SUMMARY (basic) 4/18/25 ciT1zen science

Progress and challenges in developing allogeneic cell therapies.

ciT1zen science summary

Source: Progress and challenges in developing allogeneic cell therapies, Deuse, Tobias et al.Cell Stem Cell, Volume 32, Issue 4, 513 – 528.

Summary:

Reviewing the rapidly evolving field of allogeneic cell therapeutics. The central challenge in this field is overcoming immune rejection to create scalable and widely accessible "off-the-shelf" therapies. The paper highlights various gene engineering strategies aimed at generating immune-evasive cells, contrasting them with the current state of autologous cell therapies and the limited data on allogeneic cell replacement. While autologous therapies avoid initial immune rejection, the paper questions their absolute immunologic inertness and emphasizes the potential of allogeneic cells, particularly those engineered for comprehensive immune evasion, to revolutionize the treatment of diseases ranging from cancer to autoimmunity and regenerative medicine. The development of "hypoimmune" cells, which evade both adaptive and innate immunity, is presented as a promising path forward, with recent preclinical data in various disease models showing significant potential.

Main Themes and Important Ideas/Facts:

1. The Promise and Challenge of Allogeneic Cell Therapeutics:

- The field of cell therapeutics is advancing rapidly, with the potential to treat a wide array of diseases.
- While autologous cell therapies (using a patient's own cells or iPSC derivatives) have been the initial focus to avoid immune rejection, allogeneic cell sources from healthy donors offer significant advantages in terms of scalability and manufacturing.
- **"therapeutics derived from allogeneic cells could be scaled and made available for a much larger patient population if immune rejection could reliably be overcome."**
- The primary obstacle hindering the widespread adoption of allogeneic cell therapies is the host immune system's rejection of foreign cells.
- The paper emphasizes that achieving reliable immune evasion is crucial for the future success of allogeneic cell therapies.

2. Questioning the Immunologic Inertness of Autologous Cells:

- The assumption that autologous cells are always immunologically neutral is challenged.
- **"The notion that products derived from autologous cells are always immunologically inert and accepted as self deserves questioning."**

- Neoantigens can arise during the ex vivo engineering and expansion of autologous cells due to mutations or genetic drift.
- The immune system can detect and respond to these neoantigens, leading to rejection even of autologous cell products.
- **"Immunogenic antigens can undergo unchecked amplification in the absence of immune surveillance and render the cell product immunogenic when transplanted back into the same cell donor."**
- Studies in immunocompetent mice and humans have demonstrated immune responses to engineered autologous cells.

3. Mechanisms of Allogeneic Immune Rejection:

- Allogeneic T cells, specifically αβT cells recognizing alloantigen peptides bound to MHC molecules, play a central role in graft-versus-host disease (GvHD).
- Knocking out the *TRAC* gene to prevent TCR-α chain expression is a common strategy in allogeneic αβT cell therapies to mitigate GvHD.
- Innate immune cells like γδT cells and natural killer (NK) cells have distinct mechanisms of allorecognition.
- Beyond immune rejection, the persistence of transplanted cells can be affected by factors such as the cell type's lifespan, cellular fitness, cytokine armoring, molecular determinants, and the presence of antigen.
- **"Transplanted allogeneic immune cells can vanish for multiple reasons (Figure 1). The most obvious is immune rejection by the host immune system, but the lifespan of the cell type, cellular fitness, cytokine armoring, molecular determinants, the presence or absence of stimuli, and the preconditioning can also have a major impact."**

4. Strategies for Immune Evasion:

- The paper distinguishes between achieving immune evasion (avoiding detection and destruction) and establishing immune tolerance (active unresponsiveness). The focus of the review is on immune evasion.
- **"The aim for circumventing immune rejection of cell therapeutics should not be confused with the establishment of immune tolerance..."**
- The concept of "hypoimmune" cells is introduced, where immune evasion is achieved by avoiding T cell detection and providing a dominant blocking signal to the innate immune system.
- Key gene engineering strategies for immune evasion are discussed, targeting interactions with T cells, NK cells, and macrophages (Figure 2).
- **Avoiding T cell detection:** Knockout of *B2M* and *CIITA* genes to deplete HLA class I and II presentation, respectively.
- **Inhibiting NK cells:** Overexpression of CD47 (engaging SIRPα), and exploring agonistic ligands for other inhibitory NK cell receptors like TIM3 and CD300a, or overexpression of HLA-E or HLA-G.

