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ASSESSMENT OF CYTOKINE RELEASE OF CAR-T CELL THERAPY PRODUCTS ON MOUSE MODELS

Cao Yang, Joinn (Suzhou) Pharmacology Department

At present, T cell-based tumor immunotherapy methods, such as CAR-T cells, enable T cells to directly kill tumor cells through non-MHC-dependent pathways. Great results have been achieved in clinical treatment of multiple hematological tumor diseases, such as B-cell lymphoma and acute lymphoblastic leukemia. However, while killing tumor cells, T cells are activated in large numbers, and cause a waterfall response of the immune system, resulting in the release of a large number of cytokines, which is clinically called cytokine release syndrome (CRS). It is currently one of the most serious clinical side effects of CAR-T cell therapeutical products. This article describes a mouse model used to evaluate the cytokine release intensity of CAR-T cell therapy products.

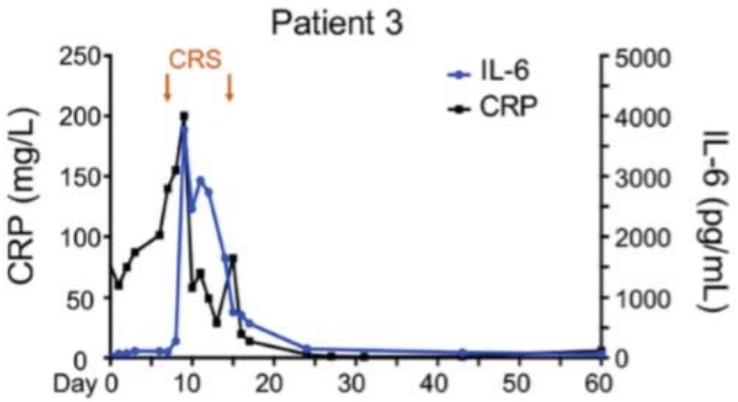


Figure 1 Clinically common cytokine release syndrome[1]

In pre-clinical research, researchers usually use immuno-deficient tumor-bearing mouse model as the experimental system, in which human-derived tumor cells/tissues provide antigens necessary for CAR-T cell activation, and mice with low immune functions provide a good environment for the colonization and expansion of CAR-T cells. Similar clinical effects can be observed in the above- mentioned experimental system, such as inhibition/regression of tumor growth, prolongation of animal survival period, and proliferation of CAR-T cells, but the cytokine release observed under normal circumstances is limited.

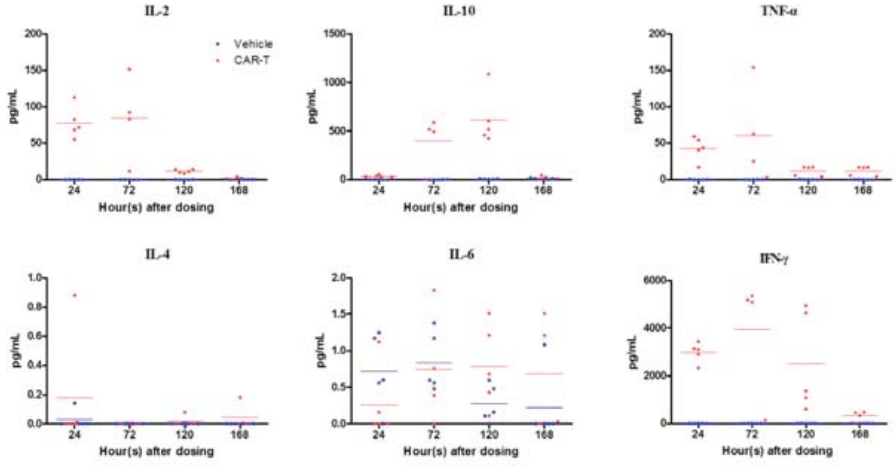


Figure 2 After CAR-T cell infusion, the serum cytokine level of tumor-bearing mice can be observed

