Introduction

Glucose transporter 1 (Glu1) is the main glucose transporter on T cells. We have shown that Glu1 level is increased on activated CD4+ T cells in people infected with HIV and this was associated with immune activation and low CD4 T cell count (Palmer et al, AIDS 2014).

In this activated state, instead of breaking down glucose through oxidative phosphorylation to form ATP, glucose is broken down via aerobic glycolysis to lactic acid, and generating precursors for cell wall synthesis and growth.

However, glycolysis is only moderately efficient in energy production so we postulated that a metabolic shift from oxidative phosphorylation to glycolysis results in metabolic exhaustion and death of CD4 T cells. We postulate that inhibition of glycolysis would suppress activation-driven CD4 T cell death.

CD4 T cell activation is associated with increased glucose uptake and aerobic glycolysis

Materials and methods

Cell surface: CD4
Metabolism: Glu1
Exhaustion: PI3K, mTOR
Senescence: CD28, CD57

Figure 2. Immunometabolic analysis using flow cytometry

Results

1. GLUT1 IS ELEVATED IN IMMUNOLOGICAL NON-RESPONDERS TO cART

Figure 3. Glucose metabolic activity in CD4+ T cells is increased during HIV infection and remains elevated during ART especially in immunological non-responders. A: HIV CD4 T cell count <500, and ≥2 years on ART.

Figure 4. There is an inverse relationship between the percentage of CD4+Glut1+ T cells and CD4 cell count in HIV+ cART patients.

2. GLUT1 EXPRESSION IN ACTIVATED T CELLS

Figure 5. Metabolic inhibitors (AS, TEM) suppress lactate accumulation of CD4 T cells activated with PMA and I.L-2. AS: PI3K, mTOR; TEM: temsirolimus and mTORC1 inhibitor, UT: activated but not treated with inhibitors.

Figure 6. Metabolic inhibitors suppress PI3 kinase (Glu73) and mTOR (p70S6K) signaling.

3. SORTING OF CD4+ GLUT1+ CELLS

Figure 7. Flow cytometry analysis of CD4+Glut1+ and CD4+Glut1+ cell death in the presence or absence of the mTORC1 inhibitor temsirolimus.

Conclusions

We propose a new paradigm by which CD4+ T homeostasis in HIV+ subjects is controlled by their metabolic phenotype, irrespective of treatment status. ‘CD4+ T cell metabolic exhaustion’ is a potential mechanism by which CD4 T cell death occurs.

Therapies that specifically target glucose metabolic pathways in CD4+ T cells could be exploited to improve immunological recovery in HIV+/cART subjects or enhance longer term remission without cART.

Reference:

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