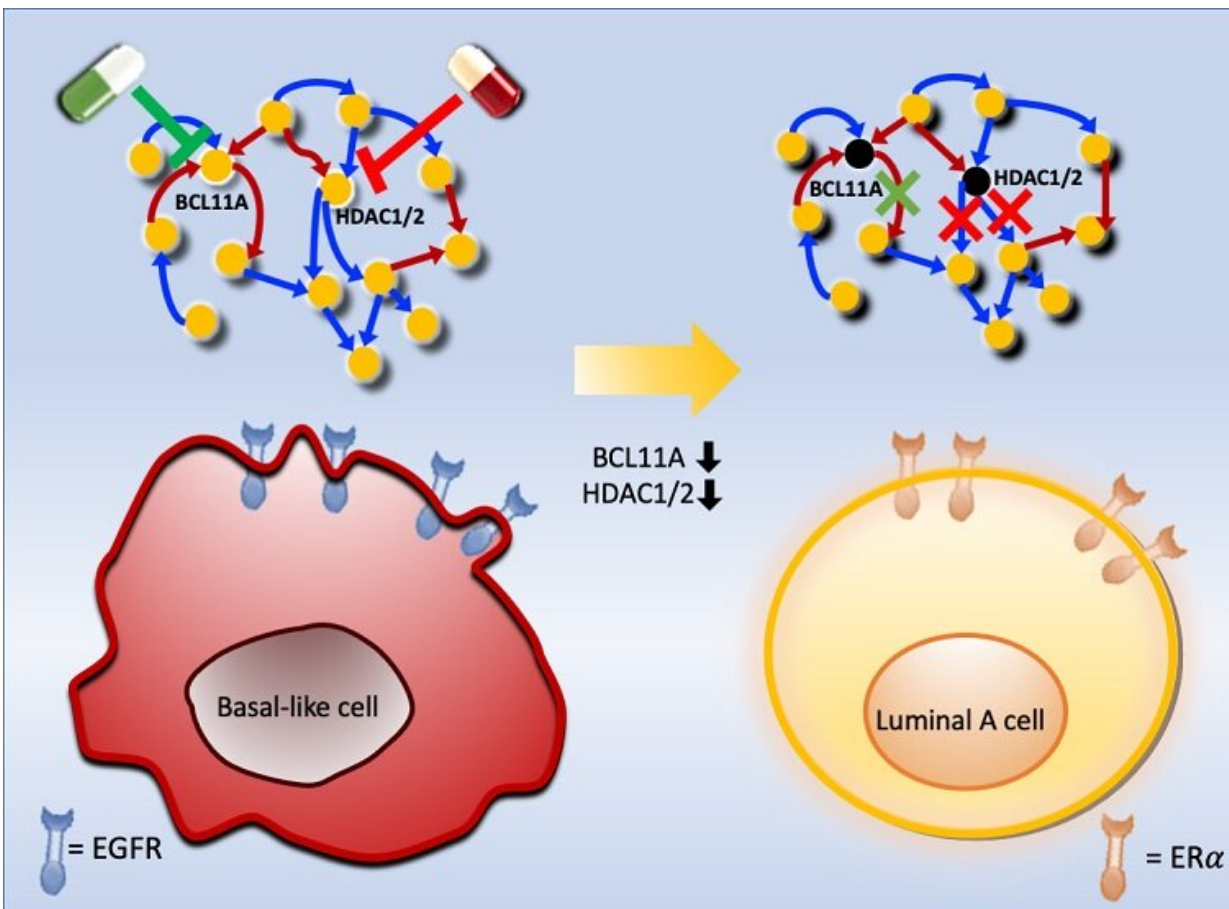


Connecting the dots to find new treatments for breast cancer

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Professor Kwang-Hyun Cho and colleagues have developed a mathematical model and identified optimal targets reprogramming basal-like cancer cells into hormone therapy-responsive luminal-A cells by deciphering the complex molecular interactions within these cells through a systems biological approach. Credit: Korea Advanced Institute of Science and Technology

Scientists at KAIST believe they may have found a way to reverse an aggressive, treatment-resistant type of breast cancer into a less dangerous kind that responds well to treatment. The study involved the use of mathematical models to untangle the complex genetic and molecular interactions that occur in the two types of breast cancer, but could be extended to find ways for treating many others. The study's findings were published in the journal *Cancer Research*.

Basal-like tumors are the most aggressive type of [breast cancer](#), with the worst prognosis. Chemotherapy is the only available treatment option, but patients experience high recurrence rates. On the other hand, luminal-A [breast cancer](#) responds well to drugs that specifically target a receptor on their cell surfaces, called estrogen receptor alpha (ER α).

KAIST systems biologist Kwang-Hyun Cho and colleagues analyzed the complex molecular and genetic interactions of basal-like and luminal-A breast cancers to find out if there might be a way to switch the former to the latter and give patients a better chance to respond to treatment.

To do this, they accessed large amounts of cancer and patient data to understand which genes and molecules are involved in the two types. They then input this data into a [mathematical model](#) that represents genes, proteins and molecules as dots and the interactions between them as lines. The model can be used to conduct simulations and see how interactions change when certain genes are turned on or off.

"There have been a tremendous number of studies trying to find therapeutic targets for treating basal-like breast cancer patients," says Cho. "But [clinical trials](#) have failed due to the complex and dynamic nature of cancer. To overcome this issue, we looked at breast cancer [cells](#) as a complex network system and implemented a systems biological approach to unravel the underlying mechanisms that would allow us to reprogram basal-like into luminal-A breast cancer cells."

Using this approach, followed by experimental validation on real breast cancer cells, the team found that turning off two key gene regulators, called BCL11A and HDAC1/2, switched a basal-like cancer signaling pathway into a different one used by luminal-A cancer cells. The switch reprograms the cancer cells and makes them more responsive to drugs that target ER α receptors. However, further tests will be needed to confirm that this also works in animal models and eventually humans.

"Our study demonstrates that the systems biological approach can be useful for identifying novel therapeutic targets," says Cho.

The researchers are now expanding its breast cancer network model to include all breast cancer subtypes. Their ultimate aim is to identify more drug targets and to understand the mechanisms that could drive drug-resistant cells to turn into drug-sensitive ones.

More information: Sea R. Choi et al, Network Analysis Identifies Regulators of Basal-Like Breast Cancer Reprogramming and Endocrine Therapy Vulnerability, *Cancer Research* (2021). [DOI: 10.1158/0008-5472.CAN-21-0621](https://doi.org/10.1158/0008-5472.CAN-21-0621)

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