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Protein 'map' could lead to potent new cancer drugs

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Imperial chemists have gained fresh insights into how a disease-causing enzyme makes changes to proteins and how it can be stopped.

The scientists hope their findings will help them to design drugs that could target the enzyme, known as N-myristoyltransferase (NMT), and potentially lead to new treatments for cancer and inflammatory conditions.

They have already identified a molecule that blocks NMT's activity, and have identified specific protein substrates where this molecule has a potent impact.

NMT makes irreversible changes to proteins and is known to be involved in a range of diseases including cancer, epilepsy and Alzheimer's disease.

In a study published in the journal *Nature Communications* chemists used living human cancer cells to identify more than 100 proteins that NMT modifies, with almost all these proteins being identified for the very first time in their natural environment.

The scientists mapped all of the proteins and also established that a small drug-like molecule can block the activity of NMT and inhibit its ability to modify each of these proteins, suggesting a potential new way to treat cancer.

Lead researcher Professor Ed Tate, from the Department of Chemistry

at Imperial College London said: "We now have a much fuller picture of how NMT operates, and more importantly how it can be inhibited, than ever before. This is the first time that we have been able to look in molecular detail at how this potential drug target works within an entire living cancer cell, so this is a really exciting step forward for us."

"This 'global map' allows us to understand what the effects of inhibiting NMT will be. This means we can determine which diseases it might be possible to combat by targeting NMT, enabling us as a next step to explore how effective such treatments could be," added Professor Tate.

The researchers spent several years developing a specialised set of tools to identify and examine NMT and the proteins it changes. They began by conducting a detailed large scale study exploring proteins under the control of NMT, but the scientists still needed information on the function of these proteins and how they are modified.

Next they used mass spectrometry to quantify the effect of a NMT inhibitor molecule. To examine this interaction, they induced a process called apoptosis, which programmes a cell to die - for example because its DNA has been damaged. This process is essential in cancer chemotherapy, and is very often deactivated in drug resistant cancers. Until now scientists knew that NMT modified only a handful of protein during apoptosis, but the results of this study identified many new proteins affected by NMT, suggesting new ways to combat drug resistance.

Reflecting on the next stage of research, Professor Tate said: "On the back of these results we are looking to test a drug that will have the most potent impact on blocking NMT's ability to modify proteins, and we have started working with collaborators at the Institute of Cancer Research and elsewhere on some very promising therapeutic areas. We are still at an early stage in our research but we have already identified

several very potent drug-like NMT inhibitors that are active in animal disease models, and we hope to move towards clinical trials over the next five to ten years."

More information: Thinon, E. et al. "Global profiling of co- and post-translationally N-myristoylated proteomes in human cells" *Nature Communications*, September 2014. dx.doi.org/10.1038/ncomm5919

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