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# CHEO scientist advances biotherapeutics as published in Cancer Cell

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Oncolytic virology uses live viruses to sense the genetic difference between a tumor and normal cell. Once the virus finds a tumor cell, it replicates inside that cell, kills it and then spreads to adjacent tumor cells to seed a therapeutic "chain reaction". As reported in today's issue of *Cancer Cell,* Dr. David Stojdl, a scientist from the Children's Hospital of Eastern Ontario Research Institute at the University of Ottawa has found a way to trick resistant cancer cells into committing suicide following oncolytic virus therapy.

When it comes to using oncolytic viruses to fight cancer, the outcome is a consequence of a battle between the genes that the virus has and the genes that the human host has. Using a technology called RNA Interference (RNAi) Dr. Stojdl's research team was able to systematically search through the entire human genome to find genes [that when inhibited] would make the viruses up to 10,000 times more potent at killing tumor cells without harming healthy cells. "Until now, scientists in our field have been focused on engineering the genes in the oncolytic virus itself to make them work better, and that has worked well to a point. This is the first study to look at all of the genes in the human genome to determine which ones we should manipulate to help the oncolytic therapy work better," said Dr. Stojdl.

Dr. Stojdl's research team has identified a series of genes that magnify the impact of oncolytic viruses. These genes normally control the endoplasmic reticulum stress response, or unfolded protein response. In essence, when the cell environment is toxic the cells have a tough time

folding proteins. "A properly folded protein doesn't expose many sticky parts on its surface. Cells don't like mangled proteins because they get sticky. If you have sticky parts they combine with other proteins to make large, toxic 'balls' of protein - and this can kill the cell," explained Dr. Stojdl in layman terms.

"To deal with this 'sticky situation', the cell turns on a few pre-programmed rescue systems that either turbocharge the folding process or slow down the production of new proteins until the cell can catch up. If this doesn't work, the cell commits suicide to stop the damage from spreading," explained Dr. Douglas Mahoney lead author of the study and member of the Stojdl lab.

Dr. Stojdl's team has identified a way to short-circuit these rescue systems so that tumor cells go straight to suicide and healthy cells stay intact. The strategy works by applying a mild stress to the cells to force them to turn on these rescue systems. But when these cells encounter an oncolytic virus, instead of trying to fix the unfolded proteins, the cell is triggered to commit suicide.

This triggering effect also works with some common chemotherapeutics that are used in cancer clinics around the world today.

Provided by Children's Hospital of Eastern Ontario Research Institute