment/alone or as new herbal therapy for improving 5year survival, and part of syndecans in pathogenesis and detailed SERM and SERD's in avoiding post menopausal fractures and for BC therapy [9-12].

METHODS

Here we performed a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like Triplenegativebreastcancer (TNBC); apoptosis; autophagy; steroid hormones; Estrogenic Actions; Progesterone; Nuclear Hormone Receptors; Estrogenreceptor α -36 (ER α 36); Estrogenreceptor- β (ER β) Glucocorticoid Receptors (GR) Androgen Receptors (AR); Non Genomic Effects NF κ B; GnRH family members from 1995 till date in May 2024.

RESULTS

We found a total of 1000 articles out of which we selected 117 articles for this review. No meta-analysis was done.

Steroid Hormone Effects in TNBC

Generally invasion capability stimulated by steroid hormone has been displayed to be nuclear receptor based. Nevertheless, BC's which are hormonal reactive possess a common signaling transduction pathway as with ER α negative BC's and the format in both was not mutually exclusive. Numerous fold resident hormone receptors and enrolled circulating hormones performed their part in ER α independent carcinogenesis events of TNBC. Therefore the hormonal imbalance is key in TNBC, the manner visualized in luminal BC's [13]. Figure 1 displays a summary regarding estradiol and progesterone and the manner they influence transcriptional controlling [rev in ref 14].

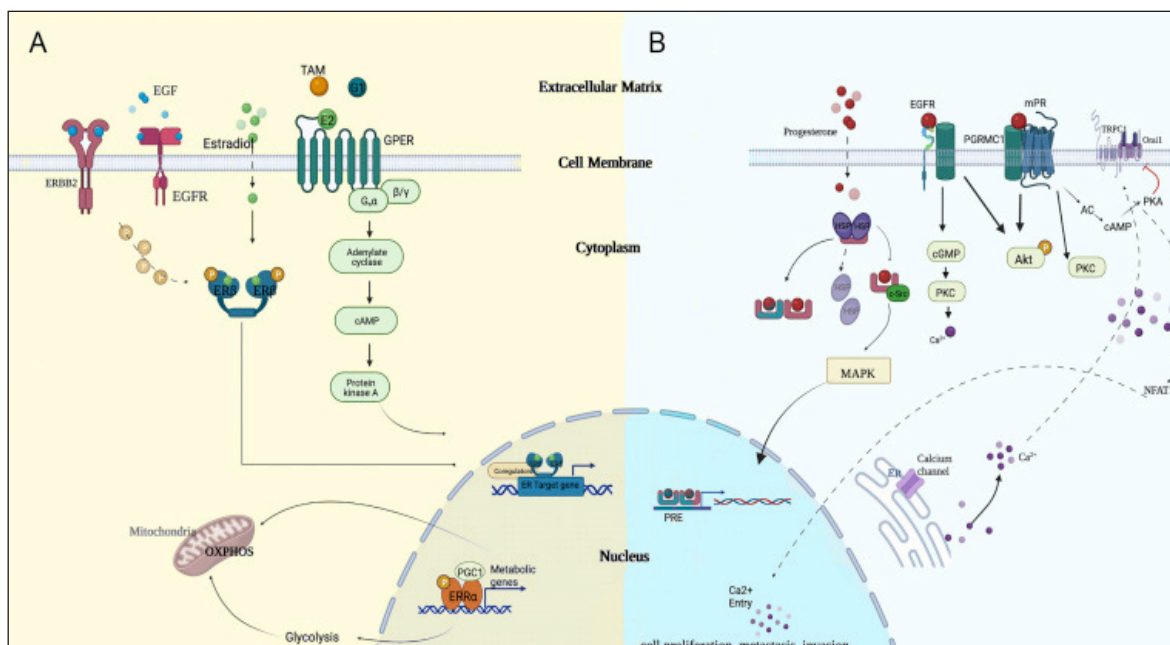


Figure 1. Courtesy refno-14-Potential modes of genomic and non-genomic approaches of (A) estradiol and (B) progesterone, which cooperated in regulating the carcinogenesis process. cGMP, cyclic guanosine monophosphate; EGF, epidermal growth factor; ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinase; NFAT1, nuclear factor of activated T cell; OXPHOS, oxidative phosphorylation; PGC1, proliferator activated receptor-gamma co-activator 1; PKC, protein kinase C; PRE, progesterone reactive element; TAM, tamoxifen.

Estrogenic Actions

Steroid hormones circulating in the periphery, particularly estrogen's liberated from their organs aid in the tumorigenic actions in patients with BC. Estrogen was existent in 3 kinds for instance i) estrone(E1)ii) estradiol(E2) and iii) estriol(E3[15]). The main isoform E2 gets biogenerated by aromatase from the androgenic precursors[16]. E2 which is lipophilic possesses the capacity of modulating genomic signaling through canonical nuclear started receptor effects (via ERα and ERβ)or non genomic signaling through membrane surface and intracellular receptors[17]. Canonically, the combination of E2-ER- impact their actions by binding to estrogen response element(ERE) at the promoter of target gene.

Although, with the lack of ERα, estrogens and xenoestrogens have been isolated for the working over tumor microenvironment(TME) through their respective receptors. E2 working is as stimulating "do not eat me" signaling by consolidating CD47-SIPR2(sphingosine-1-phosphate receptor-2-receptor) crosstalk and twisting the antiphagocytic action of M2 microglia[5,18]. Additionally, E2 elimination was advantageous from the therapeutic perspective as it corroborated and displayed escalating

tumor cell tropomyosin kinase receptor B(TrkB) signal controlled by E2 in premenopausal TNBC women and therefore diminished the risk of brain metastasis(BM) [1]. The preclinical model illustrated that E2 elimination based upregulation of Brain derived neutrotrophicfactor (BDNF) in ERα positive reactive astrocytes, followed by activation of TrkB demonstrated the carcinogenic part of estrogens in TNBC. In contrast to mice whose E2 were believed to be depleted, E2 shielded TNBC cells from the oncorepressive actions of the defense system[19].

Sartorius et al.[20], posited an innovative strategy with regards to endogenous E2 modulated brain metastasis colonization in which upregulation of EGFR ligand which had been characterized stimulated paracrine actions of E2 in an E2 reactive brain microenvironment caused sensitization of EGFR downstream pathway[20]. These studies reported that the E2 fueling worked and widened the therapeutic repercussions of tumor immune micro environment(TIME)- for instance ER positive mesenchymal stem cells and tumor associated macrophages(TAM). In view of E2 possesses the capacity of promoting immune escape in BM of TNBC,it might be believed to be a candidate for targeted therapies in case of primary breast lesions. The neuroprotective

and antiinflammatory actions of estrogen in the central nervous system(CNS), gets modulated by the pacy activation of the extracellular signal –regulated kinase (ERK1/2) independent of ER- ERE classical pathways [21]. The evolution of TME in the CNS occurred and generated an immunorepressive characteristic at the time of BM [22], and the TNBC subkinds were further tilted towards the immune evasion phenotype in contrast to luminal subkinds[23]. The TME in TNBC continues to be uncharted with the situations in stimulating anti inflammatory and immunorepressive capability of E2 in the manner BM was what warrants research .

