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Molecular Pathways Underlying the Pathogenesis of Triple-Negative Breast Cancer

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Annotation: Breast cancer remains the most prevalent malignancy among women worldwide, with triple-negative breast cancer (TNBC) representing one of its most aggressive and clinically challenging subtypes. TNBC, defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, accounts for 10–15% of all breast cancers but contributes disproportionately to global mortality. The pathogenesis of TNBC is driven by multiple genetic and molecular alterations, including BRCA1/2 and TP53 mutations, PTEN loss, and homologous recombination deficiency (HRD), which promote genomic instability. Epigenetic dysregulation, such as aberrant DNA methylation and non-coding RNA alterations, further contributes to tumor progression and immune evasion. Additionally, the activation of oncogenic signaling pathways—including PI3K/Akt/mTOR, Notch, Wnt/β-catenin, and JAK/STAT—enhances cell proliferation, epithelial–mesenchymal transition, and drug resistance. These molecular features not only underscore TNBC's heterogeneity and poor prognosis but also highlight novel therapeutic opportunities, such as PARP inhibitors, epigenetic therapies, and pathway-specific targeted agents. Addressing TNBC is especially critical in regions with limited screening and treatment access, such as Central Asia and Uzbekistan, where late diagnosis and restricted availability of advanced therapeutics exacerbate poor clinical outcomes.

Keywords: Breast cancer, Triple-negative breast cancer (TNBC), BRCA1/2 mutations, Homologous recombination deficiency (HRD), Genomic instability, Epigenetic regulation, DNA methylation, PI3K/Akt/mTOR pathway, Epithelial–mesenchymal transition (EMT), Drug resistance, PARP inhibitors.

Introduction.

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality [8]. According to the latest estimates from the International Agency for Research on Cancer (IARC, GLOBOCAN 2022), approximately 2.3 million women were newly diagnosed with breast cancer globally in 2022, representing about one in four of all female cancer cases [28]. In the same year, around 670,000 women died from the disease, making breast cancer the most common cause of cancer death among women worldwide (WHO, 2023) [5]. Projections indicate that by 2050, the annual number of new breast cancer cases may rise to nearly 3.2

million, with mortality approaching 1.1 million deaths per year, driven largely by demographic growth and aging populations in low- and middle-income countries [12]. In Central Asia, breast cancer is also the most common cancer among women, though incidence rates are generally lower compared to Western Europe and North America. According to GLOBOCAN data, breast cancer accounts for approximately 18–20% of all female cancers in the region, with age-standardized incidence rates averaging 30–45 cases per 100,000 women annually. Despite these relatively lower incidence levels, mortality remains disproportionately high due to limited access to early detection and comprehensive treatment services [10]. In Uzbekistan, breast cancer constitutes the leading oncological disease among women. National estimates based on IARC data suggest that there are approximately 4,500–5,000 new breast cancer cases each year, representing nearly one-fifth of all female malignancies in the country. Mortality is also considerable, accounting for about 14–15% of all female cancer deaths annually. While diagnostic capacity and screening programs have expanded in recent years, a large proportion of patients are still diagnosed at advanced stages, contributing to persistently high fatality rates [13].

Within this broad epidemiological landscape, Triple-Negative Breast Cancer (TNBC) represents a particularly aggressive and clinically significant subtype. TNBC is defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, and it accounts for approximately 10–15% of all breast cancer cases worldwide (Bianchini et al., 2022). Despite its relatively lower prevalence, TNBC is responsible for a disproportionately high number of deaths, contributing to 15–20% of global breast cancer mortality (Bertucci et al., 2021) [6]. Patients with TNBC frequently present at younger ages, often with high-grade tumors and a higher likelihood of visceral or central nervous system metastases. Survival outcomes remain poor compared to other subtypes: the five-year survival rate is about 77% for localized TNBC, but declines to 12% in metastatic disease (American Cancer Society, 2023). The aggressive nature of TNBC, combined with the absence of established hormone or HER2-targeted therapies, underscores its importance in breast cancer research and clinical management. These challenges are particularly relevant in regions such as Central Asia and Uzbekistan, where limited screening programs and restricted access to advanced therapeutics may exacerbate already poor prognostic outcomes [11]. The pathogenesis of triple-negative breast cancer (TNBC) is highly complex and involves a combination of genetic, epigenetic, and signaling abnormalities that contribute to its aggressive clinical behavior. Genetic alterations play a central role, with germline and somatic BRCA1/2 mutations strongly associated with TNBC development, alongside frequent mutations in TP53 and alterations in PIK3CA as well as loss of PTEN, all of which promote genomic instability and tumor progression. A hallmark of TNBC is the disruption of DNA repair pathways, particularly homologous recombination (HR) deficiency, which impairs the ability of tumor cells to accurately repair double-strand DNA breaks. This genomic instability accelerates tumor evolution and underlies the heightened sensitivity of some TNBCs to PARP inhibitors. Epigenetic mechanisms also contribute significantly. Aberrant DNA methylation patterns and dysregulated microRNAs (miRNAs) are frequently observed, leading to silencing of tumor suppressor genes and dysregulation of oncogenic networks [23]. Several oncogenic signaling pathways are implicated in TNBC pathobiology. These include activation of the PI3K/AKT/mTOR pathway, which promotes cell proliferation and survival; dysregulation of the Notch and Wnt/β-catenin pathways, which drive stemness and epithelial-to-mesenchymal transition (EMT); and activation of the JAK/STAT pathway, which enhances inflammatory signaling and immune evasion. Taken together, these molecular alterations define TNBC as a heterogeneous but biologically aggressive subtype of breast cancer. A deeper understanding of these mechanisms provides the foundation for the development of targeted therapeutic strategies, which will be discussed in subsequent sections [33].

