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Review Article

A Review on Biomarkers for Predicting Radioresistance and Role of Natural Radiosensitizers in Triple-Negative Breast Cancer

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ABSTRACT

Breast cancer mortality rate is fifth among all cancer and increasing day by day due to modern lifestyles. Its molecular subtype is classified as per their significant receptor expression, such as estrogen receptor (ER), progesterone receptor (PR) & human epidermal growth receptor 2 (Her2). Triple-negative breast cancer (TNBC) is an aggressive subgroup among breast cancer subtypes and clinically challenging to treat due to loss of all three receptor (ER/PR/Her2) expression. Treatment modalities of TNBC include surgery, chemotherapy, radiotherapy and immunotherapy. Postoperative radiation therapy (RT) improves locoregional control and overall survival in TNBC patients. The powerful ionizing radiation (IR) response to RT is contributed by the inherent radiosensitivity of the tumor, which is influenced by genes associated with the cell cycle, DNA damage repair, apoptosis, etc. This review article narrates the role of biomarkers obtained through data mining and manual curation of published literature to predict radioresistance in patients receiving radiotherapy. Further, the role of natural radiosensitizers in overcoming radioresistance for effectively managing TNBC is also discussed.

INTRODUCTION

Around one in four incidences of cancer among women worldwide are breast cancer cases.[1, 2] In India, for the past 25 years, breast cancer (BC) has ranked as the second most frequent type of malignancy.[3, 4] At the end of 2020, almost 7.8 million women were diagnosed with breast cancer.[5] Breast cancer incidence rate changed with an annual percentage between 0.4–0.6 among women in India over the last two decades.[6] Breast cancer subtypes are classified based on their receptor status (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), as well as the proliferation status of Ki67. Perou *et al.,* (2000) divided breast cancer into four major clinical subgroups., e.g., ER-positive luminal type, basal type, HER2 enriched and normal-like (Table 1). This luminal type is further subclassified into Luminal A, Luminal B and Luminal C. Triple-negative breast cancer (TNBC) is distinguished by the lack of ER, PR & Her2/neu receptors on their cells, which makes them not suitable for targeted therapy and hence difficult to treat breast cancer subtype.[7] The TNBC incidence rate in India is higher than in the rest of the world.[8] It presents a high proliferation rate, a higher rate of metastases to the brain, liver and lungs and affects younger patients than the other breast cancer subtypes.[9-12]

Molecular Classification of TNBC

Many researchers have classified and characterized TNBC at molecular levels in recent decades. Lehmann *et al.,* (2011) categorized into six TNBC subtypes based on

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Table 1: Molecular subtypes of breast cancer

Subtype	*Prevalence (%)*	*IHC (Immunohistochemistry) Status*	*Other markers*	*Mitotic grade*	*Prognosis*
Luminal-A	50–60	[ER+/PR+], HER2-, Ki67-	CK8/18	Low	Good
Luminal-B	15–20	[ER+/PR+], HER2-/+, Ki67+		High	Bad
HER2	15–20	[ER-/PR-], HER2+		High	Bad
Basal (TNBC)	8–37	[ER-/PR-], HER2-, basal marker+	CK5/14/17 Laminin, EGFR	High	Worst
Normal	5–10	[ER+/PR+], HER2+, Ki67-	CK5-/EGFR-	Low	Good

ER = estrogen receptor, PR = progesterone receptor, HER2 human epidermal growth factor receptor 2, CK = cytokeratin, EGFR = epidermal growth factor receptor

their gene expression status and ontology analyses as (a) basal-like (BL1/ BL2), which depicted higher expression of cell cycle genes and its signaling growth factor; (b) Immunomodulatory (IM), which revealed a greater expression of immune-related pathways; (c) mesenchymal (M), represented genes responsible for the differentiation and growth of mesenchymal cells.; (d) Mesenchymal stem-like (MSL), which exhibited mesenchymal features but decreased proliferation; and (e) luminal androgen receptor (LAR), which shows activation of hormones-related pathways, respectively. Five years later, the same group had reclassified with tumor-infiltrating lymphocytes (TILs) joined with stromal cells into IM and MSL subtypes. So, TNBC is recharacterized as BL1, BL2, M and LAR (TNBC four-type classification). Elsawaf *et al.,* (2013) classified TNBC expressing histology, immunohistochemistry (IHC) and transcriptome profile. They classified four groups of expressed cytokeratin (CK) as luminal, basoluminal, basal A and basal B for TNBC tumors. Among all other subtypes, the BL1 type has the best prognosis.[13] In such a way, Burstein *et al.,* (2015) classified TNBC into four stable groups labeled LAR, mesenchymal (MES), basal-like immune-suppressed (BLIS), and basal-like immune-activated (BLIA) with its gene expression profiling and copy number variations (CNVs). BLIS had poor survival compared to other types, whereas BLIA had better survival.[14] In recent work, Jezequel *et al.,* (2019) used transcriptome profiling to classify three distinct subtypes (C1, C2, and C3). TNBC tumors in the C1 group had better prognoses due to their molecular apocrine nature, while C2 and C3 exhibit basal-like characteristics. The C2 group had an aggressive and immune-suppressed phenotype, while C3 had a good immune check point response.[15]

