Are MCPIP1 and MCPIP3 analogous or opposite players in the maintenance of skin function?

Keratinocytes build the outermost layer of skin. They play a crucial role in skin immunity and epidermal repair. Co-ordinated processes of keratinocyte proliferation, differentiation and migration ensure proper epidermis function. Disruptions of the balance between these processes can result in the development of skin disorders, such as psoriasis or atopic dermatitis.

MCPIP1 and MCPIP3 belong to the MCPIP family of proteins, which have RNase properties. So far, the MCPIP1 protein has been the most extensively studied. It negatively regulates the half-life of transcripts encoding proteins related mainly to inflammation (e.g. IL-6, IL1-β), but also other processes such as apoptosis or differentiation. Available data describing the role of MCPIP3 protein is very limited. It has been shown that mice deficient of MCPIP3 do not develop autoimmunity. This is in contrast to the MCPIP1-knockout mice, which develop severe systemic inflammatory syndrome.

Published data indicate that both MCPIP1 and MCPIP3 are transcriptionally activated in human psoriatic epidermis. We have previously shown that the loss of MCPIP1 function specifically in murine keratinocytes impairs epidermal proliferation and differentiation balance. As a result, it progressively leads to the impairment of skin integrity and development of skin inflammation. Moreover, mice deficient of keratinocyte MCPIP1 are more susceptible to the development of psoriasis-like inflammation. Our preliminary results indicate that MCPIP3 protein is expressed in healthy human skin, but its expression profile is different compared to that of MCPIP1. We hypothesize that MCPIP3 protein is also involved in the regulation of keratinocyte biology and is essential for proper function of epidermis.

Within this project we will utilize an unique model of conditional knockout mice that lack MCPIP3 specifically in epidermis. This model will be utilized to investigate the function of MCPIP3 in the regulation of proliferation and differentiation of keratinocytes as well as susceptibility to the induced inflammatory and allergic reaction of the skin. These research will enable to identify similarities and differences the two RNases, MCPIP1 and MCPIP3, play in skin biology. In parallel to the mice studies, we will develop *in vitro* models to identify set of proteins interacting specifically with MCPIP1 and MCPIP3 RNases in normal human keratinocytes, which will provide mechanical understanding of their activity.

This project will result in the description of the function of MCPIP3 protein in skin biology. The identification of molecular factors and signaling pathways that contribute to the maintenance of epidermal homeostasis is an enabling step for the development of novel therapeutic strategies towards the treatment of skin-related disorders.