Mitochondrial metabolism of glycerol as a regulator of homeostasis and pathology of lymphocytes

Upon sensing infection, T lymphocytes are activated to rapidly proliferate and differentiate to fight the disease. Activation of a T cell occurs by triggering of the T cell receptor (TCR). One of the still puzzling phenomena happening after TCR binding is a rapid and transient generation of low, thus non-toxic amount of reactive oxygen species (ROS). This "oxidative signal" was found to be necessary for expression of genes required for proper T cell activation and proliferation.

Surprisingly, pioneering research performed by the applicant established that this "oxidative signal" is generated in controlled fashion by the "powerhouse of the cell" – the mitochondria. It was also found how on the molecular level TCR "talks" to the mitochondria by reeling necessary intracellular signals. The applicant also extensively characterized the biochemical phenomena happening at the mitochondria, which lead to production of potentially dangerous ROS to enable T cell proliferation and mounting of the acquired immune response However, the detailed mechanisms by which the oxidative signal is generated are still unclear. What's more - they await a practical application in therapy.

One of the proteins found by the applicant to be crucial for the generation of the "oxidative signal" is an enzyme, glycerol phosphate dehydrogenase (GPD2/mGPDH), which is localized on the inner mitochondrial membrane. This finding is of utmost interest since GPD2 is an enzymatic hub connecting glycolysis, mitochondrial respiration, and lipid flux. Thus, GPD2 integrates the three metabolic pathways fundamental for T cell activation, proliferation, and differentiation. Interestingly, recent research by others demonstrated that GPD2 regulates generation of the "oxidative signal" in macrophages - the mediators of innate immunity and that GPD2 acts as a guardian against cell death induced by accumulation of toxic lipids – ferroptosis. Therefore, GPD2 emerges as an interesting, putative therapeutical target.

It was reported that T cells take-up extracellular glycerol and turn it into glycerol-3-phosphate (G3P) for fatty acid synthesis. Since GPD2 metabolizes glycerol-3-phosphate in the mitochondria an intriguing question arises: could glycerol influx potentiate GPD2-dependent generation of the oxidative signal.? Indeed, applicant's preliminary data using T cells from mice lacking GPD2 protein (GPD2 KO mice) or when treated with iGP-1, a GPD2 inhibitor, indicate that T cell could use mitochondrial glycerol metabolism for activation, proliferation, and survival. Glycerol influx and GPD2 may not only modulate mitochondrial ROS production/T cell activation-induced gene expression but also influence lipid storage and toxicity. To further investigate this observation and to find out what really happens with the glycerol taken up by the T cell the applicant will apply a metabolic tracing method (GC-MS, tracing of 13C-U-glycerol, 13C-U-glucose and 13C-U-glutamine metabolism), lipid profiling (LC-MS) and lipid storage analysis (confocal microscopy) using T cells and MEF lines (WT and GPD2 KO). It is also planned to investigate T cell function in vivo by using applicant-generated GPD2 KO x OT-1 Tg+ mice harboring a TCR of single specificity against ovalbumin protein.

World-wide obesity is a single most serious risk factor responsible for unprecedented rise in mortality from diabetes, heart disease and cancer. The adipose tissue of the obese is infiltrated by the activated immune cells, which create a state of chronic inflammation. It is this inflammatory state, which inevitably leads to a disease. Strikingly, glycerol concertation while low in blood is exceptionally high in the adipose tissue. Therefore, it is possible that activated T cells which infiltrate adipose tissue of the obese use glycerol to maintain proliferation and pro-inflammatory state. Since hyper-activated T cells are known to be responsible for adipose tissue inflammation, it is interesting to test, if treatment directed against GPD2, mitochondrial use of glycerol and generation of the oxidative signal would inhibit T cell activation in adipose tissue of the obese. This approach would potentially yield effective means to prevent adipose tissue inflammation, thus development of diabetes or cancer.