

Module 12 Assignment

585.751 Immunoengineering

1. (100points) The immune system plays a key role in tissue engineering and regenerative medicine that is still being elucidated. Answer the following questions about tissue engineering and the immune system:

1. (10points) What are the 3 major components of a biomaterial for tissue engineering?

- **Cells:** typically, precursor stem cells for the tissue type being regenerated or replaced (in some cases differentiated cells).
- **Scaffold/Matrix:** designed to be biodegradable, and porous so that cells can migrate through the scaffold. It provides structural support to allow the cells to attach as they're forming the tissue and their migration; and shape designed to fill the tissue defect.
- **Bioactive cues:** are different signals on the scaffold to allow for attachment and migration; including signals to cells for proliferation, and differentiation.

2. (45points) List 3 ways in which the immune system has been shown to be involved in tissue regeneration (either from the lecture videos or your own research).

- **Macrophage-Mediated Tissue Regeneration**

Macrophages (M2a and M2c) are mainly triggered by IL-4 and contribute to the wound healing process by producing extracellular matrix (ECM) proteins like fibronectin, which activate fibroblasts. Regulatory macrophages (M2b) help limit inflammation and promote tissue regeneration. Macrophages also influence the repair of various tissues such as neurons in spinal cord injuries, osteoblasts in bone defects, and myogenic cells in muscle injuries. For example, in muscle repair, macrophages contribute to the proliferation and differentiation of myoblasts, while in central nervous system (CNS) injuries, they play a role in the remyelination of neurons.

- **Immune Cells in Angiogenesis and Vascular Remodeling**

Immune cells play an important role in vascular remodeling and promoting angiogenesis, which are essential for revascularizing regenerating tissues to ensure they receive sufficient nutrients and O₂. A variety of immune cells, including M1 and M2c macrophages, dendritic cells, mast cells, eosinophils, and neutrophils, secrete pro-angiogenic mediators that stimulate the formation of new blood vessels from existing ones. Later, M2a, M2c macrophages, NK cells, and CD4⁺ T-cells, induce arteriole genesis and vascular remodeling via secreted mediators.

- **Regulatory T Cells (Tregs) in Modulating Inflammation and Tissue Repair**

Tregs are involved in tissue regeneration and repair by modulating the inflammatory response. They help neutralize inflammatory cytokines and inhibit neutrophil extravasation. Tregs promote apoptosis of neutrophils and enhance the phagocytosis of dead neutrophils, clearing the inflammatory site. Additionally, they inhibit the activity of M1 macrophages and encourage the polarization towards the M2 phenotype, which is more conducive to healing. Tregs also suppress effector T-cells, further supporting tissue repair and regeneration. Research has also shown that Th2 T-cells are important mediators at scaffold remodeling.

3. (45 points) Briefly describe 3 ways in which a biomaterial for tissue engineering can be designed to modulate the immune system in order to improve regeneration.

- **Manipulating Physicochemical Properties**

The design of biomaterials can be tailored by adjusting their physicochemical properties, such as degradability, hydrophobicity, topography, and cross-linking density. Choosing between synthetic and naturally derived materials also impacts how immune cells respond to the implant. These modifications can influence the recruitment and activation of immune cells, driving specific phenotypes in macrophages and T cells that are conducive to regeneration.

- **Pro-inflammatory Modulator Delivery**

Biomaterials can be engineered to release pro-inflammatory modulators, such as growth factors, cytokines, and chemokines. These substances help initiate the immune response necessary for tissue repair by promoting the recruitment and activation of immune cells at the site of injury.

- **Anti-inflammatory Modulator Delivery**

This includes:

Cytokines and Chemokines: Encapsulating cytokines within the scaffold to promote the polarization of immune cells towards anti-inflammatory phenotypes, such as M2 macrophages over M1, and increasing Th2 cells relative to Th1.

Cell Recruitment: Using chemokines to attract regulatory immune cells like Tregs or mesenchymal stem cells (MSCs) to the site of injury.

MiRNA Targeting: Incorporating immunoregulatory miRNAs into the biomaterial to modulate immune cells like neutrophils and macrophage anti-inflammatory phenotypes.

(Or a combination of initially pro-inflammatory modulators followed later by anti-inflammatory modulators)