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EDITORIAL

CAR-T CELL THERAPY CAUSES INFLAMMATION BY IL-1 WHICH ACTIVATES INFLAMMATORY CYTOKINE MAST CELLS: ANTI-INFLAMMATORY ROLE OF IL-37

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Chimeric antigen receptor (CAR) T cells are genetically modified T cells that act against cancer. When CAR-T cells are administered they can trigger inflammatory cytokines and increase toxicity. Interleukin (IL)-1 is the classic cytokine that mediates inflammatory reactions including those that occur in CAR-T-cell therapy. IL-1 also induces IL-33 in mast cells (MCs), amplifying the allergic reaction. IL-37 (ILF7) is an IL-1 family member which binds IL-18 receptor alpha (IL-18Rα) chain and suppresses innate and acquired immunity. IL-37 is an anti-inflammatory cytokine which inhibits pro-inflammatory cytokines including IL-1 and IL-33. Here, we hypothesize that inflammation and toxicity generated in tumor CAR-T therapy could be inhibited by IL-37, contributing to an improvement in the treatment of tumors with CAR-T therapy.

New cancer therapies open new hopes, but their toxicity is still a serious problem to be solved (1). Important adverse occurrences are allergy and inflammation, which can also cause fatal events (2). Chimeric antigen receptor T (CAR-T) has emerged as a new anti-tumor therapy, with the ability to stimulate the immune system (3). CAR-T is a genetically modified engineered receptor that produces a chimeric receptor of artificial T cells used in immunotherapy (4). This T receptor is chimeric because it has the function of binding the antigen and activating T cells, capable of affecting specific proteins.

CAR-T therapy can cause remission in patients with tumors resistant to conventional therapies; but this therapy has turned out to be very toxic by several mechanisms, and it can also affect antigens of normal tissue associated with the tumor and may cause patient death (5). The most important toxicity of CAR-T cells is pro-inflammatory cytokine release (6). These reactions occur after treatment with CAR-T cells, provoking tumor lysis and cytokine release, followed by anaphylaxis syndrome, fever, neurological toxicity, tachycardia, and hypotension (7). In fact, in the serum of patients treated with CAR-T cells a wide variety of inflammatory cytokines are found. The inflammatory reaction produced by the

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cytokines released by the CAR-T cells can activate other immune cells, such as macrophages and mast cells (MCs), which, in turn, produce other pro-inflammatory cytokines, aggravating the situation. Treatment with CAR-T can provoke a systemic inflammatory response mediated by inflammatory cytokines, such as interleukin (IL)-1 and IL-33, in frequent events (8). Therefore, it is important to apply an aggressive anti-inflammatory therapy in patients treated with CAR-T immunotherapy. In this therapy, pro-inflammatory cytokines are produced that activate the immune cells, including macrophages and MCs to produce and release other pro-inflammatory cytokines, aggravating the patient status (8). Macrophages primarily release IL-1 which in turn activates the MCs to generate IL-33, creating an allergic inflammatory phenomenon (9). In addition, IL-18, a cytokine of the IL-1 family polarizes CAR-T cells, provoking an acute inflammatory response, an effect that can be inhibited by IL-37, since it has been demonstrated that this cytokine plays its biological inhibitory role through IL-18 receptor alpha binding (IL-18Rα) (10).

Mast Cells

MCs are bone marrow immune cells derived from hematopoietic stem cells and reside in all the vascularized tissues and serous cavities, where they mature (11). MCs participate in both innate and adaptive immune responses and are a potential source of cytokines/chemokines, which mediate allergic disease (12-13). They can be activated by various molecules through the Toll-like receptors, and IL-1 receptors, without degranulation and without the intervention of IgE (14-15).

In MC pathway activation, intracellular calcium (Ca^{++}) is regulated by PLC, and PKC results in the formation of IP3 and diacylglycerol (DAG). MAPK, ERK, JNK and p38 participate in the transcription of cytokines and subsequently the generation of proteins (11). The production of IL-1 family, is strongly involved in the inflammatory process (16).

IL-1

IL-1 is one of the most important regulators of innate immune responses and participates in numerous inflammatory processes (17). IL-1 is the classic pro-inflammatory cytokine that includes two distinct ligands: IL-1 alpha (IL-1α) and IL-1 beta (IL-1β), which bind the IL-R1 receptor by mediating inflammatory phenomena. IL-1β, which is the most studied, is inducible and is released by the splitting of caspase-1 (17).

The inflammation that is created in CAR-T therapy with the activation of immune cells generates pro-inflammatory cytokines, mainly IL-1 (8). At this point IL-1 causes an inflammatory network by activating other immune cells including the MCs to produce IL-33, which actively participates in the allergic reaction.

IL-33

IL-33 (formerly IL-1F11) is a pro-inflammatory cytokine of the IL-1 family and is produced by several immune cells including macrophages and

Table I. *Organs that may be more frequently affected by toxicity after infusion of pro-inflammatory cytokine-releasing CAR-T cells.*

ORGANS	SOME EFFECTS
Brain	ataxia, headache, tremor, seizures
Blood	neutropenia, thrombocytopenia, lymphopenia
Liver	hyperbilirubinemia, transaminitis
Kidney	acute kidney injury
Lungs	hypoxia, tachypnea
Heart	hypotension, tachycardia

MCs (18). In addition, IL-33 generated by MCs contributes to allergic reactions (19). IL-33 acts through the ST-2 receptor of which there are two types, a transmembrane receptor (ST2L) and a soluble receptor (sST2) (18). IL-33 is released after cellular injury and/or necrosis by alerting. It contributes to inflammatory and allergic states and is expressed in various organs and cells, including lymphoid cells (20).

CAR-T therapy is a new potentially curative method for cancer. However, adverse reactions such as allergic phenomena, where MCs also participate, still remain obstacles to overcome. The generation of IL-33 from MCs and macrophages contributes to the inflammatory and allergic state (20). Therefore, inhibition of this cytokine with IL-37 may be a new strategy for an improvement of CAR-T therapy (21).

Interleukin-37

IL-37 has emerged as an important inhibitor of immune and inflammatory responses, and it has achieved remarkable efficacy in the treatment of inflammatory diseases (22). IL-37 binds to the IL-18R receptor and at low concentrations is capable of inhibiting innate immune reactions, reducing activation of the MyD88 receptor (23). IL-37 is mainly produced by macrophage cells after activation of the toll-like receptors (TLR) which leads to the formation of mature IL-37 through the action of caspase 1. IL-37 could abolish systemic inflammation and neurotoxicity caused by pro-inflammatory cytokines, including IL-1 and IL-33 with prolonged survival. This therapy could offer a new strategy in the treatment with CAR-T. cells.

The gene expression of IL-37 shows an up-regulation of messenger RNA in tumors including melanoma. This enhancement occurs mainly in Treg cells and in granulacites, which probably also include MCs. The up-regulation of IL-37 messenger RNA in tumors indicates a defensive state that the organism uses in neoplasia (24).

The inhibition of IL-1 and IL-33 with IL-37, a new anti-inflammatory cytokine, could be a new therapy, even if the indications of administration are still to be determined. However, treatment with IL-37 which is immune suppressant should be carried out with great care, because it could negatively affect the immune system and may cross-react with the good receptors which are not expressed on tumor cells.

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