Hitching a ride: Misfiring drugs hit the wrong targets

August 25 2016

It probably isn't surprising to read that pharmaceutical drugs don't always do what they're supposed to. Adverse side effects are a well-known phenomenon and something many of us will have experienced when taking medicines.

Sometimes, these side effects can be caused when a drug hits the wrong target, binding to the wrong protein. However, the difficulty of tracking this process means that little research has been carried out.

Now, a new study led by scientists at the University of Oxford and published in *Nature Chemistry* has shown how a series of anti-HIV protein inhibitor drugs can interfere with the processing of a protein known as prelamin A, essential for maintaining the shape of human cells and directly related to ageing.

The researchers used mass spectrometry - a long-established way of identifying molecules by measuring their mass - to observe directly the drugs' 'hitchhiking' on the wrong protein.

Professor Dame Carol Robinson of Oxford's Department of Chemistry, corresponding author on the paper, said: 'The "hitchhiking" of drugs on incorrect targets is a common problem but isn't much studied, as it can be difficult to observe directly. You have to know which proteins to look for, and only then can you target these proteins for further research.

'The results of this study surprised us, as the drugs target HIV proteases

and were not thought to bind the human metalloprotease that is involved in processing prelamin A.'

The researchers found that the anti-HIV drugs lopinavir, ritonavir and amprenavir each blocked the processing of prelamin A.

Professor Robinson added: 'The association between some anti-HIV drugs and premature ageing has been suspected for some time through observation of patients undergoing treatment, but it hasn't been proved at the molecular level. There have also been other highly publicised drugs with off-target protein side effects, including an anti-diabetes drug that caused heart attacks in some patients.

'Now that we have developed this mass spectrometry-based approach, we anticipate that it will have widespread application, since it is likely that many drugs that are designed with a specific target in mind end up hitchhiking on other protein targets. It could even be used during the drug development process to determine if drugs are binding to the wrong targets at the molecular level.'

More information: Shahid Mehmood et al, Mass spectrometry captures off-target drug binding and provides mechanistic insights into the human metalloprotease ZMPSTE24, *Nature Chemistry* (2016). DOI: 10.1038/nchem.2591

Provided by University of Oxford