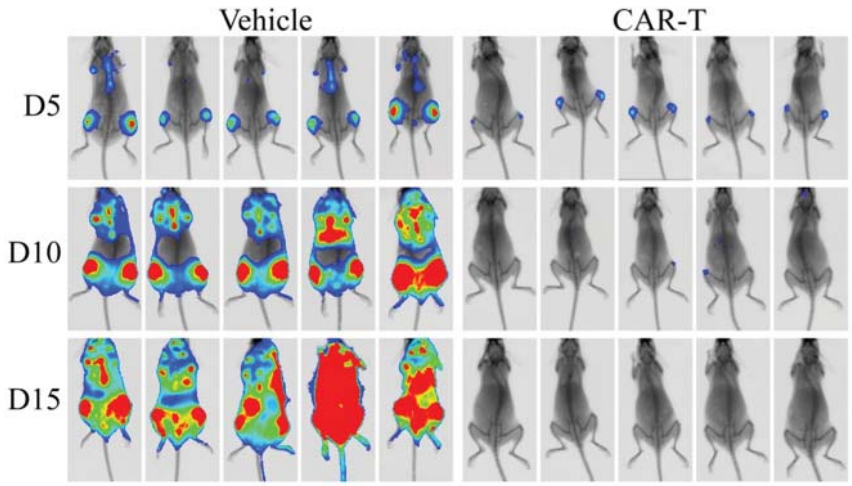
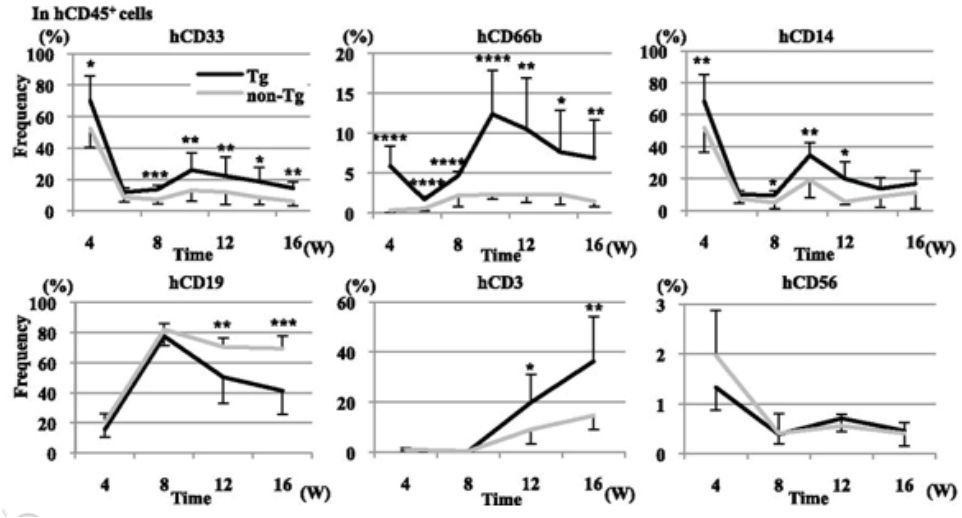


Figure 3 After CAR-T cell infusion, the tumor burden of mice is reduced

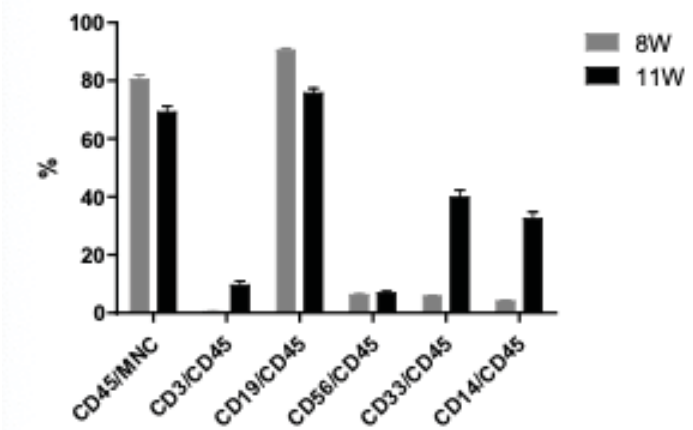
According to the research by Margherita Norelli et al[2], high levels of cytokine release can be observed in immune-reconstituted NSG-SGM3 mice. At the same time, there is evidence that the occurrence of CRS may be related to the activation of myeloid-derived cells. This explains why the cytokine release levels observed in immunodeficient mice lacking myeloid-derived cells or humanized PBMC and HSC mice are significantly different from the clinical ones.

