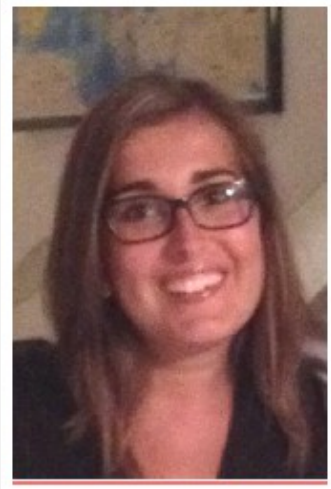
ImmunoTools *special* Award 2019



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The effect of mtDNA deletion on the production of memory cells

Background

Mitochondrial diseases are multisystem and heterogeneous disorders characterized by a multitude of symptoms: anaemia, myopathy, lactic acidosis, CNS abnormality, endocrine abnormalities, renal disease, sensorineural deafness, and retinal involvement. To date the number of cases continue to increase. Several are the clinical abnormalities; they usually begin in childhood but also adults could be involved in. The fundus shows pigmentary retinopathy, with a salt-and-pepper appearance, but vision remains good in most patients. Systemic involvement includes chronic progressive external ophthalmoplegia (CPEO), with ptosis being the most common complaint, and cardiomyopathy. Other variable features are short stature; cerebellar symptoms; weakness of muscles of the face, pharynx, trunk, or extremities; and progressive hearing loss (1). Most of the time premature death occurs because of cardiac conduction defects.

Kearns-Sayre (KSS) syndrome is a kind of mitochondrial disease characterized by several dysfunctions. People with Kearns-Sayre syndrome have a single, large deletion of mtDNA, ranging from 1,000 to 10,000 DNA nucleotides. The cause of the deletion in affected individuals is unknown. The mtDNA deletions that cause Kearns-Sayre syndrome result in the loss of genes important for mitochondrial protein formation and oxidative phosphorylation. The most common deletion removes 4,997 nucleotides, which includes twelve mitochondrial genes. Deletions of mtDNA result in

impairment of oxidative phosphorylation and a decrease in cellular energy production. Regardless of which genes are deleted, all steps of oxidative phosphorylation are affected. Researchers have not determined how these deletions lead to the specific signs and symptoms of Kearns-Sayre syndrome, although the features of the condition are probably related to a lack of cellular energy.
Most cases of Kearns-Sayre syndrome are not inherited; mitochondrial disorders can appear in every generation of a family and can affect both males and females. Males that are affected do not pass mitochondrial traits to their children.

Our preliminary data demonstrated that patients with Kearns-Sayre syndrome have impaired T and B cell phenotypes compared to the healthy controls. In particular in a pilot population of 10 patients we stained peripheral blood mononuclear cells with fluorescent antibody and analysed the cells with flow cytometry. We noticed an increase of transitional B cells and a significant decrease of both memory B cells and CD8+ memory cells.
To date no evidence supports the correlation of the mitochondrion impairment with a possible defect of the immune system. The possibility to work in a paediatric hospital gives me the chance to collect many samples and evaluate both B and T phenotypes to verify a possible correlation between this preliminary immune evidences and the need of energy in the production and maintenance of memory cells. Glucose, glutamine, and fatty acids are three potential sources of carbon for growth and energy. Glucose uptake, which increases dramatically after B cell activation (2-4), provides the substrate for glycolysis and use of the two resultant pyruvate molecules for Krebs (citric acid) cycle entry. However, glucose-derived carbon is likely also needed for anabolism and a net increase in the mass of molecules (e.g., lipids, nucleic acids) synthesized during G1 and S phases. At present, the balances among the varied processes (net contributions of glucose versus glutamine to ATP generation or to increased biomass) have not yet been quantified for B lineage cells and only partially in the T cells.

The requested **ImmunoTools** antibodies will allow the staining of cells and the evaluation of both B and T cells phenotypes in patients and controls. Therefore, it would be advantageous to include cytokines to stimulate cells in vitro and verify the downstream production of memory B cells and antibodies.

ImmunoTools *special* AWARD for **Sara Terreri** includes 25 reagents

FITC conjugated anti human : CD3, CD4, CD8, CD11c, CD38, CD45RA, IgG, IgE, IgM

PE conjugated anti human: CD8, CD24, CD11c, CD27

APC conjugated anti human: CD38, CD45RA

Recombinant Human Cytokines: rh IL-21, rh IL-4, rh IL-2

DETAILS more AWARDS

References

1. Tsang SH, Aycinena ARP, Sharma T. Mitochondrial Disorder: Kearns-Sayre Syndrome. Advances in experimental medicine and biology. 2018;1085:161-2.

2. Caro-Maldonado A, Wang R, Nichols AG, Kuraoka M, Milasta S, Sun LD, et al. Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. Journal of immunology. 2014;192:3626-36.

3. Cho SH, Ahn AK, Bhargava P, Lee CH, Eischen CM, McGuinness O, et al. Glycolytic rate and lymphomagenesis depend on PARP14, an ADP ribosyltransferase of the B aggressive lymphoma (BAL) family. Proceedings of the National Academy of Sciences of the United States of America. 2011;108:15972-7.

4. Dufort FJ, Bleiman BF, Gumina MR, Blair D, Wagner DJ, Roberts MF, et al. Cutting edge: IL-4-mediated protection of primary B lymphocytes from apoptosis via Stat6- dependent regulation of glycolytic metabolism. Journal of immunology. 2007;179:4953-7.