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Mitochondrial ROS drives autoimmune CD44^{hi} effector/memory T cell hyperactivation

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Naive, activated and memory T cells have different metabolic profiles. During TCR activation, mitochondria translocate to immunological synapse and produce reactive oxygen species (ROS) that are essential for correct T cell activation, antigen-specific T cell expansion and IL-2 production. Antigen-experienced memory T cells, especially hyperactivated effector/memory T cells in lupus models, strongly rely on mitochondrial metabolism. Nonetheless, the role of mitochondrial ROS (mROS) in effector/memory T cell functions remains undefined. We showed that, compared with the primary activation of naïve cells, mROS accumulation in re-challenged effector/memory cells occurs much faster and with greater intensity. This suggested that mROS activation plays a critical role in effector/memory T cell activation. In fact, mROS abrogation (using DPI, an inhibitor of ROS-producing mitochondrial complexes) led to complete inhibition of effector/memory T cell phenotype, as seen by down regulation of CD44 expression marker. These findings were corroborated in Fas-deficient T cells isolated from lupus model lpr mice. We found that hyperactivation of lpr effector/memory T cells, associated with elevated production of IFN-gamma (a key cytokine associated with disease development in lupus models), was accompanied by increased mROS activation in these cells. In addition, mROS abrogation led to a significant decrease in CD44^{hi} lpr effector/memory T cell accumulation and their hyperactivation status. Overall, our data point to mROS as key regulator of effector/memory T cell functions, and its pharmacological modification may serve as a potential target for treatment of autoimmunity.

Biography

Gorjana Rackov has expertise in immuno-oncology and passion for developing innovative therapies and improving healthcare. She obtained her degree in Molecular Biology and Physiology from University of Belgrade, Serbia in 2010 and moved to Spanish National Centre for Biotechnology (Madrid), to study macrophage and T cell activation during infection and autoimmune disease. She completed her PhD thesis, at Autonomous University of Madrid in 2015, unraveled a critical role for cell cycle inhibitor p21 in generation of mROS, production of proinflammatory cytokines and interferons, as well as activation of MAPK and NF-kappa B pathways. Currently, she works as a Postdoctoral Researcher in IMDEA Nanoscience Institute, developing a monoclonal antibody-based immunotherapy for high-grade brain tumors. Her long-term goal is to develop an original research line and pursue a career of independent group leader.

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