Threat of Biocompatibility due to Allogeneic Cells in Tissue Regenerative Matrices

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Introduction:

Not every molecule secreted by an allogeneic donor cell is biocompatible in the host tissue. The fact is: "No two individuals' tissues are immunologically biocompatible." The purpose of this article is to highlight our misconception about adding a third person's living cells to enhance the tissue regenerative value of a scaffold. We just take such products meant for the treatment of wounds and analyze them here as a general review.

The genome makeup of fibroblasts differs between individuals and thus, fibroblasts of one person will not express similar proteins in another person. This is one of the key scientific factors why allograft cells like fibroblasts are not that much compatible with the host tissue. The molecules secreted by the fibroblasts of a different human may not be compatible with the host tissue due to the genomic difference between the two human individuals.

Several company products that incorporate the fibroblast of a third person in their matrices to function as a universal tissue regenerative cell system may not be ideal.

Methods:

We notice there are varied matrices in the current usage. Among such scaffold biomaterials, we address the purpose and cell delivery potentials of different matrices in a separate review article. In general, from a scientific point of view, only certain molecules are proven to be immunologically safe based on the high degree of amino acid sequence homology. One such matrix is Type-I collagen which has maximum homology with other species of Type-I collagen, either Allograft or Xenograft. Accordingly, the allogeneic cell incorporation in all kinds of matrices may not be appreciated from the effective functioning of such cells. Besides this awareness, the major misconception to be reviewed is that there may be deleterious end-result through the secretion of bio-incompatible molecules by those donor cells. Let us see the details in the coming sections of this article.

Discussion & Conclusion:

Overall impacts of allogeneic cells especially fibroblasts or keratinocytes and dermal Langerhans and dendritic cells of allogeneic origin in host tissue upon usage for treatment are being discussed here. Further, we also add the fate of allogeneic Stem cells in the host tissues. Immune rejection of allogeneic keratinocytes can be explained by the difference in HLA expression and cytokine production[1]. Under a controlled animal model, it has been well established that allogeneic fibroblasts transplanted into mouse skin cause rejection of the skin implant by inflammatory immune response[2].

Fibroblasts from different donors display inter-individual variable responses to innate immune stimuli, that may translate into a stromal-specific inter-individual response variability[3].

Further, in the wounds covered with allogeneic fibroblasts, the epithelization was slowest[4].

It is also reported that the allograft with viable cells when transplanted on a healthy recipient, rejection occurs within 2 weeks. Such rejection is mediated by the activation of T cells which is directed primarily against the Langerhans cells of the epidermis and Dendritic cells of the dermis[5,6].

With respect to Stem cell incorporation, Embryonic Stem Cells (ESCs) may not be safe; as they may cause immune rejection and stimulation of tumor formation. Therefore, ESCs are rarely employed for the treatment of Diabetic Foot Ulcers (DFUs)[7,8].

Moreover, the stem cells derived from the umbilical cord may lead to immunological rejection due to their allogeneic nature and thus their immunogenicity must be carefully evaluated prior to their use in clinical applications[9].

In conclusion, it is in the hands of the product developers and regulators to further investigate the safety concerns of allogeneic cell-incorporated wound matrices. This concept of a potentially negative impact can also be extrapolated to frozen cadaver skin applications. A thorough review of our literature survey documents that there is no single well-accepted cell-seeded product in the market that supersedes other tissue regenerative products currently.

Matrix Type	Allogeneic Cell Types	Purpose
Xenograft type I collagen with cultured cellular matrix	Human neonatal fibroblasts & keratinocytes	Treatment of venous ulcers and diabetic foot ulcers
Synthetic polymer scaffold seeded with fibroblast	Human neonatal fibroblasts	Treatment of venous ulcers and diabetic foot ulcers
Xenograft collagen coated nylon mesh seeded with fibroblast	Human neonatal fibroblasts	Treatment of full-thickness skin wounds
Cryopreserved human skin with live skin cells	Human skin cells	Treatment of venous, diabetic foot, pressure ulcers & burns
Cryopreserved human chorionic placental tissue with 70% living cells	Human placental tissue cells	Treatment of acute and chronic wounds
Xenograft type I collagen sponge cultured with fibroblast	Human skin fibroblasts & keratinocytes	Treatment of chronic wounds and skin graft donor sites
Xenograft collagen cultured with fibroblast	Human dermal fibroblast & keratinocytes	Treatment of deep partial thickness burns
Xenograft collagen cultured with fibroblast	Human fibroblast & keratinocytes	Treatment of muco-gingival conditions

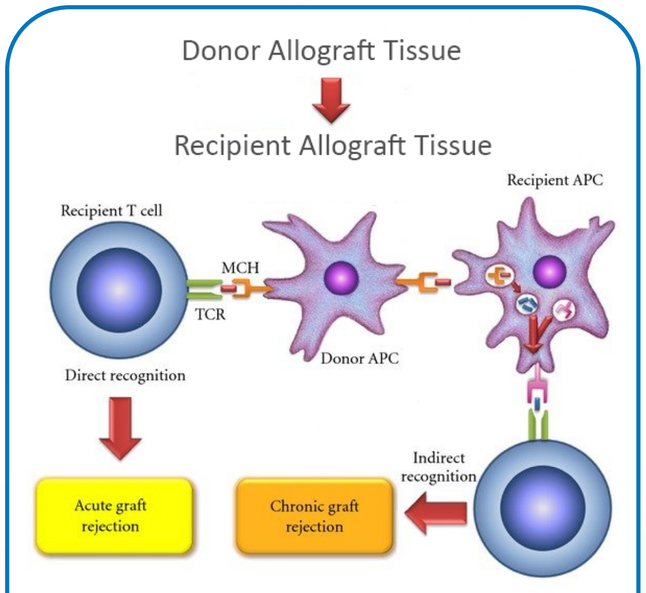

Fig. 1: Biological Pathway of Allograft Rejection

References:

1.https://stemcellres.biomedcentral.com/articles/10.1186/s13287-019-1203-3#ref-CR44
2.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9340901
3.https://www.frontiersin.org/articles/10.3389/fimmu.2020.569331/full
4.https://pubmed.ncbi.nlm.nih.gov/15836851/
5.https://www.ijburns.com/article.asp?issn=0971-653X;year=2018;volume=26;issue=1;spage=66;epage=71;aulast=Agarwal
6.Janeway, C.A., Travers, P., Walport, M. and Capra, D.J., 2001. Immunobiology (p. 600). UK: Garland Science: Taylor & Francis Group.
7. https://pubmed.ncbi.nlm.nih.gov/22221581
8.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8844366
9. https://pubmed.ncbi.nlm.nih.gov/24635168

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