TOUTES DIRECTIONS

DENDRITIC CELLS

One SIGN, different paths

When an invading pathogen meets a dendritic cell (DC) it is greeted by several cell surface receptors that work together to tailor a fitting immune response. A new report published in *Nature Immunology* reveals how one receptor creates further specificity by altering cytokine production levels in response to binding particular pathogen carbohydrates.

DC-specific ICAM3-grabbing non-integrin (DC-SIGN; also known as CD209 antigen) is one of several pattern recognition receptors, which are expressed by DCs and recognize various highly conserved molecules expressed by microorganisms. Signals from DC-SIGN modulate the signalling pathways that result from the activation of Toll-like receptors (TLRs). Unlike TLRs, of which there are numerous family members, each of which binds a specific molecule, the single DC-SIGN receptor binds various pathogen-expressed carbohydrate ligands, but it was not known whether these different carbohydrates could trigger distinct downstream pathways.

This study showed that interaction of DC-SIGN with ligands containing mannose induced a different profile of cytokine production from interactions with ligands containing fucose. The team found that mannose-expressing pathogens (and assorted mannose ligands) prompted DCs to increase production of interleukin-10 (IL-10), IL-12 and IL-6. Fucose-containing ligands, however, led to increased production of only IL-10; production of both IL-12 and IL-6 was decreased. These different cytokine production profiles could in turn induce or inhibit specific subsets of T helper cells.

The carbohydrate-specific cytokine profiles of the DCs were associated with changes in the composition of the signalosome complex linked to DC-SIGN. In quiescent DCs, the DC-SIGN signalosome was made up of the scaffolding proteins LSP1 (lymphocyte-specific protein 1), KSR1 (kinase suppressor of Ras 1) and CNKSR1 (connector enhancer of KSR1) and the protein kinase RAF1. Following binding of mannose-expressing pathogens, such as mycobacteria and HIV-1, additional proteins that activated RAF1 were recruited to the DC-SIGN signalosome. This activation was shown to be necessary for the observed increase in cytokine production. By contrast, binding of fucose ligands from pathogens such as *Helicobacter pylori* led to the disbanding of the signalosome complex, as KSR1, CNKSR1 and RAF1 became dissociated. LSP1 remained associated with the signalosome and, in line with this, cytokine regulation in fucose-exposed DCs was LSP1 dependent and RAF1 independent.

Exactly how the signalosome composition is altered by the two carbohydrates is unknown. The authors suggest that it results from the way in which mannose and fucose interact with DC-SIGN. The two carbohydrates bind the receptor in a similar manner but have slightly different amino acid interactions. This subtle difference might be sufficient to induce a conformational change in DC-SIGN and so switch the signalling pathways.

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ORIGINAL RESEARCH PAPER Gringhuis, S. I., den Dunnen, J., Litjens, M., van der Vlist, M. & Geijtenbeek, T. B. H. Carbohydrate-specific signaling through the DC-SIGN signalosome tailors immunity to *Mycobacterium tuberculosis*, HIV-1 and *Helicobacter pylori*. *Nature Immunol.* **10**, 1081–1088 (2009)