

Psoriasis is a common genetically determined chronic immune-mediated skin disorder, characterized by frequent clinical relapse. This disease is characterized by pruritus, pain, erythema, and thickened scales. The continuous inflammation of psoriatic skin is caused by intense immune cells infiltration. Numerically dominant and characteristic component of the inflammatory infiltrate in psoriasis are neutrophils.

Neutrophils are the largest fraction of white blood cells and the first cells to be recruited to infected or sterile wounded tissues where, in addition to providing immune protection, they may also contribute to healing and recovery. In the defense against pathogens, neutrophils use various mechanisms like: phagocytosis, generation of reactive oxygen species, extrusion of genomic DNA as neutrophil extracellular traps, and release of cytotoxic granules.

Pro-inflammatory activity of neutrophils, so needed in the organism protection, causes however exacerbation of psoriatic symptoms. In this project we will investigate the possibility of neutrophil activity modulation by acyl-CoA:diacylglycerol acyltransferase 1 (DGAT1).

DGAT1 is an enzyme, which have the potential to regulate cell activity and functional outcomes on multiple levels. Its primary function is the synthesis of triacylglycerols (TGs), a major form of storage energy in mammalian cells. Resting neutrophils accumulate TGs, which can be utilized for membrane lipid synthesis (necessary during phagocytosis) or to provide energy essential during immune response. It is a strict cross-talk between metabolism and immune response, and it was suggested that the neutrophil's lipid alterations may modify the physiology of these cells, and therefore, the host defense mechanism(s).

In addition, DGAT1 takes part in retinoic acid (RA) storage. RA, the active metabolite of vitamin A, is a potent signal molecule, which can directly modulate gene expression in target cells and influence on a wide range of physiological processes, including immune response. RA regulates neutrophil maturation and differentiation. In addition, therapeutic administration of RA exert anti-inflammatory effects in dermatological diseases, such as psoriasis.

Since DGAT1 regulate the homeostasis of lipids and retinoids, the purpose of this project will be to know the role of DGAT1 on the regulation of neutrophil functions in psoriasis. In the present project we set a hypothesis, that DGAT1 by controlling lipid storage and reduction of retinoic acid availability, enhances pro-inflammatory activity of neutrophils in psoriasis. Hence DGAT1 deficiency or inhibition may lead to reduction of psoriasis symptoms.

In this project, we propose to investigate the effect of DGAT1 on the development of inflammation in the skin in a mouse model of psoriasis. Research on this issue will be pursued in stages and the scope of work will primarily involve analysis of: psoriasis development (including changes in skin morphology and physiology, and leukocytes infiltration), lipid accumulation and neutrophils metabolism, and retinoic acid signaling in neutrophils. Research will be performed on wild type mice and mice with a genetic deficit of DGAT1.

We assume that DGAT1 may play a role in regulating neutrophil functions during immune responses, and inhibition of DGAT1 activity decrease neutrophil pro-inflammatory activity, which in turn can lead to reduction of psoriatic symptoms. The results of the proposed project will significantly increase the knowledge about neutrophils action under physiological and pathological conditions. They will also contribute to a better understanding of the regulation of inflammatory processes in psoriasis. In addition, if our hypothesis is confirmed, DGAT1 will be a promising pharmacological target in the treatment of psoriasis.