Inflammatory Breast Cancer is Associated with Hyperactivated Mitogen Activated Kinase

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Inflammatory Breast Cancer (IBC) is a distinct clinical subtype of locally advanced breast cancer, with a particularly aggressive behavior and poor prognosis. Clinically, IBC typically presents with rapidly progressive breast warmth, erythema and edema [1]. It is now well established that adjuvant systemic therapy improves survival in patients with early-stage breast cancer [2]. Breast cancer is highly curable if diagnosed at early stage. Recent progress in diagnosis and therapy has increased the survival of women in estrogen-dependent breast cancer. However, despite advances in multidisciplinary treatment, the prognosis of IBC is less favorable than that of non-IBC, with a 3-year survival of about 40% [3,4]. Activation of NF-κB in inflammatory breast cancer is associated with loss of Estrogen Receptor (ER) expression, indicating a potential crosstalk between NF-κB and ER. It has been shown that NF-κB activation is not exclusively limited to IBC but more general to ERα- breast tumors.

Determination of estrogen receptor (ER) status of invasive breast carcinoma is useful as a prognostic and predictive factor and has become standard practice in the management of this type of cancer. Breast cancer presents as either estrogen positive (ERα+) or receptor negative (ERα-). ERα + tumors have a better prognosis in terms of increased disease-free survival and respond to hormonal therapies such as tamoxifen [5-7]. Whereas, ERα- breast cancers have a worse prognosis and are associated with a more aggressive phenotype, are resistant to anti-estrogens, and frequently present with elevated growth factor receptor expression and/or signaling with resultant p42/44 Mitogen Activated Kinase (MAPK) signaling [8-10]. Signal transduction by way of Mitogen Activated Protein (MAP) kinases is an integral part of many cellular responses. These responses include proliferation, differentiation, and cell death. Upwards of a dozen highly genetically conserved MAP kinase families have been identified since their initial discovery in yeast. In mammalian cells, several distinct MAPKs have been identified. These include Extracellular signal Regulated Kinase (ERK) 1/2 cascades, c-Jun N-Terminal Kinase (JNK) or Stress Activated Protein Kinase 1 (SAPK1), and p38 MAPK also known as SAPK2. ERK 1/2 are often activated by mitogens and regulate cell growth and differentiation, while the JNK and p38 MAPK are poorly activated by mitogens and typically function in stress responses such as inflammation and apoptosis [11,12].

It has been reported that hyperactivation of MAPK directly represses ERα expression in a reversible manner. IBC is characterized by MAPK hyperactivation in comparison to non-IBC, potentially due to overexpression of EGFR and/or ErbB2. The activation of NF-κB and the frequent ER independency of IBC tumors can be explained in this context. The reexpression of ERα in established ERα- breast cancer cell lines has only been previously shown via inhibition of DNA methylation or histone deacetylation in those cell lines in which the ERα promoter has been shown to be methylated [13-15]. The methylation of ERα promoter is presumably a means of permanent repression secondary to some other down-regulating event. The down-regulation of ERα expression by hyperactive MAPK is a more direct mechanism and is dynamic and reversible (i.e., the down-regulation is reversed by the inhibition of MAPK activity and occurs again shortly after return of MAPK activity). Bayliss et al. [13] reported that in addition to hypermethylation of the ERα promoter, hyperactivation of MAPK resulting from over expression of EGFR or erbB-2 can also be directly responsible for the lack of ERα expression in ERα - tumors. Importantly, this MAPK-mediated down-regulation of ERα expression can be targeted to result in reexpression of ERα. In fact, it has recently been shown that in a small study of 10 ERα- / erbB-2+ patients treated for various lengths of time with Herceptin, 3 patients reexpressed ERα [13]. Another study by Massarweh et al. [14] suggested that this mechanism can also be exploited in ERα+ / erbB-2+ tumors that lose ERα expression during treatment. It was found that resistance to estrogen deprivation/fulvestrant in an ERα+ / erbB-2+ MCF-7 xenograft model was accompanied by upregulation of MAPK activity and loss of ERα expression, and subsequent cotreatment with Iressa resulted in inhibition of MAPK activity and increased ERα expression.