Treatment Management of TNBC

For solid tumors, there are four main treatment options: surgery, chemotherapy, radiation therapy, and immunotherapy.[16] These core pillars are surgery, chemotherapy, radiotherapy, and immunotherapy, shown in Fig. 1 as the main approach for treating TNBC. Breast cancer is being recently treated by immunotherapy and targeted therapy.[17] Here, it mainly introduced radiotherapy for TNBC.

Fig. 1: The main four pillars for the treatment of TNBC

Radiotherapy in TNBC

Radiation therapy is mainly done in early breast cancer, followed by breast-conserving surgery (BCS) and post-mastectomy in locally advanced breast cancer patients.[18] According to new research, radiation after lumpectomy and mastectomy improves overall patient survival.[19] In clinical trials from Canada and Denmark, results for post-mastectomy radiation treatment increased by 9–10% overall survival rate than those who did not receive radiotherapy.[18, 20, 21] This conclusion, however, varies with a patient-based meta-analysis of randomized therapeutic studies.[22] There are various causes for the disparity. In meta-analyses, clinical trials were performed long ago with older radiotherapy techniques and their fractions given higher doses to the heart, which resulted in cardiac arrest compared to modern radiotherapy techniques.[23] The reanalysis of previous clinical trials showed a reduced mortality risk linked to radiotherapy for 12.4% ($p < 0.001$), significantly to recent trails included.[24, 25]

Compared to other breast cancer subtypes, patients with TNBC mainly undergo radiotherapy after mastectomy or conservative breast surgery (BCS).[26] Comparing other breast cancer subtypes of mastectomy to TNBC patients with early stages (T1-2N0) BCS followed by radiation therapy might not show similar results due to the aggressive form of cancer.[27] TNBC patients with gene BRCA1 mutation or BRCA1 nonfunction protein tumors are mainly radiosensitive and have no double-strand break repair via homologous recombination, so it responds well to postoperative RT.[28] Numerous survival analyses revealed that TNBC patients who received BCS + RT had better overall survival (OS) than only mastectomy and mastectomy + RT.[29-31]

Breast cancer guidelines by the National Comprehensive Cancer Network (NCCN) suggest postoperative RT in patients with breast-conserving surgery (BCS), despite their lymph node metastasis status. Various studies reported a beneficial survival rate from this protocol. Overall, radiotherapy has improved the survival rate in TNBC patients. However, patients undergoing total mastectomy with postoperative radiotherapy still a topic of debate.[30]

Radiation Types and Mechanisms for Radiotherapy

Radiotherapy (RT) is a treatment modality using high-energy ionizing rays or radioactive substances to stop the growth or kill the tumoral cells. The ionizing radiation damages cell organelles and macromolecules (DNA & protein) of both normal and cancer cells and blocks cell division ability and further proliferation.[32] There are two mechanisms of radiation-induced cell death. One is a direct effect of radiation on cellular components, e.g., DNA lesions. Second, an indirect effect of radiation causes DNA damage via generating free radicals such as reactive oxygen species (ROS) due to the cell's ionization or excited water content mainly leads to cellular damage to macromolecules and cell death. Ionizing radiation (IR) generates many types of the lesion in DNA, such as base and sugar modification, DNA-protein cross-links, DNA single-strand breaks (SSBs) and double-strand breaks (DSBs), ultimately leading to chromosomal aberrations (CA) production.[33]

Different types of radiation and their sources were used for radiation therapy, as shown in Fig. 2. Typically, radiation treatment involves daily fractions of 1.5 to 3 Gy (Gray) for many weeks. During two successive fraction interval time, normal cells quicker regain its normal function via repair mechanism compare to tumor cells.[34] There are two methods for delivering radiation at the tumor location. External beam radiation is delivered from outside the body by directing high-energy rays (photons and particle radiation) to the specific site of the tumor. This method is most used in clinical practice. Internal radiation, or brachytherapy, is given from within the body using radioactive sources sealed in catheters or inserted directly into the tumor's core. This method is applied in specific malignancies such as prostate and breast cancer, where retreatment is needed due to its short-range effects.[35]

Radiation treatment might take hours, days, and weeks to kill cancer cells. The target of radiation in the cell is DNA. Radiation causes DNA damage in cancer cells, which results in cell death. The mechanism is shown in Fig. 3. Generally, radiation is applied to cancer cells, which results in genomic instability and cellular death via mitotic catastrophe, apoptosis, necrosis, senescence, and autophagy.[36-38] Latest innovations and advancements in radiation therapy improved precision in dose delivery and target selection. Such intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy

