**LINC01871, IMPLICATED IN SJÖGREN'S DISEASE PATHOGENESIS, IS REGULATED BY INTERFERON-Г AND CALCINEURIN SIGNALING**

M. L. Joachims, B. Khatri, C. Li, K. L. Tessneer, J. Ice® F. A. M. Stolarczyk, N. Mats, K. Grundahl, S. Glenn, J. Kelly, D. Lewis, L. Radfar, D. Stone®, J. Guthridge, J. A. James®, R. H. Schröder®. T. W. B. W. Liley, J. Wren, P. M. Gaffney®. C. Montgomery®, K. Sivils, D. Schleiss®, B. Schwikowski®, X. Mariette: None declared, Jacques-Eric Gottenberg: Grant/research support from: None declared, Wan Fai Ng: None declared, Tsutomu Takeuchi: None declared, Xavier Jean Sibilia: None declared, Fanny Monneaux: None declared, Hélène Dumortier: None declared, Cédric Schleiss: None declared, Benno Schwikowski: None declared, Disclosure of Interests: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Objectives:**
- **Methods:** This work was supported by the Innovative Medicines Initiative 2 Joint Undertaking (IM2 JU) (NECESSITY grant 806975). The Joint Undertaking received support from the European Union’s Horizon 2020 Research and Innovation Programme and from the European Federation of Pharmaceutical Industries and Associations. This work was also supported by R01 AR65953 Beth the NIH, United States. The contents are the sole responsibility of the authors and do not necessarily the official views of the NIH.
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**THE CELLULAR METABOLISM OF SLE NK CELLS IS PRIMARILY ALTERED AT THE LEVEL OF MITOCHONDRIAL RESPIRATION.**

N. Fluder, M. Humbel, F. Bellanger, A. Horisberger, C. Fenwick, C. Ribli, D. Comet. Lausanne University Hospital, Immunology and Allergy, Lausanne, Switzerland

**Background:** Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease, involving the development of autoreactive cells and autoantibodies. Natural Killer (NK) cells are innate immune cells that mediate the interaction between the innate and adaptive immune system, however their role in SLE is incompletely understood. SLE NK cells are decreased in peripheral blood, exhibit reduced cytotoxicity, and impaired cytokine production (1, 2). Furthermore, SLE NK cells present phenotypic alterations: increased expression of CD38 and altered upregulation of SLAMF7 after activation (3). To date, few studies evaluated the molecular mechanisms underlying NK cell dysfunction in SLE.

**Objectives:** We examined the metabolic activation of SLE NK cells.

- First, we characterized the cellular metabolism of SLE NK cells by assessing glycolysis and oxidative phosphorylation (OXPHOS) at basal level. Then, we evaluated how cellular metabolism can be manipulated to enhance NK cell function. In this perspective, we examined how the ligation of CD38 with daratumumab (DARA) and SLAMF7 with elotuzumab (ELO) modulate metabolic activation of SLE NK cells.

- **Methods:** NK cells of cryopreserved PBMC from SLE patients were isolated. Glycolysis and OXPHOS were studied using XF96 Seahorse. Expression of metabolic receptors (CD71, GLUT-1, CD98), mitochondrial function (mitochondrial membrane potential, mass) and calcium influx were investigated.
Results: 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 metabolite transporters CD71, GLUT-1 and CD98. 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 the cellular metabolism 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 present in SLE NK cells and contribute to a better understanding of the pathogenesis of the disease.

References:

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