

DC-SIGN and mSIGNR1 with

Estella A. Koppel and Teunis BH Geijtenbeek PhD
Molecular Cell Biology & Immunology, VU University Medical
Center, van der Boerhorststraat 7, 1081 BT Amsterdam, The
Netherlands.
t.geijtenbeek@vumc.nl



What is known about mSIGNR1?

Estella Koppel and Teunis Geijtenbeek: mSIGNR1 is a murine homologue of the human C-type lectin Dendritic Cell-specific ICAM3-grabbing nonintegrin (DC-SIGN) (1). Five murine DC-SIGN homologues have been identified at mRNA level: mDC-SIGN and mSIGNR1 to 4, but so far protein of only mDC-SIGN and mSIGNR1 has been detected in tissues (2,3). Hence, research has focused on mDC-SIGN and mSIGNR1. Although mDC-SIGN is expressed on a dendritic cell (DC) subset (2), it does not bind multivalent pathogen ligands (Gramberg et al., 2006). In contrast,

mSIGNR1 has a similar carbohydrate binding specificity to DC-SIGN, (4), interacting with pathogens, such as HIV-1, *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* (5). However, mSIGNR1 is expressed by specific macrophage subsets such as marginal zone macrophages in spleen, peritoneal macrophages, subcapsular and medullary macrophages in lymph node but not by DCs (3,6). Recently, mSIGNR1-deficient mice were generated by Lanoue et al., providing an excellent tool to study for the first time the role of one of the murine DC-SIGN homologues *in vivo* (7).

What is the *in vivo* role of mSIGNR1?

Estella Koppel and Teunis Geijtenbeek: *In vitro* experiments have demonstrated that mSIGNR1 interacts specifically with several *S. pneumoniae* serotypes (8). Spleen, with its highly specialized lymphoid compartment, is pivotal to an effective immune response against *S. pneumoniae*. We therefore used mSIGNR1-deficient mice to study the role of mSIGNR1 in *S. pneumoniae* infections. Strikingly, mSIGNR1-deficient mice succumbed to intranasal infection with *S. pneumoniae* in contrast to wild-type mice (9). Our data demonstrate that the mSIGNR1-deficient mice were unable to raise early antibodies against the pneumococcal antigen phosphorylcholine (PC). Marginal zone B cells, that reside in close proximity to marginal zone macrophages,

are involved in the production of these early antibodies. Therefore, we hypothesized that mSIGNR1, through the capture of *S. pneumoniae*, is involved in the production of early neutralizing antibodies by marginal zone B cells perhaps by directly activating them (9). Peritoneal infection of *S. pneumoniae* using mSIGNR1-deficient mice demonstrated that mSIGNR1 is also essential for the uptake and degradation of *S. pneumoniae* (7), indicating that it may have a role in antigen transfer to MZ B cells (9). In conclusion, mSIGNR1 is involved in the early immune defense against *S. pneumoniae* infection by inducing rapid antibody responses as well as capture and phagocytosis of the bacteria (7,9).

Are there any differences between mSIGNR1 and DC-SIGN?

Estella Koppel and Teunis Geijtenbeek: Yes, there are differences between these C-type lectins. Most impor-

tant are the differences in their expression. DC-SIGN is expressed by DCs, and upon inflammation by some macrophage subsets (10,11), whereas mSIGNR1 is not expressed by DCs but by specific macrophage subsets such as marginal zone macrophages, and the liver sinusoidal endothelial cells(3). Its expression pattern is similar to the human homologue of DC-SIGN, L-SIGN (3,12).

There are also some differences in carbohydrate specificities but it is unclear yet whether these differences contribute to distinct pathogen recognition (4).

Can binding of pathogens like *S. pneumoniae* to DC-SIGN cause immunomodulatory effects on dendritic cells?

Estella Koppel and Teunis Geijtenbeek: DC-SIGN functions as a broad-spectrum pathogen receptor. It recognises a great variety of pathogens, including viruses, mycobacteria, bacteria and parasites. Strikingly, the immune responses initiated by the interaction of DC-SIGN with these various pathogens differ between pathogens: *Mycobacterium tuberculosis*

interaction leads to immune suppression (13), whereas *Helicobacter pylori* shifts the Th1/Th2 balance away from a host favourable outcome (14). We have demonstrated that DC-SIGN interacts with several but not all *S. pneumoniae* serotypes and their polysaccharides. However, results suggest that DC-SIGN is not involved in modulation of DCs by *S. pneumoniae* (15).

Do you believe that your findings can help to develop more potent vaccines?

Estella Koppel and Teunis Geijtenbeek: An intensively investigated area of research at the moment is the targeting of C-type lectins to induce stronger cellular immune responses against pathogens. Our data suggest that perhaps DC-SIGN and mSIGNR1 are necessary to induce proper

antibody responses, which would indeed be useful in the design of vaccines. Thus, targeting of these receptors with specific carbohydrate structures of pathogens could accordingly help vaccine development by inducing specific T and B cell responses.

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