

Research project report

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Acylcarnitines, mitochondrial fitness & immunometabolism: novel target for healthy aging

Metabolic diseases are characterized by both altered mitochondrial function and chronic inflammation status, thus, indicating that there is a possible link between immunity and mitochondrial function. Our previous data indicated that accumulation of acylcarnitines, fatty acid oxidation intermediates, inhibits glucose and pyruvate metabolism, oxidative phosphorylation in mitochondria and may further decrease fatty acid oxidation. It could be hypothesized that acylcarnitines play a pivotal role in the regulation of energy metabolism and mitochondrial functioning, and, thus, could determine healthy aging and response to inflammation. The aim of the present study was to discover the role of acylcarnitines in the mitochondrial functionality/fitness in immune cells under physiological and pathological conditions.

To investigate the physiological role of fatty acid oxidation in immune cells in collaboration with Dr. L. Plakane (University of Latvia, Department of Human and Animal Physiology) the cycle ergometry experiments were performed in healthy volunteers. Our results showed that:

- 1) maximal lipolysis and fat oxidation rate are reached in a fasted state during low intensity exercise;
- 2) low intensity exercise improves bioenergetics and increases fatty acid oxidation in peripheral blood mononuclear cells (PBMCs) and may contribute to the anti-inflammatory phenotype.
- 3) there is a bioenergetic crosstalk between muscles and circulating cells like PBMCs

The investigation of role of mitochondria and fatty acid oxidation in pathological conditions (acute inflammation) in collaboration with Immunology group (Dr. J. Frič) of Center for Translational Medicine, International Clinical Research Center, St. Anne's University Hospital Brno (Czech Republic) showed that:

- 1) changes in energy metabolism pattern in monocytes and macrophages are time dependent – the fatty acid oxidation is stimulated in the early phase of inflammation, while with the progression of inflammation FAO becomes depressed and results in accumulation of acylcarnitines; meanwhile mitochondrial function is partially disturbed in the early phase but not in the later phase of inflammation;
- 2) calcineurin/NFAT signalling is involved in the regulation of fatty acid metabolism during inflammation;
- 3) the accumulation of acylcarnitines in immune cells slows down the anti-inflammatory response, and may cause immunoparalysis.

Overall, the results of the present project showed that targeting acylcarnitine accumulation and mitochondrial functionality/fitness is perspective strategy for healthy aging.

L'OREAL Baltic „For Women in Science” fellowship supported the progress of postdoctoral project “*Novel treatment strategy for the correction of energy metabolism in sepsis*”. In addition, 3 manuscripts for publication in SCI journal are in preparation and participation in the conferences was supported:

Publication:

- **Makrečka-Kuka M**, Liepinsh E, Murray AJ, Lemieux H, Dambrova M, Tepp K, Puurand M, Käämbre T, Han WH, de Goede P, O'Brien KA, Turan B, Tuncay E, Olgar Y, Rolo AP, Palmeira CM, Boardman NT, Wüst RCI, Larsen TS. Altered mitochondrial metabolism in the insulin-resistant heart. *Acta Physiol (Oxf)*. **2020** Mar;228(3):e13430. doi: 10.1111/apha.13430.

Manuscripts:

- Liepinsh E, Makarova E, Plakane L, Konrade I, Liepins K, Sevostjanovs E, Grinberga S, **Makrečka-Kuka M**, Dambrova M. Low-intensity exercise stimulate bioenergetics and increase fat oxidation in mitochondria of blood mononuclear cells from sedentary adults. *submitted*
- Hortová-Kohoutková M, **Makrečka-Kuka M**, Kucera L, Tidu F, Valcikova B, De Zuani M, Burilova P, Bartonova J, Mytníková A, Sevostjanovs E, Polansky O, Kubasova T, Rychlik I, Helan M, Sramek V, Dambrova M, Liepinsh E, Zareie A, Sedlacek R, Uldrijan S, Fric J. Calcineurin -NFAT axis controls immunometabolic reprogramming of human monocytes and contributes to immunoparalysis in sepsis. *In preparation*
- **Makrečka-Kuka M**, Videja M, Korzh S, Hortová-Kohoutková M, Fric J, Dambrova M, Liepinsh E. The accumulation of long-chain acylcarnitines but not mitochondrial dysfunction slows down the macrophage polarization for anti-inflammatory phenotype. *In preparation*