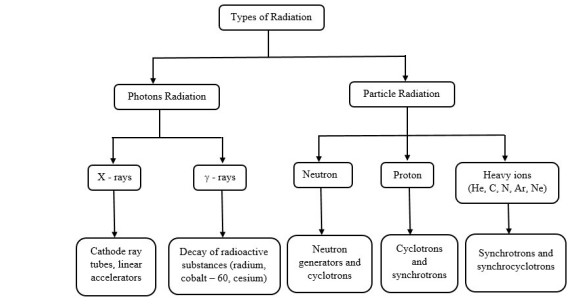

Fig. 2: Various types and sources of radiation used in radiotherapy

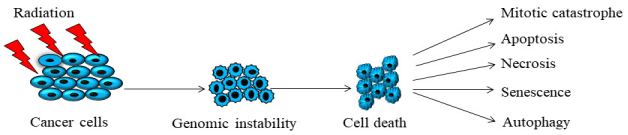

Fig. 3: Types of cell death induced by cell radiation

(IGRT) techniques allow an accurate dose delivery to tumor cells with lesser damage to surrounding normal tissue.[39, 40]

Radiosensitivity

The term "radiosensitivity" refers to cells or tissue more responsive to the harmful effect of ionizing radiation. Damage due to IR has different cellular radiosensitivity in each cell cycle phase. The cell cycle's G1 or S phases are damaged, preventing or delaying the S phase's transition. If double-strand breaks (DSBs) are produced during the G2 phase of the cell cycle, then cell entry into mitosis is postponed. The G2/M phase hast the most radiosensitivity, followed by the G1 phase, while the S phase has the lowest levels.[41] Hence, radiosensitizing agents and anticancer drugs might potentially cause cell death via stopping from the G2/M phase.[42] It has been observed that the pathways for repair by IR-induced DSBs are the same as that of naturally occurring DSBs. These processes include non-homologous end-joining (NHEJ) and homologous recombination repair (HRR), and single-strand annealing (SSA), which is a subtype of HRR.[43]

H2AX is a type of histone H2A variant mainly conserved in mammals.[44] Hence, its deficiency causes irreparable lesions, creating ionizing radiation-induced foci (IRIF) and making cells more sensitive to IR.[45] Whenever double-strand breaks (DSBs) occur, rapid phosphorylation of H2AX (called ɣ-H2AX) occurs immediately. As a result of this process, proteins related to DNA repair such Nbs1, DNA-PK, BRCA1, and RAD51, accumulated at the damaged site of DSBs. Several proteins related to DSB repair are being phosphorylated before regathered to the IRIF site.[46] Phosphorylated versions of these proteins such as MDC1, RAD51, ATM, MRN complex, RNF8/KIAA0646, RNF168 and BRCA1-A complex.[47, 48] Existing research has shown that some ɣ -H2AX foci continue to exist at the site of DSBs even after repair is complete.[49] The precise role

of IRIF is still not known. However, it could have a role in chromatin alterations, late repair, apoptosis, the activity of certain kinases and phosphatases and cell cycle checkpoint signaling.[50,51] One potential use of IRIF-induced damage cells is communicating with adjacent normal tissue. This allows the bystander effect to transfer IR-induced damage signals to nearly healthy tissue without being directly exposed to IR.[52]

It is shown that the ability of DSBs repair mainly affects the radiosensitivity of cancer cells. Different methods in which cells react to ionizing radiation include activation of DNA repair pathways, cell cycle checkpoints, apoptosis, inflammatory responses etc. They are genetically mutated in genes associated with DNA repair mechanisms.[51]

Ionizing radiation (IR) indirectly damages DNA via ROS production from the radiolysis of water, which can further damage macro-molecules like carbohydrates, proteins, and DNA. Intracellular enzymatic and nonenzymatic antioxidants engaged in many pathways enable cells to prevent from harmful effects of ROS. It is possible to define enhanced radiosensitivity in normal tissue surrounding tumor cells by genetic variation in genes that participate in this pathway.[53] Few studies have found a link between oxidative stress-related gene polymorphism and acute toxicity for the radiosensitivity effect.[54, 55]

Radioresistance

Ionizing radiation (IR) is the most efficient therapy for treating solid tumors. However, radioresistance is developed during cancer treatment or is inherently resistant.[56] Radioresistance is when tumor cells or tissue repair the radiotherapy-induced changes effectively before the second exposure and become resistant to the IR. These are complex processes involving multiple pathways, factors, and mechanisms, as depicted in Fig. 4.[57, 58]

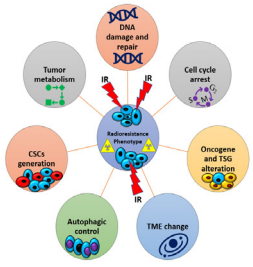

Fig. 4: The mechanism of radioresistance after ionizing radiation.

