OPUS Dec2022 Abstract

In this project we are going to investigate an essential skin protein, called profilaggrin, produced by the cells forming the uppermost layer of the skin, which is the epidermis. These cells, called epidermal keratinocytes, produce profilaggrin and store it in granules until it is needed. The reason why the cells do this is that filaggrin, which is released from profilaggrin by enzymes, is cytotoxic, which means that it causes cell death. Death of keratinocytes is needed at the top layer of the epidermis because this is how the shedding part, known as a horny layer is formed. However, premature death of the cells is unwanted as it would result in multiple problems with the skin barrier, causing it to be very leaky.

Apart from storing profilaggrin safely in the granules, keratinocytes have additional mechanisms which they use to control profilaggrin level in their cytosol, for example they can actively degrade it or remove its excess. However, this means that the level of the protein would go down, which is not good for the barrier function, so these mechanisms are used if there is a danger of accumulation.

We investigate these mechanisms in the context of atopic dermatitis (AD), a very common skin disease linked to allergy and asthma. AD patients suffer from a problem with dysfunctional, “leaky” skin barrier, resulting from low amount of profilaggrin and filaggrin in their skin. In our previous studies we could observed greater removal of the protein in AD patients, which we believe may contribute to the reduced function of the skin barrier, which gives symptoms to those patients. Now we want to test if the patients have a problem in containing the protein inside of their keratinocytes.

We will use a Nobel-price winning technology, so called CRISPR, to modify profilaggrin and observe profilaggrin storing granules, which we will do both in cells cultured in a dish, as well as cells which we grow in 3D model that resembles epidermis. We will measure how much profilaggrin can escape from the modified cells to define the requirements for the cell to activate it storage abilities. Then we will also link this to mutations in the profilaggrin gene, to observe if AD patients can form granules and if it is possible to force this process artificially.