Editorial

Understanding Oestrogen Receptor Function in Breast Cancer and its Interaction with the Progesterone Receptor. New Preclinical Findings and their Clinical Implications

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Oestrogen antagonists have been used for decades for the treatment of patients with oestrogen receptor (ER)-positive breast cancers, to the benefit of many millions of women worldwide. However, the clinical outcomes of these women vary considerably, something that has been an important focus for research, but an unresolved issue. One key observation has been that patients with ER-positive and progesterone receptor (PR)-positive breast cancers tend to have better clinical outcomes than those with ER-positive, PR-negative tumours.

PR is an oestrogen-regulated target gene and for many years the accepted explanation was that PR-positivity was a passive marker of a functional ER (Figure 1A). ER-positive, PR-positive tumours were more likely to be sensitive to treatment with ER antagonists and therefore have a better outcome. Conversely, ER-positive, PR-negative tumours were thought to have a ‘non-functional’ ER and therefore less likely to respond to anti-oestrogens.

However, recently published preclinical data [1] suggest an alternative explanation, namely that PR activity can change where ER binds to DNA, directly modulating ER function and thereby potentially improving the tumour response to ER antagonists (Figure 1B). This is important, as such combination endocrine therapies might lead to improved clinical outcomes. These new preclinical data shed new light on where ER makes contact with DNA and the importance of parallel pathways that can influence the DNA binding profile and, ultimately, activity of the ER complex in breast cancer.

Where Does Oestrogen Receptor Make Contact with DNA?

It might be thought that after stimulation by oestrogen, ER binds to DNA and regulates the transcription of genes encoded immediately adjacent to the ER binding site. In
fact, transcription factor mapping techniques [e.g.
cromatin immunoprecipitation-sequencing (ChIP-seq)] have
shown that in most cases, ER regulates its target genes from
considerable distances. ER and its associated proteins (termed
co-factors) bind to ER binding sites and, subsequently, DNA
loops form to bring this ER complex adjacent to its distant
target genes. Interestingly, when ER-positive, PR-positive (good
outcome) tumours are compared with ER-positive, PR-negative
(poor outcome) tumours, the ER DNA binding sites are distinct,
with different genes being switched on and off as a result [2].

How Does Oestrogen Receptor Make Contact with DNA? The Role of Oestrogen
Receptor-interacting Proteins

ER function is heavily influenced by ER-binding proteins,
which can make the DNA more accessible for the ER com-
plex, or assist in stabilisation of the ER–DNA interaction. A
comprehensive list of these proteins can be obtained using
unbiased techniques like rapid immunoprecipitation mass
spectrometry of endogenous protein (RIME), in which the
protein of interest is pulled out of cell lysates with an
antibody and mass spectrometry used to discover which
other proteins it physically associates with. Using this
technique, over 100 ER-binding proteins have been identi-
fied, including FoxA1 and GATA3, as would be expected [3].
Out of these, the pioneer factor FoxA1 has been found to be
essential for ER function, by stabilising ER–DNA in-
teractions. In the absence of FoxA1, ER-positive breast
cancer cells stop growing [4], revealing a dependence on
FoxA1 for ER functioning. These findings make FoxA1 itself
a major focus of research, including understanding the
structural interactions between ER and FoxA1, the role of
potential chemical FoxA1 post-translational modifications
and the discovery of chemical inhibitors that block FoxA1
function. Interestingly, in addition to the known ER-
interacting protein, PR was purified as an ER associated
protein, suggesting a putative functional role for PR in the
ER complex.

An Alternative Explanation to the ‘Non-
functional’ Oestrogen Receptor Theory

For many years, the ‘non-functional’ ER theory has been
used to explain why ER-positive, PR-negative breast can-
cers have a worse clinical outcome. However, there are
now multiple reasons to think that this theory might be
too simplistic. First, in patients with metastatic ER-
positive breast cancer, resistance to one endocrine ther-
apy does not necessarily mean resistance to another
drugtherapy; indeed, it is standard of care for pa-
tients to be managed with sequential endocrine therapy in
the absence of rapidly progressive visceral disease. Sec-
ond, we know from preclinical oestrogen-responsive
models that continued tumour proliferation is dependent
on the ER-binding protein FoxA1, implying maintenance of
a functional ER complex. In support of this, recent dis-
coversies have revealed that ER is frequently mutated in
metastases that arise from ER-positive breast cancers
[5–7] and the mutations occur in a predictable part of ER
that renders ER independent of oestrogen. These new
findings support a role for a functional, albeit constitutive,
ER complex in endocrine-resistant patients. In fact, the
non-functional ER theory has been challenged before
[8,9], but perhaps it is only now that we are able to pro-
pose a plausible alternative; namely that PR expression is
not just a passive consequence of an active ER; but that PR
can actively reprogramme ER binding to alternative sites
and PR negativity might actually contribute to an altered,
but still functional, ER complex. The loss of PR can be the
cause, not the consequence of altered ER activity and
tumour progression. An alternative explanation for low PR
levels has been identified, namely a frequent deletion in
the genomic regions that encode the PR gene (PGR),
essentially removing the PR ‘molecular handbrake’ that
can sequester and inactivate ER. This raises the possibility
that we can activate this ‘molecular handbrake’ by
Potential Clinical Significance

The potential clinical significance of these findings is clear. First, the addition of a progesterone agonist might enhance the anti-proliferative activity of anti-oestrogen therapies and therefore prove a more effective combination therapy. Clinical data already exist that suggest that the PR agonist megestrol acetate (‘Megace’) may help control tumour growth in patients with ER-positive metastatic breast cancer after aromatase inhibitor treatment failure. In a single-arm phase II study, 48 postmenopausal ‘hormone-sensitive’ patients were treated with megestrol acetate at the dose of 160 mg daily. The treatment was reasonably well tolerated and yielded a clinical benefit rate of 40%, with a median duration for this benefit of 10 months [10]. It should also be noted that there is a body of evidence supporting the use of low-dose PR agonists as supportive therapies to help ameliorate the hot flashes associated with anti-oestrogen therapy [11]. A second important motive for such combination therapy is therefore to improve the quality of life for women taking anti-oestrogens. This is even more important at a time when the intensity [12] and/or duration [13] of adjuvant endocrine therapy is being increased for many patients.

As the preclinical findings described here are translated into the clinic, a number of key questions remain. First, can we confirm in the clinic that the addition of a PR agonist enhances the anti-proliferative activity of anti-oestrogen therapy? Second, what is the lowest dose of progesterone therapy that can achieve a significant biological effect with an acceptable side-effect profile? Third, and most importantly, can the combination of a PR agonist with an ER antagonist improve clinical outcomes for both metastatic and early stage breast cancer patients. Clinical trials are currently being set up to test these and other questions, in an attempt to improve the outcome for millions of patients diagnosed with ER-positive breast cancer every year.

References