MedicalXpress

Efficient treatment a step closer in the fight against cancer-causing herpes

February 13 2014

Herpes virus proteins are more 'spaghetti-like' than previously thought, which provides a vital clue in the search for an efficient treatment against a type of herpes which causes a form of cancer known as Kaposi's sarcoma.

That's according to researchers from The University of Manchester who have discovered that the virus protein uses its flexible arms to pass on viral building blocks to the proteins of cells that it hijacks.

The latest part of this research is published in the February edition of *PLoS Pathogens* which has uncovered how the protein of cells hijacked by the herpes virus take on a 'spaghetti-like' structure.

The research provides the first ever molecular insight of how the herpes virus RNA, a type of molecule which helps to decode the generic blueprint of a virus, is transferred between viral and cellular proteins, thus helping the virus to hijack a cell. Dr Tunnicliffe, who is the first author of the paper, said: "Viruses cannot survive or replicate on their own - they need the resources and apparatus within a host cell to do so."

In their studies, funded by the Biotechnology and Biological Sciences Research Council, the research team developed and used a new methodology which revealed how exactly flexible proteins interact together and with RNA.

Dr Tunnicliffe continues: "We have developed a novel technique which

reveals how flexible molecules work together; this allowed us a glimpse of how the virus is able to compromise the workings of the cell that it infects."

The research team has been using NMR – a technique related to the one used in MRI body scanners and capable of visualising molecules at the smallest scales – to examine how small components of herpes virus help it to multiply by binding themselves with other large molecules; this produced images of a monkey herpes virus protein interacting with mouse cellular protein and viral RNA. These images were then used to develop a 3D model of how viral RNA is recognised by this herpes virus protein and then passed on to the cellular protein of the host.

Although the model system studied here used protein from a species of herpes virus - which is only transmitted between squirrel monkeys, without actually doing much harm to them - these monkey herpes viruses are structurally very similar to viruses causing Kaposi's sarcoma in humans. Understanding how monkey viruses work may help to find ways to prevent this type of cancer in humans.

Senior researcher Dr Alexander Golovanov, from the Manchester Institute of Biotechnology and Faculty of Life Sciences, said: "Initially proteins were thought to interact only as fitting rigid bodies – as a lock and key, for example. The fitting key is inserted into the lock, and that sets the rigid mechanism of a lock in action. Then the understanding evolved - it was found that not all protein 'keys' are rigid, some are more like boiled spaghetti which can still operate the rigid lock successfully, by adjusting its shape."

Dr Golovanov continues: "Just recently, the 'fuzzy' protein complexes were discovered - it is as if not only the 'key' is made of flexible boiled spaghetti, but also parts of the lock itself are made of boiled spaghetti. This 'spaghetti mechanism' still manages perform a defined complex

function, despite lacking rigidity. The viral proteins behave a lot like such spaghetti."

He added: "Unfortunately, no effective antiviral treatment is currently available, which suppress viral replication efficiently enough. Finding a weak spot in the virus, which can be used to prevent Kaposi's sarcoma in the future, therefore would make a significant breakthrough."

Professor Melanie Welham, BBSRC Executive Director of Science, said: "This is an interesting technique which will help us understand more about the herpes virus and could be applied in virology research more generally. This is the type of excellent bioscience research underpinning health that BBSRC seeks to fund to deliver social and economic benefits for all."

More information: 'Competitive and Cooperative Interactions Mediate RNA Transfer from Herpesvirus Saimiri ORF57 to the Mammalian Export Adaptor ALYREF,' by Richard B. Tunnicliffe, Guillaume M. Hautbergue, Stuart A. Wilson, Priti Kalra, and Alexander P. Golovanov, *PLoS Pathogens*, 2014.

Provided by University of Manchester