Novel Machine Learning Technique Identifies Populations of Stimulated Mesenchymal Stromal Cells with Immunosuppressive Activity

A technique developed at FDA for computer-assisted analysis of thousands of images of stimulated human mesenchymal stromal cells (MSCs) identifies morphological characteristics that could serve as quality control markers during large-scale manufacturing of immunosuppressive cell therapies.

“Morphological profiling using machine learning reveals emergent subpopulations of interferon-γ-stimulated mesenchymal stromal cells that predict immunosuppression”

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The potential medical benefits of immunosuppressive MSCs

Treatment of immune-system-based disorders
- Therapies: Immune system disorders, such as graft-versus-host disease, type 1 diabetes, and multiple sclerosis.
- Tissue and organ transplants: Preventing immune rejection of tissue grafts and organ transplants.

The problem this work addresses

Functional heterogeneity is a barrier to many promising cell therapies
- Functional heterogeneity: Donor-to-donor and intra-population variation in the ability of MSCs to suppress immune system activity after being stimulated in vitro with Interferon-γ (IFN-γ).
- Wide variations in clinical trial outcome: Outcomes from clinical trials using stimulated MSCs obtained from different human donors and grown in different bioreactors by different manufacturers vary widely, which complicates studies of potential MSC-based immunosuppressive therapies.

One potential solution to the problem of functional heterogeneity

Functionally-relevant morphological profiling (FRMP) and Visual stochastic neighbor embedding (viSNE)
- FRMP: 1) Quantifies subcellular, single cell, or multicell morphological attributes of MSCs (e.g., cell perimeter, cell radius, nuclear perimeter; 2) identifies correlations between the number of cells in distinct morphological subpopulations and the degree of immunosuppression displayed by different preparations of MSCs.
- viSNE: Machine learning technique that identifies specific subpopulations of stimulated MSCs that share certain morphological attributes.
- Quality control markers: FRMP/viSNE enables identification of specific morphological attributes that predict whether any one of several populations of MSCs responded to IFN-γ by developing the ability to suppress two key immune T cells, CD4+ and CD8+.

How viSNE is used to find MSCs with immunosuppressive potential

Grouping MSCs according to morphological traits linked to immunosuppressive activity
- Grouping MSCs according to shared morphological traits: viSNE was used to group stimulated MSCs into 14 different clusters, based on which traits each cell shares with other MSCs in that cluster.
- Linking morphological traits with immunosuppressive activity: viSNE links each cluster of MSCs having shared morphological traits to the relative ability of those clusters to suppress CD+4 and CD+8 T cells. This identifies the sets of morphological characteristics that reflect immunosuppressive activity.

The potential role of FRMP/viSNE in stem-cell-based therapies

Supporting large-scale manufacturing by understanding functional heterogeneity
- Facilitating large-scale production in bioreactors: FRMP/viSNE could facilitate identification of immunosuppressive MSC preparations and optimize manufacturing methods.
- Broader therapeutic uses of FRMP: Unlocking the potential medical benefits of different human donors and grown in different bioreactors by different manufacturers. Such understanding could support optimized production of safe and effective MSC-based immunosuppressive therapies. This strategy might also be successfully used to assess how other types of stem cells respond to different growth factors, thus providing critical insights into how best to develop stem-cell-based therapies for a variety of disorders.