

## LETTER TO JCP

# Expression of DC-SIGN in human foreskin may facilitate sexual transmission of HIV

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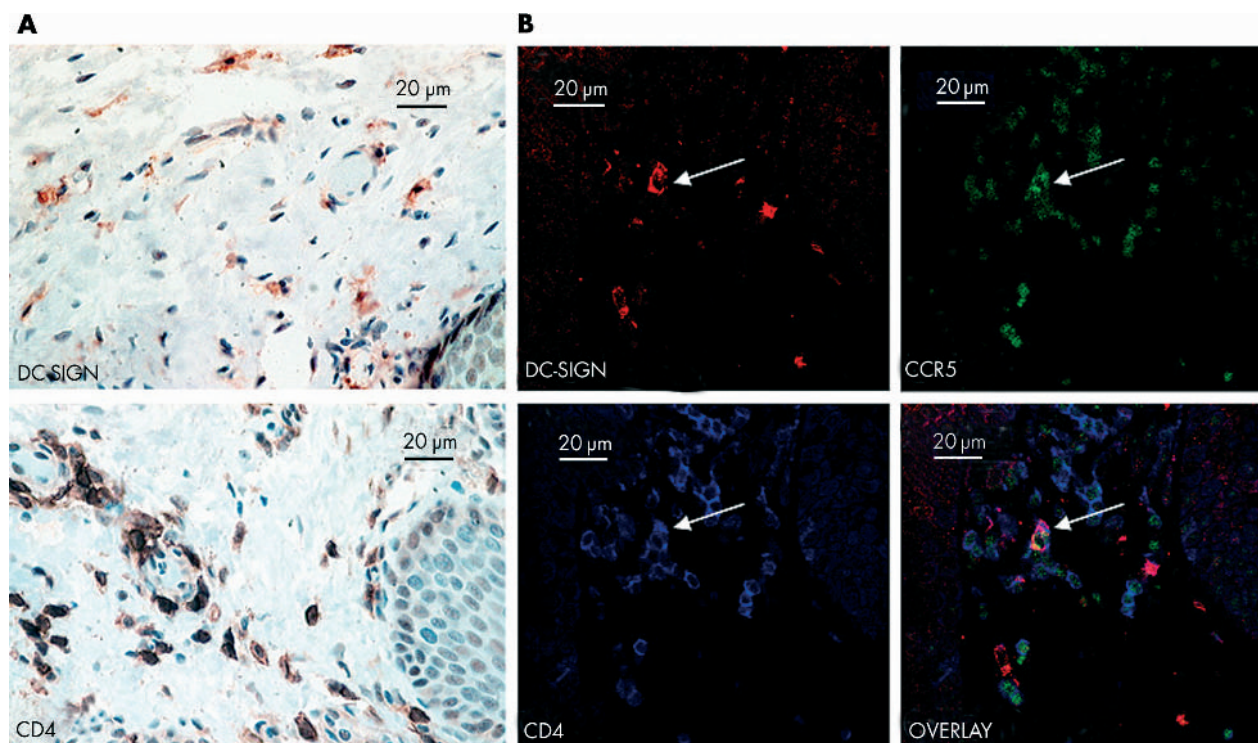
This study demonstrates that the human immunodeficiency virus (HIV) binding C-type lectin DC-SIGN is coexpressed with CD4 and CCR5 on dendritic cells/macrophages in human foreskin. It is hypothesised that DC-SIGN may contribute to the sexual transmission of HIV in the foreskin, by enabling infection of permissive cells in cis and/or in trans.

amounts of CD4.<sup>2</sup> We have examined the potential contribution that the C-type lectin DC-SIGN (dendritic cell specific intercellular cell adhesion molecule grabbing non-integrin) may make to HIV transmission in the foreskin.

