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Review Paper

Novel Way to Kill the Cancer Cells

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ABSTRACT

Stanford university reseachers have designed a molecule that grabs on to two different proteins in cancer cells, ultimately killing by making two proteins together using "molecular glue" which plays an important role in binding and stabilizing protein - protein interactions in biological systems. Make the cancer cells to self distruct.

INTRODUCTION

Our bodies divest themselves of 60 billion cells every day through a natural process of cell culling and turnover called apoptosis. These cells - mainly blood and gut cells - are all replaced with new ones, but the way our bodies rid themselves of material could have profound implications for cancer therapies in a new approach developed by Stanford Medicine researchers. They aim to use this natural method of cell death to trick cancer cells into disposing of themselves. Their method accomplishes this by artificially bringing together two proteins in such a way that the new compound switches on a set of cell death genes, ultimately driving tumor cells to turn on themselves. The researchers describe their latest such compound in a paper published Oct. 4 in Science. The idea came to Gerald Crabtree, MD, a professor of development biology, during a pandemic stroll through the forests of Kings Mountain, west of Palo Alto, California. As he walked, Crabtree, a longtime cancer biologist, was thinking about major milestones in biology. One of the milestones he pondered was the 1970s-era discovery that cells trigger their own deaths for the greater good of the organism. Apoptosis turns out to be critical for many biological processes, including proper development of all organs and the fine-tuning of our immune systems. That system retains pathogen-recognizing cells but kills off self-recognizing ones, thus preventing autoimmune disease. It occurred to me, Well gee, this is the way we want to treat cancer," said Crabtree, a co-senior author on the study who is the David Korn, MD,

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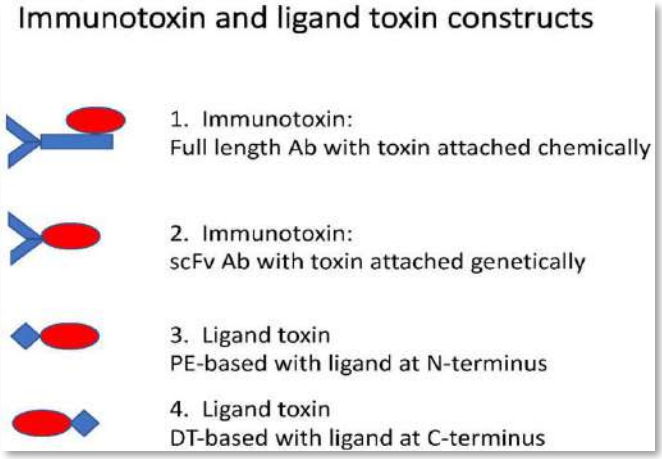
Professor in Pathology. "We essentially want to have the same kind of specificity that can eliminate 60 billion cells with no bystanders, so no cell is killed that is not the proper object of the killing mechanism." Traditional treatments for cancer - namely chemotherapy and radiation - often kill large numbers of healthy cells alongside the cancerous ones. To harness cells' natural and highly specific self-destruction abilities, the team developed a kind of molecular glue that sticks together two proteins that normally would have nothing to do with one another.

Targeting Receptors on Cancer Cells

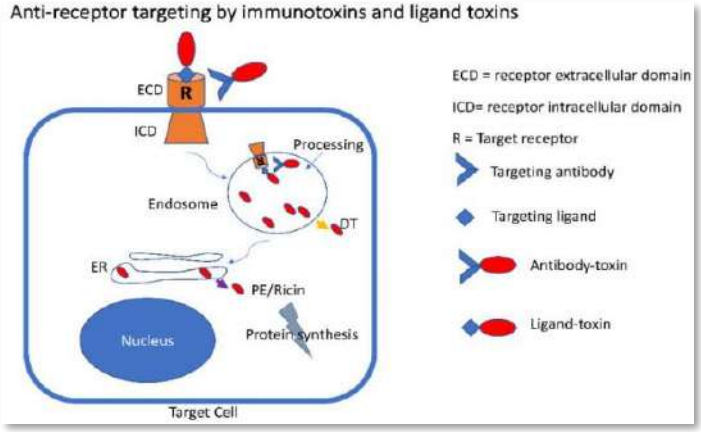
Cancer cells frequently upregulate surface receptors that promote growth and survival. These receptors constitute valid targets for intervention. One strategy involves the delivery of toxic payloads with the goal of killing those cancer cells with high levels of specific receptors. Delivery can be accomplished by attaching a toxic payload to either a receptor-binding antibody or ligand. Antibody-toxin agents are called “immunotoxins” while ligand toxins retain their own designation. Receptors provide an entry pathway for the delivery of cytotoxic drugs or proteins to the cell interior. Here, we confine our discussion to the use of bacterial or plant protein toxins that act catalytically within cells to inhibit protein synthesis. Generally, the cell-binding domain of the toxin is replaced with a ligand or antibody that dictates a new binding specificity (Figure 1). Further, while this review will cover both antibody-toxin and ligand-toxin therapeutics, it is important to highlight key differences among these two types of chimeric molecules. Anti-receptor antibodies rarely stimulate signaling pathways while ligands certainly will. Additionally, the effectiveness of ligand-toxins can be blocked by high local concentrations of endogenous ligand which is rarely an issue with antibody-based agents. Finally, anti-receptor antibodies, unlike ligands, can target portions of the external domains of receptors that are not directly involved in ligand binding—thus there may be many more binding sites available to antibodies than to ligands.