Progesterone

One other elemental steroid hormone alias progesterone (P4) constituted of canonical activation of nuclear effects and non canonical activation of membrane effects imparts its progestogenic effector downstream targets akin to estrogen [24]. Therefore the progesterone receptor (PR), might be categorized into the nuclear progesterone receptors (nPR) and non genomic receptors for instance membrane progesterone receptors (mPR) and progesterone receptor membrane constituent 1 (PGRMC1) [25].

As illustrated by whole genomic actions of progesterone, once reactivation takes place in TNBC, P4 resulted in upregulation of genes, inimical for cell proliferation and invasion and constantly hampered the sustenance of genomic stability[26]. Anticancer characteristics of P4 target genes isolated in endocrine TNBC have insensitivity, which gave a provision of innovative endocrine approaches . Conversely, apart from progesterone metabolites alias 5 α dihydro progesterone(5 α P) and 3 α HP elicited converse actions over the evolution of TNBC, that gets significantly escalated by 5 α P whereas repressed by 3 α HP[27], whereas greater quantities of 3 α HP: 5 α P was implicated in the conservation of physiological situations in a non tumor milieu . Therefore the summary is P4 as per circumstances elicits its antitumor actions in TNBC.

NUCLEAR HORMONE RECEPTORS WORKING IN THE FORM OF TRANSCRIPTION FACTORS

Despite no expression of ER α and PR, other hormone transcription factors synergistically start endocrine signaling cascades that possessed the capacity of working as activators by possessing the equipment of endocrine network transponders-alias convey radiosignals through ER α independent pathways - androgen receptors(AR)

[28,9], glucocorticoid receptors (GR)[30] and unique ER isoforms. The manner described earlier ER α negative leading to immunohistochemical staining (IHC), could not be implicated in lack of endocrine effectiveness in TNBC.

Estrogen receptor α -36(ER α 36)

As a canonical ER α (ER α 66), ER α 36 was quoted by Wang et al.[31], in 2005, to possess a truncated length of 36kda [31]. In contrast to ER α 66, ER α 36 might be simultaneously expressed in TNBC and modulate transduction of estrogen signaling [32], that was initially isolated to be expressing a particular transcriptomic signature in TNBC[33]. Despite the absence of both transcriptional domains, the DNA binding domain and the dimerization binding domain bestowed ER α 36 with a dominant negative controlling of the transactivation working signaling via ER α 66 and ER β [34]. ER α 36 was implicated in genomic mechanistic modes of carcinogenesis and invasion, despite with an inferior percentage in contrast to non genomic effects. The intactness of the necessary domain ER α 36 whose potentiation takes place for dimerization with ER α and translocation into nuclear ER α to start nuclear effects. Nevertheless, equivocal conclusions lie behind the force meant for counteraction amongst ER α 36 and ER α 66. Wang et al. [31], displayed that tamoxifen working was as an ER α agonist for upregulating the expression of the aldehyde dehydrogenase 1A1(ALDH1) in cancer stem cells (CSCs) that possess a key part in the sustenance of the cancer stemness characteristics[35]. This **observation** strengthened the genomic mechanistic modes of ER α 36 independent of status of ER α 66 in reaction to estrogen and tamoxifen. It was realized that truncated ER α 36 and ER α 66 reciprocally crosstalked and were constrictive. An earlier study showed the controlling part of ER α 36 for downregulating ER α 66 expression through upregulating EGFR [36]. Apart from that ER α 66 possessed the capacity of crosstalking with ERE-half area in intron1 of the ESR coding area and thereby hampering ER α 36 transcription action[37]. Additionally, a recent study reported that ER α 36 in communication with GPER hampered nuclear factor κ B(NF κ B) modulated proinflammatory action and expression of downstream tumor necrosis factor alpha(TNF α) and interleukin-6 (IL-6) in TNBC[38].

Estrogen receptor- β (ER β)

In contrast to indicated part of ER α over the effectiveness regarding endocrine strategies ER β expression occurred in CSCs, normal epithelial cells, stromal cells and TNBC and organization were believed to be absence of specificity[39].

ER α and ER β have been isolated to be homologous, sharing a considerable likeness with DNA binding domain although they both have their own ligand binding and their transcriptional activation working domains. Other than ER β 1, all the rest of ER β isoforms (β 2-5) got disabled for their combination with the connecting ligands independently and their dimerization with ligand binding was only feasible with ligand binding domain ER α / ER β 1 for the activation of negative estrogen correlated signaling pathway. The genomic topography globally with regards to crosstalk amongst ER β and the oncogenic genome in breast cancer (BC) showed that ER α and ER β intersect remarkably amongst each of them regarding controlling of the target gene. In view of spatial intricateness with mitochondrion ER β believed to aid in mitochondrial DNA encoded genes working via an ERE-like sequence [32].

The manner corroborated by earlier studies ER β was foresighted as an anticipator regarding BC survival. E2/ ER β modulated hostility and stemness characteristics in BC might be partially reasoned out by downstream effects, which facilitate EGFR, vascular endothelial growth factors (VEGF), amphiregulin, wntless-related integration site (WNT) Wnt-10 β liberation [27]. The inimical sequelae resulting from ER β might be reverted by tamoxifen in ER α negative tumors. In view of the existence of ER β resulted in improvement of ER α positive BC patients that were treated by tamoxifen. Being a canonical SERM, fulvestrant hampered growth stimulating actions by negatively controlling DNA methyltransferases (DNMT), that broadened the probability of intent to treat population of ER α / ER β + BC [40].

At the time of existing simultaneous with ER α , ER β usually illustrates antagonistic effects towards proliferation and invasion [28], pointing towards a restricted output of ER α and its modulating transcriptional actions by diminishing the enrollment of c-Fos and c-Jun to the estrogen promoter [29]. In vivo study corroborated the oncorepressive part of ER β as evidenced by its elimination resulted in over expression of ER α and resulted in the combative phenotype [35]. Mechanistic modes evaluation illustrated that downregulation of cell cycle repressive tumor protein 53 induced nuclear protein 1 (TP53INP1) by ER α , had feasibility to be completely reverted by ER β , thereby, substantially diminishing occasional cyclins for instance CCNA2, CCNB1, CCNB2, CCND and CCNF [30]. As the controlling genomic evaluation presented, the gene profiles that were facilitated by ER α whereas hampered by ER β , which were focused in the working of the "cell

cycle", "xenobiotic metabolism," and "ion transport" and genes in these pathway basically were corroborated to be tumorigenesis biomarkers.