The mechanism for radiation resistance occurs due to biological changes after radiotherapy. These undesirable changes lead to treatment failure in patients receiving radiotherapy.[59]

DNA Damage Repair

Radiation may trigger DNA damage response (DDR), which keeps safe cells from their genomic instability and generates radioresistance by increasing the DDR rate. DDR activates pathways of signaling like phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and Sirtuin (SIRT), a class of histone deacetylase pathways.[60, 61] Homologous recombination is controlled by the PI3K signaling pathway, increasing DDR. PI-103, an inhibitor of PI3K, significantly increases radiation-based death in TNBC cell lines and xenografts.[62] MAPK pathway induces a cellular response by phosphorylation of XRCC1, which control oxidative stress response and increases damage repair.[63] The SIRT show a class of histone deacetylases, and its downregulation causes cell death by lowering DNA repair enzyme complexes such as MSH2, MSH6, and APEX1.[64] Human breast cancer stem cells (CSCs) are more resistant to radiation and produce less or fewer γ-H2AX foci. They repair themselves more quickly than the non-CSC population.[65] Also, radiation-induced cytotoxicity of cancer cells is prevented by CHK1 phosphorylation independently repair via non-homologous end joining.[66] However, it is known that RAD51 is involved in breast cancer stem cells.[67, 68]

Cell Cycle Arrest

The cell cycle checkpoint molecules, such as 14-3-3σ, a member of the 14-3-3 protein family, have been shown to detect IR-induced DNA damage and link this to radioresistance by halting cell cycle progression in the G2/M phase.[69] The G2/M arrest in the presence of DSB inhibits cells from entering the M (mitosis) phase.[70] After IR exposure, mammalian cells enter G2/M arrest between 0.5 to 4 hours and try to resolve the defects.[71] A higher rate of IR induces more G2/M arrest, and its recovery effect leads to cell death via mitotic catastrophes. However, cell lines have different recovery times and cycle arrest phases.[72] A deficiency of specific genes such as *PLK1*, *ATM* and *CHK1*, which are involved in G2/M regulating blockage, changes the cell cycle response to IR-induced DNA damage.[73, 74] Hence, targeting G2/M-related proteins might benefit IR-induced cell death by overcoming radioresistance in cancer patients.

Oncogene and Tumor Suppressor Alterations

Vitronectin (VTN), a cell adhesion molecule, is an example of an oncogene. The downregulation of VTN expression enhances the migration and proliferation of nasopharyngeal carcinoma (NPC) into radioresistance.[75] Current research has demonstrated that microRNAs act as a main regulator of gene expression associated with radioresistance.[76,77] miRNAs are non-coding RNA made up of 18-25 nucleotides long. They regulate gene expression by making improper complementary base pairing to 3'-UTR and suppressing mRNA translation.[78] Cancer-related miRNAs are categorized as either oncogenic or tumor suppressive. Tumors having overexpressed miRNAs (oncomiRs) are oncogenic, while downregulated are tumor-suppressive miRNAs. miR-668 overexpression is found in radioresistant cells in MCF-7 and T-47D radioresistant-derived cell lines.

The knockdown of miR-668 reversed radioresistance and increased radiosensitivity in those cell lines.[58] Certain miRNAs have a dual role, either tumor suppressor or oncomiR. The tumor suppressor miR-122 is typically downregulated in breast cancer. However, up-regulation of miR-122 encourages cell survival in radioresistant breast cancer.[79]

Changes in the Tumor Microenvironment (TME)

Many changes in the tumor microenvironment create radioresistance characteristics. Hypoxic condition in the tumor core produces adenosine triphosphate (ATP) mainly via a glycolytic pathway with lactate as the ending product change into the microenvironment acidic with low pH.[80,81] An acute hypoxic situation in the tumor activates the proangiogenic process by activating the hypoxia-related transcription factor for hypoxia-inducible factor 1 (HIF-1). Also, HIF-1 higher expression activates proangiogenic factors like as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), resulting in leaky, immature vascular blood supply, which supplies oxygen and nutrient to tumor cells.[82,83]

Tumor cells become more resistant to radiotherapy due to cytokine alteration, epithelial-mesenchymal transition (EMT-related) changes, and hypoxia. The radioresistance hypoxic cells escape immune attack by overexpressing HIF-mediated immune inhibitory molecules such as programmed cell death ligand 1 (PD-L1) on tumor cells.[84] Therefore, immune checkpoint inhibitors are anticipated to be novel therapeutic targets to achieve a radiation response in a hypoxic fraction of tumors.[85]