Immunotoxin and ligand toxin constructs. In examples 1 and 2, antibodies (blue) are joined with toxins (red) to form immunotoxins. Shown in example 1, a toxin is attached chemically to a full-length antibody. Example 2 is a genetic fusion between the single-chain Fv portion of an antibody and a toxin. In examples 3 and 4, the two most common ligand toxin constructs are shown. Example 3 shows a ligand toxin whereby the ligand (blue) is placed at the N-terminus of the construct, in place of pseudomonas exotoxin’s (PE’s) native binding domain. Example 4 shows the ligand at the C-terminus, replacing the native binding domain of diphtheria toxin (DT).

Receptors, especially those tied to oncogenic progression, represent attractive targets. In

addition to high expression levels, surface receptors can provide an efficient gateway for internalization (Figure 2). Normally, internalization by signaling receptors (e.g., growth factor or cytokine receptors) leads to receptor downregulation and destruction of both ligand and receptor. Targeted toxins can use the receptor internalization feature but must avoid destruction. Likewise, internalization by nutrient-related (e.g., lipoprotein or transferrin receptors) receptors allows for cargo uptake but recycling of the receptor to the cell surface allows additional rounds of internalization. For these receptors, the toxin must leave the recycling pathway—or risk being returned to the media. In either case, it is possible to deliver cytotoxic payloads to surface receptors on cancer cells. However, receptor expression on normal tissue represents a significant obstacle to therapeutic intervention.



Anti-receptor targeting by immunotoxins and ligand toxins. A ligand toxin is shown interacting with a target receptor at the ligand-binding site. Similarly, an immunotoxin is shown binding the same receptor but at a distinct site. Following binding, internalization results in delivery to endosomes. In endosomes, toxins are processed (often by furin-like proteases) to separate the antibody or ligand from the toxin. After the processing step, some toxins such as DT translocate directly from endosomes (yellow arrow) to the cell cytosol while others traffic further into the cell to the endoplasmic reticulum where translocation is noted for pseudomonas exotoxin (PE) and some plant toxins (purple arrow). Once in the cytosol, toxins shut down protein synthesis.

MECHANISM OF ACTION

By artificially linking two proteins together, the new complex can trigger a cascade of events within the cancer cell, leading to programmed cell death (apoptosis).

How Can Be Cancer Cells Self Distructed

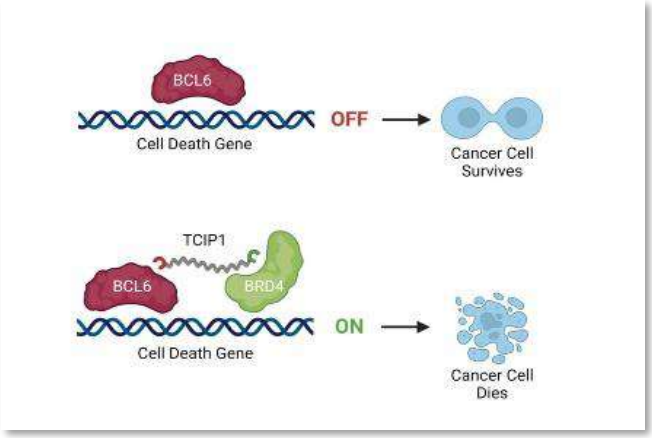
Using a "molecular glue," they connect two proteins—BCL6, which usually aids cancer survival, and CDK9, which activates cell death genes. This compound tricks cancer cells, specifically those in diffuse large B-cell lymphoma, into triggering their own destruction.

