BREAST CANCER

Untangling the role of progesterone receptors

The role of progesterone receptor (PR) signalling in breast cancer is complex and controversial. PR has largely been used as a marker of oestrogen receptor-α (ERα)-driven gene expression, yet some breast tumours that do not express PR still seem to have active ERα signalling. Furthermore, although synthetic progestins (which can also have androgenic activity) used in hormone replacement therapy have been linked to increased breast cancer risk, naturally occurring progesterone does not have this effect, and in cell lines that are both ERα$^+$ and PR$^+$, progesterone inhibits proliferation. Mohammed *et al.* have examined the functional interactions between these two hormone receptors in mouse and human breast tumours, and they found that activation of PR changes the pattern of ERα chromatin binding, resulting in the expression of antiproliferative genes.

> PR activation in oestrogenic conditions reduces ERα-driven proliferation

Lara Crow/NPG

In agreement with previous data, the authors confirmed that in the presence of oestrogen, treatment with progesterone or a synthetic progestin (R5020) induced a physical interaction between ERα and PR in two breast cancer cell lines (MCF-7 and T-47D). Analyses of genome-wide binding profiles of ERα using chromatin immunoprecipitation followed by sequencing (ChIP–seq) indicated that the genomic distribution of ERα changes when PR is activated by progesterone or R5020, and that the newly bound sites predominantly contained progesterone-responsive elements but not oestrogen-responsive elements, indicating that DNA binding is probably PR dependent. Moreover, the PR-dependent ERα chromatin binding sites were enriched for binding of histone acetyltransferase p300, a transcriptional co-activator. Collectively, these data suggest that the interaction between PR and ERα might affect downstream gene expression.

Indeed, expression of genes that are largely antiproliferative increased, and the resulting gene signature was associated with a good prognosis in a cohort of 1,959 patients with breast cancer.

To understand the role of PR in the context of ERα activation *in vivo*, the authors looked at MCF-7 and T-47D xenograft tumours. Tumours grown in the presence of oestrogen and progesterone were smaller than those grown in the presence of oestrogen alone, even though PR expression was induced in both cases. As in the cells grown *in vitro*, genome-wide reprogramming of ERα binding occurred in the xenograft tumours, as measured by ChIP–seq. In addition, combination treatment of xenograft tumours with an ERα antagonist (tamoxifen) and progesterone inhibited oestrogen-stimulated tumour growth more than tamoxifen alone. Similar data were obtained from primary human breast tumours grown in an *ex vivo* culture system: oestrogen promoted the growth of cells in these cultures, but co-treatment with oestrogen and R5020 slowed growth.

Further analysis of PR expression levels in human breast tumours revealed that many ERα$^+$ tumours with low PR expression have homozygous or heterozygous loss of the gene encoding PR (*PGR*). Furthermore, patients with ERα$^+$ tumours that also had *PGR* loss had a worse prognosis than those whose tumours retained *PGR*.

These data suggest that there is functional crosstalk between ERα and PR, such that PR activation in oestrogenic conditions reduces ERα-driven proliferation. Furthermore, in ERα$^+$ breast tumours that retain PR expression, PR agonists might be beneficial therapeutically.

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ORIGINAL RESEARCH PAPER
Mohammed, H. *et al.* Progesterone receptor modulates ERα action in breast cancer. *Nature* http://dx.doi.org/10.1038/nature14583 (2015)