- **Modulating activating NK cell ligands:** Knockout of stimulatory ligands to elevate the activation threshold.
- **Protecting from antibody-mediated rejection:** Overexpression of truncated CD64 to block IgG binding or expression of membrane-tethered or secreted IgG proteases (IdeS).
- Partial immune evasion strategies, such as retaining certain HLA molecules for matching, face challenges regarding reliability, universality, and potential for rejection.
- Strategies involving the expression of T cell immune checkpoint ligands (PD-L1, CD80/CD86) or secretion of inhibitory agents (TGF-β, IL-10, IL-2 mutein) have shown varying degrees of success.

5. The Hypoimmune Platform (HIP) Concept:

- The HIP concept, involving knockout of *B2M* and *CIITA* and overexpression of *CD47*, is presented as a comprehensive immune evasion strategy.
- **"The hypoimmune platform (HIP) concept is a specific hypoimmune strategy, comprising knockouts of the B2M and CIITA genes to achieve HLA class I and II depletion and overexpressing CD47, that has been shown to fully protect engineered cells from all allogeneic adaptive and innate immune cells..."**
- CD47's interaction with SIRPα on macrophages ("don't eat me signal") and its more recently discovered inhibitory effect on NK cells are highlighted.
- Preclinical studies in a HIP mouse model (MHC I/II deficient, CD47 overexpressed) showed normal viability and no increased risk of viral infections or tumors.
- Transplantation of HIP cells in immunocompetent allogeneic mice demonstrated long-term survival and function without triggering immune responses.
- **"Hypoimmune cells escape all cellular and humoral cytotoxicity and are able to survive and persist within ongoing rejection."** (referring to Figure 3)

6. Application of Immune Evasion Strategies in Different Cell Types and Diseases:

- **Immune Cell Therapies (CAR T/NK Cells):**Allogeneic CAR T cells with *TRAC* knockout are in clinical development.
- IL-15 or IL-21 armoring can enhance the persistence of CAR NK cells.
- The potential for repeated redosing without loss of efficacy is a key advantage of allogeneic immune cell therapies.
- HIP engineering has been applied to primary human CD19 CAR T cells, demonstrating protection from allorejection without sorting.
- **Cell Replacement Therapies (Islet Cells for Diabetes, Cardiomyocytes for Heart Failure, Neurons for Parkinson's):**Autologous iPSC-derived cells are being tested to avoid immune rejection in diseases like Parkinson's and diabetes.
- Clinical trials using unprotected allogeneic embryonic stem cell-derived islet cells for type 1 diabetes require chronic immunosuppression.
- Encapsulation devices offer a physical barrier but face challenges with oxygenation.

- Partial immune evasion strategies for islets (HLA class I/II depletion alone) have had limited preclinical success.
- HIP-engineered iPSC-derived and primary human islets have shown promising preclinical results in allogeneic and autoimmune diabetic models, achieving engraftment and glycemic control without immunosuppression.
- **"Human islets derived from HIP iPSCs were transplanted into immunocompetent, allogeneic, diabetic humanized mice and showed resistance against allorejection. Survival, engraftment, and alleviation of diabetes could be achieved, and no immune response against HIP islets was observed."**
- HIP-edited primary rhesus monkey islets demonstrated blood glucose control in allogeneic diabetic cynomolgus monkeys for over half a year without immunosuppression.
- Early clinical results of unmodified allogeneic islet transplantation without immunosuppression show initial signs of cell survival and function.
- Preclinical studies with HIP-engineered cardiomyocytes showed survival and improved heart function in allogeneic mice.

7. Other Considerations:

- The role of "veto cells" in allogeneic cell products, which can induce immunomodulation, is briefly discussed.
- "Stealth transgenes" are being explored to evade host immune responses against the transgene itself.
- The potential for viral persistence in HLA-depleted hypoimmune cells requires further investigation.
- Manufacturing and quality control are critical aspects for the clinical translation of allogeneic cell therapies.

Conclusion and Outlook:

The paper presents a compelling overview of the significant advancements in engineering immune-evasive allogeneic cell therapeutics. The development of comprehensive strategies like the hypoimmune platform holds immense promise for creating universal "off-the-shelf" therapies that can overcome the limitations of autologous approaches and the need for immunosuppression. While challenges remain, the preclinical data, particularly with HIP-engineered cells in various disease models, provides a strong and optimistic outlook for the future clinical success of allogeneic cell therapies.

Conflicts of Interest:

- "T.D. is a consultant to Sana Biotechnology and owns stock. T.D. is a consultant to Shinobi Therapeutics and owns stock. S.S. is an employee of Sana Biotechnology and owns stock. T.D. and S.S. have patent applications covering immune evasion topics." This disclosure highlights potential biases and the active involvement of the authors in the development of these technologies.