The Breast Cancer gene 1 (BRCA1) and Breast Cancer gene 2 (BRCA2) encode proteins that are essential mediators of the DNA damage response, particularly in the repair of double-strand breaks (DSBs) through the homologous recombination (HR) pathway [24]. Since their discovery in the early 1990s, it has been well established that individuals carrying germline BRCA1/2 mutations face a significantly increased lifetime risk of developing malignancies such as breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer, compared to the general population [3]. BRCA1 and BRCA2

play a critical role in maintaining genomic stability by ensuring the faithful repair of DSBs. HR is considered an error-free repair mechanism, predominantly active in the late S and G2 phases of the cell cycle, when a sister chromatid is available as a repair template. Recognition of DNA damage begins with ATM and ATR kinases, which detect DSBs and activate downstream signaling cascades by phosphorylating DNA repair effectors, including BRCA1. BRCA1 is a multifunctional nuclear phosphoprotein that contains several domains, among which the BRCA C-terminal (BRCT) domain is particularly important for protein–protein interactions involved in DNA repair and cell cycle regulation [17]. Upon DNA damage, BRCA1 is recruited to DSB sites through its association with the MRN complex (Mre11-Rad50-NBS1) and CtIP, where it promotes DNA end resection at the 5′ ends of the breaks, generating single-stranded DNA (ssDNA) overhangs. At this stage, BRCA2—together with PALB2—facilitates the recruitment and loading of Rad51 recombinase onto ssDNA. Rad51 then mediates strand invasion into the homologous template on the sister chromatid, allowing precise repair of the break. Through this highly coordinated process, BRCA1 and BRCA2 ensure genomic stability and suppress tumorigenesis [15].

DNA double-strand breaks contribute to the initiation of tumorigenesis and are normally repaired by homologous recombination repair (HRR). Deficiency of this pathway (homologous recombination deficiency, HRD) results in an increased reliance on alternative DNA repair pathways, such as non-homologous end joining (NHEJ), which are more error-prone. As a result, HRD leads to the accumulation of somatic mutations, genomic rearrangements, and chromosomal instability [29;7;22;26]. Pathogenic mutations within key genes involved in HRR, including BRCA1 and BRCA2, may result in HRD, and germline mutations in these genes are associated with a significantly increased risk of breast and ovarian cancer. Additionally, promoter DNA hypermethylation of BRCA1 has been shown to result in HRD. Overall, the biological process of homologous recombination is complex, and HRD can be caused by many different factors that converge on the same phenotype. Identification of HRD status allows the stratification of patients for targeted therapy with poly (ADP ribose) polymerase (PARP) inhibitors, which exploit the dependency of HRD cancer cells on alternative DNA repair pathways, resulting in synthetic lethality. In addition, tumor cells with HRD are often more susceptible to other DNA-damaging agents, such as platinum-based chemotherapies [35; 21; 32; 25].

Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNA (ncRNA) regulation, are pivotal in cancer development and progression. DNA methylation typically occurs at CpG islands in the promoter regions of genes, silencing tumor suppressor genes in many cancers [4]. Histone modifications, such as acetylation and methylation, regulate chromatin structure, influencing gene expression. The enzymes involved in these modifications, such as histone deacetylases (HDACs) and histone methyltransferases, are often dysregulated in cancer, leading to aberrant transcriptional activation or repression [30]. Non-coding RNAs, particularly microRNAs and long non-coding RNAs (lncRNAs), further modulate gene expression by affecting mRNA stability and translation. These epigenetic mechanisms are reversible, making them attractive targets for therapeutic intervention. Drugs targeting DNA methylation and histone modifications, such as DNA methyltransferase inhibitors (DNMTis) and HDAC inhibitors, are actively explored for cancer therapy, demonstrating promising results in hematologic and solid tumors [1]. Epigenetic modifications, particularly DNA methylation, are intimately involved in TNBC's immune evasion strategies. DNA methylation is a critical epigenetic mechanism that adds a methyl group to the cytosine ring within CpG islands, primarily in gene promoters. This process is catalyzed by DNA methyltransferases (DNMTs), such as DNMT1, DNMT3A, and DNMT3B, which play a crucial role in maintaining gene silencing. Aberrant DNA methylation is prevalent in tumors, with variations in methylation levels across different regions exerting distinct impacts on gene transcription (Figure 1). Aberrant DNA methylation, particularly promoter hypermethylation, leads to the transcriptional repression of tumor suppressor genes, contributing to cancer initiation and progression. On the other hand, increased CpG site methylation within gene bodies can enhance gene expression, potentially by stabilizing the transcript. Blagitko-Dorfs et al. discovered that the combined use of DNMT and HDAC inhibitors can

downregulate oncogenes such as MYC in acute myeloid leukemia cells through the demethylation of gene bodies. This demonstrates that targeting gene body demethylation may represent a viable epigenetic therapeutic strategy. DNA methylation can silence the expression of immune-related genes, including those involved in antigen presentation and interferon signaling pathways, which are critical for an effective immune response [34].

The PI3K/Akt/mTOR pathway regulates several essential physiological cellular processes, including survival, growth and migration. Role in Protein Translation Once activated, mTORC1 plays a central role in translation initiation by phosphorylating its two main substrates: ribosomal S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4 E-binding protein 1 (4E-BP1) [18]. In fact, phosphorylation of 4E-BP1 leads to the release of eukaryotic translation initiation factor 4E (eIF4E), which then initiates protein translation at the 5′ end of mRNAs. In addition, S6K1 phosphorylation promotes the assembly of the translation initiation complex by phosphorylation of ribosomal protein S6 and eIF4B [9]. Role in Epithelial Mesenchymal Translation: Epithelial–mesenchymal transition (EMT) is a process by which an adherent epithelial polar cell acquires a mesenchymal phenotype. This process, essential for cell migration during embryogenesis and organogenesis, is strongly implicated in cancer metastasis. EMT is enhanced by the PI3K/Akt/mTOR pathway. In fact, mTORC1/eIF4E axis enables protein translation, and mTORC2 acts at the post-translational level by stabilizing Snail. Also, PTEN loss decreases cell polarity and commits cells to EMT. Role in Apoptosis: The PI3K/Akt/mTOR pathway play also a central role in apoptosis inhibition. Indeed, the anti-apoptotic proteins B-cell lymphoma 2 (Bcl-2) and X-linked inhibitor of apoptosis protein (XIAP) are frequently overexpressed in PIK3CA-mutated TNBC cells [16]. In addition, the eIF4F complex activated by mTORC1 promotes Myeloid Cell Leukemia-1 (MCL-1) anti-apoptotic protein translation. Akt downregulated apoptosis through inhibitory phosphorylation of the pro-apoptotic protein bcl-2 antagonist of cell death (BAD) and Forkhead box O (FoxO) transcription factors 3 and 1, which are involved in the regulation of apoptosis. Role in Autophagy Regulation: Moreover, mTORC1 inhibits autophagy by phosphorylating key autophagy markers such as autophagy-related protein 13 (ATG13) and Unc-51-like autophagy activating kinase 1 (ULK1) and by promoting the cytoplasmic retention of the lysosomal gene expression modulator Transcription Factor EB (TFEB), thereby enhancing cell survival [27]. Role in Cell Morphogenesis: The other subunit of the mTOR complex, mTORC2, also contributes to tumor development. It promotes cell morphogenesis and migration through phosphorylation of protein kinase C δ and α, which regulates actin cytoskeleton dynamics. In addition, PTEN also exerts a non-phosphatase activity that contributes to chromosome stability and enables it to act as a scaffolding protein in the nucleus and the cytoplasm. Role in DNA Repair: Independently of mTOR, PI3K and Akt play fundamental roles in genome stability and DNA repair. Notably, interactions between PI3K and homologous recombination (HR) are essential for the repair of DNA double-strand breaks. Furthermore, Akt induces the degradation of the transcription factor Forkhead box (Fox) O3 and FoxO1, thereby enabling the expression of FoxM1 and exonuclease 1, which regulate the expression of Breast Cancer 1 (BRCA1), BRCA2 and RAD 51, key components of the HR system. Activation of the HR system repairs DNA double-strand breaks. This increases cell survival and generates drug resistance by maintaining the genetic integrity of cells damaged by treatment. Role in Chemoresistance: In addition to its established role in oncogenesis, the PI3K/Akt/mTOR pathway is strongly implicated in chemoresistance. Several commonly used chemotherapies in TNBC promote Akt phosphorylation, thereby altering drug response. Once activated, Akt enhances the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which subsequently promotes Multidrug-Resistant (MDR) protein expression, leading to drug resistance through cellular efflux [14]. Moreover, PI3K/Akt/mTOR can lead to immune evasion. In fact, PTEN loss has been associated with resistance to anti-PD-1/PD-L1 therapies by impairing T-cell CD8+ infiltration and promoting angiogenesis through vascular endothelial growth factor (VEGF) overproduction. These chemoresistance mechanisms result in widely variable drug responses. For example, the pathologic complete response (pCR) rate reaches 52% for the BL1 subtype but drops to just 10% for LAR subtype and 0% for BL2 tumors. PI3K/Akt/mTOR Pathway Alterations in TNBC: The main alterations of the PI3K/Akt/mTOR pathway involve activating mutations in PI3K and downregulation of PTEN, both of which drive

