Helping the immune system to combat cancer

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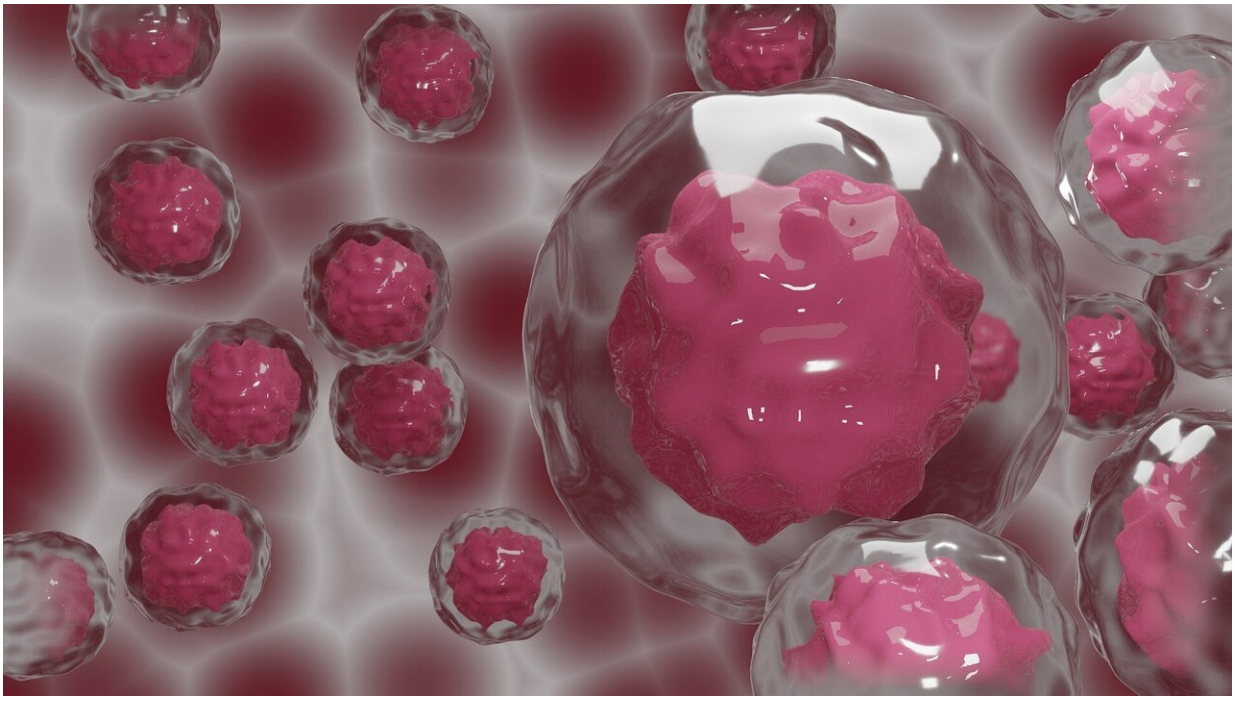

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Cancers sometimes escape our immune defenses because of the over-activity of molecular signaling systems, called checkpoint processes. Now we may be able to fight back using a new range of molecules, researchers in China report in the *European Journal of Medicinal Chemistry*.

"We have been working on the discovery of anti-cancer agents for more

than 15 years and we believe these molecules have a real future in cancer therapy," says Jianjun Chen of the research team at Southern Medical University in Guangzhou, in China.

A problem for T-cells

The team's molecules act against a protein involved in checkpoint processes known as PD-L1. This molecule protrudes from the surface of cells, including cancer cells, and can bind to a protein called PD-1 carried by T-cells of the immune system. The T-cells have the potential to destroy tumor cells, which they bind to via several proteins, some of which activate the anti-tumor activity while others inhibit it.

When PD-L1 on a tumor cell binds to PD-1 on a T-cell this generates an inhibitory signal, which can lead to destruction of the T-cell. This plays an important role in regulating the immune system in health, but can dampen down the immune attack on cancer.

Chen explains that the binding of PD-L1 on cancer cells to PD1 on T-cells is one of the most significant mechanisms that can allow cancers to evade the attack of the immune system.

Dual action

The drugs discovered by the researchers act against PD-L1 in two ways. They inhibit the activity of the protein by binding to it, but they also promote its degradation. The team explored the potential of 28 molecules based on the compound resorcinol diphenyl ether, each with a somewhat different structure but all similar to a category of drugs known as PROTACs (proteolysis targeting chimeras).

The chimera label indicates that the drugs consist of two distinct

functional parts, joined by a linker group. One part binds to a target protein, while the other part binds to a protein that initiates the destruction of any proteins it is attached to. 'Proteolysis' literally means the breakdown of protein.

A first, and an extra

"This is the first time a PROTAC molecule has been found to inhibit and degrade the PD-L1 protein," says Chen. It could therefore be a significant breakthrough towards new cancer therapies given the role of PD-L1 activity in suppressing the immune system's response against cancer.

The research also revealed that the most potent of the molecules the team are exploring has some additional potential. "We found it could moderately reduce the levels of PD-L1 in a manner different from the mechanism of PROTACs," Chen explains. This different mechanism involved degradation of PD-L1 by lysosomes, which are involved in routine removal of waste materials within cells.

The team now plan more detailed studies to work out the precise mechanism of their molecules' actions before hopefully moving towards candidates for clinical trials.

More information: Binbin Cheng et al. Discovery of novel resorcinol diphenyl ether-based PROTAC-like molecules as dual inhibitors and degraders of PD-L1, *European Journal of Medicinal Chemistry* (2020). DOI: 10.1016/j.ejmech.2020.112377

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