Autophagy

Autophagy is an evolutionary metabolic procedure in which autophagosomes and lysosomes engulf cytosolic substances to give metabolic precursors for macromolecule synthesis under nutrient-stress conditions.[86] The common characteristic of cancer is proliferation, which generates metastasis and develops nutrient deficiency. Chemotherapy and radiotherapy caused genotoxic stress, whereas hypoxia and an acidic tumor environment caused metabolic stress. Additionally, autophagy keeps alive damage organelles and mitochondria.[87] Autophagy protects cancer cells from DNA breakage, organelle damage and decreased susceptibility to anticancer therapy.[88]

The use of autophagy inhibitor, 3-methyadenine (3-MA) or chloroquine (CQ), dramatically decreased clonogenic survival efficiency in irradiated MDA-MB-231 radioresistant cell line.[89] These results indicate the inhibition of the autophagy process might increase sensitivity towards TNBC. Other research showed that autophagy inhibition resulted in low checkpoint kinase 1 (Chk1) levels, which disturbed the DNA repair process and slower DNA double-strand break repair via homologous recombination.[90] From *in-vitro* and xenograft mice model using MK-8776, a Chk1 inhibitor, improved the radiosensitivity in TNBC cell lines by preventing the autophagy process.[91]

The Generation of Cancer Stem Cells (CSCs)

Cancer stem cells (CSCs) play a major role in developing and relapsing tumor after post-therapy. According to a well-established definition, CSCs are tumor cells with uncontrolled cell division and can regrow entire tumor.[92] The CSC environment consists of numerous soluble factors, direct cell-cell adhesion surface molecules and extracellular matrix (ECM) substances. Tumor niches for CSC induce oxygen demand in stress conditions and further allow self-renewal, differentiation, and resistance to treatment of the CSCs.[93] The CSCs are mainly protected in the hypoxic area during radiation compared to other cells via low ROS production and activating hypoxia-inducible factor (HIF) signaling pathway.[94] The transcription factors HIF-1α and HIF-2α both main regulators of gene transcription for hypoxia response elements (HREs) that activate oncogenic signaling such as Notch, Hedgehog and Wnt (wingless-related integration site) pathway.[95-97] For CSCs maintenance, repopulation and radioresistance are required to activate these signaling routes during and after therapy.[98-100]

Identification of CSCs done by their cell surface marker, such as CD 44 significance (present on CSC in cancer of the brain, liver, lung, ovaries, prostate, esophagus, pancreas, colon, stomach, breast and head and neck region) and CD 133 in some types of tumor (found in cancer of brain, lung, liver, stomach, colon, ovaries, skin, head and neck region). CSCs might vary phenotypically and functionally based on different types of cancer.[101, 102]

The CSCs for colorectal cancer develop radioresistance via up-regulation of SOX2 in PI3K/AKT signaling.[103] Breast cancer stems from cell-induced radioresistance via mesenchymal-epithelial transition plasticity nature by the N2f2-Keap1 pathway.[104]

Tumor Metabolism

Several researchers have determined that radioresistance is closely related to tumor metabolism's alternations.[105,106] Clinically, the mitochondrial or glycolytic pathway changes alter the radiation sensitivity.[107] The Warburg effect, a specific feature of a hypoxic tumor, is characterized by an increase in the rate of glucose absorption, active glycolysis, greater amounts of lactate formation, and a reduction in mitochondrial oxidative phosphorylation, which lowers intracellular ROS levels.[108-110]

The glucose transporter, such as glucose transporter 1 (GLUT1), transcription factors such as HIF-1 and cellular metabolites such as lactic acid mainly influence the effectiveness of radiation therapy. High amounts of GLUT1 are seen in radioresistant tumor cells. They are linked to control of several signaling pathways,

including MAPK and PI3K/AKT, oncogene activation, tumor suppressor inactivation, promote hypoxia and many other processes.[111,112] It was discovered that tumor tissue had higher levels of lactic acid than healthy tissue.[113] It can encourage radioresistance, tumor recurrence, metastasis, and poor prognosis in many malignancies.[114] Greater lactic acid production and hypoxia-induced radioresistance negatively impact cancer-associated stromal cells, primarily controlling angiogenesis by influencing fibroblast and endothelial cell proliferation, differentiation, and maturation.[115, 116] Lactic acid prevents the activation of various immune cells, including T-cells and dendritic cells, by disturbing their metabolism and facilitating immunological escape.[117,118] Additionally, tumor-associated fibroblasts produce hyaluronic acid, encouraging cell migration, VEGF production and neovascularization.[119] Many studies have shown that HIF-1 encourages tumor metastasis and invasion and prevents radiation effects.[120] Additionally, HIF-1 release cytokines such as VEGF and PDGF, inducing tumor angiogenesis and developing radioresistance in endothelial cells, allowing tumor recurrence and vascular proliferation.[121,122]

