With CryoEM, researchers obtain exquisite view of the androgen receptor, a key protein in prostate cancer

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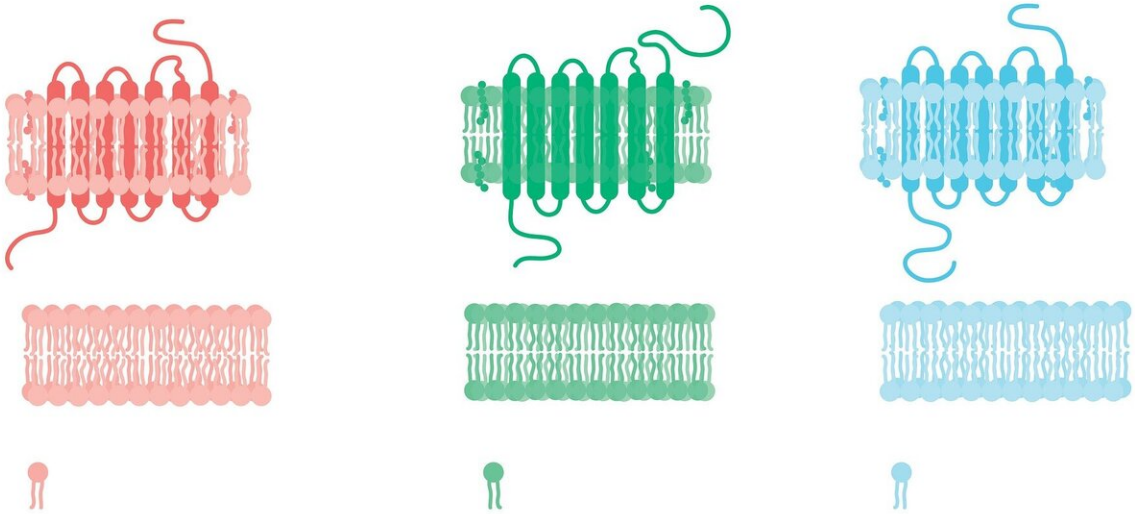

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Scientists at Memorial Sloan Kettering Cancer Center (MSK) have glimpsed never-before-seen details of the human androgen receptor—the protein inside of cells that responds to male-typical hormones like testosterone. Their research, published April 20, 2022, in the journal *Molecular Cell*, identifies unique features of the receptor that distinguish it from other hormone receptors and provide clues to how

androgen signaling goes awry in prostate cancer.

"We know a lot about the androgen receptor from studies conducted at the level of about 10,000 feet," says Charles Sawyers, Chair of the Human Oncology and Pathogenesis Program at MSK who researches the biology and treatment of prostate cancer. "But to get close to the real action, you need to go down to the atomic level, and we were able to get much closer to that goal with this study."

To obtain this closer look, Dr. Sawyers partnered with Elizabeth Wasmuth, a structural biologist who did her graduate work at the Sloan Kettering Institute and is now doing a joint postdoctoral fellowship at MSK and The Rockefeller University. Dr. Wasmuth has expertise in using cryo-electron microscopy (cryoEM) to study the atomic details of molecules and is interested in using that knowledge to solve long-standing problems in cancer biology.

"People have been trying for years to get structural data of the androgen receptor, but it's been super challenging," Dr. Wasmuth says. "Basically, for this study, we had to throw the whole kitchen sink at it."

A eureka moment

One of the biggest challenges was the fact that the androgen receptor by itself does not dissolve readily in solution, which is a precondition for being able to use cryoEM to visualize it. Instead, gobs of the receptor remain stuck together in a kind of "snot ball," Dr. Sawyers says.

What he calls a "eureka moment" came when they added another protein into the mix—a known cancer-causing protein called ERG. Just like that, the combination went into solution. "Suddenly we had something to look at," he says.

There were still many challenges to overcome, and the researchers had to be resourceful. In addition to MSK's cryoEM, the team also relied on cryoEM instrumentation at the New York Structural Biology Center, Rockefeller, and the Janelia campus of the Howard Hughes Medical Institute.

New explanations for old observations

The androgen receptor is what's called a nuclear hormone receptor. It moves between the cell cytoplasm and the nucleus, where it turns on genes that maintain male-typical features. The conventional model for how nuclear hormone receptors work is that they basically form two main shapes. One shape predominates when the receptor is inactive and floating free in the cytoplasm; the other shape forms after an androgen hormone binds to it. That duplex then moves into the nucleus, where it binds to DNA and turns on genes. This how the estrogen receptor is known to work, for example.

By contrast, the cryoEM pictures that Dr. Wasmuth obtained showed that the androgen receptor was far more flexible in the shapes it could form. In particular, it could form different DNA-binding shapes, enabling it to turn on a wide range of genes, depending on which conformation it was in—something not seen before in this family of receptors.

"The androgen receptor doesn't follow the rules," Dr. Wasmuth says.

The different three-dimensional shapes created by these movements also allow the androgen receptor to interact with other proteins that change its shape—so-called allosteric interactions. One protein it can interact with in this way is ERG, a main driver of prostate cancer.

This shape-shifting ability helps explain some long-standing observations

about androgen hormones, including the fact that they play many roles in development and adulthood. The androgen receptor is simply more versatile in the sets of genes it can turn on compared with other nuclear receptors. In fact, recent findings even suggest that it can affect T cell responses to immunotherapy.

What's next for this research?

While the pictures they've assembled of the androgen receptor are the most detailed to date, the researchers hope to improve on these results, by going down to even deeper atomic resolution. Once they do, it might be conceivable to think about designing drugs to block particular movements of the androgen receptor—to prevent its interacting with ERG, for example.

Being able to conduct such interdisciplinary studies, where scientists from different fields can closely collaborate, scientists say, is a unique feature of the research environment at MSK, including the Sloan Kettering Institute and The Rockefeller University.

"It speaks to the culture and community in the amazingly rich research triangle here on 68th Street," Dr. Sawyers says.

"I really don't think this work could have been on anywhere else, to be honest," Dr. Wasmuth adds.

More information: Elizabeth V. Wasmuth et al, Allosteric interactions prime androgen receptor dimerization and activation, *Molecular Cell* (2022). DOI: 10.1016/j.molcel.2022.03.035

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