

Schistosomiasis: role of DC-SIGN

with

Irma van Die, PhD; Glycoimmunology Group, Department of Molecular Cell Biology and Immunology, VU University Medical Center, van der Boerhorststraat 7, 1081 BT Amsterdam, the Netherlands
im.vandie@vumc.nl



During schistosomiasis, how can parasite-derived glycoconjugates manipulate immune response of the infected host?

Irma van Die: *Schistosoma mansoni* and other parasitic helminths generate a large array of glycan antigens that occur on the parasite surface (attached to proteins and lipids) and within secreted polysaccharides. Many of these carbohydrate antigens are foreign to the host, and are highly antigenic (1). Increasing evidence indicates that schistosome carbohydrate antigens are potent inducers of Th2 responses, and specific carbohydrate antigens can stimulate the production of different classes of glycan-spe-

cific antibodies, not only IgM, but also Th2 associated IgG and IgE. Interestingly, helminths also show molecular mimicry, by expressing similar glycan antigens as found within their hosts. We established that several of the carbohydrate antigens of schistosomes are recognized by human lectin receptors that occur on dendritic cells or macrophages (2). Binding of these host lectin receptors to the parasite glycoconjugates may provide a specific signal to the immune cells and modulate their function.

How can different schistosome glycan antigens interact with the lectin receptor DC-SIGN?

Irma van Die: DC-SIGN (Dendritic-cell specific ICAM-3 grabbing non-integrin, CD209) is a human C-type lectin receptor that is abundantly expressed on immature dendritic cells, together with a variety of other lectin receptors (3). DC-SIGN interacts with many pathogens (2), and indeed recognizes several different carbohydrate antigens of *Schistosoma mansoni*. DC-SIGN interacts with egg glycoproteins through Le^x and LDNF

glycan antigens (4,5), and with glycolipids via Le^x and pseudo-Le^y (6). To understand how different glycan antigens can interact with DC-SIGN, the binding mode of Le^x in DC-SIGN was determined by molecular modeling (5,6) based on the crystal structure of DC-SIGN (7). Interestingly, the binding domain of DC-SIGN seems to be flexible, allowing interaction with different glycan ligands (see Figure 1).

How important is DC-SIGN in Schistosomiasis?

Irma van Die: The functions of lectin receptors such as DC-SIGN for dendritic cell function are not yet fully understood. It is thought that lectin receptors in concerted action with Toll-like receptors control the balance between induction of immunity versus tolerance in dendritic cells. We currently can only speculate about the importance of this interaction in schistosomiasis. Inter-

estingly, glycoconjugates derived from virulent *Mycobacterial* strains, as well as from *Helicobacter pylori* can induce the production of IL-10 from immature dendritic cells via interaction with DC-SIGN (8,9). This is important since IL-10 may induce a regulatory T-cell network that can suppress overly strong Th2 responses, which could also be relevant in schistosome infections.

Is the interaction with the carbohydrate antigens Le^x, LDNF and pseudo-Le^y limited to schistosomes?

Irma van Die: DC-SIGN can mediate multiple functions in the immune system since it mediates cell-cell interactions between different immune cells, but it is also involved in pathogen recognition. Interaction of DC-SIGN with Le^x is not limited to schistosomes. Recognition of *Helicobacter pylori* by DC-SIGN is also Le^x mediated (8). In addition, DC-SIGN interacts with human neutrophils through Le^x antigens on Mac-1, an interaction that induces DC maturation (10). LDNF is found on

many pathogenic helminths, and also on a limited number of human glycoproteins. However, the interaction of DC-SIGN with LDNF from other sources than schistosomes has not yet been reported, and whether interaction indeed occurs may be dependent on the abundance and spacing of the LDNF antigens on a particular glycoprotein. Interaction of DC-SIGN to pseudo-Le^y may be limited to schistosomes, since pseudo-Le^y has so far not been found elsewhere.

Is there any hope to re-manipulate the parasite-mediated alteration of the immune response?

Irma van Die: There is always hope of course. It may be possible that DC-SIGN plays a crucial role in the regulation of Th cell responses during parasitic infections, and perhaps can be targeted to modulate such responses. It has been shown however that DC-SIGN can also act as an internalization receptor, and thus may enhance uptake and processing of parasite glycan antigens. Its function may be dependent on whether and which other receptors (lectin receptors and/or Toll-like receptors) are triggered simultaneously. There are many different lectin receptors on DC that may recognize the same, or

different glycan antigens on the same protein. For example human MGL, which is also a lectin receptor on immature DC, recognizes similarly to DC-SIGN the LDNF glycan antigen, but in contrast does not recognize Le^x (11). It will be very important to get more insight in how glycan antigens in concerted action with other glycans or lipid/protein antigens that may be present on the same molecule trigger multiple receptors, and to understand the functional consequences. We should learn a lot more before we know whether and how DC-SIGN can be used to re-manipulate the immune response.

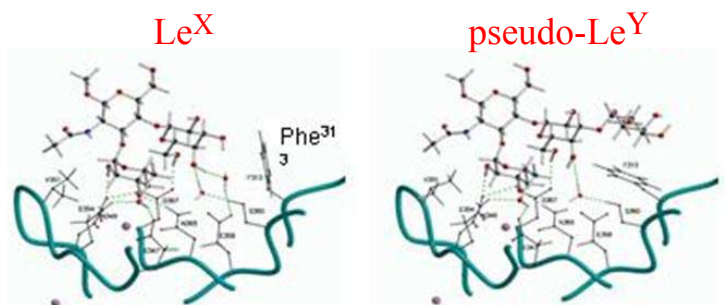


Figure 1: DC-SIGN can interact with both Le^x trisaccharide and pseudo-Le^y tetrasaccharide. Calcium ions are represented by purple spheres. The model of DC-SIGN complexed with Le^x predicts that a substituent on the 2-OH group of galactose in Le^x, such as in Le^y or LDNF, is acceptable (5,7). However, linkage of a fucose to the 3-OH group of galactose, such as in pseudo-Le^y, would give a steric conflict with the side chain of Phe³¹³. Interestingly, we observed binding of soluble DC-SIGN-Fc, as well as cellular expressed DC-SIGN, to pseudo-Le^y (6). To fit a fucose on position 3 of galactose into the model, the orientation of the side chain of Phe³¹³ was slightly changed, a movement that does not cost significant energy and allows a perfect stacking with the galactose-linked fucose (6). We propose that the secondary binding site of DC-SIGN is flexible due to the capacity of the Phe³¹³ side chain to change orientation, and that pathogens such as *S. mansoni* may use this property to target DC-SIGN.

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