

Review

“The Infinite Maze” of breast cancer, signaling pathways and radioresistance



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ABSTRACT

The parallel growth in our understanding of tumor biology and genetics might be the key to understanding local recurrence after optimal treatment is applied. Data suggest that genetic alterations and breast cancer molecular subtypes have an effect on radiotherapy efficacy and that the HER2, EGFR/PI3K/Akt signaling pathways play a pivotal role in modulation of post-irradiation survival. These pathways have been found to be involved in radiosensitivity and/or radioresistance, tumor cell proliferation, and hypoxia. Therefore, affecting the functional activity of key players combined with radiotherapy might be the future of breast irradiation.

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Introduction

The vast majority of breast cancers is sporadic and attributed to numerous somatic genetic alterations; consequently, each individual tumor has a unique genetic milieu.^{1–3} The frequency and distribution of mutations redefine the histology-based taxonomy of breast cancer. The approval of trastuzumab in 1998 was a landmark in the new era of “targeted therapy”, since trastuzumab significantly improved patient outcome and paved the way for the advent of “tailored therapy” for breast cancer.^{4,5} The human epidermal growth factor receptor type 2 (HER2) status was also found to be important in determining the preferred chemotherapy regimen.⁶ While medical anti-tumor treatment has evolved significantly (and is still evolving) according to molecular subtypes, radiotherapy principles have not changed. Adjuvant radiotherapy techniques, regimens and volumes (whole breast, partial, accelerated, etc.) are determined according to clinical factors such as patient-related (BRCA status, age, co-morbidities), tumor-related (histology, size, location, number of foci, grade, lymphovascular invasion),

lymph node status (number involved, number dissected), and surgical factors (margins, type of surgery).^{7,8} This is demonstrated in the 2011 St. Gallen publication entitled “Strategies for subtypes—dealing with the diversity of breast cancer”, in which considerations for adjuvant radiotherapy were according to the clinical factors mentioned previously and were barely associated with molecular subtypes.⁹

A “molecular” phenotype that is commonly included in adjuvant radiotherapy guidelines is the estrogen receptor (ER) status. Patients with ER positive and other features of low-risk breast cancer can be considered for accelerated partial breast irradiation.^{10–12} With the results of the EORTC “young boost” trial,¹³ it appears that adjuvant breast irradiation has reached the limit of dose escalation and physical–technical features that can be manipulated to further improve treatment efficacy.^{13–15} Consequently, the curative potential of radiotherapy is limited by the intrinsic radioresistance of the tumor cells.

The concept of radiosensitive and radioresistant tumor cells is well recognized in different tumor cell clones. With the new understanding of different molecular phenotypes of breast cancer tumor cells, clinicians and radiobiologists were intrigued by their influence on dose–response curves. These genetic changes have a “prognostic signature” which translates into different responses to various medical treatments and survival, yet the magnitude of their

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effect on radiotherapy was hardly explored. The aim of this review was to investigate the current data on breast cancer subtypes and potential radioresistance.

Breast cancer subtype classifications and signaling pathways

Intrinsic breast cancer subtypes can be segregated into two major groups according to the ER status: ER-positive group [luminal A, luminal B], ER-negative group [basal-like, claudin-low, HER2-enriched] and normal breast-like (this subtype is not clearly defined).¹⁶ The nomenclature has been changed with the identification of new subtypes (according to gene expression) and their unique prognostic features. Therefore, care must be taken when reading clinical trial reports as the nomenclature may differ between trials.³ The definition of these subtypes is not an easy task, as creating validated assays for clinical use and universal grading systems is a major difficulty and is still evolving.

Importance of Erb receptor family and intracellular signaling pathways

A more intensively researched breast cancer subtype is the HER2-enriched. About 15–30% of breast cancers display over-expression or gene amplification of HER2 (ErbB2)^{17–19} which is a part of the ErbB receptor tyrosine kinase (RTK) family that is comprised of “HER1 (EGFR, ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4).”

These tyrosine kinases have a critical role in cellular growth. It was found that these kinases are often up-regulated in numerous cancers, including breast carcinoma.²⁰ The over-expression of HER2 was found to be of great importance since its activation triggers multiple downstream pathways required for the abnormal proliferation of cancer cells.²⁰ The activation of HER2 is

achieved by the formation of homodimers or heterodimers with other part of the ErbB receptor tyrosine kinase family. This dimerization results in phosphorylation of specific tyrosine residues in intracellular domains of the receptor, which leads to the activation of the Ras/Raf/mitogen-activated protein kinase. The fundamental importance of this pathway in neoplastic cell proliferation in humans has been confirmed by the clinical success of therapeutics that target tyrosine kinases, such as trastuzumab. Fig. 1 is a schematic illustration of the intracellular pathways resulting from HER2 activation, however, the complexity of tumor behavior is even higher since more pathways are involved in tumor progression and since HER2 and PI3K themselves are also involved in controlling apoptosis, DNA repair, perfusion and hypoxia. Figs. 1 and 2 illustrates potential targets to overcome radioresistance.

