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Commentary

Challenges for CAR Macrophages in Cancer Immune Cell Therapies

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DESCRIPTION

There has been a surge in interest in using immune cell therapy to treat solid tumours in recent years. Chimeric Antigen Receptor (CAR) arose in response to the need to use engineered cell products for much more effective treatment, inspired by the pattern that T-cell Antigen Receptor (TCR) created immunological synapse boosts immune activation of cytotoxic T cell. CAR is a chimaera protein that consists of an extracellular antigen recognition domain, a transmembrane domain, and an intracellular domain. The extracellular domain is made up of a single-chain variable segment that recognises antigens and a hinge region. A costimulatory domain and a signal transduction domain make up the intracellular domain.

As a result, the CAR has been engineered to boost immune cell targeting efficacy and trigger cell antigen dependent activation. Recently, chimeric antigen receptor CAR-T cell therapy has shown promising results in the treatment of hematologic malignancies. Nonetheless, there are still challenges in applying CAR-T cell therapy to solid cancer, such as off-target effects, poor efficiency against infiltrating tumour lumps, and CAR-T cell exhaustion due to immunosuppressive Tumour Micro Environment (TME), as well as antigen loss or decrease in solid tumour cells. Furthermore, the high costs associated with CAR-T cell treatments have limited the broad use of CAR-T in clinical treatment. As a result, great attention has been placed on developing new options, such as optimising chimaera antigen receptors, increasing T-cell capacity, utilising the various properties of subsets of T cells or NK cells, and producing so-called off-the-shelf universal cells. Despite these enormous efforts, efforts to optimise CAR-T cells remain far from complete.

Macrophages are widely known for their particular roles in immunological modulation as well as their ability to invade solid malignancies. Macrophages have traditionally been classified as highly malleable cells that perform a variety of roles including as pathogen eradication, cellular debris clearing, inflammatory response modulation, and contribution to tissue formation and homeostasis. All of the research indicates that macrophages will be a new option for cancer immune cell treatment. However, research has shown that in the presence of various cytokines and antigens, macrophages could remain in two polarised states, namely, classically activated macrophages M1 and alternatively activated macrophages M2. As a result, efforts have been attempted to convert M2 macrophages to M1 macrophages or to adoptively transplant genetically engineered CAR-macrophages into patients.

Influence of macrophages on the tumour microenvironment, as well as an overview of the three primary sources of human CAR macrophages and their involvement in cancer cell elimination, to offer a foundation for future research.

Despite significant progress in clinical treatment, many problems remain, including Cytokine Release Syndrome (CRS), CAR neurotoxicity, and medication resistance. CAR modified macrophages, on the other hand, have shown promising anti-tumor activity in recent years, following T and NK cells.

CAR-macrophages provide various advantages over CAR-T cells. T cells have a restricted ability to access the tumour environment because to the matrix-forming physical barriers that exists throughout the tumour cells, whereas macrophages may easily immerse in the cancer environment. It should be highlighted that TAMs play important roles in tumour invasion, immunosuppression, and metastasis. Furthermore, CAR-macrophages phagocytose cancer cells, improve antigen presentation, and increase T cell cytotoxicity. Finally, CAR-macrophages are less toxic and have a shorter lifespan than T cells.

More research is needed to demonstrate the efficacy of CAR macrophages in immunotherapy. Because macrophages cannot multiply on their own *in vitro* or *in vivo*, their small cell quantity poses a substantial hurdle in CAR macrophage immunotherapy. Furthermore, little is known about the macrophage dosage required *in vivo*. Exogenous macrophages cross the lung and primarily remain in the liver, reducing therapeutic efficacy. Finally, keep in mind that the TME is extremely complex, necessitating additional research to better present understanding.

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