hyperactivation of the pathway. In TNBC, PIK3CA mutations occur in 10.2% of cases, with a higher frequency in the LAR subtype (46.2%) compared to other subtypes (4.5%). Approximately 80% of PIK3CA somatic mutations involve three hotspot mutations, each affecting a single amino acid. E542K and E545K, located in exon 9 (helicase domain), disrupt interactions with the SH2 domain of the p85 regulatory subunit. H1047R, in exon 20 (kinase domain), upregulates activation of downstream PI3K signaling proteins. Mutations in the p85α subunit are less frequent but can also activate the PI3K pathway [31]. Additionally, PIK3CA amplification can result in allelic dose-dependent activation of the pathway. A reduction in PTEN expression of 20% may be sufficient for the development of mammary tumors. PTEN expression is decreased in 19% of BCs and in up to 35% of TNBCs, particularly in BL subtypes. Loss of PTEN, and, therefore, of its 3′-phosphatase activity, leads to an increase in PIP3, constitutively activating the PI3K pathway, which promotes cell proliferation and tumor progression. PTEN loss can be caused by allelic inactivation leading to loss of function and homo- or heterozygous deletions. Promoter hypermethylation can also silence PTEN expression at the transcriptional level [19]. Furthermore, post-transcriptional modifications, such as microRNA-498 overexpression, are linked to decreased PTEN expression and function. Finally, PTEN protein can undergo various post-translational modifications, such as phosphorylation, acetylation, oxidation and ubiquitination, which can alter its activity. The Akt1 E17K hotspot mutation is the most common Akt-related alteration, promoting Akt1 binding to PIP3 and stimulating its activation. Although Akt1 mutations are uncommon (3%), they are more frequently observed in TNBC expressing androgen receptors [20].

Conclusion.

Triple-negative breast cancer (TNBC) represents one of the most aggressive and therapeutically challenging subtypes of breast cancer, accounting for a disproportionate share of mortality despite its lower prevalence. The absence of ER, PR, and HER2 expression underscores its heterogeneity and limits the efficacy of conventional targeted therapies. The pathogenesis of TNBC is driven by a complex interplay of genetic alterations, including BRCA1/2 mutations, TP53 mutations, and PTEN loss, alongside homologous recombination deficiency (HRD), which promotes genomic instability. Epigenetic reprogramming, such as aberrant DNA methylation and dysregulated non-coding RNAs, further enhances tumor progression and immune evasion. In parallel, activation of oncogenic signaling cascades, notably the PI3K/Akt/mTOR, Notch, Wnt/β-catenin, and JAK/STAT pathways, contributes to tumor cell proliferation, survival, epithelial–mesenchymal transition (EMT), and drug resistance. Collectively, these molecular mechanisms define TNBC as a biologically aggressive and clinically complex disease. A deeper understanding of these pathways not only highlights the challenges in clinical management but also provides a rationale for developing novel therapeutic strategies, including PARP inhibitors, epigenetic drugs, and pathway-specific targeted agents. Such approaches hold promise to improve outcomes, particularly in regions with limited access to early detection and advanced treatments, such as Central Asia and Uzbekistan.

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