Editorial

Breast Cancer: Novel Therapeutic Targets

BREAST CANCER

Breast carcinoma is the commonest cancer in women globally, in both developed and developing countries, and also the leading cause of malignancy-associated deaths [1]. The GLOBOCAN project estimated that there were 1.38 million newly diagnosed breast cancer cases worldwide in 2008, and that the disease accounted for more than 458,000 deaths [2]. In the United States of America alone, cost of medical care for cancer patients in 2010 was estimated to be US$125 billion [3]. Of this, US$16.5 billion would be used in the management of patients with breast cancer. The figure is expected to rise to US$20.5 billion by 2020. The direct cost of medical and nursing care of cancer patients contributes to less than half of the economic burden of cancer [4, 5]. The major impact comes from indirect morbidity and mortality costs and the loss of productivity.

Several factors are well established to be associated with a greater risk of breast cancer [6]. Mutations in the *BRCA1* and *BRCA2* genes significantly increase the incidence of breast cancer. Early menarche, an older age at first full-term pregnancy and late menopause are known to increase a woman's risk of developing breast cancer, and suggest the importance of hormonal status in this malignancy. Exposure to ionising radiation has also been linked to an elevated risk of breast cancer. In contrast, a healthy diet, limitation of alcohol intake, and regular physical activity may help in the primary prevention of this disease [7].

Early diagnosis and advancement in treatment modalities are important strategies in the management of breast cancer patients. Analysis of survival trends of women with breast cancer during the period 1996 to 2005 showed a large improvement, with a relative risk of 0.94 [3]. Clinical breast examination and screening by mammography have been shown to reduce patient mortality [8-12]. However, there are conflicting reports that question the effectiveness of screening programmes [13, 14]. Indeed, in 2009, the US Preventive Services Task Force recommended reducing the frequency of screening by mammography from once a year to once every two years, and restricting the use of biennial screening to women in the 50 to 74 age group [15]. Overdiagnosis, false positives and associated problems must always be borne in mind in the assessment of breast cancer screening programmes [16, 17].

TARGETS FOR TREATMENT OF BREAST CANCER

Depending on the stage and other clinicopathological considerations, current breast cancer treatment may involve surgery, radiotherapy, chemotherapy and systemic adjuvant or neoadjuvant therapy. Much effort has been put into the discovery of novel strategic targets and anti-cancer drugs that may be able to significantly improve patient prognosis. Recognition of the key role of hormonal regulation in breast cancer led to targeting of the oestrogen receptor using tamoxifen and other selective oestrogen receptor modulators, resulting in improved patient survival [18-21]. A complementary approach using aromatase inhibitors such as anastrozole and letrozole to block oestrogen biosynthesis has also been demonstrated to be clinically effective [22, 23].

Overexpression of epidermal growth factor receptor 2 (ERBB2) is predictive of worse clinical outcome in breast cancer patients [24]. Targeting the ERBB2 receptor using trastuzumab, a recombinant humanised monoclonal antibody that binds to the receptor, has produced dramatic results in patients with HER2-positive breast cancer [25-27]. Lapatinib, an inhibitor of HER2 and epidermal growth factor receptor signalling, has also been shown to reduce disease progression [28, 29].

In recent years, heparan sulphate proteoglycans have emerged as a potential therapeutic target for breast carcinoma [30]. Changes in the glycosaminoglycan moiety per se or in the expression levels of proteoglycans have been shown to regulate tumour growth and disease progression [31-35]. The compound phosphomannopentaose sulphate, which inhibits the heparanase enzyme, has been demonstrated to reduce breast cancer growth and distant spread to draining lymph nodes [36]. Other possible strategies that capitalise on the biological roles of heparan sulphate proteoglycans for cancer treatment include disruption of the biosynthesis of these molecules, and using antibodies or prodrugs to bind to the molecules [37-40].

In this issue, Mohanraj and Oh examine the potential targeting of the insulin growth factor system for cancer treatment, while Lai *et al.* review the possible exploitation of metallothioneins for this purpose. Raju *et al*. provide evidence that novel pyrazole derivatives possess anti-cancer activities. Potential treatment options for aggressive triple negative breast tumours are reviewed by Teng *et al.* It is hoped that continual research efforts would lead to improvements in clinical outcome for breast cancer sufferers, thereby reducing the personal and societal impact of this disease.

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