Challenge based learning (CBL)

Modification and engineering of extracellular matrix enzymes to reverse and resolve fibrosis

Note for teachers: A CBL user guide can be found at www.jandeboerlab.com/TissueEngineering with instructions and tips to run an effective CBL teaching session.

Background and vision

The extracellular matrix (ECM) is a ubiquitous and dynamic network of macromolecules that forms a scaffold for cells, tissues and organs. The ECM is organized in a tissue specific manner and is constantly undergoing remodeling due to its interaction with proteins, growth factors and other bioactive molecules. Thus, the ECM can continuously change the microenvironment the resident cells are exposed to. These ECM changes can alter processes like homeostasis, cellular proliferation, differentiation, tissue development, cellular adhesion, and migration. In addition, the ECM can guide the body's response to injury. Abnormal response and/or chronic tissue injury results in excessive accumulation of ECM in and around damaged organs. This causes scarring or fibrosis and, if unchecked or uncontrolled, can lead to organ failure. A long-term goal of the healthcare industry is to develop therapeutic methods to prevent or control organ fibrosis.

Motivation and stakeholders

Fibrotic diseases of organs (kidneys, lungs, liver and heart) remain a major health problem globally and account for one third of all deaths worldwide. Even though organ transplantation is currently used to manage organ failure, reasons such as shortage of organs, complications due to life-long immunosuppression in transplant patients, and transplant rejection make this option less than ideal. The study of the fibrosis process reveals that it shares common but complex cellular and molecular pathways across organs. Fibrosis is also neither static nor irreversible since matrix-degrading enzymes produced by the ECM play an important role in tissue remodeling and wound healing. Targeting these enzymes by regulating their expression can be an efficient tool for limiting or reversing fibrosis. Solutions to mitigate organ fibrosis should consider the needs, requirements and regulatory, financial and technical boundary conditions defined by stakeholders such as patients suffering from fibrotic diseases, the clinicians involved in their care, biomaterial scientists and bioengineers.

Problem definition

At the moment, there are no approved treatments that use targeted administration of matrix-degrading enzymes to control fibrosis and associated organ failure. There is a need for a strategy where an off-the-shelf implant carrying matrix-degrading enzymes could be activated at the fibrosis site.

Challenge

To design a biomaterial-mediated strategy by delivering engineered enzymes to increase their matrix-degrading activity to target organ fibrosis without sacrificing the tissue's normal structure and function.

Learning framework

Reading the Extracellular Matrix chapter and related literature will help you to understand that:

1. ECM is highly heterogenous and the composition varies between tissues. Revise and understand the basic components and organization of the ECM that are commonly encountered in all tissues.
2. Fibrosis results in inflammation caused by a variety of stimuli, which leads to excessive deposition of ECM components. Describe what triggers fibrosis and what steps are involved in this process.
3. Describe the molecular mechanisms that trigger fibrosis which are shared across tissues and organs.
4. Understand the pathologic signaling pathways involved in fibrosis.
5. Define tissue regeneration and how it is different to fibrosis.
6. Describe the ECM factors and pathways responsible of tissue regeneration after injury.

For a more focused examination of the challenge, read scientific literature and create a mind map to include information about the following:

7. The triggers for the resolution of fibrotic tissue. Include the function of fibroblasts, myofibroblasts and fiber-degrading enzymes.
8. Study the delivery modes to locally restrict the activity of matrix-degrading enzymes. Include strategies to control the dosage of these enzymes at the injury site.

9. Understand the different strategies being used by tissue engineers to slow down or disrupt fibrosis to regain organ function.
10. Describe the common targets in the ECM pathway that can be used to reverse fibrosis.
11. Describe and understand the different types of implants (natural and synthetic) being used to reverse fibrosis. Also, study the potential response the hosts can triggered upon implantation of such materials.
12. Understand the mechanism of action of matrix-degrading enzymes involved in fibrosis.

End Product
A three-minute video explaining the solution of your challenge. Please include your motivation and the steps to execute your solution.