Cell Reports Medicine

CellPress
OPEN ACCESS

Preview

Boosting NAD: An opportunity for metabolic reprogramming of Th17 cells in psoriatic disease

Eva Reali[1,*]
[1]Department of Translational Medicine, University of Ferrara, via Luigi Borsari 46, 44121 Ferrara, Italy
*Correspondence: eva.reali@unife.it
https://doi.org/10.1016/j.xcrm.2023.101163

Metabolic reprogramming of CD4 T cells has become an opportunity for adjunctive therapies. Here, Han et al. show that boosting NAD^+ blunts systemic Th17 responses and increases antioxidant pathways through arginine and fumarate-mediated activation of NRF2 transcription factor.

NAD^+ has gained renewed attention as a pivotal molecule in energy metabolism, being part of fundamental metabolic pathways including glycolysis and fatty acid metabolism.[1] It generally reflects a cellular switch from glucose metabolism to the fatty acid metabolism. In addition, it is a cofactor for NAD^+-dependent enzymes catalyzing non-redox reaction such as sirtuins, the NADase CD38, and Poly (ADP-ribose) polymerase, thus also regulating DNA repair, stress response, and immune cell functions. The link between NAD^+ and the maintenance of systemic health and homeostasis has been clearly established, and low NAD^+ levels have been associated with several disease conditions, including metabolic and neurodegenerative disease and diseases related to aging.[1] Hence, there is growing interest in understanding how NAD^+ metabolism influences the pathogenesis of the diseases and impacts their progression.

In common with aging conditions, chronic inflammatory and autoimmune diseases have dysregulated activation of immune cells and altered crosstalk with adipose tissues and hepatocytes with consequent dysregulation of metabolic pathways associated with systemic inflammation, atherosclerosis, and insulin resistance.[2] In the field of T cell immunometabolism, several concepts have been added in recent years.[3,4] Akkaya et al. in 2018 showed that CD4 T cell activation is accompanied by a shift to glycolysis as a source of energy even in the presence of oxygen. This phase corresponds to an early mitochondrial remodeling with and increase in volume size and number and increased production of reactive oxygen species and to a sustained increase of glucose transporter GLUT-1 in prolonged activation.[5] On the other hand, a study by Han and colleague in 2021 has evidenced that the restrain of the response by T cell could occur in the context of caloric restriction after fasting when glucose was not available. NAD^+ boosting is a component of caloric restriction, and it is likely that specific products of cell metabolism can transmit signals to immune cells to limit their activation and regulating T cell fate and polarization. The study, performed on peripheral blood mononuclear cells from 28 healthy subjects, showed that 24-h fasting increased the expression of FOXO4, a member of the forehead box O transcription factor family, that is usually negatively regulated by insulin signaling. FOXO4 in the fasting state blunts CD4 T cell responses through FKBP5 induction and decreased expression of Tbx21, RORγt, and GATA-3 transcription factors of Th1, Th17, and Th2 polarization. This concept reinforces the evidence that glucose deprivation and low insulin level can restrain the CD4 T cells response.[6]

In this issue of *Cell Reports Medicine*, Han and colleagues[7] extend the concept of NAD^+ modulation to the context of psoriasis, a chronic inflammatory skin disease that is associated with systemic comorbidities including atherosclerosis, obesity, and metabolic syndrome. The study aims to investigate the applicability of NAD^+ salvage pathway intermediates to boost NAD^+ in psoriatic disease and to investigate the mechanism underlying the T cell reprogramming by interfering with NAD^+ metabolism.

The authors report a series of experiments performed on CD4 T cells isolated from peripheral blood of healthy subjects and psoriasis patients, cultured under different polarizing conditions activated with αCD3/CD28 and treated with nicotinamide riboside (NR) to boost NAD^+. On these cells, the authors measured the cytokine secretion, the gene expression by RNA-seq followed by gene enrichment analysis, pathway analysis, and metabolomics analysis.[7] From the study, it emerges that NR treatment reduces Th1 and Th17 responses, with a more pronounced effect on Th17. Notably, blunting of IL-17 expression by CD4 T cells occurs both in Th0 and in the Th17 polarized state through the regulation of the *RORC* transcription factor expression.

It also emerges that NR induces upregulation of oxidative stress genes including sequestosome 1 (*SQSTM1*), which is more pronounced in psoriasis patients' derived T cells. The reduction of reactive oxygen species is linked to the activation of the transcription factor NRF2 regulating antioxidant response element (ARE)-mediated gene expression. Knocking down the *NRF2* gene by siRNA in CD4 T cells abolished IL-17 blunting as well as the the increased expression of oxidative stress response genes induced by NR. From the metabolomics analysis, the authors associated the effect of nicotinamide riboside with the biosynthesis by arginine succinate lyase of arginine and fumarate, which in turn inhibit ROS through activity of NRF2 transcription factor.

