New research could provide key to overcoming resistance to HER2 targeted cancer treatments

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Scientists from the School of Pharmacy & Pharmaceutical Sciences, Trinity College Dublin have made a significant discovery of a new biomarker which may help overcome resistance to newer and more targeted anti-cancer drugs, such as Herceptin, for HER2 positive cancers. These findings may also help the early identification of patients who will benefit more from these treatments.

The researchers, led by Professor Lorraine O'Driscoll, Associate Professor of Pharmacology, Trinity, studied breast cancer cells and their extracellular vesicles (exosomes), which are 'packages' of information released out of cells. They discovered a molecule called Neuromedin U (NmU) which is strongly associated with resistance to the new anti-cancer drugs for HER2 positive cancers. This suggests NmU could be used as a biological marker to indicate the likelihood of responsiveness in a particular patient and may also be very important in the management of resistance to these drugs. The findings have just been published in leading international, peer reviewed journal: *Cancer Research*, the most frequently cited cancer journal in the world.

About one quarter of breast cancer patients are known as being HER2 positive, where the protein HER2 is found at greater amounts on cancer cells compared to normal cells and which is associated with a poorer prognosis for the patient. A relatively new range of targeted anti-cancer drugs became available in recent years to treat patients with HER2

positive breast cancer and some other cancers such as HER2 positive gastric cancer. The best known one is Herceptin (trastuzumab), but there are other newer drugs in this family, including lapatinib, neratinib, afatinib, pertuzumab, T-DM1.

Speaking about the challenges some patients face with these newer anti-cancer drugs, Professor O'Driscoll said: "Many patients with HER2 positive tumours gain huge benefit from these drugs. Unfortunately, however, some who seem suitable candidates based on a HER2 test, don't gain the maximum intended benefit from these treatments. They may have a natural level of resistance to the treatment which is not detectable with currently available tests, while some other patients respond at first but may then become unresponsive or develop resistance to the treatments."

Professor O'Driscoll continued: "Clinicians urgently need ways of predicting which patients with 'HER2 tumours' are likely to gain real benefit, both to ensure patients are given the optimal treatments and to ensure these very costly drugs are used where they will have the most benefit. Our discovery may offer a new way to predict or identify both innate and acquired resistance, overcome it and potentially block or prevent resistance. This would allow patients to get the full benefit from these particular anti-cancer treatments and help other patients to be more quickly identified and receive the treatment options which are more appropriate for them."

The scientists also found that the levels of NmU outside the cells reflects that within the cells indicating it may be used as an 'extracellular' blood-based marker. This could allow clinicians to access and sample the levels of NmU through a minimally-invasive blood test compared to testing biomarkers within tissues.

They also found that by tweaking NmU's amounts in the cells, they could

restore sensitivity to this family of anti-cancer drugs and offer an approach which may help prevent or overcome the serious resistance problem.

The research team conducted other studies which found that blocking NmU also significantly slowed the tumour's growth in the body and they plan to conduct further studies in this area.

The intellectual property has been protected to facilitate the translation of these discoveries to the benefit of patients with two patents pending in Europe and the US. This will be aided by the team's collaboration with the All Ireland Oncology Research Group (ICORG).

More information: cancerres.aacrjournals.org/con … CAN-13-2053.abstract

Provided by Trinity College Dublin