

## **The effect of Western diet modified with vegetable oils on the healing process of skin wounds in mice**

Skin ability to heal wounds results from its condition, which is significantly influenced by genetic factors as well as age, sex and diet. Currently, popularity of so-called 'Western diet' (WD), which is a high-fat diet rich in saturated fatty acids (SFAs), mostly animal-based, simple carbohydrates and salt, has grown. Overconsumption of WD, has dramatically increased prevalence of obesity and obesity-associated metabolic disorders, that are manifested by impaired wound healing such recognized as chronic or non-healing wounds. Non-healing, diabetic ulcers are one of the best documented examples demonstrating detrimental effect of WD overconsumption on skin wound healing in human. Macrophages play a key role in the pathogenesis of chronic or non-healing wounds. Dysregulation of pro-inflammatory (M1 phenotype) and reparative (M2, anti-inflammatory) effector functions of macrophages lead to the development of chronic inflammation in the skin. Literature data show that SFAs, which constitute the main component of all fatty acids (FA) in a WD, stimulate macrophages to amplify the inflammatory response, and thus they contribute to impair wound healing. In contrast to animal-based fat, vegetable oils are rich predominantly in unsaturated FA. Rapeseed oil demonstrates unique composition of FA characterized by high content of monounsaturated FA (MUFAs; over 60%) and polyunsaturated FA (PUFA, over 30%), that are mostly classified as 'essential FA' (EFA). However, palm oil, the most widely used oil in the world, consists in half of SFAs.

The aim of the project is to show that changing eating habits by partial substitution of dietary animal fat by plant oils improves skin wound healing by reducing pro-inflammatory effect of WD and restoring skin ability to heal wounds via repair (scarring). Additionally, a comparative analysis of the effect on skin between diet rich in rapeseed and palm oil will be performed. To achieve our goal, experimental mice will be fed modified versions of laboratory animal WD in which 50% of the animal fat content will be replaced with rapeseed or palm oil, and standard WD (control). In post-injured skin samples collected from animals at the inflammatory and remodeling phase of wound healing, we will determine: (a) macrophage phenotype and their functional features, (b) inflammatory markers expression, (c) markers of reparative healing. In the *in vitro* experiments there will be investigated the mechanism underlying the effect of diet on interactions between macrophages and dermal fibroblasts, and the role of the CD36 (FA transporter) and Wnt/ $\beta$ -catenin pathway in establishing these interactions. Single cell RNA-sequencing (scRNA-seq) and chromatin profiling (scATAC-seq) will provide detailed molecular – level information on the impact of diet on intact and post-injured skin cell populations.

Results obtained in the proposed project will provide important information of the immunomodulatory role of dietary vegetable oils (rapeseed and palm) and their impact on skin condition that determines the tissue capacity to heal wounds. Investigating the interactions between macrophages and dermal fibroblasts, describing the importance of CD36, as well as demonstrating the role of the Wnt/ $\beta$ -catenin pathway that acts as mediator and effector pathway of these interactions, might reveal potential therapeutic targets for the treatment of chronic and non-healing wounds. Moreover, considering the FA profile of the tested plant oils, we assume that in the context of skin wound healing our studies will show that the effect of rapeseed oil consumption is superior over those observed for palm oil. In this way, obtained results can contribute to the promotion of consumption of local products and lead to regional development as Poland is European leader of rapeseed oil production. Finally, by demonstrating that the modified version of the WD proposed in the project has a beneficial effect on skin condition and wound healing process, obtained results will strengthen the recommendations for replacing animal products with plant-based food in a daily, balanced diet.