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The role of mitochondrial DNA mutations in chronification of inflammation

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Abstract

Objectives: Defective mitophagy caused by mutations in mtDNA, may cause disturbance in the formation of innate immunity, leading to chronic inflammation. In this work, we have established the ability of ybrids carrying mtDNA mutations to form innate immune tolerance.

Method: Cybridswere created by fusion of mtDNA-free THP-1 cells with platelets isolated from patients with mtDNA mutations associated with progression of atherosclerosis. The genotyping of cybrids detected heteroplasmy of number mtDNA variants in genes MT-RNR1, MT-TL1, MT-TL2, MT-CYB, MT-ND2 and MT-ND5.The ability of cells to form Innate immune tolerance was evaluated by two-challenge protocol: the 1st hit with 1 μg/ml of LPS for 16h and the 2nd hit with 1 μg/ml of LPS for 4h. The secretion of TNF and IL-1 was evaluated by ELISA.

Results: In the case of the intact THP-1 line, an adequate response to LPS stimulation as well as the ability to form innate immune tolerance was observed. For the HSM-1 and LSM-1 cybrids, the secretion of TNF and IL-1 did not exceed 10 pg/ml, which indicates that these cybrids are insensitive to LPS. HSMAM-3 cells exhibited increased pro-inflammatory response to LPS as well as total inability to form immune tolerance.

Conclusions: Cells differing in the mitochondrial genome and carrying atherogenic mutations were dramatically different in their immune response from intact THP-1 cells. Two cybrids did not respond to inflammatory stimulation, but the third line lacked tolerance of innate immunity. Presence of such cells in the focus of inflammation could complicate the resolution of the inflammatory response contributing to the chronification of inflammation.

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Biography

Zhuravlev is PhD-student working in Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Moscow.

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