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Atomic Model Reveals New Details about the Virus that Causes Cervical Cancer

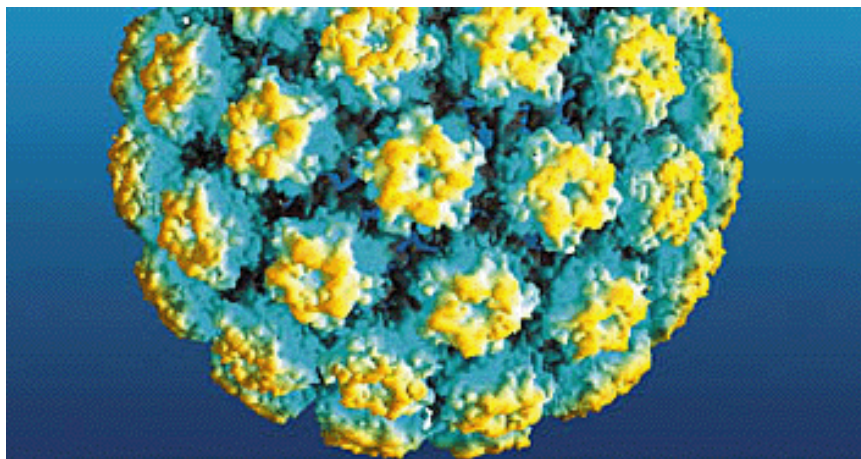


Image Title: The illustration shows a view of the molecular surface of the atomic model of papillomavirus generated by HHMI investigator Stephen C. Harrison and colleagues. - Courtesy of the Harrison Laboratory

New studies reveal that papillomavirus — the major cause of cervical cancer — may look somewhat different to the immune system than researchers had previously thought.

The researchers used a hybrid technique, integrating images of the virus obtained by electron microscopy with x-ray crystallography data, to discover new details about the surface of the papillomavirus. The studies provide information that may aid in developing an effective vaccine against papillomavirus, which is estimated to infect about 20 million people in the United States, according to the Centers for Disease Control and Prevention.

Human papillomavirus is the most prevalent sexually transmitted infection, affecting 50-75 percent of sexually active men and women at some point in their lives. Although the majority of the more than 100 types of

papillomavirus are relatively benign, nearly all cervical cancers are associated with infection by one of the cancer-causing types of papillomavirus. Cervical cancer is the second most common cause of cancer in women worldwide.

A research team led by Howard Hughes Medical Institute investigator Stephen C. Harrison published the new atomic models of outer coat of the papillomavirus in an article in the September 16, 2002, issue of the European Molecular Biology Organization (EMBO) *Journal*. Harrison, who is at Childrens Hospital and Harvard Medical School, collaborated on the studies with Yorgo Modis and Benes Trus, who is at the National Institutes of Health.

Previous structural studies in Harrisons laboratory showed that the principal subunit of the virus outer coat, or capsid, is constructed of a five-sided (pentameric), ring-like molecular unit. Harrison and his colleagues crystallized a 12-pentamer assembly to produce smaller virus-like particles (VLPs) and to study in detail how the pentamers are linked to one another in the VLPs.

These VLPs are much smaller assemblies than the 72-pentamer assembly that from electron microscopy studies we knew to make up the papillomavirus capsid, said Harrison. That difference left open some puzzling questions about the mode of association of the pentamers in the full-size virus particle, as opposed to the mode of association of the pentamers in the small VLPs.

Although Harrison and his colleagues would have preferred to use x-ray crystallography to determine the structure of the capsid, it was not possible to culture enough of the virus to obtain the crystals necessary for crystallographic studies. Instead, they decided to start with the most detailed electron microscopy images of the virus they could obtain. They used those images as the scaffolding upon which they attempted to build a coherent atomic model of the entire virus, using information about the structure of the pentamer subunits from Harrisons structural studies of VLPs.

We thought that this approach might reveal details of the viral structure we hadnt understood before, and we turned out to be right, said Harrison.

The scientists discovered that an arm of the pentamer subunit that connects it with its neighbor is arranged differently in the full-size capsid than in the VLP. Using geometric and chemical bond constraints that they deduced had to exist in the full virus, the scientists developed a rearranged model of the arm — which they called an invading arm model — by which the pentamers link to one another.

Imagine that you have your hand on your waist, and youre rubbing elbows with the person next to you, said Harrison. Thats the type of connection that exists between pentamers in the small virus-like particles. But in the virus, the invading arm arrangement suggests that you each have your hand on the other persons waist, with your elbow extended.

According to Harrison, these differences in how the viral subunits are connected suggest that the outer coat of the virus might appear differently to the immune system. This is important news for researchers developing vaccines against papillomavirus.

Merck, MedImmune, and other companies and research groups are using virus-like particles produced using recombinant protein from eukaryotic cells as the basis for their vaccines, said Harrison. The invading arm model we have developed affects the conformation of loops on the viral surface that are known to be involved in its antigenicity — or ability to elicit an immune response. So, in thinking about the structure of the particles they use in their vaccines, vaccine developers would want to consider whether this new understanding of viral assembly might be used to modify or enhance the protective immunity they want their vaccines to achieve, he said.

The studies also demonstrate the value of integrating electron microscopy data with x-ray crystallography data, said Harrison. We wanted to push the boundary of this technique, he said. We wanted to show that if we obtain the highest possible resolution electron microscopic images of a virus — and we also have additional atomic structure information of part or all of a subunit — that we can come up with a valid model for the whole virus.

More broadly, said the researchers, the technique they used — integrating electron micrographic virus images with x-ray crystallographic data about viral subunit structure — constitutes a useful tool for understanding viral and other biological structures.