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Editorial

Resistance in Breast Cancer Chemotherapy: Patterns and Mechanisms

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Breast Cancer Drug Resistance

Breast cancer is one of the leading causes of cancer-associated death among the female population worldwide [1]. One of the reasons of breast cancer morbidity is chemotherapy failure. Despite the increasing arsenal of anticancer agents and the advent of molecular targeted therapies, drug resistance in cancer is not uncommon [2].

Types of drug resistance in breast cancer

In breast cancer, both intrinsic or *de novo* and acquired types of drug resistance are reported [3]. In the case of intrinsic resistance, before receiv¬ing chemotherapy, resistance-mediating factors pre-exist in the bulk of tumour rendering the therapy inef¬fective. Acquired drug resistance, on the other hand, can emerge during the course of the treatment for tumours that were initially responding to the same therapy. This eventually leads to treatment failure and ultimately to progression of the disease and tumour recurrence.

Mechanism of drug resistance

In general, both pharmacokinetic factors *viz.,* absorption, distribution, metabolism and elimination (ADME) of the drug, as well as pharmacodynamic properties of the compound may contribute to the development of resistance. For example, inadequate access of the drug to the tumour cell, poor infusion rate or influx, decreased drug uptake, excessive drug metabolism by detoxifying enzymes and efflux due to overexpression of drug transporters, all of which might contribute to the mechanisms underlying acquired resistance. The anticancer activity of a drug can also be limited by drug inactivation or lack of activation, alterations in the expression levels of the drug target, triggering of adaptive prosurvival responses, and importantly, changes in drug-induced apoptosis [4].

Patterns of drug resistance in breast cancer

In breast cancer, there is evidence of both *de novo* as well as acquired resistance, not only for traditional drugs, such as doxorubicin and paclitaxel, but also for targeted chemotherapeutic agents such as tamoxifen. Prominent examples include doxorubicin resistance by overcoming drug-induced senescence [5], tamoxifen resistance by overexpression of HER2/neu (HER2) and the estrogen receptor (ER) [6], and trastuzumab resistance by cyclin E amplification/overexpression in HER2-positive breast cancer patients [7].

In many instances, breast cancer therapy failure occurs mainly due to emergence of recurrent endocrine-resistant tumours. Altered growth factor signalling, mediated by EGFR and insulin-like growth factor I receptor (IGF-IR), is also responsible for the development of anti-estrogen resistance [2]. A recent evidence suggests the involvements of micro-RNAs in the regulation of multi-drug resistance (MDR) in breast cancer. Specifically, overexpression of the microRNA (miR)-106b~25 cluster leads to generation of doxorubicin resistance in breast cancer cells by overcoming doxorubicin-induced senescence [5].

It has also been suggested that the tumour microenvironment could play important roles in breast cancer therapy resistance, endocrine resistance [8]. Elevated stromal gene expression predicts resistance to neoadjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC), implying that stromal activation could be involved in chemotherapy resistance in breast cancer [9]. The

relatively small proportion of stem-cell-like populations known as the tumour-initiating or progenitor cells also potentially exacerbate drug resistance [10]. Importantly, breast cancer stem cells are reported to be highly resistant to both radiation therapy as well as chemotherapy [11]. This emphasises the need for developing therapeutic strategies targeting cancer stem cells.

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