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Oestrogen receptor mutations and their influence on breast cancer growth

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CHAPTER ONE

GENERAL INTRODUCTION

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REASONS FOR THIS STUDY

Oestrogen is a modulator of cellular growth and differentiation of cells associated with reproduction and mammary gland development (Dixon, 1995). Oestrogens are also involved in the growth and development of normal and mammary cancer cells (Millar, 1989). The mechanism by which the effects of oestrogen are mediated in both normal and neoplastic cells involves specific intracellular receptors ER $\pm$ and ER ^{2} (Kaufman, 1991). These are members of the steroid/thyroid/retinoid receptor-gene superfamily. Upon activated nuclear translocation, their presence has been an indicator of a favourable prognosis in breast cancer, even in cases where the tumour is sensitive to endocrine therapy with agents such as tamoxifen. Unfortunately, a large proportion of patients develop resistance towards this treatment (Clarke and McGuire, 1988). The study of ER $\pm$ and ER ^{2} variants has identified several variants (Fuqua et al, 1991; Wang and Miksic, 1991; Fuqua et al, 1992; Zhang et al, 1996; Chappell et al, 2000; Panda Speirs, 2001; Pedraza et al, 2002; Taylor et al, 2010). And it has been suggested that ER variants may play a role in the development of drug resistance. These variants have also been found to coexist with wildtype ER and may

function. This study attempted to examine these variants and their clinical relevance as well as their significance with respect to the role they each may play in the pathogenesis of breast disease.

In order to examine the role of these variants in the progression of disease, the T47D cell line was utilized as a model for the effects of various breast cancer ERs. The T47D cell line is an ER⁺ positive cell line that has been found to be sensitive to tamoxifen, a selective ER modulator, and is therefore a good model for studying the effects of oestrogen on ER⁺ cells. The effects of oestrogen on ER⁺ cells are therefore important when assessing hormone responsiveness and the role of each ER⁺ exon variant or ER² region.

Tamoxifen is the most widely used hormonal therapy for breast cancer provided that the patient is ER⁺ (Fiorio et al., 1999). It has been used for the treatment of advanced disease in premenopausal women but also for the prevention in women at high risk of developing breast cancer (Levenson and Jordan, 1999). It acts as a partial agonist to ER⁺ and competitively blocks the action of oestrogen on ER⁺ cells. It binds to tamoxifen but with a higher affinity than ER⁺ does. An important drawback to tamoxifen treatment, however, is the resistance that occurs in many patients. This may also take the form of stimulation of the tumour, suggesting both oestrogen agonist and antagonist activities (Katzenebein et al., 1997; McDermott et al., 2002). The mechanism

of tamifen resistant-positive breast cancer is unknown despite early studies (Osborne, 1998; Ali and Therasse, 2002) defines the potential role of oestrogen receptor development of oestrogen resistant T-47D breast cancer by observing growth in medium containing tamifen.

The majority of breast cancer arises after menopause when ovarian production of oestrogen and progesterone declines, however, oestrogen occurs in muscle, skin and adipose through the conversion of androstenedione or testosterone and locally by the enzyme, aromatase cytochrome P450. Cytochrome P450s also involved in the conversion of cholesterol to pregnenolone, the basic precursor of oestrogens and glucocorticoids. It has, therefore, also been implicated in increasing breast cancer risk in postmenopausal women (Pau, 2004). Concentrations of oestrogen in breast tissue are reported to be significantly higher in breast carcinoma than in peripheral tissue in postmenopausal women (Szytko et al, 1985; Szytko, 1998; Chetani, 2000; Miyoshi, 2004) suggesting that oestrogen production within the breast and by breast tissue is important in stimulating proliferation in the breast. Aromatase mRNA levels have been found to be increased in breast carcinoma (Ueda et al, 1996) and in breast carcinoma (Suzuki et al, 2007) compared to normal breast tissue, suggesting that aromatase is the key enzyme for the increase in intra-tumoural oestrogen levels in breast cancer. Systemic treatment of breast cancer with aromatase inhibitors should block synthesis of oestrogen and therefore reduce the progression of breast tumours in postmenopausal women.

One of the early aromatase inhibitors that was the prototype for nonsteroidal aromatase inhibitors (C-450) Aminoglutethimide blocks several cytochrome-mediated steroid hydroxylation steps including those required for cholesterol conversion and for the aromatization of androgens to oestrogens. This line provides a model in order to establish the effects of observing growth in the presence of cholesterol and an aromatase inhibitor (in the addition of aminoglutethimide to) the growth on ER variants.

Oestrinol, a weak androgenic metabolite of oestradiol, has been used successfully as a hormone replacement therapy for postmenopausal women for the treatment of symptoms (HRT 2000). Menopausal HRT has, however, been associated with increased cancer risk (Rosenberg et al 2000) although the presence of oestrinol has also indicated some prevention of mammary carcinogenesis (Lay et al 2004). T-47D breast cancer cells grown in medium would provide information on hormone response and the effect of metabolite on ERs.

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AIM

The purpose of this thesis is to define a pattern (ER^α) and oestrogen receptor ² (ER^β) mRNA variants in clinical breast

and sequence analysis in order to establish their relative parameters, prognosis and treatment outcome and thus the of oestrogen action that occurs during tumourigenesis and acquisition of endogenous resistance. To further examine pre-disease the rate and location of variations in the exons of oestrogen receptors, aromatase inhibitors and oestrogen pathways their implications on hormone responsiveness is being examined using the human breast cancer cell line model.