Arthritis Drugs Make CAR-T Therapy Safer

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Abstract

CAR-T therapy has shown significant efficacy in the treatment of leukemia, lymphoma and other blood cancers. Novartis and Gilead Sciences have already received FDA approval for CAR-T therapy targeting the B cell antigen CD19. However, these CAR-T therapies often lead to the appearance of side effects of CRS, and even more severe neurotoxicity occurs in some patients. These toxic and side effects have become one of the important reasons limiting the widespread promotion of CAR-T therapy.

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Recently, in the two scientific papers published in *Nature Medicine*, researchers from the Memorial Sloan-Kettering Cancer Center in New York and the San Raffaele Hospital in Italy have revealed the relationship with CAR by establishing an innovative mouse model. -T therapy-related cytokine release syndrome (CRS) and causes of neurotoxicity. More importantly, they found that taking certain drugs to mice before using CAR-T therapy can prevent the development of CRS and neurotoxicity, and these drugs are currently approved for the treatment of other diseases.

CAR-T therapy has shown significant efficacy in the treatment of leukemia, lymphoma and other blood cancers. Novartis and Gilead Sciences have already received FDA approval for CAR-T therapy targeting the B cell antigen CD19. However, these CAR-T therapies often lead to the appearance of side effects of CRS, and even more severe neurotoxicity occurs in some patients. These toxic and side effects have become one of the important reasons limiting the widespread promotion of CAR-T therapy.

The CAR gene has two major components: (1) the external receptor recognizes the antigen binding site on the cancer cell (2) the internal component or signal/expression directs the T cell to the cancer binding site, via the retrovirus or lentiviral vector.

As early as 2009, when CAR T therapy was used for the first time in humans, researchers observed an increase in cytokine levels in patients. However, due to the lack of a suitable mouse model, scientists knew little about the causes of cytokine production.

Researchers from Italy used a humanized mouse leukemia model and found that the main cells that secrete IL-1 and IL-6 cytokines that cause CRS and neurotoxicity are not CAR-T cells but host monocytes. The use of tocilizumab to block IL-6 receptor activation or to eliminate host monocytes can prevent the production of CRS, but it does not prevent neurotoxicity from occurring. Tocilizumab is a drug that has been approved by the FDA for the treatment of rheumatoid arthritis and CRS produced by CAR-T therapy,

but it is a relatively large protein that cannot cross the blood-brain barrier.

More importantly, the production of IL-1 in the host was earlier than IL-6 production for several hours. In a mouse model, IL-1 can trigger the production of IL-6. This means that IL-1 is the main regulator that regulates IL-6 and other cytokines. The researchers found that the use of an IL-1 receptor antagonist called anakinra prevented both CSR and neurotoxicity. Anakinra is a drug that has received FDA approval for the treatment of rheumatoid arthritis. It is a smaller molecular weight peptide that crosses the blood-brain barrier.

Researchers from New York used another mouse model to show that IL-1 and IL-6 produced by host macrophages play an important role in causing CRS and neurotoxicity. Their research shows that the production of nitric oxide (NO) by host macrophages also plays an important role in triggering CRS. Moreover, anakinra is more effective than tocilizumab in preventing CRS, and it does not affect the anti-cancer effect of CAR-T therapy.

Next, researchers will examine the efficacy of blocking IL-1 signaling in the prevention and treatment of CRS in human patients. Ultimately, they hope to integrate IL-1 receptor blockers into CAR-T cells, thereby improving the safety of CAR-T technology.

"These are very important preclinical studies that show that there are ways to prevent serious side effects including CRS and neurotoxicity caused by CAR-T therapy, without affecting the anticancer effect. We all look forward to a better CAR T treatment for global patients," Pfizer immunized Dr. Chris Boshoff, head of cancer therapy development, said.

Author Bio
As a global company, Creative Biolabs has more than 200 talented and well-trained scientists located in different continents working closely with partners from the entire world to develop and produce medicines of tomorrow. Specifically, we are the established leading expert in TCR T development and CAR T&NK cell immune therapy development, as we offer the one-stop custom services that cover the entire new drug development pipeline. Additionally, we also offer an exclusive line of ready-to-use TCR and CAR T&NK cell construction products, such as virus packaging, purification, expansion and titer determination kits. Furthermore, we have built up a unique unparalleled CAR construction and production platform for all four CAR generations.