The 'secret weapon' of retroviruses that cause cancer

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Oncogenic retroviruses are a particular family of viruses that can cause some types of cancer.

Thierry Heidmann and his colleagues in the CNRS-Institut Gustave Roussy-Université Paris (France) have studied these viruses. They have identified a "virulence factor" that inhibits the host immune response and allows the virus to spread throughout the body. This factor is a sequence of amino acids that is located in the envelope protein of the virus. The scientists have also shown that once mutated to lose its immunosuppressive capability, this envelope protein could serve as a basis for the development of vaccines.

These findings have been published online in the *Proceedings of the National Academy of Sciences USA,* Monday 8 February 2010.

Retroviruses are viruses whose genome is made up of RNA. These viruses are unique in possessing an enzyme that enables synthesis from this RNA of a DNA molecule capable of integrating into the DNA of a host cell. The retrovirus then utilizes the cell machinery to replicate. HIV is one of the best-known retroviruses. Oncogenic retroviruses (or oncoretroviruses) are cancer-causing viruses. Numerous oncoretroviruses are associated with animal diseases. In humans, two retroviruses, called HTLV and XMRV, have been associated with a type of leukemia and with prostate cancer.

Researchers have been working on the ability of retroviruses to

propagate and persist in their hosts by escaping the immune system. They have studied the molecular basis of this process, and have shown that it is driven by the envelope protein of these viruses. First of all, this protein has an essential "mechanical" role, as it induces the fusion of viral particles with the target cell membrane, thus allowing them to penetrate into the cell. Using a mouse model of infection with a murine leukemia virus, the researchers showed that this envelope protein also has a second role that is equally essential to viral propagation in the body: it is immunosuppressive, or in other words it inhibits the host immune response in a radical manner, affecting both the "innate" and "adaptive" immune responses.

The researchers succeeded in locating the domain responsible for this property within the amino acid sequence of the envelope protein. This domain, an authentic virulence factor, is a crucial element in the arsenal that enables retroviruses to invade their host and produce their pathogenic effect. It thus becomes a target of choice for the design of novel antiretroviral therapeutic strategies, including vaccines. The results obtained by these scientists mean it will be possible to follow this path. They were able to introduce targeted point mutations into the envelope protein that could suppress its ability to inhibit the immune system which, as expected, reacted much more effectively than with the non-mutated protein, producing a high level of antibodies and inducing antiviral cellular immunity. By working on this mutated protein, it should be possible to develop vaccines for the future. Indeed, after the mouse model, the researchers were able to show that the HTLV and XMRV retroviruses associated with human diseases were both endowed with an immunosuppressive domain in their envelope protein.

More information: Schlecht-Louf, G., Renard, M., Mangeney, M., Letzelter, C., Richaud, A., Ducos, B., Bouallaga, I., and Heidmann, T. Retrovirus infection in vivo requires an immune escape virulence factor encrypted in the envelope protein of oncoretroviruses. *Proc. Natl. Acad.*

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