Exosomes are multi-vesicular endosome pathway derived micro vesicles with a 30 to 150 nm diameter.[123] The movement of exosomal cargo substances can help cancer cells become more resistant to chemotherapy and radiotherapy.[124] The resistant cancer cells increase exosome secretion, and recipient cells absorb them and activate aerobic glycolysis, which affects cancer treatment therapy. A recent publication on exosomes in CSCs reported their role in chemo-radio resistance.[124-126] Exosomal LMP1 increases surface marker $CD44^{+/high}$, generating more CSCs via PI3K/AKT signaling in nasopharyngeal carcinoma cells.[127, 128] Experimental data revealed a transfer of miR-100, miR-222 and miR-30a from exosomes produced from adriamycin and docetaxel resistant MCF-7 breast cancer cell line to drug-sensitive cell line by increasing CSCs number and encouraging non-CSCs to CSCs phenotype.[129, 130]

Biomarkers as Radiation Response Predictors

Paik *et al.,* (2004) have reported a panel of 16 cancer-related genes (Table 2) identified from 250 candidate genes from 447 patients selected on their proliferation, invasion and 10 year recurrence rate, which can classify patients into a higher and lower risk of recurrence.[131] Bougen *et al.,* (2012) studied quantitative expression levels of the selected genes mainly associated with DNA repair, cell cycle and radioresistance in breast cancer cell lines.[132] Other groups have reported an autocrine hGH (human growth hormone) mediated increase in these genes.[133] Functional antagonism of hGH reduces cell viability and clonogenic survival and increases DNA damage by radiosensitizing IR-induced cell death. In mammary cell carcinoma, an autocrine human GH (hGH) expression promotes radioresistance and is correlated with the tumor stage and lymph node metastasis.[134] Another research group have identified 10 genes listed as a radiosensitivity index (RSI). A major advantage of focusing on a radiotherapy-specific signature is that it could function as a predictive rather than a prognostic biomarker. The radiosensitivity index (RSI) was studied from five independent data sets among 621 patients examined as a signature of radiosensitivity. Further, three novel genes, *RBAP48*, *RGS19* and *TOP1* identified as radiation response predictors for a personalized clinical target of radio sensitization.[135]

Alexander *et al.,* (2017) identified cyclin E overexpression as a biomarker for combined therapy in inflammatory breast cancer (IBC). Higher expression of cyclin E suggests an aggressiveness and poor prognosis. For IBC specifically, their radio sensitization data confers that dinaciclib (CDK2 inhibitor that down-regulates DNA repair pathways) is worth combining with post-mastectomy radiation in women with triple-negative IBC (TN-IBC). They have studied eight genes associated with DNA damage repair related in Table 2. Besides this, transcription factors associated with these genes, such as c-Myc, E2F1, NF-κB and STAT3, were studied in patients and cell lines.[136] Tumor-specific cyclin E strengthens its bond with CDK2 and encourages its activity independently in the cell cycle.[137] Cyclin E is a key to switch G1-S checkpoints and allow oncogene activation. Additionally, cyclin E stimulates growth factor signaling, centrosome reduplication, and stem cell phenotype.[138] These studies revealed that with dinaciclib, down-regulating a DNA repair-related signature genes profile via inhibiting DNA damage repair mechanism ultimately leads to apoptosis.[139] The androgen receptor (AR) has been identified as the main target for radiosensitization based on the radiation treatment response observed in 21 breast cancer cell lines and combined with high throughput drug screen data. A radiosensitizer bicalutamide is the most prominent target to treat radioresistant breast cancer cell lines. Speers *et al.,* (2017) have shown significantly high expression of androgen receptors in TNBC patients.[140] Other studies have shown that expression of hypoxic markers such as carbonic anhydrase IX (CAIX), and hypoxia-inducible factor 1 alpha (HIF1A) can be used to predict overall survival (OS) in patients with locally advanced breast cancer (LABC). In their investigation, CAIX expression was greater in HER2-enriched and triple-negative patients with clinical stages (higher than IIB/T3N0).[141] These results indicated that CAIX expression correlated with the histological grade and was linked with a lack of hormone receptors, particularly triple-negative breast cancer. So, the co-expression of these two proteins CAIX and HIF1A, shows poor prognosis in TNBC patients.[142-144]

Natural Products Such as Radiosensitizer

Several natural products have been reported as potent radiosensitizers in patients supplemented before radiotherapy. They act as a protecting agent for normal tissue to IR due to their antioxidant and immune-modulatory effects.[145] Some of the essential natural compounds are listed in Table 3.

