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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 differentia
cells associated with reproduction and mammary gland dev
al, 1995). Oestrogens are also involved in the growth and development
and mammary cancers (Miller, 1989). The mechanism by which th
effects of oestrogen are mediated in both normal and neoplas
specific intracellular receptors ER± and ER² (Kuiper
members of the steroid/thyroid/retinoid receptor-gene su
activated nuclear transcriptor factors. Their presence has been an ind
a favourable prognosis in breast-cancer tumours. ER± more
sensitive to endocrine treatments such as tamoxifen. Unfort
large proportion of patients eventually develop resistance towards this tr
(Clarke and McGuire, 1988). A number of ER± and ER² variants ha
identified (Fuqua et al, 1991; Wang and Miksicek, 1991; Dotzlaw et al, 1992;
Fuqua et al, 1992; Zhang et al, 1996; Chaptal et al, 2000; Pandya and Speirs,
2001; Poola et al, 2002; Taylor et al, 2010) and it has been suggested that
ER variants may play a role in the development of drugs. These variants
have also been found to coexist with wildtype ER and may i

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

In order to examine the ion of disease-47D breast cancer cell li was utilized as a model for the effects of various breast c ERs. The 47D cell line is an ER± positive cell line that has found to be sensitive to tamoxifen, an oestrogen antagonist, to also be genetically unstable. This cell line therefore is in transition from an oestr responsive state to an oestrogen resistant state and po negative. The effects of oestrogen-17 and oestradiol therefore important when assessing hormone responsiveness and the each ER± exon variant or ER² region.

Tamoxifen is the most widely used hormonal therapy for cancer provided that the cell is ER (Fisher, 1999). Not only has it been used for the treatment of advanced postmenopausal wome and in pure but also for the prevention in women at high risk of dev (Levenson and Jordan, 1999). In breast tissue, tamoxifen binds to ER± and competitively blocks the action of oestrogen (ER²) and Oestrogen, 1997. It also binds to tamoxifen but with a higher affinity than ER± does (Fisher, 1997). important drawback to tamoxifen treatment, however, is th resistance that occurs in many patients. This may also tak stimulation of the tumour thus suggesting both oestrogen agonist an activities (Katzenellenbogen, McDonnell, 2002). The mechanism

of tamoxifen resistance in breast cancer is unknown despite e
studies (Osborne, 1998; Ali and Coombs, 2002). This study examines the pote
role of oestrogen receptor variants in the development of oestrogen resist
T-47D breast cancer cells observing growth in medium containing t

The majority of breast carcinomas arise after menopause when ovarian p
of oestrogen and progesterone decline. Oestrogen synthesis, however, also
occurs in muscle, skin and adipose through the conversion of
androstenedione or testosterone and oestrone and oestrone by the enzyme,
aromatase, a cytochrome-450 P. Cytochrome-450 P is also involved in the
conversion of cholesterol to pregnenolone, the basic pre
oestrogens and glucocorticoids. Cholesterol has, therefore, also been in
increasing breast cancer risk in postmenopausal women (Lipton et al, 2004).
Concentrations of oestrogen have been reported significantly higher in bre
carcinoma than in peripheral tissue in postmenopausal women (Lipton et al, 1985; Szyczak et al, 1998; Chettrit et al, 2000; Miyoshi et al, 2001) suggesting
that oestrogen production within the breast and by breast
in stimulating tumour proliferation in these patients. Aromatase m.RNA levels ha
been found to be increased in invasive (Utsumi et al, 1996) and invasive
(Suzuki et al, 2007) breast carcinoma compared to normal breas
that aromatase is the key enzyme for the increase in intra
oestrogen levels in breast cancer. Systemic treatment of breast cancer
with aromatase inhibitors should block synthesis of oestro
and therefore reduce the progression of breast tumo
postmenopausal women.

One of the early aromatase inhibitors was aminoglutethimide. It was the prototype for nonsteroidal aromatase inhibitors (C Aminoglutethimide blocks several cytochrome-450 mediated steroid hydroxylation steps including those required for cholesterol conversion and for the aromatization of and-Tetrad-7D cell line provides a model in order to establish the effects of observing growth in the presence of cholesterol and an aromatase inhibitor (by the addition of aminoglutethimide to) the grow on ER variants.

Oestriol, a weak oestrogen and a metabolite of oestradiol, has been used successfully as a hormone replacement therapy postmenopausal women for the medic syndromes (Takahashi, 2000). Menopausal HRT has, however, been associated with incr cancer risk (Rosenberg, 2006) although the presence of oestriol has also indicated some prevention of mammary carcinogenesis (Lykkesfeldt, 2004). T-47D breast cancer cells grown in medium could containin provide information on hormone response and the effect metabolite on ERs.

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AIM

The purpose of this thesis is to define a pattern of ER+ and oestrogen receptor ² (ER²) mRNA variants in clinical breast

and sequence analysis in order to establish their relati
parameters, prognosis and treatment outcome and thus the
of oestrogen action that occurs during tumourigenesis a
acquisition of endocrine resistance. To further examine pr
disease the rate and location of variations in the exons of
oestrogens, oestrogens, aromatase inhibitors and oestrogen p
their implications on hormone responsiveness in vivo were examined
using the human breast cancer cell line, MCF-7.