Glut1: establishing a new paradigm for HIV-1 infection by regulating glucose metabolism and activation in CD4+ T cells in HIV-1-positive subjects

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Background: Glucose metabolism in T cells

Glucose Transporter-1 (Glut1) belongs to a family of glucose transporters
Fu et al, 2004; Barata et al, 2004; Maratou et al, 2007

Glut1 and is the main glucose transporter on T cells and is regulated predominantly by immunological signals

Intracellular retention of glucose is facilitated by hexokinase (Hx) activity

Glucose is metabolized via glycolysis or oxidative phosphorylation depending on the T cell activation status
Powel and Delgoffe, 2010; Finlay and Cantrell, 2011
Glucose metabolism and T cell activation

Increased metabolic machinery is an integral component of T cell activation

*Fox et al., Nat. Rev. Immunol, 2005*

Glucose metabolism

T cell activation

TCR stimulation and mitogens induces Glucose transporter-1 (Glut1) expression on lymphocytes

*Palmer et al., unpublished*

*Fox et al., Eur J Clin Invest, 2007*

*Kinet et al., 2007*
Hypothesis and objective

**Hypothesis**
HIV-1-induced T cell activation is associated with increases glucose metabolic responses in T cells

**Objective**
Evaluate cell surface expression of glucose transporter 1 (Glut1) on T cells from HIV-, HIV+ and HIV+/cART subjects
<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>HIV+</th>
<th>HIV+/cART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>25</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Male (%)</td>
<td>96</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td><strong>Viral load (copies/ml)</strong></td>
<td>-</td>
<td>79,1740 ± 78,094</td>
<td>&lt;50</td>
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<tr>
<td><strong>CD4 cell (cells/ul)</strong></td>
<td></td>
<td>397 ± 193</td>
<td>496 ± 256</td>
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Method: Glut1 expression on T cells

- Fresh blood (The Alfred Hospital, Melbourne)
- Frozen PBMCs (UWA, USA)

Lysed red blood cells

Surface markers: CD3, CD4, CD8
Metabolic marker: Glut1
Activation marker: CD38, HLA-DR

Flow cytometry
HIV-1 infection is associated with increased Glut1 on CD4+ T cells

In HIV+: the frequency of CD4+Glut1+ T cells was independently associated with the levels of HLA-DR on CD4+ T cells.

In HIV+/cART: the frequency of CD4+Glut1+ T cells was not associated with markers of activation.

In HIV+/cART: the frequency of CD4+ Glut1+ T cells was not associated with markers of activation.
CD4+Glut1+ T cells have increased levels of markers of activation.

% CD38+HLA-DR+ cells

- Glut1+ HIV-
  - n= 14

- Glut1+ HIV+
  - n= 20

- Glut1+ HIV+/cART
  - n= 11

p<0.0001  p=0.0001  p=0.008
Inverse relationship between CD4+Glut1+ T cells and CD4 percentage in HIV+ subjects

**HIV-1 treatment naive**

\[ r = -0.71, \ p < 0.0001, \ n = 45 \]

**HIV-1/cART**

\[ r = -0.53, \ p = 0.001, \ n = 35 \]

Increased glucose metabolic activity may contribute to CD4+ T cell loss during HIV-1 infection
Aim 2

To access the functional significance of Glut1 expression on CD4+ T cells
CD4+Glut1+ T cells have high glycolytic activity

CD4+ T cells from HIV+ subjects secrete more L-lactate

Intracellular L-lactate is higher in CD4+Glut1+ T cells

HIV-1 infection increases aerobic glycolysis in CD4+ T cells in vivo

Intracellular L-lactate

CD4+Glut1-

CD4+Glut1+
Host metabolism and viral infection

Human cytomegalovirus requires a glycolytic environment for replication

Yu et al., Trends Microbiol, 2011

Glut1-mediated metabolic pathway regulates HIV-1 infection in naïve CD4+

Loisel-Meyer et al., PNAS, 2012

Are CD4+Glut1+ T cells more permissible to HIV-1 infection?
CD4+Glut1+ T cells are more permissive to HIV-1 infection in vitro

PBMCs from study participants

- Time on cART: $6 \pm 4.3$ years
- Plasma viral load: <50
- CD4 T cell count: $274 \pm 98$
- CD4+Glut1+: $57.0 \pm 18.9\%$

Incubate with HIV-1-GFP (72h) (Absence of exogenous stimuli)

- Glut1
- OX40 (PI3K)
HIV-1 infection in CD4+Glut1+ T cell subsets

PI3K activity and Glut1 expression are both required for efficient HIV-1 infection in vitro
1. Circulating CD4+Glut1+ T cells have high glycolytic activity, are significantly increased in HIV-infected subjects and were not restored to normal levels following cART

2. Glut1 may represent a novel and functional marker of CD4+T cell activation and metabolic activity

3. CD4+Glut1+ T cells with high PI3K activity are more permissive to HIV-1 infection in vitro
Model: role of Glut1 in HIV-1 pathogenesis

Inhibition may limit glucose metabolic activity and activation
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CD4+Glut1+ T cells have increased levels of markers of activation

% CD38+HLA-DR+ cells

- Glut1+
  - HIV-: n=14
  - HIV+: n=20
  - HIV+/cART: n=11

- Glut1-

p<0.0001
p=0.0001
p=0.008

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