Researchers discover new way to attack drug-resistant prostate cancer cells

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In most cases, prostate cancer is cured by surgical removal of the tumor and/or by radiotherapy. However, 20% of patients will need treatment to remove tumor cells but this treatment ceases to be effective after two or three years and the cancer develops further. Once this stage of the disease has been reached, there is no cure. A team headed by Xavier Salvatella, ICREA researcher at the Institute for Research in Biomedicine (IRB Barcelona), has discovered a new avenue through which to attack prostate cancer cells that have developed drug-resistance. Published in the journal *Structure*, part of the Cell group, the study opens up new therapeutic avenues against a disease that causes 75,000 deaths a year in Europe alone (source: European Science Hub, 2015).

A clear target and new sites of attack

The survival and proliferation of prostate tumor cells calls for highly active androgen receptor protein. The drug used to remove tumor cells interferes with this protein by binding to a specific region of the receptor and blocking its activity. “Over time, the protein accumulates alterations and mutates, and there comes a point where it is futile to target this region with drugs because, in fact, it is no longer there,” says Salvatella.

The Molecular Biophysics Laboratory, headed by Salvatella, studies the tridimensional structure and atomic movements of the androgen receptor, with the aim to find new binding sites. It has been known for some years that the protein has a small region, spanning only 20 amino acids, that is important for

tumor cell survival. The study now describes for the first time that this region—usually without a structure and therefore a priori disregarded as a drug target—has a helix shape. Upon gaining this helix—it is not known how the helix occurs—, another protein, called TFIIF, binds to it. The study reveals that this interaction stimulates the activity of the androgen receptor and, consequently, facilitates the survival and multiplication of tumor cells.

To this 20-residue motif in the androgen receptor the IRB Barcelona teams now adds the protein TFIIF as a potential therapeutic target for prostate cancer. “The fact that TFIIF is a folded protein with a more defined structure makes it easier to search for drugs that can interfere with its interaction with the motif. For prostate tumor cells that have become resistant to treatment, we believe that this interaction could be their last mechanism through which to survive and proliferate,” explains Salvatella.

“Using cells in vitro, we have seen that if we remove this region, the TFIIF protein can’t bind to the androgen receptor. So if the interaction does not occur, the androgen receptor loses activity, which is what we are interested in achieving,” says Elzbieta Maria Szulc, “la Caixa” PhD student at IRB Barcelona and co-first author of the study with Eva de Mol, a former “la Caixa” PhD student in the same lab who started this line of research.

In collaboration with experts in computational modeling, the scientists are searching for drugs that interfere with TFIIF. “We don’t know whether such drugs will have a positive effect on cells, but the data available is promising,” says Salvatella.

Source:

https://www.irbbarcelona.org/en/news/closing-in-on-advanced-prostate-cancer