NOG-EXL mice express human IL-3 and human GM-CSF with transgenic technology on the basis of NOG mice. With the support of these two human cytokines, artificial hematopoietic stem cells (HSC) used in NOG-EXL mice can be valued and differentiated more efficiently, and can support the differentiation of HSC into myeloid cells.



After transplanting cord-blood-derived CD34+ hematopoietic stem cells into NOG-EXL mice, differentiation of various types of immune cells, including T cells, B cells, NK cells and myeloid-derived cells, can be observed, which is consistent with the results reported by Ito R et al.[3]

Figure 4 After transplanting HSC into NOG-EXL mice, reconstitution of various immune cells can be observed[3]



After the HSC-NOG-EXL was given and CAR-T cells were infused, significant release of various cytokines could be observed, among which the highest release of IL-6 reached 6,000 pg/mL. However, the timing of cytokine release is earlier than that in clinical practice, and the duration is shorter.

Figure 5 8 and 11 weeks after HSC transplantation in NOG-EXL mice, the percentages of various immune cells, including T cells, B cells, NK cells and myeloid cells (n=24-30)

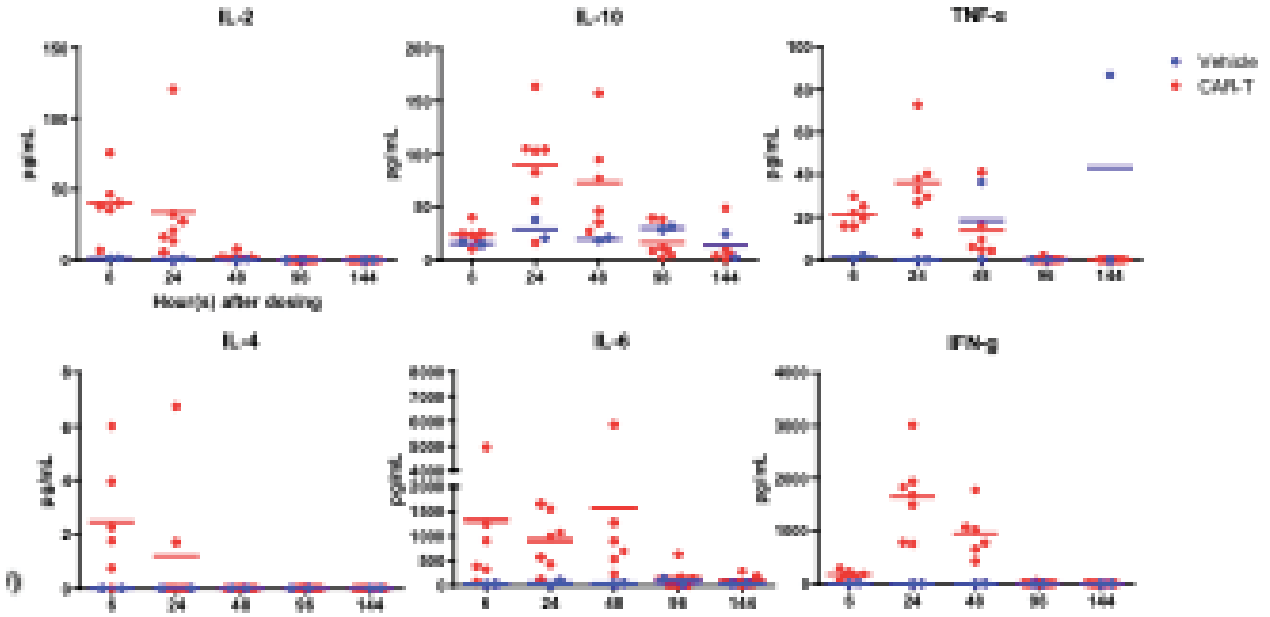


Figure 6 After CAR-T cell infusion, a significant increase in serum cytokine levels in HSC-NOG-EXL mice is observed

It can be concluded that, when researching on or predicting the cytokine release intensity of CAR-T cell products in the pre-clinical phase, immune-reconstructed NOG-EXL mice are a more suitable model than the conventional tumor-bearing mice.

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