Andrographolide (Andro)

Andrographolide (Andro) is a diterpene lactone molecule derived from plant *Andrographis paniculate* and works as a nuclear factor kappa B (NF-κB) inhibitor.[153] Andrographolide has various pharmacological benefits, including anti-bacterial, anti-parasitic, anti-inflammatory, and anticancer actions.[154] Andro inhibits extracellular signal-regulated kinase 1/2 (ERK) and PI3K/Akt signaling pathways via inactivating matrix metalloproteinase 9 (MMP-9).[146] These two signaling further reduce DNA binding transcription factors such as activator protein 1 (AP-1) and NF-κB.[155] Andro is a potential candidate for targeting p300 (histone acetyltransferase p300 HAT) signaling pathway to suppress NF-κB activation and angiogenesis via the VEGF pathway in breast cancer.[147] Andrographolide suppresses radiation-induced DNA damage by inhibiting signal transducer and activator of transcription 3 (STAT3).[156]

Table 2: List of radiation response predictive biomarker panel in breast cancer

Biomarkers	*Importance feature*	*References*
Ki67, *STK15*, *Survivin*, *CCNB1* (Cyclin B1), *MYBL2*, *MMP11* (Stromolysin 3), *CTSL2* (Cathepsin L2), *GRB7*, *Her2*, *ER*, *PGR*, *BCL2*, *SCUB2*, *GSTM1*, *CD68*, *BAG1*	Multigene panel expression assay algorithm used for distant recurrence scores in patients with tamoxifen-treated without lymph node-involved estrogen receptor-positive breast cancer	[131]
NBN, *MRE11 (MRE11A)*, *RAD50*, *RAD51*, *RAD52*, *RAD54 (ATRX)*, *BRCA1*, *BRCA2*, *RPA*, *H2AFX*, *ATM*, *XRCC4*, *XRCC2*, *XRCC3*, *ATR*, *PRKDC*, *LIGASE 4F*, *XRCC6/KU70*, *XRCC5/KU80*, *CHK1 (CHEK1)*, *CHK2 (CHEK2)*, *DCLRE1C*, *ABL*, *MDC1*, *TERT*	A novel hGHR inhibitor sensitizes an hGH-responsive tumor to radiation treatment in breast and endometrial cancer.	[132]
AR, *cJun*, *STAT1*, *PKC*, *RelA*, *cABL*, *SUMO1*, *CDK1*, *HDAC1*, *IRF1*	The clinical approach of radiosensitivity index (RSI) enhances to complete pathological response by delivering radiation doses to patients predicted as radiosensitive.	[135]
ATM, *BARD1*, *BRCA1*, *BRCA2*, *FANCA*, *MDC1*, *MSH2*, *RAD51*	The genes profile DNA damage related seen with better outcomes during radiotherapy.	[139]
AR	The probability of locoregional recurrence following radiotherapy increases in TNBC when AR expression is above the median level.	[140]
CAIX, *HIF1A*	In forty patients, CAIX and HIF1A levels were higher in the negatives of the hormone receptors.	[141]

Table 3: Enlist several such natural products reported for their role as radiosensitizers

Natural Compounds	*Possible mechanism*	*References*
Andrographolide	It inhibits cyclooxygenase (COX-2) expression and suppresses the angiogenesis process by the VEGF pathway in breast cancer cell lines such as MDA-MB-231, MCF-7, T-47D, MDA-MB-361 and BT-549.	[146, 147]
Berberine	Berberine causes cell cycle arrest and down-regulate the homologous recombination repair protein such as RAD51 in human breast cancer cell line MDA-MB-468 and MCF-7. So, berberine can act as a prominent radiosensitizer to treat breast cancer malignancy.	[148]
Curcumin	Radiation combined with curcumin initiates tumor death by attenuating NF-κB transcriptome signaling in MCF-7 cells.	[149]
L-Mimosine	The gold nanoparticles synthesized from leaf extract of *M. pudica* showed anticancer potential by arresting the cell cycle in the early phase from G0/G1 to S phase in MCF-7 and MDA-MB-231 breast cancer cell line.	[150]
Melatonin	Melatonin and irradiation treatment showed a potential radiosensitizer by activating pro-apoptosis genes like p53, suppressing the DNA damage repair process and changing tumor cell metabolism in breast cancer cell lines.	[151]
Resveratrol	It prevents HIF1-α in hypoxic conditions and increases radiosensitivity in MCF-7 breast cell lines that have undergone chemotherapy and radiotherapy.	[152]

Berberine (BBR)

Berberine (BBR) is an isoquinoline alkaloid derived from many plants of *Berberis,* such as *Berberis aristate*, *Berberis vulgaris* and *Berberis aquifolium* and other genera *Hydrastis canadensis*, *Coptis chinensis*, *Tinospora cordifolia* etc. Numerous studies have documented that BBR causes radiosensitization in cancer cells by cell cycle arrest and apoptosis.[157,158] MCF-7 and MDA-MB-468 cell lines were treated *in vitro* with BBR (15 μM) and various doses of X-ray (1-4 Gy), which showed that BBR treatment increased DSBs and down-regulated RAD51.[148] Additionally, BBR prevented STAT1 from being phosphorylated, which prevented IFN-γ from downregulating the immune checkpoint expression of indoleamine 2,3-dioxygenase 1 (IDO1). These results showed that BBR could represent a viable therapeutic substance for cancer.[159]

