Trophoblast: the new player in Regenerative Immunology

PhD Project

Immunotherapy is rapidly emerging as providing a revolution in the treatment of cancer. The centre piece of this new therapy is the advent of Chimeric Antigen Receptor (CAR) technologies which are polygenic constructs consisting of an antibody fragment (scFv), targeting a specific cancer antigen, linked to cytoplasmic signalling domains. The expression of a CAR on T-cells or NK-cells enables them to not only track down the cancer, but the engagement of the CAR with its target antigen also induces activation of the effector cells and killing of the cancer cell; they are thus designated CAR-killer cells. Despite this ground-breaking advance in cancer immunotherapy, several practical issues are preventing widespread use of CAR-killer cells in clinical trials. If the killer cells are obtained from the cancer patient (autologous), they are limited in number and quality because of the impact of chemotherapy, radiation therapy and the cancer itself. The process to create autologous CAR-cells is also expensive, time consuming and it is difficult to maintain quality control in production. Accordingly, current strategies are aimed at developing "off-the-shelf" technologies, where the allogeneic CAR-T or CAR-NK cells have been pre-prepared in large numbers, sufficient to infuse into patients on demand. The most promising of these approaches is the derivation of CAR-iNK cells from induced pluripotential stem cells (iPSC), which have been previously genetically edited to contain the nominated CAR. The advantage of this system is that the iPSCs, per se, can be expanded indefinitely, theoretically providing a limitless source of CAR-NK cells.

However, an obvious drawback of the iPSC model is that the iNK cells produced will not be genetically matched to the patient (allogeneic) and hence are likely to be rejected by the patient's immune system. This is a perennial problem with allogeneic transplants. Recently, a potentially ground-breaking solution has emerged from an understanding of one of life's great immunological paradoxes– the acceptance by the mother of her fetus, despite the production of "non-self" paternal HLA by the fetus.

One of the key underling mechanisms that restricts fetal immune rejection by the mother has recently been revealed. It is focussed on the trophectoderm layer of the blastocyst (fetal), which is in direct contact with the uterus (maternal). The rapid production and proliferation of this extra-embryonic cell layer, early in embryogenesis, generates a unique type of placental cell, the trophoblast, which provides the interface between the fetal and maternal blood, enabling nutrient and waste exchange between the mother and fetus. The most extensive contact between fetal derived cells and maternal blood cells is formed by the highly vascular embryonic placental villi which are lined by trophoblasts forming a barrier, the syncytiotrophoblast, which floats in maternal blood. The failure of the mother to reject the fetus is not, however, due to a physical barrier. What is now clear is that the trophoblasts have the unique characteristic of expressing HLA- C, -E and -G; they have limited polymorphism and restricted adult tissue distribution. These are important features, because each deliver immune suppression signals when they engage their corresponding ligands, which are highly expressed on the surface of NK cells. For example, the ligand for HLA-E is NKG2A (complexed with CD94), on NK cells. Several receptors have been identified for HLA-

G, such as CD85j/immunoglobulin-like transcript 2 (ILT2), CD85d/ILT4, and CD158d/killer cell immunoglobulin-like receptor 2DL4 (KIR2DL4).

Maternal NK cells are found in high abundance at the placental interface with the fetus. The engagement with the syncitiotrophoblast is proposed to deliver immune suppressive signals to the NK cells, very likely preventing the destruction of fetal cells and tissues. The trophoblasts also express the immune inhibitory molecules Fas Ligand, TRAIL, and Indoleamine 2,3-dioxygenase (IDO) which further suppress NK cell function.

More recently, two key additional features of trophoblasts have aroused great interest in the field of regenerative medicine: they are pluripotential stem cells and they are very easily propagated in vitro. Combined with their propensity to avoid immune rejection in the allogeneic setting, trophoblasts may represent an exciting new source of cells for production of "off-the-shelf" immune effector cells. The adaptation of this concept to the induction and characterization of "off-the-shelf" trophoblast-derived NK cells (trNK cells), and extending these to express cancer specific CARs (CAR-trNK cells) forms the basis of this novel PhD project.

The basic aims of this project are to answer the following questions:

1. Can trophoblasts be induced into phenotypic and functional trNK cells in vitro?
2. If so, does the model provide advantages over more common iPSCs as the primary source of cells?
3. How closely do the characteristics of differentiated trNK cells resemble normal blood NK cells?
4. Are trNK cells produced from trophoblasts functional in killing cancer cells in vitro and in vivo?

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Collaboration: This project will be undertaken in collaboration with Accelerated Biosciences, who will provide the trophoblasts under an MTA which is currently being negotiated, and research input from Dr. Yuta Lee, President and Founder of Accelerated Biosciences.

Selected References:

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