EORTC-NCI-AACR Symposium Press Information

Scientists identify potential new target for treating triple negative breast cancer

Scientists believe they may have found a new target for treating triple negative breast cancer – one of the more difficult breast cancers to treat successfully and for which there is no targeted therapy at present.

Triple negative breast cancer (TNBC) is a cancer that does not express receptors for oestrogen (ER), progesterone (PR) or the human epidermal growth factor (HER2). It tends to be more aggressive, occurs more often in younger women, and is difficult to treat successfully as it lacks the receptors that currently available targeted therapies such as tamoxifen and trastuzumab (Herceptin) can home in on. Surgery, followed by chemotherapy, is the usual treatment.

Now researchers in Dublin (Ireland) have found that TNBC cells respond to compounds that disrupt the signalling processes of another receptor, EGFR (epidermal growth factor receptor), high levels of which are expressed in TNBC. In a presentation to the 22nd EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Berlin today (Wednesday), Dr Patricia McGowan, a senior postdoctoral scientist at University College Dublin, said the compounds had reduced the growth of TNBC cells in the laboratory by up to 91%.

“As these cancers possess high levels of EGFR, we thought that they may be dependent on EGFR signalling,” she said. “ADAMs (a disintegrin and metalloprotease) are enzymes that are involved in the activation of EGFR binding-proteins (i.e. ligands) during the signalling process, and so we thought that inhibiting them might be a potential therapeutic option for TNBC, either alone or in combination with drugs that target EGFR, such as gefitinib.”

Dr McGowan and her colleagues tested gefitinib and a compound that specifically inhibits ADAM17 on breast cancer cell lines. The compound, known as TMI-002 (Pfizer), was similar to gefitinib in its ability to inhibit the growth of cancer cells. Gefitinib is not used in breast cancer treatment at present, but the researchers tested it to see whether inhibiting ADAM and EGFR simultaneously would work synergistically. “We did not observe any additional benefit when we combined the ADAM inhibitor with gefitinib; however, adding gefitinib 72 hours after ADAM inhibitor treatment was more effective than adding both inhibitors simultaneously, although this did not reach statistical significance.”

In addition, another, as yet un-named compound that blocks both ADAM10 and ADAM17 resulted in significant effect on a range of TNBC cell lines. “We found that it reduced the growth of these cells by up to 91%,” she said. “We have also found that treatment of TNBC cells with this compound reduced their ability to migrate, a process that is vital for the progression of cancer.

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“Triple negative breast cancers comprise 10-20% of all breast cancer cases. Women with TNBC

tend to present with higher grade, larger tumours, are younger at diagnosis, have a higher incidence of metastases and have a shorter time to recurrence compared to other breast cancer types. One reason for the poor prognosis for this group is the lack of targeted therapies for these women. Having found that an ADAM inhibitor can reduce the proliferation of TNBC cell lines, we hope that ADAMs may be a useful therapeutic target."

The scientists hope that inhibiting ADAMs might also be a possible treatment for other cancers in which members of the EGFR 'family' are active. In addition to EGFR, the 'family' consists of HER2, HER3 and HER4, and these are implicated in a number of cancers such as lung, colorectal, head and neck, and pancreatic cancers.

"Theoretically, inhibiting ADAMs should block downstream signalling from all four EGFR family members and thus potentially reduce cancer progression. We are excited that we have seen an effect in this particularly aggressive subgroup of breast cancers but propose that we will see an effect in other cancer settings also," said Dr McGowan.

"We hope to expand our investigation of these compounds using a larger panel of cell lines, moving into animal models, and eventually into clinical trials."

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Abstract no: 129. Poster on Wednesday 17 November in the Exhibition Hall (ground level) from 08.00/09.00 hrs to 18.00 hrs CET.

Notes:
[1] EORTC [European Organisation for Research and Treatment of Cancer, NCI [National Cancer Institute], AACR [American Association for Cancer Research].
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