Conferences:

- Korzh S, Hortová-Kohoutková M, Sevostjanovs E, Frič J, Liepinsh E, **Makrečka-Kuka M**. The time-dependent changes in energy metabolism pattern in immune response. *FEBS3+ Conference of Latvian Lithuanian and Estonian Biochemical Societies*, Riga, June 17-19, **2019**. Abstract book, P. 74.
- **Makrečka-Kuka M**, Kuka J, Vilskersts R, Makarova E, Dambrova M, Liepinsh E. Targeting long-chain acylcarnitine content as a novel strategy to treat cardiometabolic diseases. *SHVM 2019 17th annual scientific sessions - Targeting metabolic pathways to treat cardiovascular diseases*, Amsterdam, The Netherlands, June 23-26, **2019**. selected talk. Abstract book P. 86.
- Hortová-Kohoutková M, **Makrečka-Kuka M**, Kučera L, Valčíková B, Lázničková P1, Sedláček R, Uldrijan S, Frič J. Calcineurin-NFAT alters the energy metabolism of activated human monocytes. *1st CCP Phenogenomics Conference*. Vestec, Czech Republic, **2019**. September 12-13.
- **Makrečka-Kuka M**, Liepinsh E, Murray AJ, Lemieux H, Dambrova M, Tepp K, Puurand M, Kaambre T, Han WH, de Goede P, O'Brien KA, Turan B, Tuncay E, Olgar Y, Rolo AP, Palmeira CM, Boardman NT, Wuest RCI, Larsen TS. Altered mitochondrial metabolism in the diabetic heart. 14th Conference on Mitochondrial Physiology: *Mitochondrial function: changes during life cycle and in noncommunicable diseases - COST MitoEAGLE perspectives and MitoEAGLE WG and MC Meeting*. Belgrade, Serbia, October 13-16, **2019**.

Additionally, thanks to the L'OREAL Baltic fellowship, I was able to visit Center for Translational Medicine, International Clinical Research Center, St. Anne's University Hospital Brno (Czech Republic) to discuss obtained results and further collaboration.

Moreover, thanks to the L'OREAL Baltic fellowship, I was able to present my research, promote the science in Latvia and, hopefully, encourage younger generation to choose the carrier in science by giving following interviews:

- Interview for Latvian Radio 1, Zināmais nezināmajā June 12th, 2019, 10:07 <https://lr1.lsm.lv/lv/raksts/zinamais-nezinamaja/iepazistam-loreal-stipendijas-sievietem-zinatne-2019.gada-laurea.a118625/?highlight=makrecka>
- <http://www.la.lv/es-dzivoju-zinatne-petniece-marina-makrecka-kuka-aizravusies-ar-imunsunu-izpeti>
- <https://lvportals.lv/viedokli/306322-mekle-vielas-kas-sunam-palidzetu-parvaret-stresu-2019>
- <https://www.delfi.lv/vina/personiba-un-brivais-laiks/vina-kas-iedvesmo/vispirms-zinatniece-un-tikai-tad-sieviete-saruna-ar-tris-nozimigu-petijumu-autorem.d?id=51230341>
- Interview in journal L'Officiel Baltic Latvia Volume August/September 2019
- <https://www.mammamunteti.lv/articles/46780/zinatniece-marina-makreckakuka-pret-sunu-novecosanu-vislabak-palidz-mieriga-pastaiga-tuksa-dusa/>

Riga, March 31, 2020



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