Additionally, apart from crosstalk with ER α , interactions with AR lies behind the aid given toward antiandrogen effectiveness enhancement. The heterodimer comprised of binding competitively to AR hampered the generation of AR- AR homodimer and the blockade of the following phosphatidyl inositol 3 - kinase (PI3K) /protein kinase B (AKT) oncogenic signaling pathway. Song et al. [39], **observed** that ZEB1 (zinc finger E-box binding homeobox 1), representing an invasion promoter and whose expression takes place cooperatively with E-cadherin, got hampered by ER β , thereby attenuating its initial hostility phenotype [39].

ER β pathway working was greater over the proliferation of CSCs in contrast to ER α , acknowledged the percentage towards estrogen reaction. Nevertheless, its influence over the TNBC propagation is only at the initial stages of evaluation. Of the 3 genes controlled only by ER β , were correlated with lipid and cholesterol metabolism. Alexandrova et al. [41], isolated ER β stimulated hampering of cholesterol biogenesis modulated by miR181a-5p by utilization of small noncoding RNAs profiling for the TNBC that corroborated the association of cholesterol metabolism [41].

Maximum **observations** posited that ER β modulated tumor hampering occurred via cell arrest in G1 phase and, downregulation of cyclins. Apart from negative controlling of ER β of tumor repressive genes might be held responsible for stability failure of EGFR and repression of p53 mutagenesis. The validating proof pointed that ER β was involved in reduction of genes encoding critical constituents, positive correlated with TNBC hostility. Furthermore interactions of ER β and intranuclear molecular chaperone initiates the events of genes controlling, RNA splicing and chromatin remodeling at the transcriptional and posttranscriptional level that was corroborated by the association amongst ER β and polycomb repressor complexes 1 and 2 (PRC1/2) in events of cholesterol biogenesis in interaction proteomics [42].

This adaptive approach with regards to dualistic part of ER β continues to be controversial. A phase II Clinical trial (NCT03941730) with the goal of above detailed quandary got performed in ER β positive TNBC population that traded off activation of tumor repressive actions by E2 against refraining of tumor facilitating actions of tamoxifen in reference to pros & cons of ER β .

Glucocorticoid Receptors (GR)

As a nuclear hormone receptor GRs work as ligand activated transcription factors and have requirement for minimal need for agonist dependency on ligand for signaling actions[30]. Phosphorylation of GR that is ligand activated resulted in modifications of the feedforward signaling loop with the sensory input of TME obtained stress signals for the continuation of activation of stress signaling pathway for switching on the advancements in cancer biology in TNBC. Other than host and stress stimuli converging possessed the capacity of activating a p38 mitogen activated protein kinase(MAPK) initiated ligand independent phosphoGR and generate a signal amplifier modulated by the positive feedforward controlling of p38 MAPK[43]. Nuclear translocation once activated with the subsequent combination of glucocorticoid response element(GRE) in addition to other transcription

factors for instance NFκB along with activator protein 1(AP1), was correlated with controlling of working gene expression and risk of generation of combative modalities in reference to BC.

GR worked as a tightly controlled homeostasis machine in reference to the disturbance of TME homeostasis pointing to stress signaling factors and pathway stimulated by solid tumor necrosis and tissue remodeling suggesting any kinds of modifications in changes of GR effect would strangle feedback controlling and baseline female aiding in pathogenesis[44]. Overexpression of GR in case of nontreated TNBC anticipated bad prognosis (HR=1.73) and 24 pS134- GR based genes correlated with hampering of apoptosis in breast epithelial cells[45]. Nevertheless, the existence of GR yielded a potential target to cascade of advance tumor phenotypes, resistance to chemotherapy and androgen in therapy of TNBC[46].

