Career Development – Final Report

REGULATION OF GENE EXPRESSION IN SEBACEOUS GLANDS - Marie Curie Intra-European Fellowships (IEF) FP7-PEOPLE-2013-IEF

Results

During the fellowship, we aimed to explore and link the genetic programs and their possible regulators in sebaceous glands (SGs) that lead to their dual function of an active lipid metabolism and inflammation at the same time. Moreover, we challenged the identified changes from our studies also under pathological settings putting acne in the focus, but involved also other diseases such as rosacea and atopic dermatitis.

Major achievements:

- Toll Like Receptor (TLR) 2 and 4 activators, which are the most relevant stimuli in the studied inflammatory skin diseases, induced a significant number of genes in sebocytes. Clustering these genes revealed that they were primarily involved in inflammation and in biological functions that were so far unknown in sebocyte biology such as chemotaxis or wound healing.
- Of these functions we have characterized in details the chemo-attractant effects and the possible interaction of sebocytes with various cells of the immune system and found that sebocytes could induce lymphocyte polarization.
- Although the change in the expression levels of genes encoding proteins involved in lipid metabolism was happening only at later time points in the inflamed sebocytes, the altered lipid profile as a result, were found to be the major contributor to the dermal lipid environment. The lipid production of sebocytes therefore could modulate the homeostasis of the skin by targeting various cell types like keratinocytes and macrophages.
- We have also identified a set of marker genes for detecting inflamed sebocytes, which were reliably used also in *in vivo* settings. Our results revealed that sebocytes depending on their proliferation and lipid metabolism status have a distinct capacity to respond to TLR activators. These genes were also successfully applied to *in vitro* test the anti-inflammatory effects of various agents with a therapeutic relevance such as retinoic acid or vitamin D.
- Revealing the changes in the microRNA profile we delivered data that these non-coding gene expression modifiers have a role also in sebocytes. While in the inflamed sebocytes, microRNAs with the most abundant changes were related to the NFKB signalling, in the differentiating ones the microRNAs were targeting genes related to the c-myc pathway.
- We also confirmed similarities between sebocytes and the subcutaneous adipose tissue, showing that the adipokines, which are responsible for the inflammatory properties of the adipocytes are also partially expressed in sebocytes and released in a stimulus dependent manner. Moreover, we have selected genes/proteins for further studies that are also known from adipocyte biology, where they control maturation and lipid accumulation.

Conclusions

One of my major goals with the fellowship was to develop skills in translation research, to translate molecular processes into physiological consequences. Since our research plans were at the interface between molecular and clinical studies, the fellowship helped me to obtain experiences in sebaceous gland biology from the research aspect. Moreover, I also acquired skills to investigate the molecular mechanisms underlying the gene expression regulation of various cell-types under pathological conditions as well as in response to therapeutic interventions.

My technical platform also improved at the Karolinska Institutet by learning new molecular approaches (like the state of the art CRISP/Cas9 gene engineering, verification of *in vitro* data using Laser Capture Microdissection based RNA work, and studying the role of microRNAs in gene expression regulation).

The scientific environment provided me great opportunities to learn how to organize research and establish future collaborations. Due to the host's involvement of European and national networks and international collaborations I also had the chance to meet leading scientists in the field of genetics, immunology, cell biology, molecular biology and dermatology. By working in a multi-national and multi-cultural environment at the Karolinska Institutet I also improved my social skills.

I also followed the work of excellent PhD students and how they were supervised, which is important for my independent future research career. In addition, the training helped me to develop knowledge about organizing research units, how to incorporate collaborative partners into research projects and how to support and develop a scientific atmosphere.

A network of interactions between the Research Unit of the Department of Dermatology, Karolinska Institutet and the Department of Dermatology at the University of Debrecen has been established. Also collaborations are active with research groups at the Dessau Medical Centre, Dessau Germany and Center for Allergy and Environment, Technische Universität and Helmholtz Center München, Germany

Socio-Economic impact

The most common and therefore widely studied SG associated disease is acne, affecting 60-90% of adolescents and persisting in nearly 20% of the patients even in their later years, with an unquestionable impact on the quality of life. Our results provided important data on how the contributing factors such as the bacterial microflora, the hormone regulated mechanisms and the epigenetic factors such as microRNAs could alter SG functions. Our results are suitable for a better understanding of acne pathogenesis and also to develop novel therapies with a special focus on not inhibiting the lipid production of sebocytes, as it is the mainstream in recent drug development, but to modulate the type of lipids that these cells produce and secrete. We therefore believe that our findings are important not just in basic sebocyte research but could help the development of new therapies to treat SG associated diseases, helping millions of people.