Mitochondrial metabolism controls threshold of T lymphocyte activation aka "Lessons from the old"

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T lymphocytes (T cells) are indispensable for acquired immune response. Upon sensing infection, T cells 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) and induces spectrum of signaling, transcriptomic and metabolic changes. Surprisingly, TCR triggering was found to induce mitochondrial generation of low, non-toxic amounts of reactive oxygen species (ROS) which serve as necessary "oxidative signal" regulating transcription and T cell differentiation to specialized sub-types such as effector or memory cells. In the elderly, T cells often cannot mount an immune response due to aberrant activation and exhaustion.

The mitochondrial theory of aging states that age-acquired mutations of mitochondrial DNA (mtDNA) lead to vicious cycle of macromolecular damage due to mitochondrial ROS release. Thus, to investigate novel aspects of mitochondrial function in T cells we applied mouse model of accelerated aging – transgenic mtDNA polymerase γ (PolG) 'Mutator' mouse. These mice gradually accumulate mtDNA mutations, which lead to pre-mature aging and reduced life span. We aimed to analyze the underlying causes of T cells phenotype of aged PolG Mutator mice. To this end, we combined bone-marrow transfer-based *in vivo* approaches with metabolic flux analysis (MS-mediated monitoring of ^{13}C-labelled isotopomers).

Our results demonstrate unexpected consequences of mitochondrial impairment for T cell function. We could demonstrate how remodeling of mitochondrial metabolism controls T cell activation and how to genetically alleviate T cell dysfunction caused by accelerated aging.