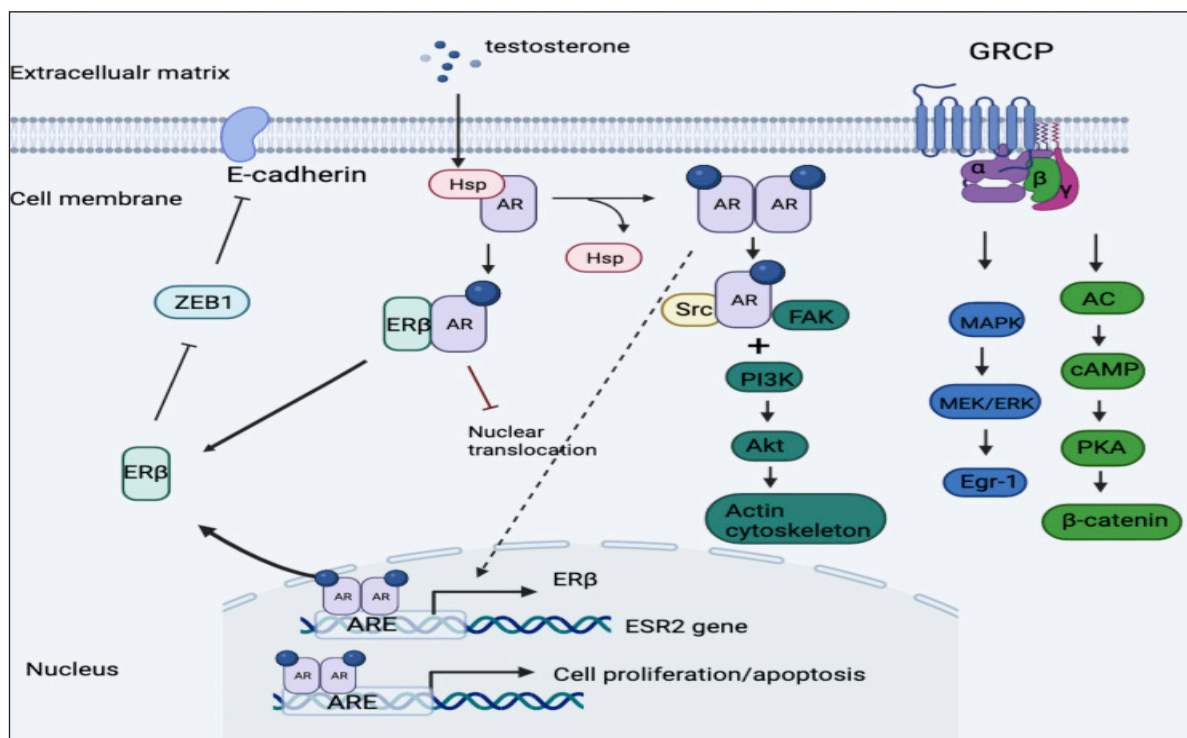


Figure 2. Courtesy ref no-13-Model of androgen-induced genomic and non-genomic actions in TNBC cells. Classical AR was divorced from the HSP and formed the homodimer once activated by a ligand, which was then transferred into nuclear actions and binding to the promotor of ESR2 gene linked to regulation of ERβ expression. Further, the expressed ERβ dimerized with AR then impeded the nuclear translocation of AR-AR homodimer and thus blocked downstream oncogenic signaling. In addition, androgen stimulation activated the classical AR/Src complex assembly, rapidly recruiting PI3K and FAK, which triggered the downstream phosphorylation and the consequent cytoskeleton changes. Besides, the G protein-coupled form of AR activated downstream MAPK/MEK/ERK signaling and induced the phosphorylation of cAMP and PKA. ARE, androgen receptor element; Egr-1, early growth response 1; GRCP, G protein coupled receptor; HSP, heat shock protein; ZEB1, zinc finger E-box binding homeobox 1.

Androgen Receptors (AR)

The existence of an androgen receptor (AR), categorized TNBC into quadruple negative breast cancer and positive AR TNBC. This AR positive TNBC garnered a variable dependence over the AR which possessed the greater universal expression in contrast to ER and PR [47]. Figure 2 displays a summary of androgenic genomic and non genomic effects in TNBC cells.

Estrogen response action through estrogen controlled genes was basically estimated by the situationally imperative fork head box protein 1 (FOXA1) as silencing modifications that interfered with the full ER α associated chromatin and transcriptome actions [48]. Despite, the part of FOXA1 as the innovator of ER α effects and the greater baseline estrogenic environment in female patients, FOXA1 expression in BC's with the ER α deficiency acquired around 30% [49]. Robinson et al. [50], displayed FOXA1 took part in transactivation of AR modulated downstream program in molecular apocrine TNBC, that was accumulating endocrine reactive genes that were akin to the luminal signatures of BC's that were ER α positive [50]. AR binding regions were rechanneled towards the objective domain where ER working occurred to start with. Thereby AR cistron working was as a hurdle on the path of carcinogenesis by ER α [51], whereas simulating the main carcinogenic program while silencing ER α [52]. Despite, FOXA1 is undetermined/inconclusive in its part as an endocrine target spot, a plethora of **observations** suggested its probability of impeding the hormone signaling independent of ER for instance - MAPK/ERK and PI3K / AKT/mTOR (mammalian target of rapamycin) pathways [53]. The cross crossing amongst ER and AR modulated signaling stepwise took place in the AR binding fashion, phosphatase and tension homolog (PTEN) that was a victim of upward controlling by ER, thereby assigning the antitumor working of AR to the diminishing output of the PI3K / AKT pathway by the upregulation of PTEN [54]. On the other hand, the activating PI3CA mutations escalation of pAKT were attenuated by hampering of AR, that gave presentation of tumor facilitating effects of AR. The other mechanistic modes **observed** that the AR being anchored to antioxidant responsive element (ARE) in the promoter of the ER β gene led to the overexpression of ER β . Apart from that synergistic hampering was found in vitro in combination with CDK4/6 hampering and antiandrogens in luminal and TNBC cell lines [55].

NON GENOMIC EFFECTS

Despite, with verifiable confirmed preferences of nuclear transcriptional ER α regarding genomic carcinogenesis, alternate isoforms of classical receptors stimulate pacy non genomic effects [56]. Non genomic effects possess the inclination to guide a pacy change through membrane disequilibrium and correlated expression activation of the 2nd messenger pathways, thereby modulating different biological reactions. For instance these receptors got considerable interest in the field of evaluation.

Estrogen Receptor α -36 (ER α 36)

In the form of an extranuclear isoform of ER α , ER α 36 modulates pacy non genomic effects by intersecting over 2 elemental signaling pathways, i) direct phosphorylation of the MAPK/ERK pathway by the activation of the c-Src [57] and ii) activation / phosphorylation of PI3K / AKT axis and hampering / phosphorylation of glycogen synthase kinase 3 β (GSK3 β), that ensures the stability and nuclear translocation of nuclear factor erythroid-2-related factor-2 (Nrf2) [58]. Nrf2 performed its necessary part in metabolic reprogramming as well as antioxidation controlling through binding with the ARE and followed by controlling metabolic correlated genes [59]. Zhang et al. [37], illustrated the mitogen activated estrogen and anti estrogen based signaling pathway via the phosphorylation of EGFR and Src by physical crosstalk, whose repression was plausible by ER α 36 knock out (KO) TNBC cells with utilization of short hairpin RNA by the bypass activation of PI3K / AKT signaling pathway [60]. Apart from signals that were being transmitted via EGFR/HER2/ERK pathway intersected towards cisplatin resistance [61].

Estrogen Related Receptor α (ERR α)

This orphan receptor referred to estrogen related receptor α (ERR α) was substantially homologous to the canonical ER α regarding target nodes, controlling elements, and region of effects [62]. In case of hormone receptor negative SKBR3 cell lines physiological dosages of E2 possess the capacity of stimulating the expression of ERR α for controlling estrogen. With the Peroxisome Proliferator Activated Receptor γ coactivator -1 α (PGC-1 α), ERR α worked in the controlling of remarkable metabolic correlated molecule. This PGC-1 α /ERR α has been acknowledged to be a key controller for the mitochondrial biogenesis and working that is applicable to the Warburg effect and energy metabolism [63]. The cholesterol-ERR α axis worked in disrupting

purine anabolism and folate metabolism by 1 carbon resource repression. Like an endogenous ligand of ERR α , cholesterol stimulated an autoinduction loop of ERR α underpinning the expression of target genes through it with its costimulatory PGC-1 α [64]. Moreover, metabolic reprogramming in an ERR α based way incorporated escalated oxidative phosphorylation(OXPHOS), tricarboxylic acid cycle(TCA alias Krebs's cycle) intermediate quantities, pentose phosphate pathway that comprised the metabolic perturbations in TNBC[65]. ERR α escalated the nicotinamide adenine nucleotide phosphate(NADPH) by the event of malate-aspartate shuttle and glucose-6-phosphate dehydrogenase (G6PD) that was further used for the expansion of the biomass generation and Reactive oxygen species(ROS) detoxification and leading to correlation of malignant phenotype in TNBC[66]. Noticeably, hampering effects to the ERR α , alias metabolic energy sensor, worked to avoid epithelial-mesenchymal transition (EMT) by directly targeting fibronectin[67].