Certain genes have the potential to mutate into oncogenes, which are a major driver of cancer. Often, these oncogenes are related to cell proliferation and disposal, so affected cells can evade apoptosis. Understandably, oncogenes and the proteins they encode are a common target for cancer treatments, but the new study, from researchers at Stanford, tackles the problem from a different angle. "Since oncogenes were discovered, people have been trying to shut them down in cancer," said Roman Sarott, co-first author on the study. "Instead, we're trying to use

them to turn signaling on that, we hope, will prove beneficial for treatment." The Stanford team targeted an oncogene protein called BCL6, which is implicated in diffuse large cell B-cell lymphoma. Mutated BCL6 will sit on DNA right near specific genes that promote apoptosis, keeping them switched off so the cancer cells can continue to grow and divide unchecked. To counter this, the scientists developed a kind of molecular glue that binds BCL6 to another protein, CDK9. This one activates genes, and in this case, it switches back on the apoptosis-associated genes that BCL6 is suppressing. In lab tests, this technique worked to kill off lymphoma cells with high potency. This particular protein pairing is very selective to diffuse large cell B-cell lymphoma. That means that unlike radiation and chemotherapy, this technique doesn't seem to affect healthy cells. In tests in mice without cancer, no major negative side effects were seen – although it does also attack some healthy immune cells. In another experiment, the team tested the molecule against 859 different types of cancer, and the only one it killed was diffuse large cell B-cell lymphoma. The researchers plan to try to alter the mechanism to target other known cancer-causing proteins, such as Ras, which is implicated in several forms of the disease. While it's certainly an intriguing mechanism, it's important to note that it's still in the very early stages. The team is currently testing the compound in mice with diffuse large cell B-cell lymphoma, with hopes that the general idea could eventually be applied to treat a wide range of cancers with extreme selectivity.

This Method Can Damage The Healthy Tissues ?

Even with careful design, there is a risk of off-target effects where the protein complex might interact with similar proteins in healthy cells, causing unintended damage.



BCL6 is only found in certain kinds of immune cells, and therapies that target BCL6 could pose potential health problems, said Dr. Staudt, whose early research helped identify BCL6 and define its role. In healthy B cells, BCL6 staves off cell death while the cells undergo the complicated process of making new antibodies—such as when a person gets a new infection or a vaccine. Like other treatments for DLBCL, there is a good chance that TCIP1 could wipe out healthy B cells and heighten the risk of deadly infections, Dr. Staudt said. But "we limit the damage" to healthy B cells by giving DLBCL treatments for short periods of time, he noted. BCL6 also reins in genes that cause inflammation. When Dr. Staudt and others created mice lacking the BCL6 gene, the mice died of an inflammatory disease, he explained.

But when the Stanford researchers gave TCIP1 to healthy mice for 5 days, there were no noticeable side effects. Although there was no evidence of

inflammation in the mice, future "clinical trials of TCIP1 or related molecules should watch out for possible inflammatory side effects," wrote Dr. Staudt and James Phelan, M.D., also of NCI's Lymphoid Malignancies Branch, in an accompanying editorial on the new study.

CONCLUSION

While the current study focuses on lymphoma, the implications could be far broader. Research has shown that nearly all cancer types share this fundamental trait of evading cell death — often by overexpressing proteins that suppress the natural death process. This hope is that similar "molecular glue" approaches could potentially be developed for other cancers by identifying and targeting their specific survival proteins. The technology has already shown promise in early testing. In healthy mice, the compound showed no obvious toxic side effects, though it did affect a specific category of immune cells that rely on the same proteins. The team is now testing the compound in mice with lymphoma to evaluate its effectiveness against cancer in living organisms. Looking ahead, the researchers have founded a biotech startup, Shenandoah Therapeutics, to advance this promising technology toward clinical trials. They are also exploring ways to adapt their molecular glue approach to target other cancer-driving proteins, including the "Ras" gene, which is involved in several different types of cancer.

This innovative approach could open up a new frontier in cancer treatment, where instead of simply blocking cancer's survival mechanisms, we trick cancer cells into activating their own self-destruct switches. If successful in clinical trials, this precision targeting could offer individuals with cancer a more effective treatment option with fewer side effects than current therapies.

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