Th17 responses and IL-17 production are key and powerful defense mechanisms at barrier tissues dependent on tightly regulated process. According to

the data presented by the authors, the Th17 response with a high pro-inflammatory potential is the most tightly linked by metabolic status of the tissue. This aspect could be highly relevant in pathologies such as psoriatic disease in both its cutaneous and systemic manifestations in which IL-17 has been shown to play a central role. Increased level of IL-17-expressing cells and cells polarized toward a Th17 phenotype were found in the circulation of patients with psoriatic disease, and a correlation with biomarkers of systemic inflammation such as C reactive protein has been reported.[8,9]

Here, the authors completed their study with a pilot clinical trial on 12 healthy subjects. NR was given as a dietary supplement showing inhibition of IL-17 secretion, increase of arginine, and the expression of genes encoding enzymes with antioxidant activity.[7] The NR supplementation has already been investigated in a previous study by the same group in the context of systemic lupus erythematosus showing a potential effectiveness in blunting inflammatory cell of innate immunity and type I interferon response in cells of these patients.[10] In addition, NR supplementation is currently under investigation in the context of an ongoing clinical trial in psoriasis patients. The opportunity to blunt Th17 responses at systemic level has an intriguing potential as an adjunctive therapy for the treatment and prevention of clinical manifestations and comorbidities in psoriatic disease.

ACKNOWLEDGMENTS

The author would like to thank the National Recovery and Resilience Plan (NRRP), Mission 04 Component 2 Investment 1.5 – NextGenerationEU, Call for tender n. 3277 dated December 30, 2021; award number: 0001052 dated June 23, 2022.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Covarrubias, A.J., Perrone, R., Grozio, A., and Verdin, E. (2021). NAD(+) metabolism and its roles in cellular processes during ageing. Nat. Rev. Mol. Cell Biol. *22*, 119–141. https://doi.org/10.1038/s41580-020-00313-x.
2. Sajja, A., Abdelrahman, K.M., Reddy, A.S., Dey, A.K., Uceda, D.E., Lateef, S.S., Sorokin, A.V., Teague, H.L., Chung, J., Rivers, J., et al. (2020). Chronic inflammation in psoriasis promotes visceral adiposity associated with noncalcified coronary burden over time. JCI Insight *5*, e142534. https://doi.org/10.1172/jci.insight.142534.
3. Chapman, N.M., and Chi, H. (2022). Metabolic adaptation of lymphocytes in immunity and disease. Immunity *55*, 14–30. https://doi.org/10.1016/j.immuni.2021.12.012.
4. Meadows, A.M., Han, K., Singh, K., Murgia, A., McNally, B.D., West, J.A., Huffstutler, R.D., Powell-Wiley, T.M., Baumer, Y., Griffin, J.L., and Sack, M.N. (2023). N-arachidonylglycine is a caloric state-dependent circulating metabolite which regulates human CD4(+)T cell responsiveness. iScience *26*, 106578. https://doi.org/10.1016/j.isci.2023.106578.
5. Akkaya, B., Roesler, A.S., Miozzo, P., Theall, B.P., Al Souz, J., Smelkinson, M.G., Kabat, J., Traba, J., Sack, M.N., Brzostowski, J.A., et al. (2018). Increased Mitochondrial Biogenesis and Reactive Oxygen Species Production Accompany Prolonged CD4(+) T Cell Activation. J. Immunol. *201*, 3294–3306. https://doi.org/10.4049/jimmunol.1800753.
6. Han, K., Singh, K., Rodman, M.J., Hassanzadeh, S., Wu, K., Nguyen, A., Huffstutler, R.D., Seifuddin, F., Dagur, P.K., Saxena, A., et al. (2021). Fasting-induced FOXO4 blunts human CD4(+) T helper cell responsiveness. Nat. Metab. *3*, 318–326. https://doi.org/10.1038/s42255-021-00356-0.
7. Han, K., Singh, K., Meadows, A., Sharma, R., Hassanzadeh, S., Wu, J., Goss-Holmes, H., Huffstutler, R., Teague, H., Mehta, N., et al. (2023). Boosting NAD preferentially blunts TH17 inflammation via arginine biosynthesis andredox regulatory control in control and psoriasis subjects. Cell Rep. Med. *4*, 101157. https://doi.org/10.1016/j.xcrm.2023.101157.
8. Diani, M., Galasso, M., Cozzi, C., Sgambelluri, F., Altomare, A., Cigni, C., Frigerio, E., Drago, L., Volinia, S., Granucci, F., et al. (2017). Blood to skin recirculation of CD4(+) memory T cells associates with cutaneous and systemic manifestations of psoriatic disease. Clin. Immunol. *180*, 84–94. https://doi.org/10.1016/j.clim.2017.04.001.
9. von Stebut, E., Boehncke, W.H., Ghoreschi, K., Gori, T., Kaya, Z., Thaci, D., and Schäffler, A. (2019). IL-17A in Psoriasis and Beyond: Cardiovascular and Metabolic Implications. Front. Immunol. *10*, 3096. https://doi.org/10.3389/fimmu.2019.03096.
10. Wu, J., Singh, K., Lin, A., Meadows, A.M., Wu, K., Shing, V., Bley, M., Hassanzadeh, S., Huffstutler, R.D., Schmidt, M.S., et al. (2022). Boosting NAD+ blunts TLR4-induced type I IFN in control and systemic lupus erythematosus monocytes. J. Clin. Invest. *132*, e139828. https://doi.org/10.1172/jci139828.