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Just a Spoonful of Sugar, HTLV-1 Style

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Host cell metabolism regulates viral infection. In this issue of *Cell Chemical Biology*, Kulkarni et al. (2017) reveal the importance of oxygen concentrations and glycolysis in the reactivation of human T cell leukemia virus (HTLV-1). Identifying the host metabolic networks that regulate infection will foster our understanding of HTLV-1-associated pathologies.

CD4 T lymphocytes are a major target of both HIV-1 and human T cell leukemia virus (HTLV-1) human retroviruses. Although extensive research has focused on the importance of antigen, cytokine, and chemokine receptor signals in promoting infection and virus reactivation, more recent studies have demonstrated the critical nature of the intracellular metabolic environment. Nutrients are essential for all cells, conditioning their survival, proliferation, and differentiation. Furthermore, distinct cell types exhibit disparate nutrient requirements, and infection is often accompanied by a metabolic reprogramming of host cells. Identifying the diverse metabolic networks that promote viral infection and activation, within the context of specific host cell subsets, will foster the development of new therapeutic strategies that target the metabolic demands of the virus.

In this issue of *Cell Chemical Biology*, Bangham and colleagues elegantly demonstrate the importance of the cell's metabolic state in regulating HTLV-1 reactivation in primary cells from infected individuals (Kulkarni et al., 2017). Whereas the vast majority of *ex vivo* infection studies are performed in atmospheric oxygen conditions (20% O_2), the oxygen tensions to which lymphocytes are exposed within lymphoid organs are significantly lower, typically on the order of 1%–5% (Caldwell et al., 2001). Kulkarni et al. (2017) studied non-stimulated PBMCs from HTLV-1-infected patients in the presence of 1%–2% oxygen and found that these more physiological concentrations significantly enhance HTLV-1 reactivation, as monitored by increased transcripts of the viral *Tax* oncoprotein, a marker of viral activation. The authors first hypothesized that reactivation was due to the activity of the hypoxia-inducible factor (HIF-1α); however, this is not likely to be correct because they found that stabilization of HIF-1α actually decreased the level of *Tax* transcripts. HIF-1α was stabilized by inhibiting its hydroxylation by prolyl hydroxylases (PHDs). PHDs are dependent on the metabolite α-ketoglutarate (α-KG), and the authors treated PBMCs with dimethyloxalylglycine (DMOG), a competitive α-KG mimetic. Notably though, the authors discovered that HTLV-1 minus-strand transcription, monitored as a function of levels of the *HBZ* (HTLV-1 basic leucine zipper factor) antisense transcript (Gaudray et al., 2002), is significantly augmented in the presence of this α-KG antagonist. It is therefore tempting to speculate that *HBZ* and *Tax* transcripts are differentially regulated by one or more of the >60 α-KG-dependent (DMOG-inhibited) dioxygenases, a group of epigenetic enzymes that includes JmjC-domain-containing histone demethylases (KDMs) and the TET (ten-eleven translocation) family of DNA hydroxylases (Zdzisińska et al., 2017). Thus, the data presented by Kulkarni et al. (2017) highlight the potential of epigenetic modifications to control the relative levels of plus-strand versus minus-strand HTLV-1 transcription.

The authors followed up on these experiments by assessing the importance of different metabolic pathways in HTLV-1 plus-strand transcription. They revealed glucose-dependent aerobic glycolysis to be a prerequisite for the efficient transcription of *Tax*. It is interesting to hypothesize that the metabolic demands of HTLV-1 alter the function of its host T cell, a proposal that is supported by recent data demonstrating that competition between T cells and tumor cells for limiting amounts of glucose alters the effector function of the former (reviewed in Buck et al., 2017). While Kulkarni et al. (2017) did not assess the role of nutrients other than glucose in HTLV-1 reactivation, amino acids such as glutamine, leucine, and arginine also play important roles in CD4 T cell proliferation (Buck et al., 2017), and decreasing alanine transport through the SNAT1 transporter has recently been shown to limit the activation of HIV-1-infected T lymphocytes (Matheson et al., 2015).

Within the CD4 T cell compartment, specific subsets exhibit distinct bioenergetic requirements, potentially leading to differences in their susceptibility to HTLV-1 infection and/or the persistence/reactivation of virus. Regulatory $Foxp3^+CD4^+$ T cells are a main reservoir for HTLV-1 in the context of pathologies such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and this subset displays a lower reliance on glycolysis than CD4 effector populations (Michalek et al., 2011). It is intriguing to consider the possibility that the increased lipid metabolism of regulatory T cells makes them less sensitive to an HTLV-1-mediated skewing of glycolytic intermediates toward virus-specific functions. It will therefore be important to evaluate the hypothesis that HTLV-1 reactivation is differentially fostered by the metabolic environment(s) of specific CD4 T cell subsets. It will also be critical to determine whether metabolic changes in HTLV-1-infected cells are associated with the progression of infected individuals from an asymptomatic carrier state (accounting for 90% of individuals) to an aggressive T cell leukemia (2%–3%) or HAM/TSP (0.25%–3%). Indeed, a large subset of HTLV-1-associated diseases can be grouped under the umbrella of

inflammatory pathologies, and it is possible that they are linked to HTLV-1-associated metabolic alterations in regulatory T cells.

