Protein folding becomes cancer treatment target

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(Medical Xpress)—A molecule that helps cancer cells to keep dividing could be a promising target for new treatments, according to research published in the journal *Oncogene*.

The Cancer Research UK-funded study looked at molecules in our cells that make sure proteins are folded properly, known as chaperones. The researchers examined the chaperone HSP90, responsible for helping to fold proteins that control cancer cell division. They revealed crucial new details about how the chaperone works alongside a partner – called CDC37 – to carry out its job and keep cancer cells growing.

Until now, researchers have focused their efforts on designing drugs to

block CDC37's role in protein folding by disrupting the way it interacts with HSP90. But this new research, carried out by scientists at the Cancer Research UK Cancer Therapeutics Unit at The Institute of Cancer Research, London, reveals the two players can act independently when folding cancer-causing proteins, thus changing the view about how best to attack them.

Proteins are the 'work-horses' of cells, carrying out all kinds of jobs, from supporting a cell's structure to creating energy, sending messages and repairing damaged DNA. In order to function correctly, proteins need to have a certain shape – this is where chaperones step in to help. Chaperones fold proteins into the right shape and keep them stable, which is critical for them to work properly.

Cancer cells divide very rapidly and the proteins that perform this task and keep the cells growing rely upon chaperones to fold correctly. By blocking the machinery that folds the proteins into the right shape, it should be possible to stop the cancer cells from growing. And because cancer cells are far more reliant on chaperones than normal cells, it should be possible to attack tumours without harming healthy tissue.

The same team has already been successful in discovering drugs that work on HSP90, with one of these – AUY922 – showing promise in the clinic. But chaperones do not operate alone. They rely on partner molecules, such as CDC37, so targeting these might be an alternative way to stop the chaperones working.

Study author Professor Paul Workman, Cancer Research UK Life Fellow and deputy chief executive of The Institute of Cancer Research (ICR) said: "Chaperones help stabilise the proteins that cancer cells need to divide and multiply, which means they present an exciting target for new treatments. We've been successful in designing drugs that work against the HSP90 chaperone and these look very promising in the clinic.

"Our new study has revealed critical details about the way HSP90 and CDC37 work together, which could be fundamental in designing drugs that target this partnership. It shows for the first time that, although both are needed to fold cancer-causing proteins, HSP90 and CDC37 do not necessarily have to bind to each other directly and so cancer cells can get around blocking their interaction. We now know that we'll need to develop new approaches."

Dr Kat Arney, science information manager at Cancer Research UK, said: "There's still a lot to learn about the various roles played by chaperones and their supporting molecules. But if we widen our net to target more of these molecules we may discover new ways of stopping cancer cells from multiplying.

"Because they divide rapidly, cancer cells are heavily dependent on chaperones, providing a weakness for us to target. Drugs that block these molecules might give us a way to stop cancers from growing any further and, combined with other treatments, give patients an even better chance of beating the disease."

Smith, J. R., et al. Restricting direct interaction of CDC37 with HSP90 does not compromise chaperoning of client proteins. *Oncogene*, 2013. DOI: 10.1038/onc.2013.519

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