The role of AMPK, FOXN1 and vitamin D in the regulation of fibrosis, wound healing and skin regeneration.

Fibrosis is a condition where tissue becomes thickened and hardened due to an excessive buildup of collagen and other extracellular components. The best example is the formation of a scar as a result of abnormal wound healing or chronic inflammation. Unfortunately, it must be emphasized, that fibrosis can affect any organ in the body.

Fibrotic disorders are responsible for 45% of all deaths in developed countries, making them one of the major health challenges. Skin fibrosis can be caused by various factors including systemic diseases, scar formation, or could be drug-induce. Formation of scar impairs the physiological and mechanical properties of the skin and subsequently leading to aesthetic and psychological distress.

During a healthy wound healing, immune, cells such as macrophages, clear damaged tissue and remove dead cells in a process called efferocytosis. If the process does not function properly, the dead cells are not removed. This results in the release of harmful molecules that cause inflammation and scarring. The process is also regulate by molecules presented on the surface of the cells. The dead, damage or unwanted cells present “eat me” signals, while molecules such as CD47 and CD24 (“don’t eat me” molecules) on the living cells prevent their removal. However, it has been demonstrated that in pathologies such as cancer “don’t eat me” signaling can block efferocytosis leading to long-term tissue damage. Recent studies have highlighted that problems with cell metabolism (bioenergetics) and inflammation are underlying issues in fibrotic diseases.

The aim of this proposal is to explore the mechanisms and potential therapeutic targets that could improve the clearance of dead cells, remodeling of fibrotic tissue and reduction of excessive scarring of the skin. We plan to investigate the role of AMP-activated protein kinase - AMPK - one of the key cellular energy sensors that can restore metabolic balance in cells. We will also investigate the biological effects of vitamin D on skin architecture and the regulation of immune cell function. Additionally, an impact of the transcription factor FOXN1 on skin regeneration including wound healing and scarring will be tested.

Our research will focus on three main tasks. At the beginning of the project (AIM 1.) we will try to understand how FOXN1 affects the development of skin fibrosis. We will prepare an animal model of skin fibrosis and assay all the markers of fibrosis. Next, we will evaluate the potential of AMPK activators, such as metformin and test the efficacy of vitamin D to enhance the clearance of dead/ damaged cells in fibrotic skin areas (AIM 2.). Finally, we will further explore how AMPK and vitamin D treatments influence the signaling pathways that prevent macrophages from clearing dead cells within fibrotic lesions and scar tissue. A mouse model of bleomycin-induced skin fibrosis, mice lacking the active FOXN1 gene, and human skin derived from fibrotic lesions and scars will be used to conduct the study.

The implementation of this proposal will expand our knowledge of the role of FOXN1 in fibrosis development. We will also aim to develop new therapeutic strategies involving AMPK activators and vitamin D that could improve skin healing, reduce scarring, and decrease fibrosis. Furthermore, the results of this project could lead to better treatments for patients with fibrotic diseases affecting other organs, such as the liver, lungs or kidneys.