Functions of PERK in autoimmune diseases and endoplasmic reticulum stress

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Autoimmune disorders affect about 5% of the population in Europe, with two thirds of the patients being female. In collaboration with the team of F. Rieux-Laucat (Institut Necker), we have identified novel causative mutations in patients with clinical evidence for familial susceptibility to autoimmune and auto-inflammatory diseases in the gene of the Protein kinase RNA-like endoplasmic reticulum kinase (PERK). PERK is the serine/threonine kinase which targets the alpha subunit of the eucaryotic initiation factor 2. However, their relationship to auto-inflammation remains unclear and needs to be established given their clinical relevance.
Accordingly, we try to characterize at cellular and immunological levels the role of PERK in autoimmunity, inflammation and the consequences of its mutations. In this purpose, bone marrow derived dendritic cells were generated from PERK KO mice and B cell were collected from human patients and immortalised with epstein barr virus (B-EBV). Owing the kinase activity of PERK on eif2a protein, the Sunrise method developed in our lab was use to study protein synthesis. Cellular homeostasie and anti-viral/anti-bacterial defence pathways were equally tested by WB, ELISA, confocal microscopy and FACS. Interestingly, primary data shows that eif2a is highly phosphorylated in wild type BMDCs. Surprisingly this phosphorylation occurs during cells differentiation and is specific of DCs. However, the depletion of PERK in those cells leads to the decrease of Phospho-eif2a in these cells. Moreover, supplementary results show a lack of lysosome maturation and an increase of mitochondrial reactive oxygen species in PERK KO cells.

Taken together these results suggests a real impact of PERK in the DCs functions. Our last experiments using SUNRISE method tend to demonstrate a specific translation associate to the eif2a phosphorylation regulation in the DCs. In this regard we plan to continue the BMDCs study to clearly determine PERK function in DC homeostasis. At the same time we will start B-EBV in order to characterize mechanisms that may be involved in autoimmune and inflammatory diseases.

Keywords : PERK, translation, eif2a, auto-inflamation, auto-immunity
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