G- Protein Coupled Estrogen Receptor(GPER)

G- protein coupled estrogen receptor(GPER), is well illustrated to be membrane bound and cytoplasm placed sex steroid hormone receptor in TNBC[68]. Specifically considerable is that SERM and SERD having ER breakdown actions were showed to be agonists of GPER, other than being the original E2 ligand, that detailed the partial mechanistic modes regarding tamoxifen escape, despite non ubiquitous acceptability of this action. Additionally, GPER worked in the form of an intermediate in the controlling of the E2 binding ERR α as well as positively influencing ligand activated ERR α working was found in reference to the overexpressed GPER that got negated by siGPER by the transfected plasmid. GPER took part in the ligand started pacy non genomic effects in TNBC through communication with phospho-ERK(pERK), phospho-focal adhesion kinase(pFAK), and cell cycle proteins for instance cyclinA and cyclinD1, that continued to possess the capacity of reacting to mitogenic estrogen signaling stimuli in the situation of hormones getting repleted[69]. A considerable percentage of evaluation displayed that GPER was responsible for the sustenance of stem cell like and self propagating characteristics through phosphorylation of protein kinase A(PKA) and BAD-Ser118 in tumor tissues[70]with jeopardized prognosis and survival. The in vitro experiment illustrated that targeting GPER in SKBR3 cell lines which had endogenous expression of GPER ensured G2/M cell cycle arrest of tumor cells[71], while tumors that were dormant kinds had

escalated proneness to a cytotoxicity action. Sequentially, endocrine treatment is anticipated to be possessing the orientation in plethora of blockade trajectories over cytoplasmic and intranuclear estrogen receptors. Dependent over considerable studies of GPER binding endocrine effects, till date validation incited remarkable variation in consensus that moved away from the fixed part as promoter of carcinogenesis and unveiled the antitumor GPER actions in variable accumulation of tumor receptor reactions. To start with i) the mechanistic modes against tumor propagation of GPER partly comprised of amelioration of mitogenesis actions of estrogen and the GPER modulated stimulation of histone H3 and caspase-3 which was followed by sequential cell apoptosis.iii) Recently it was illustrated that activation of GPER through its particular agonist G1 repressed the proangiogenic factor, for instance IL-6, vascular endothelial growth factors(VEGF) and NF κ B, thereby targeting angiogenesis and invasiveness as key dilemma of combative TNBC[72].

Differences over GPER modulated proliferation actions on BC were inclusive of growth hampering of endocrine sensitive MCF7 cells and in growth facilitating actions of ER negative SKBR3 cells[73]. Notas et al.[74], isolated the crosstalking of ER and GPER in extranuclear ER actions through the pharmacological strategies towards breast cancer cell lines T47D and MDA-MB231[74], that was in consensus with the earlier clinicopathological confirmation which associated ER and GPER expression in breast cancer in a positive[75]or in a negative manner[76]. Concisely, early membrane started effects of estrogens in BC are controlled in a complex way where the actions of GPER transcription is basically based over the simultaneous activation of the ER variants.

Non Genomic PR Signaling

Over the last variable decades a restricted pool of PR impinging over the plasma membrane(PM) has been substantially found to enact pacy progesterogenic actions in a classical independent way. The non genomic modulator was basically associated with progestin and adiponectin Q receptor family (PAQR) that got comprised of non classical G- protein coupled mPR[77]. The major pathways in pacy non genomic PR signaling were PI3K / Akt and Src/ MAPK pathways based on direct crosstalking that worked in the progestin modulated angiogenic shift through VEGF and generation of advanced metastatic phenotype[78,79]. With lack of canonical PR, in TNBC P4 started a non

canonical membrane signal with P4- PGRMC1 conjugate in the injustice of intracellular calcium homeostasis in TNBC cell lines, where P4 - based Ca^{2+} mobilization pathway faced/confronted the blockade of PGRMC1 modulated nuclear factor of activated T cells(NFAT1) intranuclear downregulation[80]. Over expression of the PGRMC1 phenotype was further associated with invasive phenotype and bad prognosis with broadened signaling of PI3K / AKT/mTOR and EGFR pathways[81]. Apart from that PR possessed the capacity of indirectly upregulating proliferation genes with signal transducers and activators of transcription3(STAT3) binding area in their promoter rather than PRE through PR started signaling complex inclusive of Src, ErbB2(1 of the 4 epidermal growth factor receptor (EGFR) tyrosine kinase family members), janus kinase(JAK1) and JAK2[82]. Naraynan et al.[83], pointed that cytoplasmic pool placed PR accumulating mainly in the G1 phase encountered replacement in the nucleus in the S phase which partially reasoned out how non genomic actions of the mPR compactly controlled the transit of the G1 / S phase and following activation of cell cycle proliferation[83].

Scientific statement by researchers displayed the biphasic actions of the progestins and non classical PR complexes in TNBC cell lines. Progesterone repressed tumor proliferation and brain metastasis in an intersecting manner through mPR [22] and reverting mesenchymal to epithelial phenotype in MDA-MB231 cell lines. Moreover, PGRMC1 was confirmed to escalate chemotherapy resistance and ameliorate apoptosis actions of doxorubicin[84].

Non Genomic AR Signaling

AR was posited to be an androgen activated transcriptional factor possessing equipment of genomic and non genomic effects. G- protein coupled receptor(GPCR) acknowledged for modulating androgen effects through 2nd messenger actions for instance Ca^{2+} efflux and ERK phosphorylation were believed to be membrane AR. The validation till now indicated that androgen stimulated reactions mARs were situationally based over variation of cell kinds and cellular milieu.[85,86]. Giovanelli et al.[85], isolated a canonical AR/ Src/ PI3K complex assembly that stimulated cytoskeletal alterations leading to motility and migration in TNBC obtained MDA-MB468 cells possessing variable quantities of expression of AR [85]. In contrast to that earlier work displayed a proapoptotic part of membrane started AR [86,87]. Further detailing, the upregulation of the inherent proapoptotic molecules for instance

Bax, cytochrome-c, and caspase3 were generated by the activation of G- protein and the following MAPK /ERK pathway and escalated intracellular zinc quantities in MDA-MB468 cells[87]. Apart from androgen triggered proapoptosis mechanistic modes controlled by mARs might be projected in the actin restructuring and stasis through AR/ Src/FAK/ PI3K signaling and downregulation of FAK and Akt[86]. The detailing previously of androgen particular transport and proapoptotic working of zinc transporter members (ZIP9) got modulated by quantities based zinc transport actions via stimulatory $\text{G}\alpha$ protein. Additionally, Kalyvianaki et al.[88], exhaustively detailed the alternate kinds of mARs via affinity binding with testosterone(T)-BSA, for instance G- protein coupled oxo- eicasonoid receptor1(OXER1) and G- protein coupled receptor family C group6 memberA(GPRC6A). They posited the importance of integrating receptors into the fashioning of further therapeutic targets[88]. OXER1 working as a particular mAR in BC got antagonized by T as per its initial cytoskeletal reorganization; thereby manipulating adhesion and migration capability[89]. GPRC6A, well acknowledged as a governing element of complicated endocrine and metabolic networks was displayed to result in activation of downstream ERK pathway and suppressing output of early growth response -1 (Egr-1) pathways upon binding with $\text{G}\alpha$ protein[90].