DC-SIGN binds HIV avidly and has been shown to facilitate HIV infection of permissive cells both in trans and in cis.<sup>3</sup> In vivo, DC-SIGN may act in cis where DC-SIGN and the HIV entry receptors CD4 and CCR5 are coexpressed, such as on maternal macrophages and fetal Hofbauer cells at the placental interface,<sup>4</sup> and on alveolar macrophages.<sup>3</sup>

Circumcised men are infected with human immunodeficiency virus (HIV) less frequently than those who are not circumcised,<sup>1</sup> suggesting that the human foreskin is important in mediating the sexual transmission of HIV. The foreskin contains macrophages that express high

**Abbreviations:** DC-SIGN, dendritic cell specific intercellular cell adhesion molecule grabbing non-integrin; HIV, human immunodeficiency virus



**Figure 1** (A) Serial sections of foreskin tissue were immunostained with rabbit anti-DC-SIGN serum, rabbit anti-CD4 (Dako, Ely, Cambridgeshire, UK), and preimmune rabbit serum (negative control; data not shown) using the immunoperoxidase technique. CD4 was expressed both by cells with a dendritic morphology and cells with an oval morphology in the superficial stroma, whereas a smaller number of similar cells expressed DC-SIGN. Further serial sections demonstrated that a large proportion of the CD4+ cells were CD68+CD3-, consistent with macrophages or dendritic cells. (B) Sections of foreskin were immunostained with rabbit anti-DC-SIGN serum, chicken anti-CCR5 serum (Aveslab, Tigard, Oregon, USA), and mouse anti-CD4 monoclonal antibody (Novacastra, Newcastle upon Tyne, UK). As negative controls, serial sections were immunostained with preimmune rabbit serum, normal chicken serum, and mouse IgG1 isotype control at appropriate concentrations. Primary antibodies were detected using Alexa-594 antirabbit serum, FITC conjugated antichickens serum (Jackson ImmunoResearch, West Grove, Pennsylvania, USA), and Alexa-633 antimouse serum (Molecular Probes, Eugene, Oregon, USA). Whereas DC-SIGN was expressed on less than 5% of CD4+ cells, all DC-SIGN+ cells (red, example marked with an arrow) expressed CD4 (blue) and CCR5 (green), the receptors required for HIV entry.

### Take home messages

- The human immunodeficiency virus (HIV) binding C-type lectin DC-SIGN is coexpressed with CD4 and CCR5 on dendritic cells/macrophages in human foreskin
- DC-SIGN may contribute to HIV transmission in the foreskin, by enabling infection of permissive cells both in cis and in trans

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### METHODS/RESULTS

We undertook immunohistochemical analysis of nine normal human foreskin specimens, using methods described previously.<sup>3,4</sup> In all cases, macrophages expressing CD4, CD68, and CD3 were seen in the superficial dermis (fig 1A). In the same location, DC-SIGN was expressed both by cells with a dendritic morphology and by cells with an oval morphology (fig 1A). These cells are consistent with dendritic cells and macrophages, respectively, both of which are permissive for HIV infection.<sup>5</sup>

Using triple labelling confocal microscopy,<sup>3</sup> we showed that all the DC-SIGN+ cells expressed both CD4 and CCR5 (fig 1B), suggesting that DC-SIGN may potentiate HIV infection of these cells in cis. Most CD4+ DC-SIGN- cells also expressed CCR5 (fig 1B), and could therefore be infected in trans by the DC-SIGN+ cells in close proximity.

### DISCUSSION

Our study provides only circumstantial evidence regarding the role of DC-SIGN in the sexual transmission of HIV, because of a lack of availability of suitable tissue. Biopsies of the penis are rarely taken, and most studies to date have used material from circumcisions. However, if human tissue were

available, population studies correlating levels of DC-SIGN expression in the penis with HIV transmission rates could provide crucially important data. Such studies could be undertaken both in circumcised and uncircumcised men, comparing the two groups of men and those contracting HIV with individuals at similar risk who do not. In addition, correlating levels of DC-SIGN expression with the probability of sexual injury in different areas of the penis could give clues to the probable importance of DC-SIGN in HIV transmission.

We suggest that DC-SIGN may contribute to HIV transmission in the foreskin, by enabling the infection of permissive cells both in cis and in trans, as has been suggested at other anatomical sites.<sup>3,4</sup>

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