Infection of cells by HTLV-1 requires viral binding and entry via the GLUT1 glucose transporter (Manel et al., 2003), and GLUT1 transcription is induced under conditions of hypoxia, at least in part via HIF1-α signaling. Irrespective of its role in HTLV-1 entry, GLUT1-mediated glucose uptake is necessary for the optimal proliferation and function of human CD4 T cells with these metabolic effects promoting infection by HIV-1, a retrovirus that enters lymphocytes in a GLUT1-independent manner (Loisel-Meyer et al., 2012). In line with significant metabolic differences between activated effector and regulatory CD4 T cell subsets, GLUT1 is expressed at significantly higher levels on the former (Michalek et al., 2011). In the context of a productive HTLV-1 infection, expression of the HTLV envelope glycoprotein would be expected to block GLUT1-mediated glucose uptake and lead to a subsequent decrease in lactate secretion. The glycolysis that is required for HTLV-1 transcription, leading to an increased expression of the HTLV-1 envelope (Env) glycoprotein, would then act as a negative feedback loop, inhibiting GLUT1-mediated glucose transport. This potential *in vivo* metabolic switch led to the hypothesis that HTLV-1-infected individuals may develop HAM/TSP because of an Env-mediated impairment of glycolysis in glial cells, resulting in a decreased secretion of lactate and a detrimental impact on neurons (Manel et al., 2004). Indeed, lactate is a major energy substrate in neurons, and glucose metabolism in astrocytes is coupled to the neuronal uptake of lactate from the extracellular environment (Pellerin et al., 1998). Further studies evaluating the interplay between glucose metabolism, HTLV-1 reactivation, and HTLV Env-GLUT1 interactions will undoubtedly provide novel insights into our understanding of the pathophysiology of HTLV-1-associated diseases.

REFERENCES

Buck, M.D., Sowell, R.T., Kaech, S.M., and Pearce, E.L. (2017). Cell *169*, 570–586.

Caldwell, C.C., Kojima, H., Lukashev, D., Armstrong, J., Farber, M., Apasov, S.G., and Sitkovsky, M.V. (2001). J. Immunol. *167*, 6140–6149.

Gaudray, G., Gachon, F., Basbous, J., Biard-Piechaczyk, M., Devaux, C., and Mesnard, J.M. (2002). J. Virol. *76*, 12813–12822.

Kulkarni, A., Mateus, M., Thinnes, C.C., McCullagh, J.S., Schofield, C.J., Taylor, G.P., and Bangham, C.R.M. (2017). Cell Chem. Biol. *24*, this issue, 1377–1387.

Loisel-Meyer, S., Swainson, L., Craveiro, M., Oburoglu, L., Mongellaz, C., Costa, C., Martinez, M., Cosset, F.L., Battini, J.L., Herzenberg, L.A., et al. (2012). Proc. Natl. Acad. Sci. USA *109*, 2549–2554.

Manel, N., Kim, F.J., Kinet, S., Taylor, N., Sitbon, M., and Battini, J.L. (2003). Cell *115*, 449–459.

Manel, N., Taylor, N., Kinet, S., Kim, F.J., Swainson, L., Lavanya, M., Battini, J.L., and Sitbon, M. (2004). Front. Biosci. *9*, 3218–3241.

Matheson, N.J., Sumner, J., Wals, K., Rapiteanu, R., Weekes, M.P., Vigan, R., Weinelt, J., Schindler, M., Antrobus, R., Costa, A.S., et al. (2015). Cell Host Microbe *18*, 409–423.

Michalek, R.D., Gerriets, V.A., Jacobs, S.R., Macintyre, A.N., MacIver, N.J., Mason, E.F., Sullivan, S.A., Nichols, A.G., and Rathmell, J.C. (2011). J. Immunol. *186*, 3299–3303.

Pellerin, L., Pellegri, G., Bittar, P.G., Charnay, Y., Bouras, C., Martin, J.L., Stella, N., and Magistretti, P.J. (1998). Dev. Neurosci. *20*, 291–299.

Zdzisińska, B., Żurek, A., and Kandefer-Szerszeń, M. (2017). Arch. Immunol. Ther. Exp. (Warsz.) *65*, 21–36.