Regardless of the different potential mechanisms for downregulating/restoring ERα expression, the reexpressed ERα must not only be functional on reexpression (i.e., induce the regulation of estrogen-responsive genes) but must also be able to regulate growth in response to estrogen/antiestrogens to be clinically relevant. Overall, these data point towards that NF-κB and MAPK might be therapeutic targets for IBC specifically and more general for ERα- breast tumors as well as for breast tumors with acquired resistance against hormonal therapy.

Current treatment methods of breast cancer, depending on the stage of cancer upon diagnosis, include surgery, radiation therapy, biological therapy, hormone therapy (e.g. tamoxifen, aromatase inhibitor) and chemotherapy (e.g. anthracyclines, taxanes). The most widely used therapy for breast cancer is the use of antiestrogen such as tamoxifen. However, the present breast cancer therapies achieve meaningful clinical results in only 30-40% of patients because drug resistance is linked to the presence of estrogen-independent pathways for breast cancer cell growth [15]. Therefore, more potent anti-breast cancer agents that combine the desired, tissue-selective effects with novel structures or new mechanism(s) of action must be developed. A number of 1,4-naphthoquinone derivatives have been found to possess powerful pharmacological effects associated with marked antimicrobial and antitumor activities [16].

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Naphthoquinones, widely distributed in nature, play important physiological roles in animals and plants. Quinone derivatives may be toxic to cells by a number of mechanisms including redox cycling, arylation, intercalation, induction of DNA strands breaks, generation of free radicals and alkylation via quinomethide formation [17,18]. As a consequence, the molecular framework of a great number of pharmaceuticals and biologically important compounds contain a quinone moiety. Representative examples of this class of compounds are the well-known anticancer drugs of the anthracycline series, doxorubicin and mitoxantrone, the action of which is believed to occur via topoisomerase II inhibition [19]. In addition, a number of naphthoquinone analogues such as plumbagin, shikonin and naphthazarin as well as 3-lapachone have also been found to inhibit topoisomerase. The MAPK signaling pathway may be initiated by activation of either the EGFR or erbB-2 growth factor receptors from which the signal is channeled via Ras, Raf, and MEK, ultimately resulting in activation of phosphorylating of MAPK and gene transcription [20]. Copeland et al. [21] reported the synthesis and effects of 2,3-Dichloro-5,8-Dimethoxy-1,4-naphthoquinone (DCDMNQ) derivatives which showed significant cytotoxicity against prostate and breast cancer cell lines. Mechanistically, it was shown that these compounds cause inhibitory effects on MAPK phosphorylation, thereby decreasing activity. Moreover, corresponding data suggest the ability of these compounds to have significant selective cytotoxicity against breast cancer cells as compared to normal bone marrow cells [22].

The abrogation of the MAPK pathway by direct inhibition of hyperactivated MAPK or possible upstream inhibition of over-expressed EGFR, c-erbB-2, or epigenetic alterations of the ERα gene promoter region, will result in re-expression of ERα. Thus, DCDMNQ may restore estrogen-dependence and anti-estrogen sensitivity in a subset of ERα- breast cancers, while contrasting the data with corresponding studies in ERα+ breast cancer cell lines. The roles of MAPK hyperphosphorylation, chromatin remodeling will provide detailed insight into the mechanisms employed by the compounds for ERα re-expression. Alternate estrogen receptor signaling pathways would further elucidate the role of these naphthoquinone analogs in breast cancer. The down-regulation of the ERα expression by hyperactive MAPK is a direct mechanism which is potentially reversible DCDMNQ analogs. However, alternative chromatin remodeling through ER regulators and histone deactylases, can potentially restore ERα expression, would increase anti-estrogen responsiveness in ERα- breast cancer cells. Therefore, ERα- breast cancer patients could benefit from combinatorial treatment with DCDMNQ analogs and conventional chemo/hormonal therapy.

References