The very reason due to which mARs were encompassed in a debatable situation with variable validation pointed to both hampering in addition to facilitative effects in breast carcinogenesis might be limited partly to the incomprehensible inclination of mAR ligand to stimulation of genomic or non genomic effects in BC cells.

Non Genomic GR Signaling

GR has been well acknowledged in fast non genomic pathway correlated with autoimmune diseases and cancer[91]. Nevertheless, minimal confirmation of non genomic actions was hypothesized in reference of cancers particularly in BC. Clarise et al.[92], detailed non genomic mechanistic modes of GR modulated apoptosis in lymphoid malignancies, mainly correlated with sequelae of cytosolic K^+ and Ca^{2+} mobilization and generation of reactive oxygen species (ROS)/ reactive nitrogen species (RNS) in association with oxidative stress(OS)[92]. Leis et al.[93], illustrated that GR possesses the capacity of counteracting the tumorigenic activity of PI3K /Akt in skin tumorigenesis and the coexpression of GR and AKT in keratinocytes suppressed the AKT guided tumor

pathways[93].As per them, non genomic GR modulated PI3K /Akt downregulation was due to transcription independent action with utilization of transcriptionally disturbed GR mutant . The distinct mechanistic mode of GR displayed disassociation of GR's from the complex possessing Src over combination with GC's and following Src liberation resulting from phosphorylation of inducible nitric oxide synthase (iNOS) and the activation of the pathway in a non genomic way[94].

ESTROGEN REACTIVE GENES ALONG WITH SIGNALING PATHWAYS

ER worked as an arbitrator in the governing of cell fate and downstream cyclin – dependent kinase4/6(CDK4/6),that were anticipated to take part in target chain of endocrine blockade.The CDK4/6 antagonists were validated to attenuate the propagation of mitogenic actions in TNBC *in vivo*, and *in vitro* studies, that illustrated the negation of cell cycle division as endocrine blockade pointing towards CDK4/6 in an ER independent way[95].

A unique TNBC subkind isolated as luminal-AR(LAR) had presentation in compact germaneness over considerable activated hormone correlated signaling pathways inclusive of steroidogenesis, porphyrin metabolism and androgen metabolism. Burstein etal. [96], performed an exhaustive genomic analysis,where they detailed molecular validation of activated estrogen downstream signaling . This pointed to reactiveness of LAR subkinds towards canonical antiestrogen/androgen approaches independent of status of ER [96], that might partly be reasoned out by the non constant status amongst expression of ER protein and ER coded gene[97]. Apart from that Williams,etal.[98], isolated a 32 gene signatures, which were centred around those obtained from ESR(encoding ER α) and its downstream target gene, thereby associating TNBC with ER reaction[98] .This BC subkind phenotypically perceived as ER negative possessed the equipment of transcriptional genes in ER positive cancers that might be directed as an endocrine approach in an ER independent, however androgen receptor based .

EPIGENETICS CONTROLLING

Equivalent to the deletion changes of hormonal receptors in metastasis at the time of distant spreading, the reacquisition of hormonal receptors through modifications in epigenetics controlling needs to be further recognized. Preclinical and clinical studies illustrated

an unproportional substantially greater rates of genetic abnormalities in TP53, BRCA1 and enhancer of Zeme Homolog 2 (EZH2) [99]. Yomtoubian etal.[100], **observed** that EZH2 hampering discriminated EZH2 high grade basal cells to an endocrine sensitive subkind by desuppressing GATA3,yielding a provision towards innovative target resensitization to endocrine substances not refrained by chemotherapy alone[100]. Recently,a study by Sharma etal.[101], evaluated the inducible restoration of working ER α and AR in SKBR3 cell line by combination of DNA methyltransferase(DNMT) hampering agents and histone deacetylase(HDACs) hampering agents that displayed the accessibility of prospective sensitivity[101].

NON CLASSICAL MECHANISTIC MODES OF ENDOCRINE SUBSTANCES

In view of main perspectives posited that existence of canonical ER α and PR were elemental to endocrine impoverishment treatment ,earlier minimal confirmation correlated present endocrine substances with the hormone signaling switching system towards the robust scientific researchers working and therapeutic targets in triple negative combative subkinds of BC, that deserved focus. Steroidal aromatase hampering agent for instance formestane and exemestane possessed the capacity of overcoming endocrine resistance of non steroidal AI's in an ER independent, however AR- based way with regards to their direct absorption into TNBC, might be by their androgenic metabolites hampering the availability of Cyclin D1 (CCND1) by histone modifications in the G1/S transit[102].

Gonadotropin releasing hormone receptor (GnRHR) portray universal expression in both the glandular tissue and malignancies.As per the **observations** of the scientists GnRHR generally were seen in over 50% of TNBC, thereby dictating them as being straight targets for GnRH analogs(GnRHa) for instance goserelin[103]. Moreover,a plethora of studies illustrated that GnRHa was implicated in leading to disturbance of an autocrine stimulatory loop where the agonists resulted in restriction on gonadal axis and shielded ovarian function from toxicity of chemotherapy in patients who were ER negative[104,105]. Apart from resulting in avoidance of generation of premature ovarian insufficiency(POI) for young BC patients,simultaneous utilization of GnRHa with chemotherapy stimulated the earlier initiation of progesterone repression and in turn quantities of receptor activator of nuclear kappa B ligand(RANKL) and

its receptor escalated the sensitivity to chemotherapy in TNBC[106]. Additionally, Matsushima-Nishiwaki et al. [107], recently unravelled raloxifene and bazedoxifene, however not tamoxifen worked as an ER β agonist in hepatocellular carcinoma (HCC) cells for abrogating, transforming growth factor1 (TGF-1)stimulated migration by particularly hampering phosphorylation of AKT[126].

Tamoxifen in general was consumed as an antiestrogen substance and Morad et al.[127], utilized its capacity of facilitating the membrane permeability regardless of ER status and efficaciously modulated the ceramide metabolism for optimization of its actions over toxicity[108].

The tamoxifen controlled transcriptional action revealed tamoxifen positively induces pluripotency of BC[109]. Moreover, the ATLAS trial confirmed that a continued tamoxifen regimen attained clinical advantage through a so called sleeping approach resulting in total cancer cells switching toward a dormant status, switching off local or metastatic relapse[110].

