Review Article

Pathways of triple negative breast cancer

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Abstract:

Breast malignances is among the most predominant malignancies in females worldwide. Annually, more than 1.5 million women (25 percent of all female cancer patients) are diagnosed with breast cancer each year**.** Sex, age, gene mutations, family history and an unhealthy lifestyle are among the risk factors which can raise the chance of breast cancer**.** Women are 100 times more likely than men to get breast cancer**.**

Breast cancer:

The word breast cancer is an umbrella term for many breast cancer sub-types. These subtypes of breast cancer differ in their clinical presentation, reveal distinct patterns of gene expression, and have different genetic and molecular features. Breast cancer is a condition in which the breast tissues become malignant cells. This happens in both sexes, but is very rare in males[1]. Breast cancer encompasses a heterogeneous group of diseases. It is composed of numerous biological subtypes that have discrete behaviors and responses to therapy. Gene expression studies identified several distinct breast cancer subtypes. These studies divide breast cancers into subtypes that diverge significantly in prognosis as well as in the therapeutic targets existing in the cancer cells[2].

Triple-negative breast cancer (TNBC):

TNBC is considered to be the worst type of breast cancers as it usually behaves more aggressively and accounts for approximately 20% of all breast cancers. The TNBC subtype is characterized as ER-negative, PR-negative and HER2-negative. Lacking target receptors makes the treatment challenging. TNBC is more common in women younger than 40 years of age and African-American women[3].

Pathways of Triple negative breast cancer:

ER, PR and HER2 are rarely expressed in TNBC, and accounting approximately for 16% of all breast cancer cases[4]. TNBCs show a disparity among racial groups, with premeno-pausal African and African American women representing higher rates of diagnosis. TNBCs were more commonly diagnosed in younger women, also Hispanic and non-Hispanic women of lower socioeconomic statuses are among reported groups[5, 6].

Solid tumors consist of heterogeneous sub-populations, also different genetic polymer-phisms determine the prognosis of the patients[7-9]. Although TNBC tumors display relatively simple molecular phenotypes, they are inherently heterogeneous. In particular, diverse morphology, signaling pathway activity and gene expression were declared in TNBCs. Thus, TNBCs have intricated clinicopathological features to the detriment of the prognosis of TNBC patients[4]. Recently, with gene expression profiling, TNBC can be categorized into diverse subtypes. Six subtypes have been confirmed with unique gene expression patterns: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), immunomodulatory (IM), and mesenchymal (M) [10].

EGFR dysregulation is the furthermost frequently recognized in TNBC tumors; 60–80% of TNBC tumors were informed to have elevated EGFR expression[11, 12]. EGFR expression is more frequent in younger women and is correlated with higher survival, lower hormone receptor (ER, PR) levels and genomic instability[13] as EGFR signal cascade promotes cell proliferation, inhibition of apoptosis, angiogenesis and metastatic spread[14]. Thus, EGFR is predicted to subrogate major signaling

pathways of breast cancer triggered by activation of HER-2, ER, PR proteins which are thereby absent in TNBC[14] as studies have reported high *EGFR* gene copy number in TNBCs[15].

EGFR triggers Ras-MAPK signaling in TNBC[16], and since HER2 is expressed in basal-like breast cancers that compose 70-90% of clinical TNBCs, Ras-MAPK signaling could be affected through HER2-dependent mechanisms in those patients[17]. These perceptions provide rationale for inspecting these RTKs and multiple components of the downstream Ras-MAPK signaling pathway as attractive targets in TNBC[18].

Copy number variations of specific genes from the Ras/MAPK pathway have been elucidated to be associated with TNBC, in spite of the incidence of alterations in the Ras/MAPK signaling pathway was confirmed to be less than 2% in TNBC. For instance, a higher mortality rate is correlated with the over-expression of ERK in TNBC patients[19].

However, specific genetic defects along the Ras/MAPK pathway, including the absence of PTEN, negative regulators of MAPK signaling, and certain regulatory micro (mi)RNAs, as the let-7 family, are also anticipated to play an imperative role in TNBC progression. The Ras/MAPK pathway suppresses tumor immunegenicity via impacting the tumor antigen presentation process in TNBC cells; combining MEK inhibition and programmed death-1 (PD-1)/ programmed death ligand 1 (PD-L1) inhibitors of immune checkpoint enhanced the therapeutic proficiency in comparison with solo treatment in a murine syngeneic TNBC model[20].

The PI3K/AKT/mTOR pathway dysregulation occurs commonly in TNBC. PI3KCα-activating mutations are detected in 24% of TNBC patients[21], and PTEN loss mutations, including functional suppression and promoter silencing, are annotated in 25–30% of TNBC cases[22-24]. In regard to outcome, the AKT and mTOR hyperactivation are related to the poor prognosis of TNBC patients. This data elucidates multiple alterations in the PI3K/ AKT/mTOR pathway in TNBC and are considered as attractive therapeutic targets[4].

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