Researchers wake up viruses inside tumors to image and then destroy cancers

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Researchers have found a way to activate Epstein-Barr viruses inside tumors as a way to identify patients whose infection can then be manipulated to destroy their tumors. They say this strategy could offer a novel way of treating many cancers associated with Epstein-Barr, including at least four different types of lymphoma and nasopharyngeal and gastric cancers.

In the March 1 issue of Clinical Cancer Research, a team of radiologists and oncologists from Johns Hopkins Medical Institutions describe how they used two agents already on the market – one of which is the multiple myeloma drug Velcade – to light up tumor viruses on a gamma camera. The technique is the first in the new field of in vivo molecular-genetic imaging that doesn't require transfecting tumors with a "reporter" gene, the scientists say.

"The beauty of this is that you don't have to introduce any reporter genes into the tumor because they are already there," says radiologist Martin G. Pomper, M.D., Ph.D. "This is the only example we know of where it is possible to image activated endogenous gene expression without having to transfect cells."

A variety of blood and solid cancers are more likely to occur in people who have been infected with the Epstein-Barr virus (EBV), but not everyone with these cancers has such infections. For those who do, researchers, such as Hopkins oncologist and co-author Richard F. Ambinder, M.D., Ph.D., have been working on ways to activate the

reproductive, or "lytic" cycle, within the virus to make it replicate within the tumor cell. When enough viral particles are produced, the tumor will burst, releasing the virus. In animal experiments, this experimental therapy, called lytic induction therapy, results in tumor death.

As the first step in this study, researchers screened a wide variety of drugs to see if any of them could reawaken the virus. They were fortunate in that one of the genes that is expressed upon viral lytic induction is EBV's thymidine kinase (EBV-TK), an enzyme that helps the virus begin to reproduce. This kinase is of interest because researchers know its "sister" kinase, the one produced by the herpes simplex virus, can be imaged by an injected radiolabeled chemical (FIAU), which can then be imaged using a gamma camera.

"To perform molecular-genetic imaging, we have always had to infect cells with active herpes simplex virus so that they can replicate, express TK, and only then could we use the FIAU tracer to make the cells light up," Pomper says. "So we were hoping to find a way to turn latent Epstein-Barr virus on in these cancers, and use the thymidine kinase it then produces to enable us to see the virus-associated tumors with radiolabeled FIAU."

The researchers screened 2,700 agents until they hit upon Velcade, a targeted chemotherapy drug already approved for use in multiple myeloma. "We were both surprised and lucky," he says. "Velcade is a proteasome inhibitor, but it also induces the lytic cycle thereby activating the TK in the Epstein-Barr virus. Once the TK is activated, we can image the tumors."

To test their findings, the researchers used mice carrying human Burkitt's lymphoma, a cancer often associated with Epstein-Barr viral infection. Tumors glowed in mice given Velcade followed by an injection of FIAU, but not in mice that weren't given Velcade. Mice

whose Burkitt's lymphoma did not contain Epstein-Barr virus also did not respond to either Velcade or FIAU, according to researchers.

"Velcade woke up the virus in the tumors, which increased viral load by 12-fold, all the while cranking out TK," Pomper says. "An injection of FIAU made it easy to image the tumors with virus in them."

The method is highly sensitive, he says: as few as five percent of the cells within the tumor mass needed to be induced into the lytic cycle in order to be detected.

Not only can FIAU light up the tumors, it can also potentially kill them, Pomper says. For imaging purposes, FIAU can carry a radionuclide that emits a low energy gamma photon, but it can also be engineered to carry therapeutic radionuclides, which are lethal to cells in which TK is activated.

Results of this study suggests that this strategy could be applied to other viruses associated with tumors, and that other drugs may potentially be used to activate these viruses, Pomper says. "Velcade is only one of an array of new, as well as older agents, that can induce lytic infection, and a particular agent could be tailored for use in a specific patient through imaging," he says.

Source: American Association for Cancer Research