Nevertheless, the debatable mechanistic modes of tamoxifen; it worked as an agonist or non canonical ER (for instance GPER)or an antagonist over canonical ER α in BC was present even now. Acconcia et al.[111], illustrated that capability of tamoxifen binding with extranuclear protein that was pertaining to particular crosstalking which was responsible for variable transcriptional results,in which tamoxifen led to enrollment of transcriptional co- suppressors in the breast and transcriptional co-activators in endometrium [111]. Zekas et al.[112], isolated in an ER α / GPERpositive estrogen reactive BC cell line-MCF-7, tamoxifen worked mainly as a GPER selective agonist for pacy transactivation of EGFR and sequentially inactivate GFP fused fork head box protein03 (FOXO3) in a GPER modulated ER α independent way transitory time scale[112]. Recently one more study validated the carcinogenic part of tamoxifen, where Ca²⁺ mobilization and overexpression of kinin B receptor occurred, portraying one more GPCR was illustrated to promote proliferation and metastasis in BC[113]. Pertaining to GPER positive cell lines regardless of ER α , tamoxifen possessed an off target action, which upregulated the expression of aromatase by enrollment of c-Fos and c-Jun to reactive elements residing in promoter areas of aromatase through GPER and leading to sustenance of endocrine resistance[114].

All the work presented above pertaining to tamoxifen realize non canonical ER modulated mechanistic modes

of tamoxifen, in BC and additionally repurposing of tamoxifen for escalating its adaptability and applicability in TME in TNBC. Furthermore, Devoy et al.[115], more recently in 2024 added another part of tamoxifen advantageous actions. Briefly 17 β -estradiol (E2) possesses the capacity of directly facilitating the growth of ER α -negative cancer cells via activation of endothelial ER α in the TME, thereby escalating a normalized tumor angiogenesis. ER α works in the form of a transcription factor(TF) via its nuclear transcriptional AF-1 as well as AF-2 transactivation working, however membrane ER α possesses a significant part in endothelium. The goals of the current study were to infer the respective parts of these two pathways in ER α -negative tumor growth. Furthermore, Devoy et al.[116], detailed the effects of tamoxifen, a SERM in ER α -negative tumors growth and angiogenesis, since they had recently illustrated that tamoxifen influences vasculature working via complicated modulation of ER α action. They grafted ER α -negative B16K1 cancer cells into immunocompetent mice mutated for ER α -subfunctions along with tumor growths were evaluated in these variable models in reaction to E2 and /or tamoxifen treatment. Moreover, assessment of RNA sequencings was performed in endothelial cells in reaction to these various treatments and corroborate by Real Time- Polymerase Chain reaction (qRT-PCR), in addition to western blot. They illustrated that both nuclear and membrane ER α effects are needed for the pro-tumoral actions of E2, whereas tamoxifen completely ameliorated the E2-induced *in vivo* tumor growth, via hampering of angiogenesis however caused facilitation of vessel normalization. RNA sequencing pointed that tamoxifen hampers the E2-induced genes, however further initiates a particular transcriptional program controlling of angiogenic genes and differentially controlled glycolysis, oxidative phosphorylation and inflammatory reaction in endothelial cells. Thereby concluding such **observations** yield corroboration that tamoxifen particularly hampers angiogenesis via a reprogramming of endothelial gene expression through controlling of certain TF's, which might open innovative favourable strategies for management of cancer therapies impacting the TME of ER α -negative tumors[115].

ROLE OF GUT MICROBIOTA (GM) IN TNBC

Bacterial inhabitants of the body possess the capacity of working in different stages of cancer starting, propagation, and treatment. These bacteria might be distal to the primary tumour, for instance gut microbiota(GM), or

local to the tissue, prior or subsequent to tumour growth. BC has been well evaluated pertaining to this issue. Of the BC types, TNBC is more hostile, has lesser treatment strategies in contrast to receptor-positive breast cancers, possesses a full greater inimical prognosis greater rates of recurrence. Thereby, a deep insight of the bacterial impact over TNBC propagation and treatment is of considerable significance. Regarding this, Gut Microbiota (GM) might be implicated in different stages of tumour propagation. It might either repress or facilitate carcinogenesis via liberation of carcinogenic metabolites, sustenance of proinflammatory milieu and /or the facilitation of epigenetic alteration in our genome. It further possesses the capacity of modulating metastasis and recurrence via crosstalking with the immune system and has been recently illustrated to impact chemo-, radio-, and immune-therapies. Furthermore, bacteria have also been

observed to possess placement in normal and malignant breast tissue. A plethora of studies have now detailed breast and breast tumour microbiome, with the tumour microbiota of TNBC possessing the minimal taxonomic variation among all breast cancer types. Here, particular situations of TME- low O₂, leaky vasculature and immune repression - are validating tumour selective bacterial growth. This innate bacterial capability might aid in their use as administration of substances for therapeutics or as diagnostics. The review by FebrissyC [116], aimed to evaluate the present information over bacterial germaneness to TNBC and its plausible utilization at the time of evaluating certain of remaining unanswered queries regarding mechanistic modes reinforcing the observed effects. This further aids in increasing E2 signaling as seen in normal circumstances (see figure 3 displaying the same) [rev in ref 117].

