

Progesterone, glucocorticoid, but not estrogen receptor mRNA is altered in breast cancer stroma

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Abstract

Our laboratory has previously found that anti-mitogenic nuclear receptor mRNA is elevated in late stage tumours and this study was performed to scrutinize the possibility of cancer-stroma crosstalk using hormone signaling in these tissues. RNA levels in stromal tissue were examined for the estrogen α , estrogen β , androgen, progesterone and glucocorticoid nuclear receptors by a semi-quantitative PCR. Significant differences in expression between the cancer stroma and control tissue were seen, analyzing for both cancer grade and estrogen receptor status. Stroma and control tissue were significantly different for the progesterone and glucocorticoid nuclear receptors ($p = 5.908 \times 10^{-7}$ and 2.761×10^{-5} , respectively). Glucocorticoid receptor also showed a significant increase to mRNA levels in the stroma of estrogen receptor negative tumours ($p = 5.85 \times 10^{-5}$). By contrast, the estrogen receptors α and β , those most closely associated with breast tissue growth, showed no significant change in mRNA ($p = 0.372$ and 0.655 , respectively). Androgen receptor mRNA also remained unaffected ($p = 0.174$).

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1. Introduction

Breast cancer is a great source of morbidity and mortality in the developed world, being the most common cause of cancer death in Australian women and affecting roughly 1 in 10 women, with rates varying slightly by country [1,2]. The development and progression of cancers is a multi-stage process,

involving numerous perturbations to normal cellular functions, especially to those genes which control cellular growth, cellular differentiation and DNA repair [3,4]. Over time, these alterations combine to change normal cells into cancerous ones that typically no longer respond to normal control stimuli and grow with great rapidity.

Recent studies are showing that there is significant crosstalk between cancer and apparently healthy cells. These studies also indicate that the stroma of a tumour also plays a role in its development and progression and that this apparently

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healthy stromal tissue may have suffered some damage itself [5,6]. Stromal tissue may show changes which are characteristic of tumour growth well before there is any sign of abnormal morphology or behaviour in the tissue that will eventually form the tumour [7]. Studies have also indicated that the expression of genes in the stroma of a tumour may differ significantly from expression in normal, healthy tissue. These changes include the unusual expression of genes involved in wound healing and inflammation, such as desmin, smooth muscle α -actin, myosin, collagenases, and other remodeling proteins [6–9]. In tumours that are more advanced, stromal cells may show more extreme perturbations to gene expression, characterised by alterations in growth patterns and rates, though these may also be present prior to tumourigenesis and may be one of the mechanisms that assist in tumour formation [7]. There are numerous ways in which stroma and tumour can influence one another, including the release of molecules that remodel the extracellular environment directly, as well as releasing signaling molecules that affect the transcription of genes in nearby cells [6–9]. It has still not been determined if the relationship between tumour and stroma is initiated by the stroma, the tumour, both together or is capable of being initiated by either one [7,9].

The nuclear receptors are a family of proteins which accept incoming signals from various molecules, and then alter gene expression or affect cell behaviour directly [10–12]. The nuclear receptors that receive signals from hormones such as estrogen and testosterone often affect cellular growth and differentiation, and have been used as successful treatment avenues, so how these genes behave in cancer is of great interest. Studies on stromal signaling have found that estrogen can be produced and released from breast stroma into nearby tissue, inducing growth in the tumour [13]. The effects of the nuclear receptor genes vary depending on tissue and these effects can be modulated by the presence of specific co-factors in the cells, as well as the presence of different splice variants. The relative concentrations of these factors can radically change the effect of receptor stimulation, making the pathways involving these genes highly complex [14,15].

The estrogen receptor (ESR) is one of the most important factors in breast cancer. There are two forms of ESR, the products of different genes, termed ESR α and ESR β . Both ESR receptors play a large role in cellular metabolism and especially in the breast. The primary ESR form, ESR α , is a

mitogenic factor in the breast, a function which is also common to other tissues [16]. Together, the two forms modulate one another's effects, having a number of other effects, including maintaining bone density in both men and women [17]. Some advanced breast tumours will lose expression of ESR, either because the gene becomes disabled and they already produce the needed growth factors themselves or else the receptor is mutated into a permanently active state [18]. In these breast cancers the cell does not respond to estrogen stimulation and will often respond poorly to other drugs that rely on the manipulation of estrogen mediated pathways, like tamoxifen.

The progesterone receptor (PgR) has many functions in various tissues, and primarily it acts as an antagonist to several other members of the steroid receptor family, including the estrogen receptor [12]. As such, it is quite important in breast cancer, and its continued expression in a tumour is a good prognostic factor, indicating that the tumour will be more responsive to hormone based treatments [19]. The expression of PgR is up-regulated by estrogen stimulation [19], this feedback relationship serving to keep signaling from both receptors balanced. Retaining this particular mechanism of ESR control is part of what makes ESR/PgR positive tumours sensitive to hormone treatments.

Similarly to PgR, the glucocorticoid receptor (GR) is growth suppressive in the breast [20]. Part of this anti-proliferative effect may be due to an ability to promote differentiation, since activated glucocorticoid receptor has been observed to induce tissue differentiation in murine cancers [21]. Additionally, the glucocorticoid receptor has been found to be a general antagonist for estrogen in breast tissue [20]. Glucocorticoid treatments have been used in breast cancer, though like estrogen based approaches, some individuals show resistance to it. It has been observed that estrogen acts to down-regulate the expression of the glucocorticoid receptor gene [20], which may contribute to the resistance some tumours show to glucocorticoid treatment.

The androgen receptor (AR) mediates a number of functions, not only in male specific tissues, but also in other areas, including the breast and nervous system [22]. The androgen receptor is important in breast cancer because of the inhibitory effect that androgen stimulation has on breast tissue growth. This anti-proliferative effect is believed to be dependant on AR itself, rather than interaction with estrogen or ESR, due to the fact that combined

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