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High throughput microscopy quantifies regulation of estrogen receptor

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High throughput microscopy that uses robots and special microscopes and techniques to generate thousands of images of a cell in a short time enabled researchers at Baylor College of Medicine in Houston to describe how the genetic message of estrogen receptor-alpha is regulated, a finding that could have implications for breast cancer.

In a report in the current issue of the Public Library of Science-ONE, Dr. Michael A. Mancini and his colleagues showed that estrogen receptor-alpha's response depends on the manner of regulation.

"All of this is leading to personalized medicine, said Mancini, associate professor of molecular and cellular biology at BCM and director of the Integrated Microscopy Core at the College. "We will some day be able to get functional assays of this kind on individual people. We have laid the groundwork to do patient samples."

Estrogen receptor activity is regulated in two manners. One is called ligand- or steroid-dependent in which the receptor has to bind to a small molecule to become active. The other is independent of the ligand and requires the action of another kind of molecule, such as a growth factor to become active.

Mancini, also a researcher in the Dan L. Duncan Cancer Center at BCM, and Dr. Valeria Berno, a postdoctoral associate in his lab, along with colleagues established a system that allows multiple quantitative "single-cell" analyses of how estrogen receptor regulates that transcription of

genetic messages. (Transcription refers to the translation of a genetic message into the protein that carries out a function within a cell. Various factors can influence the extent to which such messages are translated within the cell).

The cell line contained elements that lit up when estrogen receptor is activated. The estrogen receptor was marked with a green fluorescent protein. When it lights up, it enables researchers to “see” through a microscope the actions of a protein on the estrogen receptor.

The technique allowed them to see the receptor move in and out of the nucleus, bind to DNA and remodel the chromatin molecule that makes up the cell’s chromosomes.

The system enabled them to differentiate the manner in which estrogen receptor responded to a ligand (estradiol) and to a growth factor (epidermal growth factor).

“This would never have been possible without the combination of manual and high throughput microscopy,” said Mancini. The high throughput approach involves using a robot to fix slides with cells, stain them, put them under a microscope, focus and take photographs.

“You put it in the microscope, come back and all the pictures are taken,” said Mancini. This particular experiment involved tens of thousands of such photographs, he said.

“You can look at DNA occupancy of receptor and coregulators, chromatin modeling and transcription (the translation of the genetic message) at the same time in the same image, this is a good example of why the approach is being called “high content analysis” he said. “What is really exciting is not only how fast we can collect the data, but the image analysis toolbox is expanding at a remarkably fast rate. This is the

beginning of high throughput systems biology."

Maureen Mancini, a research associate at BCM, helped overcome a major hurdle by making the cell line that allowed the scientists to see what was happening.

"We are able to look at the receptor affected by the two different types of stimulation. They are now distinguishable because of this research," he said.

Source: Baylor College of Medicine