GvHDHub

aGvHD

EHA 2019 |The role of iNKT cells in CAR immunotherapy and acute graft-versus-host disease prophylaxis

Anna Bartus Zara Kassam | Jul 04, 2019

At the 24th European Hematology Association (EHA) Congress in Amsterdam, Professor Anastasios Karadimitris from Imperial College London, London, United Kingdom, gave a presentation about invariant NKT (iNKT)-cells on Saturday, June 16. iNKT-cells control a variety of immune responses with the enhancement of anti-tumor and anti-pathogen responses, as well as protection from auto-immunity and allo-reactivity, especially in acute graft-versus-host disease (aGvHD).[1]

iNKT-cells are a rare type of T cells (a subset of TCRab T cells with patterns of adaptive and innate immune responses) and represent <0.1% of cells in the blood, with the ability to migrate and home into different tissues. These cells are controlled by non-polymorphic CD1d cells presenting a specific glycolipid HLA class I-like molecule. It was hypothesized that iNKTcells received from third-party donors would offer an 'off-the-shelf' treatment option for aGvHD.[2-4]

iNKT-cells for CAR immunotherapy

- In the last couple of years, chimeric antigen receptor (CAR)-T cell immunotherapy has been demonstrated to yield durable responses in patients with hematological malignancies
- A single dose of 2nd generation CAR19-iNKT-cells without in vivo cytokine support in comparison with CAR19-T cells shows superior anti-lymphoma effect in vivo through dual targeting of CD19 by CAR19 and of CD1d
- V. administered CAR19-iNKT cells rapidly reduced the number of secondary central nervous system lymphoma cells due to higher expression of integrins by iNKT-cells in order to move across the blood-brain barrier
- Upregulation of CD1d expression in lymphoma and CLL B-cells with all-trans retinoic acid leads to the augmentation of the anti-lymphoma effect of CAR19-iNKT-cells
- The pre-clinical potential of CAR-iNKT-cells in other CD1d-expressing malignancies such as multiple myeloma should be further explored
- The evaluation of CAR-iNKT-cells in the clinical setting is already underway

iNKT cells for aGvHD prophylaxis

- aGvHD is mediated by allogeneic T-cells
- Allo-iNKT-cells are not involved in aGvHD development, as a consequence, these cells would represent a promising platform for 'off-the-shelf' CAR immunotherapy without the necessity of TCR deletion
- Previous studies have shown that donor iNKT cells may prevent aGvHD without increasing relapse rates[5]

- Pre-clinical and clinical data showed that donor iNKT cells are able to prevent aGvHD without increasing the risk of disease relapse: transfer of donor CD4+ iNKT cells in the presence of alpha-galactosylceramide, a glycolipid that selectively and powerfully stimulates iNKT-cells, prevents the development of experimental aGvHD in an HLA mismatched setting
- Donor iNKT-cells were shown to be more than 10 times more effective than T_{regs} for aGvHD prophylaxis in mice without affecting the graft-versus-leukemia effect[6]
- Early posttransplant iNKT cell recovery can predict the occurrence of aGvHD and improved overall survival through a

Conclusions

- Pre-clinical and clinical evidence supports a critical role of donor iNKT cells in protection from aGvHD
- iNKT cells provide an optimal platform for chimeric antigen receptor-based immunotherapy of blood cancers
- iNKT cell-based, 'off-the-shelf' immunotherapy could be sourced from allogeneic, healthy donors without risk of aGvHD

References

1. Karadimitris A. Invariant NKT cells as a platform for CAR immunotherapy and prevention of acute graft-versus-host disease. EHA 2019.
2. Salio M. *et al*. Biology of CD1- and MR1-restricted T cells. Annu Rev Immunol. 2014;32:323–366.
3. Bendelac A. *et al.* The Biology of NKT Cells. Annu Rev Immunol. 2007;25:297–336.
4. Tian G. *et al*. CD62L+ NKT cells have prolonged persistence and antitumor activity in vivo. J Clin Invest. 2016;126:2341–2355.
5. Yang J. *et al*. Adoptive therapy by transfusing expanded donor murine natural killer T cells can suppress acute graft-versus-host disease in allogeneic bone marrow transplantation. Transfusion. 2010;50:407–417.
6. Leveson-Gower DB. *et al*. Low doses of natural killer T cells provide protection from acute graft-versus-host disease via an IL-4-dependent mechanism. Blood. 2011;117:3220–3229.
7. Rubio MT. *et al*. Early posttransplantation donor-derived invariant natural killer T-cell recovery predicts the occurrence of acute graft-versus-host disease and overall survival. Blood. 2012;120:2144–2154.