MONOCYTE-DERIVED DENDRITIC CELLS HAVE A DISTINCT IMMUNOMETABOLIC STATUS SUSTAINED BY PYRUVATE METABOLISM IN PLASMODIUM INFECTION

Theresa Ramalho[1], Kely Matteucci[2], Milton Pereira[1], Douglas Golenbock[1], Ricardo Gazzinelli[1,2,3]

[1]Infectious Diseases and Immunology Division, Department of Medicine, University of Massachusetts, Worcester, USA; [2]Platform for Translational Medicine, Oswaldo Cruz Foundation, Ribeirao Preto, Brazil; [3]Institute Rene Rachou, Oswaldo Cruz Foundation, Belo Horizonte, Brazil

The World Health Organization estimates that more than 90% of Plasmodium infections cause malaria-related deaths in endemic areas. This rate is attributed to intensified immune response against Plasmodium, which correlates with alterations in carbohydrate and lipid metabolism. Our group showed that a rhythmic alteration in systemic TNFa levels is followed by periodic changes in glucose levels and Plasmodium cycle. In this scenario, murine splenic monocyte-derived dendritic cells (MODC) amplify the influx of CD8+ T cells into the brain, triggering a lethal neuropathy in a model of malaria. Herein, our metabolomics indicated that MODCs of Plasmodium-infected mice accumulated mitochondria-derived phospholipids and a broken TCA (Krebs) cycle. Also, our RNAseq data suggested that MODCs were hyperenergetic and activated PPARg pathway. Indeed, Plasmodium infection promoted PPARg activation downstream IFNgR in splenic CD11b+ cells. It is known that PPARg activation induces GLUT1 translocation to plasma membrane, which culminates into glucose uptake in immune cells. In fact, we found that PPARg deficiency in myeloid cells reduced GLUT1 protein expression induced by Plasmodium infection in $CD11b^+$ cells. PPARg deficiency also reduced the high levels of mtROS and damaged mitochondria in MODCs, corroborating the fact that PPARg promoted glucose uptake and intensified pyruvate input into mitochondria of those cells. Once in mitochondria, pyruvate disrupted the TCA cycle due to itaconate and mtROS accumulation. In another work, our group shows that the high GLUT1 expression in liver, spleen and brain culminates in high glucose uptake in those organs, and GLUT1 is exclusively expressed in myeloid cells. This is consistent with a less hypoglycemic state observed in PPARg-deficient mice, indicating that the axis IFNgR/PPARg/GLUT1 contributes to hypoglycemia in Plasmodium infection. In this work, we also found that PPARg deficiency reduced the frequency of $MHCII^+CD80^+CD86^+$MODCs, suggesting that such metabolic status induced by Plasmodium in MODCs contributes to immunological synapse and neuropathy. Together, our results indicate that in malaria, a broken TCA cycle associated to PPARg activation in MODCs could promote adaptive immunity and rhythmic changes in systemic glucose levels. These findings would suggest PPARg as a therapeutic target to treat individuals with malaria-related neuropathy.