Molecular discovery puts cancer treatment in a new perspective

July 11 2013

Researchers from the University of Copenhagen and the National Institutes of Health have obtained ground-breaking new knowledge about proteases - important enzymes which, among other things, play a role in the development of cancer cells. The findings may be significant for the development of cancer drugs, and have just been published in *Journal of Biological Chemistry*.

Cancer cells can exploit an over-production of proteases to force their way into the body.

In a joint effort with the National Institutes of Health, a group of researchers from the University of Copenhagen have taken a step closer to being able to design a more effective anticancer treatment by mapping a previously unknown molecular mechanism.

The group has been working with proteases, important enzymes which are responsible for maintaining different types of tissues in the body while also being involved in many -diseases, including cancer. Cancer cells can exploit an over-production of proteases to force their way into the body so they can quickly grow and create a space for themselves in which to spread.

"So far, we have been unable to treat cancer patients with drugs which can effectively stop cancer cells from spreading, but having now discovered that an important function of proteases has been overlooked, we have the possibility of designing new drugs. So far, cancer drugs have

primarily been shaped to stop the proteases from cleaving and thereby activating processes, but this is probably insufficient. Surprisingly, our studies show that proteases perform another function in addition to cleaving; they are also able to bind to one another, besides from cleaving, and kick-starting various cellular processes," says Stine Friis, a postdoc at the Department of Cellular and Molecular Medicine at the University of Copenhagen. She has spearheaded the new research in collaboration with the National Institutes of Health.

Overlooked functions for proteases

One example of proteases making a positive difference is in connection with wound healing. When tissue is damaged, a molecular mechanism starts whereby a protease cleaves and activates the next protease, which then cleaves and activates a third protease, and so on. In other words, it sets off a repair mechanism – a kind of domino effect whereby a single protease can issue a small signal to a whole string of proteases. However, this mechanism can also be exploited by cancer cells, enabling them to spread.

"My generation of molecular biologists learned that proteases are enzymes which are capable of cleaving and activating other proteases, and that this molecular mechanism – called proteolysis – is their sole function. However, our new research findings show that proteases have functions which until now have been overlooked. Yet the key to designing effective drugs is to understand all the molecular mechanisms that make the cancer grow," says Stine Friis.

Bind instead of cleave

More specifically, the research group has worked with two proteases, matriptase and prostasin, which are both essential for maintaining

healthy cells in the skin, intestines and other organs. However, in contrast to what has so far been believed, the two proteases do not activate one another by one cleaving the next, i.e. through proteolysis. In fact, prostasin's role in activating matriptase is surprisingly independent of this mechanism. Instead of cleaving one another, the two proteases bind to each other, which is most unusual, and thereby start important processes.

Through knowing about this previously overseen but vital function of how proteases activate the cell's signals, researchers hope to improve our understanding of how proteases operate in the body. And not just in normal circumstances, but also in situations where something malfunctions with the protease balance, such as in cancer.

"Hopefully our new findings will inspire others to think outside the box, opening the doors to innovation with drugs aimed at regulating protease activity, such as anticancer drugs. The drugs we design today are developed to halt the cleaving process, but even though it is stopped, some proteases can apparently continue to transmit signals by binding to instead of cleaving one another. If we can stop the binding, we should be able to develop better drugs, which in the long term will bring us closer to developing successful cancer treatments. If you only understand how one half of an engine functions, it's almost impossible to repair it," says Stine Friis.

About proteases

Proteases are important enzymes which, among other things, play a role in the development of cancer cells. The proteases in our bodies are active all the time. In connection with wound healing, the process of proteolysis is initiated to repair the damaged tissue.

Proteolysis is the molecular mechanism whereby a protease cleaves and

activates the next protease, which then cleaves and activates a third protease, and so on. The mechanism is a kind of domino effect, whereby a single protease can issue a little signal to a whole string of proteases.

It is important to have balanced protease levels – when they are out of balance and there is too much of them, things go wrong.

Researchers have produced models of mice with excessive levels of the proteases matriptase and prostasin, and those mice with too much protease develop a predisposition to skin cancer. The mice are used to study proteolysis.

Cancer does not necessarily develop in all cases where the mice have excessive protease levels, but when it specifically involves matriptase and prostasin, it does. Previous research has also shown that cancer patients have raised matriptase levels.

Provided by University of Copenhagen