Curcumin

Curcumin is a rotatory polyphenolic compound suitable for various animal cancer models, like lung, pancreas, breast, colon, breast, skin, kidney, and blood. Curcumin has been used in ancient Ayurvedic and Chinese medicines since ages. Treatment of MCF-7 cells with curcumin (100 nM) induced cell death via suppression of radiation-induced NF-κB DNA binding activity by attenuating expression of NF-κB signaling. In recent decades it has been used as an anticancer agent in several clinical trials in animals and humans. Curcumin contains several properties like antioxidant, anti-inflammatory, antiproliferative and anti-angiogenesis.[160,161] Experimental evidence has been generated by applying a higher dose of curcumin to demonstrate an antiproliferative effect on specific cancer cell lines and xenografts models.[162] The STAT3 protein is a transcription factor of the STAT family, associated with cancer development. The use of curcumin inhibits STAT3 phosphorylation in various types of cancers.[163,164] curcumin can inhibit hypoxia-induced NF-κB signaling, leading to enhanced radiosensitivity.[149,165]

L-Mimosine

L-Mimosine (β-N(3-hydroxy-4-pyridone)-α-amino propionic acid) is a toxic type of L-amino acid that is abundant in leaf and seeds plant *Leucaena glauca* or *Mimosa pudica*.[166] It has been observed that mimosine arrests DNA synthesis of cancer cells grown in a laboratory. Mimosine treated breast cancer cell lines cannot form a cell cycle from G0/G1 to the S phase due to its ability to chelate metal ions.[167] *M. pudica* coated gold nanoparticles anticancer activity significantly shows DNA single-strand breaks in breast cancer cell lines.[150]

Melatonin

Melatonin (N-acetyl-5-methoxy tryptamine) is an indoleamine mostly released at night during dark hours by the pineal gland. Several studies concluded that when given along with radiotherapy, melatonin might increase therapeutic efficacy and protect normal cells from adverse effects while undergoing treatment. Melatonin is a low-toxicity antioxidant and anti-inflammatory substance with radiosensitive and radioprotective properties. Melatonin increases the production of reactive oxygen species (ROS), proteins associated in estrogen biosynthesis are synthesized, tumor cells are unable to DNA repair, angiogenesis is modulated, inflammation is reduced, apoptosis is induced, preadipocyte differentiation is stimulated, and metabolism is altered. These are mechanisms of radiosensitization by melatonin.[168] Melatonin treatments reduce the number of cells in S phase. Additionally, melatonin pretreatment in the MCF-7 cell line reduced the expression of RAD51 and DNA-PKCs compared to cells that were just exposed to radiation alone.[169, 170] Melatonin further inhibits tumor growth by decreasing glycolysis and increasing oxidative phosphorylation. Through the activation of p53 and TRAIL ligand, melatonin increases apoptosis in cancer cells.[151]

Resveratrol (RV)

Resveratrol (RV) is a naturally occurring polyphenol in fruits and vegetables, including those consumed by humans like raisins, mulberries, grapes, and peanuts.[171,172] *In-vitro* studies have shown that it inhibits and suppresses tumor growth as an antiproliferative agent, possibly by inhibiting apoptosis or anti-angiogenesis.[173] The colony number for breast cancer spheroid of MCF-7 cells is greatly reduced by resveratrol (RV) combined with 5-fluorouracil (5-FU) and radiation together.[152] Resveratrol increases radiosensitivity and suppresses the expression of HIF1-α protein by controlling the protein translation mechanism.[174]

Summary

This review article provides an in-depth exploration of biomarkers that hold promise in predicting radioresistance and identifying natural radiosensitizers in triple-negative breast cancer (TNBC). By examining the latest research findings and clinical studies, this comprehensive review aims to shed light on the complex interplay between TNBC biology, radiation response, and potential biomarkers that can aid in personalized treatment strategies. Through a systematic analysis of various biomarkers, including genetic, epigenetic, and protein-based markers, this review highlights the need for accurate prediction of radioresistance to optimize treatment outcomes in TNBC patients. Additionally, identifying natural radiosensitizers, such as botanical compounds and natural agents, offers a novel way to enhance radiotherapy's efficacy while minimizing associated toxicities. Overall, this review provides valuable insights into the current landscape of biomarkers for predicting radioresistance and natural radiosensitizers in TNBC, paving the way for future

research and the development of personalized therapeutic interventions.

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