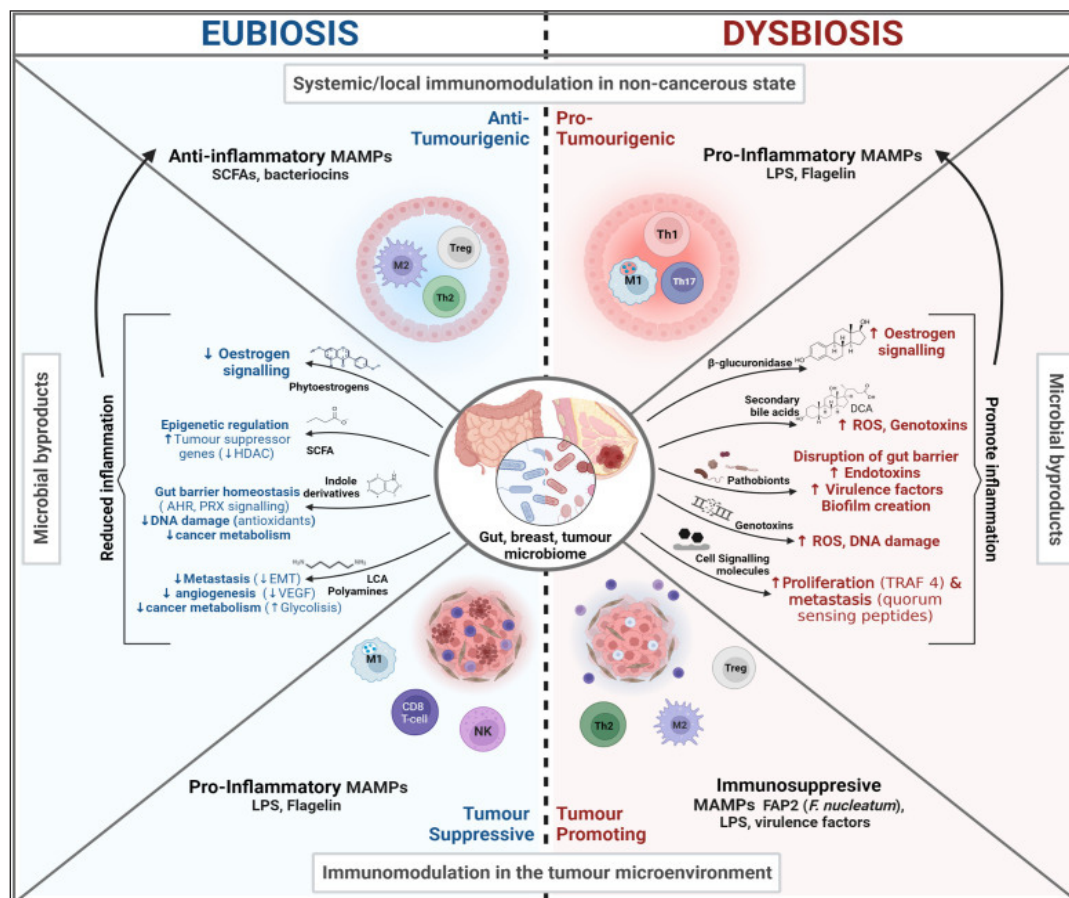


Figure 3. Courtesy ref no-116-The microbiome influence in Cancer. In eubiosis the microbiome promotes our health status and prevents oncogenesis and tumor progression by influencing the immune system, promoting gut barrier integrity, and influencing cell signaling. Conversely, during dysbiosis there is a loss of barrier integrity that can lead to potentially harmful bacterial translocation, chronic inflammation in distal sites and the production of cancer promoting bacterial by-products.

Furthermore, Puig Saenz et al.[117], detailed a holistic approach in reference to cancers believed to be tough to treat on the basis of GM for instance immunotherapy in

glioblastoma ,Triple negative breast cancer, and advanced prostate cancer[117], see Figure4

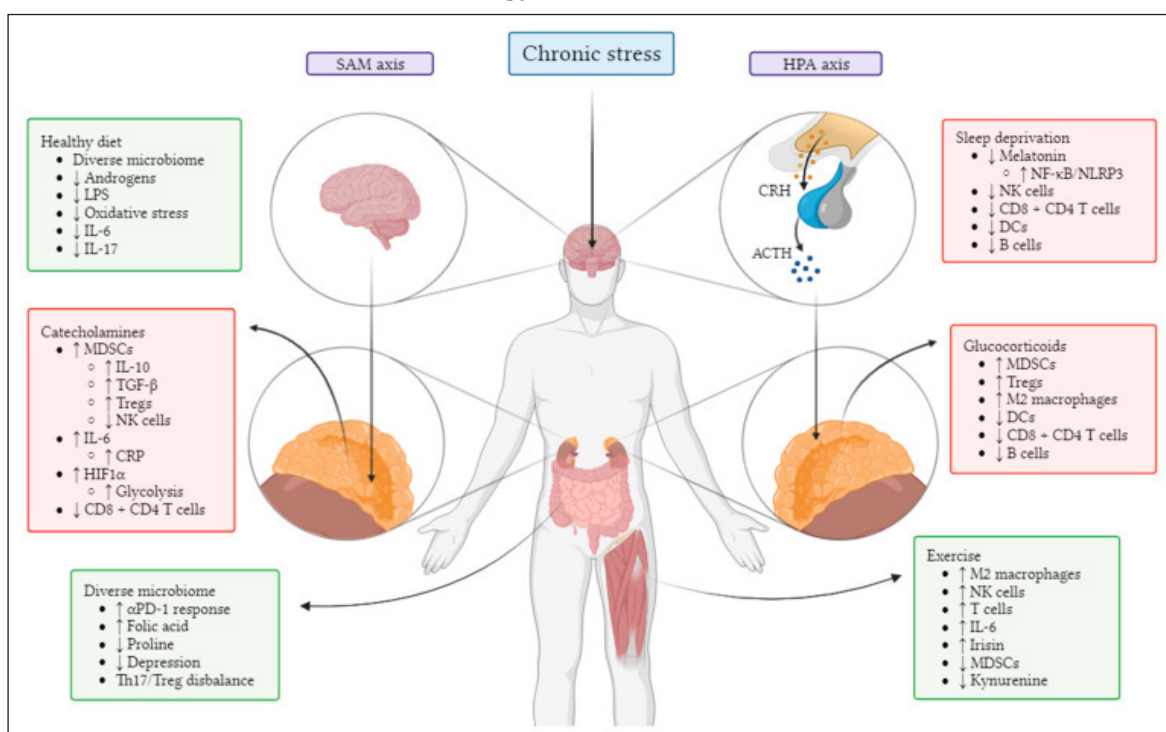


Figure 4. Courtesy ref no-117-Mechanisms of immune modulation by physical and psychological factors. Abbreviations: SAM, sympathetic-adreno-medullar; HPA, hypothalamic-pituitary-adrenal; DCs, dendritic cells; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; HIF1α, hypoxia-inducible factor-1α; CRP, C-reactive protein; TGF-β, transforming growth factor-β; LPS, lipopolysaccharide.

Here they emphasized on role of GM,GC,SNS,Stress axis impacting various neurotransmitters, glucocorticoids actions on tumorigenesis,over immune system etc in detail[117].

CONCLUSION

Thus here we have tried to appreciate the necessary part of endocrine networks which had not been well realized thus far. Here we try to detail how we can repurpose certain of the agents like tamoxifen and attempt to further charge and vitalize the milieu in ERα negative milieu and hormonal analogues (agonists and antagonists) possess a key part in avoidance of carcinoma evolution, which posited relooking pertaining to signal transduction and interactions with genetic codes. Complex TME and intratumor heterogeneity diminished the effectiveness of canonical chemotherapy remarkably in receptor deficient subkinds, which escalates the transitional and upgraded endocrine topography of TNBC rather. Thereby endocrine approaches might be done with the idea of medicine

meant for sustenance and buttressing as well during time period of chemotherapy 's cytotoxicity receding which needs to be reproduced in further studies .

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