MedicalXpress

New strategies work to put cancer on the firing line

January 3 2008

Dr. Yukai He wants to put cancer in the bull's eye."Cancer really comes from us," the Medical College of Georgia Cancer Center immunologist says of the scary reality that cancer cells are our own cells gone awry. That means our immune system doesn't always see cancer as a horrific invader.

"Tumors and T cells, the cellular arm of the immune system and the main player in anti-tumor immunity, cohabitate for many years before the tumor grows," says Dr. He, who recently was named one of the first Georgia Research Alliance Distinguished Investigators, a new initiative to support outstanding young investigators.

The tumor is smart, he says, changing just enough to stay out of the line of fire.

He and collaborators at Memorial Sloan-Kettering Cancer Center in New York, the University of Chicago and now MCG are putting together a package they believe will place it dead center.

The researchers are packaging an antigen gene that will alert the immune system in a novel viral vector delivery system while quashing the body's misguided efforts to protect a tumor.

The treatment could one day follow tumor surgery and chemotherapy in patients when recurrence is likely, says Dr. He, who came to MCG in August from the University of Pittsburgh. It also could work for

persistent viral infections such as HIV and human papillomavirus, parasitic diseases such as malaria and bacterial infections such as tuberculosis.

It is antigens – proteins on or in all cells – that get the attention of the immune system. Dendritic cells present antigens to T cells so that the host immune system will be alerted.

Using animal models of melanoma, researchers at Sloan-Kettering are taking key antigens and modifying them just enough to get the attention of T cells but still result in an immune response that targets the cancer.

Dr. He is looking for the best way to deliver modified antigens, identifying which dendritic cells actually present the antigens to T cells, so he can use a delivery mechanism that also gets their attention. He's using the lentivector, the backbone of HIV minus most of the genes, as the basic mode of transportation. The vector – obviously good at getting in and surviving in the body – will ideally help generate a potent, memorable immune response that eradicates cancer or an infection in the first place then leaves an immune army waiting should it return.

Vaccination is by far the most effective approach for preventing infectious diseases. These vaccines stimulate B cells to produce antibodies to neutralize targeted bugs. These conventional vaccines are generated by inactivating microbes or attenuating their virulence. For example, the Salk Polio vaccine, first used in the1950s, was made from dead virus, and the Sabin Polio vaccines were from the attenuated virus, in which the infectious part of the virus was inactivated. Scientists next took advantage of the B cell's ability to produce antibodies by identifying the most prominent antigen expressed, cloning it and giving it to patients to impart immunity from future infections. Tradeoffs of this type vaccine include a potentially weak immune response since it's not the whole virus, but that also means it can't cause disease.

However, some persistent viruses such as HIV and malignant tumor lack a single protein that would inspire sufficient neutralizing antibodies, prompting researchers such as Dr. He to turn to development of T cell vaccines. So far, the most effective and safest way of stimulating T-cell immunity is with recombinant viral vectors, including the lentivector Dr. He is using. Recombinant viral vectors, already under study in HIV vaccine clinical trials, appear safe and effective.

Another important difference from conventional vaccines is that tumor vaccines need to work where tumor growth is established. Tumors impede the work by not just flying under the radar screen but actually suppressing the immune response. Two of Dr. He's MCG colleagues discovered one of those suppressive mechanisms.

Dr. Andrew Mellor, director of the Immunotherapy Center and Georgia Research Alliance Eminent Scholar in Immunogenetics, and Dr. David Munn, pediatric hematologist-oncologist, showed in work published in 1998 in Science that fetuses use the enzyme IDO – indoleamine 2,3-dioxygenase – to locally disable a pregnant woman's immune system and avoid rejection. Subsequent studies demonstrated that tumors also use IDO for protection by activating regulatory T cells, which has a suppressive effect on the anti-tumor immune response. "Hopefully our collaboration will enable a comprehensive treatment package that includes a T cell vaccine and an IDO inhibitor to optimize the therapeutic effect in cancer patients," Dr. He says.

Source: Medical College of Georgia