UNLOCKING BREAST CANCER TUMORS' DRUG RESISTANCE

A troubling phenomenon in breast cancer treatment is that some patients' tumors become resistant to treatments over time. Scientists at the University of Cincinnati in Ohio are researching a nanotechnology-based method of discovering why this happens to help physicists develop new treatments for those patients. Recently, their efforts were supported by a $450,000 grant from ‘Susan G. Komen for the Cure®’. The latter is the world’s largest breast cancer organization, as well as the largest source of nonprofit funds dedicated to fighting breast cancer with more than $1.9 billion invested to date.

The vast majority—about 75%—of human breast cancer patients have estrogen receptor (ER)-positive tumors, explained Xiaoting Zhang, the postdoctoral fellow and assistant professor of Cancer and Cell Biology, who is heading the University of Cincinnati research team. Zhang said that selective estrogen receptor modulators (SERMs), such as tamoxifen and the aromatase inhibitor letrozole, have been used in the treatment of these patients.

"Unfortunately, up to half of all ER-positive tumors either do not respond to these hormonal therapies or, after initial successful treatment, the tumors recur as endocrine-resistant breast cancer," noted Zhang, who added that it has been recognized that activation of the tyrosine kinase HER2 is one of the major mechanisms contributing to endocrine resistance. "However, although blockage of ErbB-2/HER2 with the monoclonal antibody trastuzumab (Herceptin) has been successfully used as a second-line treatment, again, the resistance to this therapy is also quite high. Hence, further development of novel strategies to selectively block the activities of these pathways to treat HER2 and ER-positive breast cancer is urgently needed."

The academic scientist said that greatest challenges in this research are to find the proper therapeutic target and a suitable delivery system to target it. "I think we have identified both and are in a very good position to carry this research forward." Zhang and his colleagues previously showed that transcriptional coactivator MED1 is required for estrogen receptor-dependent transcription and estrogen-dependent breast cancer cell growth. To further study
the role of MED1 in human breast cancer, the University of Cincinnati researchers stained MED1 for its protein expression using human breast cancer tissue microarray.

"Our statistical analyses revealed that MED1 expression levels are highly correlated with HER2 positive status of the human breast cancer tissue samples examined," reported Zhang. This is consistent with previous studies indicating the MED1 gene is localized at HER2 amplicon and often co-amplified with HER2. The team’s further studies indicate that MED1 is not only over-expressed, but also activated by HER2 signaling pathway in human breast cancer. "Importantly, we found that knockdown of MED1 significantly sensitized HER2 over-expressing cells to tamoxifen treatment," stressed the university professor.

These results indicate MED1 as a novel key downstream crosstalk point of ER and HER2 pathways and suggest that targeting MED1 could simultaneously block these two pathways, thus overcoming the resistance of tumors to current endocrine and anti-HER2 therapies. "Furthermore, it is well known that the currently used hormonal therapeutic agents often elicit severe unwanted side effects in other normal estrogen-responsive tissues (for example, uterus and bone), even in patients who have benefited from the current endocrine therapies," pointed out Zhang. "Our most recent studies published in PNAS showed that MED1 plays a rather tissue-specific role in vivo in mediating estrogen receptor functions in breast, but not in uterus and bone, suggest that targeting MED1 could also potentially overcome these unwanted side effects of current medicine."

In this particular study, Zhang and company will combine RNA nanotechnology with recent advancement of small RNA biology to target MED1. "It has traditionally been hard to target these transcriptional co-activators by small molecules because their lack of enzymatic activities," he explained. "Recent discoveries of RNAi technology have made it possible to specifically target the RNA transcript of any desired gene to block their protein expression. It is naturally fitting that we choose to deliver the small interference RNA against MED1 into cancer cells by using a pRNA nanodelivery system derived from phage phi29 because this will form a drug delivery system composed of all RNAs."

The Cincinnati scientist cited a number of practical advantages of devising a whole RNA system as a drug delivery system. Most notably, RNAs are known to
elicit little or no immune response, unlike other macromolecules. Importantly, recent advancement in RNA nanotechnology field has allowed the generation of stable RNA nanoparticles in vivo with highly desirable pharmacokinetics and dynamics. "To specifically target this nano drug delivery system into cancer cells, we will conjugate folate that binds folate receptor, which is highly expressed in cancer cells to this system. In addition, we are also currently developing a RNA-based tool to directly bind HER2 receptor or its partner EGFR for the delivery of this nanodelivery system into HER2 positive type of breast cancer," remarked Zhang.

The University of Cincinnati professor’s research in this area began with the support of a Joanne and Michael Masin Young Investigator Award from the Breast Cancer Alliance of Greenwich, CT. Since then, Zhang has been supported by the Hormone Research Foundation, Komen for the Cure Foundation, a University of Cincinnati Cancer Center startup and pilot grant, and a Ride Cincinnati award. "With this support, I have been able to extensively investigate the basic biology of transcriptional cofactor MED1 in breast cancer and publish a number of papers in the journals such as Molecular Cell, PNAS, EMBO J, Endocrinology, and Journal of Biological Chemistry," he commented.

Based on the information obtained in these basic research studies, Zhang and his colleagues are convinced that MED1 represents a unique opportunity for breast cancer treatment. Therefore, the team has decided to take on more translational approaches to directly target this protein for breast cancer therapy. Their current research is supported, in addition to the Komen Award, by a Department of Defense Breast Cancer Research Program IDEA Award, University of Cincinnati Center for Clinical and Translational Sciences Junior Investigator Award, and seed money from the Ohio Cancer Research Associates.

"We should have a laboratory prototype of this nano delivery system within a year or so and have it tested both in vitro and in vivo in animal models in the next 2 to 3 years," said Zhang.

When asked what trends he sees using nanotechnology to create innovative drug delivery systems, the academic research replied, "I would see people taking advantage of recent advances in RNA nanotechnology and increasingly using RNA as a nanoplatform for therapeutic purposes. In addition, I would see people further exploiting the multivalent nature of RNA nanotechnology
and building different aspect of therapeutic functions (tumor cell targeting, disruption of drug target functions, and combined therapy through directly crosslinking with current medicine (for example, hormonal- and chemotherapeutic drugs)) into one delivery system."

Zhang offered some advice to technology developers to meet these trends in RNA nanotechnology. "It is critical to be able to synthesize large scale (at least milligram level), long RNA (> 100nt) at high quality and low price. It is also important to develop the technology to increase the efficiency and decrease the cost for crosslinking additional chemical moieties such as above hormonal and chemotherapeutic drugs to the RNA."

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