Objectives: Genes implicated in immune regulation [1]. LINC01871 surface and secreted protein expression changes, respectively, in response to immune stimuli. -/- cells and the parental HSB2 cells. Parental HSB2 T cells, -/- clone with altered expression of many genes, implicated in expression with longer stimulation (2d).

Conclusion: LINC01871 is regulated by calcineurin signaling. Treatment of primary human T cells with anti-CD3/CD28 to mimic true TCR engagement resulted in a modest decrease of LINC01871 expression at early time points, followed by an increase in expression with longer stimulation (2d).

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Conclusion: First, we examined the cellular metabolism of SLE NK cells compared to healthy cells. We observed that OXPHOS is significantly increased in SLE NK cells (Figure 1A), whereas glycolysis was normal (Figure 1B). Furthermore, the mitochondrial mass and membrane potential (by FACS (Figure 1C) and confocal microscopy) were increased in SLE. Electron microscope imaging showed profound alterations in SLE NK cell mitochondrial ultrastructure (Figure 1D). No significant differences in the expression of key metabolite transporters involved in mitochondrial fueling (CD71, GLUT-1, CD98) was observed in SLE NK cells compared to healthy controls.

Second, we examined how ligation of DARA and ELO influences the metabolism of healthy NK cells. Our data showed that ELO primarily enhances NK cell OXPHOS (Figure 1E), whereas DARA mainly increases glycolysis. Consistently, ELO also increases mitochondrial membrane potential and expression of OXPHOS. These findings provide important insights on the alteration in SLE NK cell mitochondrial ultrastructure (Figure 1D). No significant alterations in SLE NK cell mitochondrial ultrastructure (Figure 1D). No significant differences in the expression of key metabolite transporters involved in mitochondrial fueling (Figure 1E).

Results: Next, we examined the effect of DARA and ELO on SLE NK cells. While stimulation with DARA adequately increases glycolysis in SLE NK cells, engagement with ELO fails to properly increase OXPHOS (Figure 1F), expression of cell surface transporters, mitochondrial membrane potential and mass.

Conclusion: Our data suggest that SLE NK cells exhibit alterations in cellular metabolism, primarily involving mitochondrial respiration. In contrast, glucose metabolism is similar to that of healthy NK cells. Additionally, ELO and DARA mediate the activation of healthy NK cells through the engagement of different metabolic pathways: OXPHOS and glycolysis, respectively. Therefore, priming SLE NK cells with ELO is unable to adequately engage their dysfunctional mitochondrial respiration. These findings provide important insights on the alteration in SLE NK cell mitochondrial ultrastructure (Figure 1D).

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ACTIVATION OF THE CELLULAR INTEGRATED STRESS RESPONSE IN LABIAL SALIVARY GLANDS FROM SJÖGREN’S SYNDROME PATIENTS.

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Background: Sjögren’s syndrome (SS) is a chronic autoimmune disease characterized by inflammation of the exocrine glands and severe symptoms of eye and mouth dryness. Disorders in the saliva secretion process have been associated with oxidative and endoplasmic reticulum (ER) stress in combination with inflammatory responses. The integrated stress response (ISR) is a stress mechanism that allows cells to modify their gene expression program to restore homeostasis and promote their survival against various extrinsic and intrinsic stress signals, such as hypoxia, nutrient deprivation, viral infections, inflammatory factors (cytokines, chemokines, inflammasomes), and accumulation of unfolded proteins in the ER, among others (1). The ISR is regulated by four kinases: PERK, PKR, HRI and GCN2, that dimerize and autophosphorylate to become active and each one responds to different stress stimuli. The signaling pathways that are activated in response to stress factors stimulate the phosphorylation of eIF2α, which causes a transient inhibition of global protein synthesis and induction of synthesis of some specific genes like ATF4 and NFKB. ATF4 induces the transcription of genes involved in metabolism and nutrient uptake, redox status, and regulation of apoptosis. Dephosphorylation of eIF2α is the ISR termination signal to restore protein synthesis and is mediated by the PPP complex, which recruits the catalytic subunit PP1c and one of its two regulatory subunits: GADD34 or CREP.

Objectives: To evaluate the presence and functional state (phosphorylation) of the ISR sensing kinases: PERK, PKR, HRI and GCN2; the levels of eIF2α/p-eIF2α and the key ISR transcription factors ATF4 and NFKB, as well as subunits of the complex involved in the ISR termination: PP1C, GADD34 and CREP in labial salivary glands (LSG) of SS-patients.

Methods: Biopsies of LSG from 12 SS-patients and 11 control subjects were studied. The levels of mRNA, protein and phospho (p)-protein of the ISR components were determined by RT-qPCR and Western blotting.

Results: Our results show increased levels of p-PERK/PERK ratio (11/11), PKR (7/11), p-PKR (5/11), p-PKR/p-PKR ratio (7/11), eIF2α (5/11) and ATF4 (11/11) in LSG from SS-patients compared to control subjects. No significant changes were found in mRNA levels of HRI, GCN2, and GADD34 between LSG from SS-patients and control subjects. Decreased protein levels of HRI (8/12), p-GCN2 (6/11), eIF2α (6/11), p-eIF2α (6/11), NFKB (7/11), and p-NFKB (12/12) were found in LSG showing scarce parenchyma and high fibrosis and fat infiltration. On the other hand, PP1c and CREP showed decreased mRNA and protein levels in all SS-patients LSG. Interestingly, Ro autoantibodies and focus score were negatively correlated with PP1c and NFKB mRNA and protein levels whereas positively correlated with PKR mRNA levels.

Conclusion: The overexpression and activation of some ISR kinases together with the decrease in the PP1C/CREP phosphatase complex suggests a continuous activation of ISR, resulting in p-eIF2α to remain activated in LSG from SS-patients. This would explain the high protein levels of ATF4 and of target genes involved in the antioxidant response in LSG from SS patients suggesting that ISR activation plays a key role in pro-survival response to cellular stress.

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