Redesigned protein opens door for safer gene therapy

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The 'fusion' protein could lead to safer, more effective retroviral gene therapy.

A fusion protein engineered by researchers at KU Leuven combining proteins active in HIV and Moloney murine leukaemia virus (MLV) replication may lead to safer, more effective retroviral gene therapy.

Gene therapy involves inserting healthy genetic material into a diseased cell. Using a carrier derived from a retrovirus, the genetic material is

smuggled into a human cell where, once inside, it integrates itself into the cell's DNA. But gene therapy is not without risks. If integrated too near a carcinogenic gene, the newly introduced genetic material can also induce disease-causing mutations.

In gene therapy, the delivery vehicle is not the retrovirus itself, but a viral vector: a derivative form of the retrovirus that retains its proteins but not its DNA. One of the most widely used viral vectors is derived from MLV. But this particular virus-borne carrier is both a weapon and a risk. It can cure disease but, if inscribed in the wrong place in a cell's DNA, it can also cause leukaemia.

A separate protein, which plays a role in HIV, does not have that problem. It only integrates itself in 'safe' places in the host cell's DNA.

The researchers put one and two together to create a safer viral vector: "We developed a fused protein with the head of the protein that HIV uses and the tail of the protein that MLV uses," Dr. Rik Gijsbers explains.

Writing in *Cell Reports*, the researchers say their retrofitted retroviral vector works: "Our experiments with cell cultures show that in the presence of this protein, the viral vector always inscribes itself in a safe place, just as it does in the HIV virus," says Dr. Gijsbers.

Several years ago, scientists successfully used viral vectors derived from MLV to treat a congenital immune system abnormality in children. Some of these children later developed leukaemia. "In these cases, the viral vector embedded itself near a carcinogenic gene," explains Professor Zeger Debyser, the corresponding author. "This disrupts the gene and leads to a higher leukaemia risk – a serious setback for gene therapy. It put a heavy damper on gene therapy's future development."

Until recently, it was not known how or why retroviruses inscribed themselves near cancer genes. Research by the Molecular Virology and Gene Therapy research group at KU Leuven sheds new light on this enigma. Their previous research into HIV proved essential, says Dr. Jan De Rijck: "In 2003, we discovered that HIV uses a particular protein as an anchor to embed itself into the host cell. We asked ourselves whether MLV used a different protein in a similar way, and that was indeed the case. The BET (bromodomain and extraterminal, eds.) proteins we found are the anchors of MLV." This discovery led the KU Leuven researchers to develop the fusion protein.

Though the initial results are promising, more research is needed to refine them, says Dr. Gijsbers. "But this definitely opens new avenues in the search for a new generation of safe viral vectors in gene therapy, particularly for various blood diseases."

More information: www.cell.com/cell-reports/full … 2211-1247(13)00563-9

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