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Cervical cancer: first 3D image of an HPV oncoprotein

For the first time, researchers from the Laboratoire biotechnologie et signalisation cellulaire at the Strasbourg-based Ecole supérieure de biotechnologie (CNRS/Université de Strasbourg) and Institut de génétique et de biologie moléculaire et cellulaire (CNRS/Université de Strasbourg/Inserm) have solved the three-dimensional structure of an important oncoprotein involved in cell proliferation and in the development of the human papilloma virus (HPV). Type 16 (HPV 16), which causes cervical cancer, is the most dangerous of human papilloma viruses. This work, published in *Science* on 8 February 2013, should make it possible to identify and improve medication to block the protein and prevent it from causing tumors.

Cervical cancer is one of the most common cancers in the world, ranking second in terms of mortality among women. It is caused by so-called “high-risk” (1) human papilloma viruses (HPV), of which type 16 (HPV 16) is the most dangerous. After infecting a healthy cell, HPV must stimulate it to multiply in order to reproduce itself. The viral proteins E6 and E7 cause cell proliferation and the development of cervical cancer, which is why they are known as “oncoproteins”.

For the first time, researcher Gilles Travé and his team at the laboratoire Biotechnologie et signalisation cellulaire (CNRS/University of Strasbourg) working in collaboration with researchers led by Jean Cavarelli and Bruno Keiffer of the Institut de génétique et de biologie moléculaire et cellulaire (CNRS/University of Strasbourg/Inserm) have solved the three-dimensional structures of E6 proteins in type-16 human papilloma virus and its type 1 bovine equivalent (BPV 1). The same researchers had already solved the structure of E6 in HPV 16 in 2012 (2), but this time the E6 proteins have been “caught” in the process of capturing target cellular proteins. The complete structure of an E6 protein—which is very tricky to produce in the laboratory—had remained unsolved for almost 30 years.

Success depended on two factors: the development of methods for isolating protein E6 as well as the use of nuclear magnetic resonance (NMR) (3) and crystallography (4) techniques. Having dealt with various aggregation and purification problems, the researchers succeeded in obtaining protein E6. The challenge then was to keep it in its folded form (so as to preserve its ability to organize itself and thus be biologically active). NMR and crystallography data made it possible to determine the structure of the E6 protein and obtain a high-resolution 3D “photograph”.

The three-dimensional structure of the E6 protein capturing its target reveals the exact molecular mechanism of its carcinogenic activity. It also explains the protein’s remarkable ability to act as a viral terrorist and hijack many of the functions of the infected cell. This breakthrough is crucial for cervical

cancer treatment, as it should make it possible to identify and improve medication to prevent the protein from causing tumors.

(1) High-risk strains : HPV viruses are classified as high-risk or low-risk depending on their ability to cause cancer. The main high-risk strains of human papilloma virus are types 16, 18, 31, 33 and 51.
(2) Zanier K, Ould M'hamed Ould Sidi A, Rybin V, Boulade-Ladame C, Rybin V, Chapelle A, Atkinson RA, Kieffer B, Travé G. Solution structure analysis of the HPV16 E6 oncoprotein reveals a self-association mechanism required for E6-mediated degradation of p53. *Structure* 2012, 20(4):604-617.
(3) Nuclear magnetic resonance: a method for studying biological molecules, which measures resonance in the nuclei of certain atoms. It is used to determine the structure of proteins.
(4) Crystallography: a method for determining the atomic structure of a crystallised protein by x-ray diffraction.

Bibliography

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