3. Materials and methods

We examined 14 specimens of normal breast tissue that originated from cosmetic breast surgery (mean age: 35 years; standard deviation (S.D.) 11 years); 7 specimens of normal breast tissue that originated from primary tumour containing breast mastectomy specimens (mean age: 57 years; S.D. 14 years) and 41 specimens of primary breast carcinoma (mean tumour per cent is 89%; S.D. 18%) (mean age 64 years; S.D. 6 years) for the presence of wild-type and variant hERα.

4. Results

Firstly, we found that the presence of wild-type hERα, relative to the total amount of hERα present, differs markedly ($P < 0.0001$) between normal breast tissue (median: 85% wild-type hERα; S.D. 5%) and breast tumours (median: 74% wild-type hERα; S.D. 17%). Secondly, the hERα variants with altered function that are present in normal breast tissue are mainly one-exon deleted splicing variants (median: 100%; S.D. 11%), whereas in breast tumours only half of all variants lacks just one single exon (median: 50%; S.D. 22%) ($P < 0.0001$). Interestingly, despite age effect and the presence or absence of cancer, there are no apparent differences between both groups of normal tissue.

5. Conclusions

Thus, this indicates that the higher amount and different molecular structure of the variants detected in breast cancer are specific for tumour tissue and not for the complete breast with malignant disease. Furthermore, our results suggest that hERα-dependent oestrogen responsiveness of breast tissue will change during tumour outgrowth, indicating that specific hERα variants may play a role in breast cancer development or progression.

Abstract: P27

The modulation of oestrogen receptor-alpha activity by melatonin in MCF-7 human breast cancer cells

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1. Introduction

We have previously demonstrated that the pineal hormone, melatonin, can suppress oestrogen receptor-α (ERα) gene transcription and repress the mitogenic oestrogen-response pathway in human breast tumour cells.

2. Objective

To address the relationship between the oestrogen response pathway and the growth-inhibition observed in response to melatonin. To investigate the cell signalling pathway(s) by which melatonin, via its mt1 G-protein coupled receptor, modulates ERα activity, we examined the effect of melatonin on intracellular cyclic adenosine monophosphate (cAMP) levels in MCF-7 cells.

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3. Materials and methods

MCF-7 cells were transiently transfected with an oestrogen response element (ERE)-*luciferase* reporter construct, and pretreated with melatonin (10^{-9} to 10^{-8} M) for 30 min, followed by 17β-oestradiol (10^{-9} M), or with each compound alone. Pretreatment of cells with melatonin significantly reduced the oestradiol induction of ERα transactivation as measured by changes in luciferase activity. Gel mobility shift assays demonstrated that pretreatment of cells with melatonin for 6 h, followed by oestradiol for 6 h, resulted in decreased ERα-ERE binding activity when compared with extracts from oestradiol-treated cells.

Melatonin inhibited forskolin- and pituitary adenylate cyclase activating protein (PACAP)-induced cAMP accumulation by 66 and 25% respectively. Furthermore, treatment of MCF-7 cells with pertussis toxin (an inhibitor of G-protein coupled receptors) abrogated mt1 (melatonin) modulation of ERα transactivation and cell growth, while MCF-7 cells stably transfected with and overexpressing the mt1 melatonin receptor showed a greater degree of growth-suppression in response to melatonin.

4. Conclusion

Combined with our previous data showing melatonin suppression of ERα phosphorylation, these studies suggest that melatonin directly modulates the activity of ERα. Thus, these data further indicate that, in addition to regulating signal transduction pathways that impinge on ERα expression, melatonin, via its mt1 receptor, can act as a biological modifier to affect receptor function by altering oestradiol-mediated ERα transactivation, modulating the DNA binding activity of the ERα, and by modifying ERα transcriptional regulation of growth-regulated genes to repress the growth of human breast cancer cells.

Abstract: P28

Identification of a novel human oestrogen receptor (Delta receptor) and it's chromosomal localisation

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We introduce for the first time in the literature a novel new human oestrogen receptor defined as delta (Δ) receptor. It has a molecular weight of approximately 67.5 kDa consisting of 695 amino acids. The Δ receptor has a half-life of approximately 9–16 h, and some anti-oestrogenic action. It is encoded by a gene localised to chromosome 14 in close proximity to the genes related to Alzheimer's disease. Thus, it is located on the same chromosome as oestrogen receptor (ER) β.

This new discovery could help to explain the different actions of oestrogens and anti-oestrogens (tamoxifen) in the body. We address for the first time the hypothesis that there is a new receptor with both agonistic and antagonistic effects; this will open a revolution in the field of treatment of malignant oestrogen-dependent tumours and hormone replacement therapy. The detection of this kind of receptor was carried out by monoclonal antibodies studies since there is a homology between ERΔ and ERα and ERβ.

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