In recent years, a second downstream pathway that plays a major regulatory role in proliferation and survival of mammalian cell was revealed. This pathway also involves tyrosine kinase receptors by both direct recruitment and/or lateral signal propagation (sometimes through RAS) to other ErbB RTK family members and involves phosphatidylinositol 3-kinase (PI3K), Akt and the phospholipase C γ (PLC γ)/protein kinase C (PKC) pathways.²⁰ The Akt family of serine/threonine protein kinases (PKB), similarly to the Ras/Raf/mitogen-activated protein kinase, is considered as key regulators of cell proliferation, survival, metabolism, and tumorigenesis. Recent studies have implicated Akt in modulating DNA damage responses and genome stability.²¹

Activation PI3K mainly results in generation of PIP3 in the membrane, which functions as a second messenger to activate downstream pathways that involve Akt and other proteins.²² The PIP3 phosphatase that is evidently primarily involved in oncogenesis is PTEN (also named MMAC1). PTEN is a 3-position lipid phosphatase that converts PIP3 back to PIP2. It was isolated initially

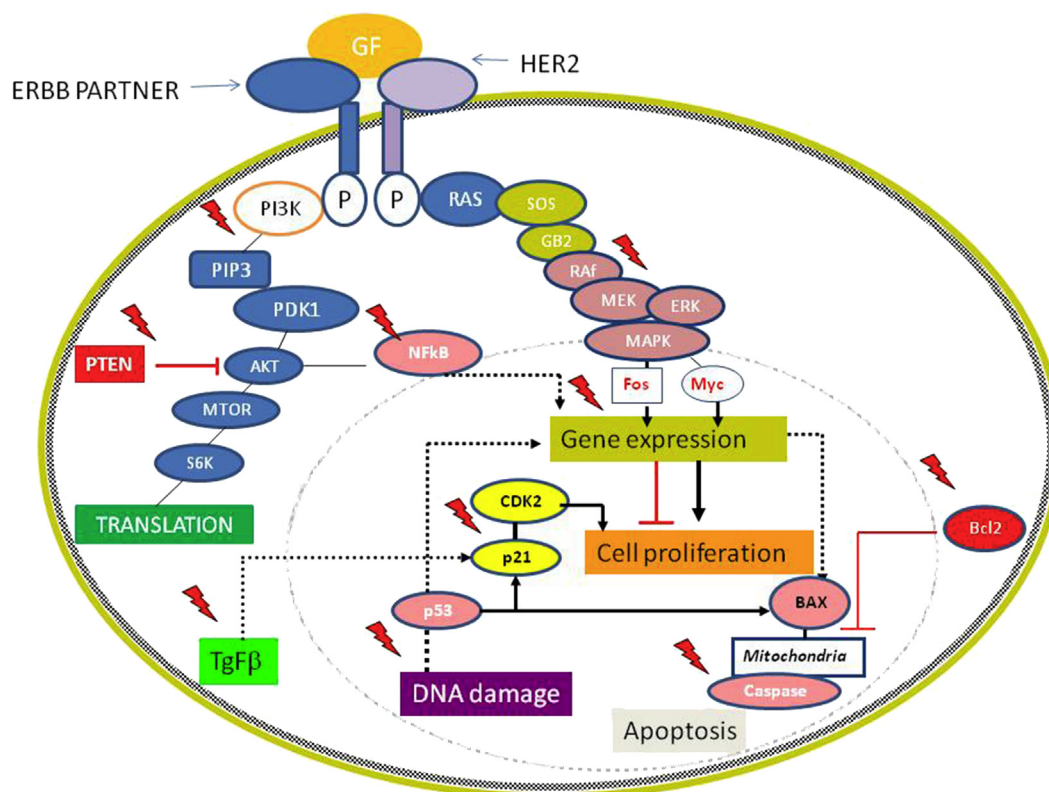


Fig. 1. The interaction between ionizing radiation (⚡) and intracellular pathways resulted by HER2 activation.

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