DENDRITIC CELLS

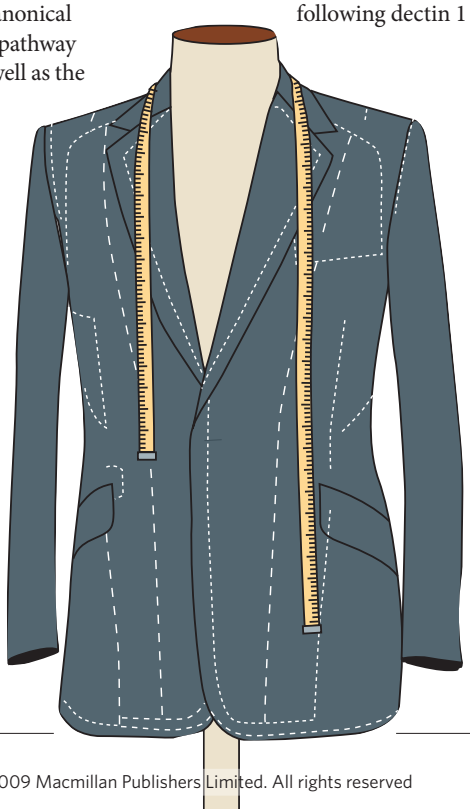
Tailoring T-helper-cell responses

A report published in *Nature Immunology* has characterized the signalling pathways by which dendritic cells (DCs) induce adaptive immunity to fungal infections following stimulation of the C-type lectin receptor dectin 1.

The activation of naive T cells by DCs is central to the differentiation of T helper (T_H)-cell populations that are required for host defence against an invading pathogen. Effective immunity to fungal infections, such as *Candida albicans*, requires the generation of T_H1- and T_H17-cell responses. In this study, Gringhuis *et al.* examined the signalling pathways that are activated downstream of dectin 1 to determine how cytokine production — and thereby T_H-cell differentiation — is regulated by human DCs during infections with fungal pathogens that express ligands for dectin 1.

Unlike other pattern-recognition receptors, dectin 1 ligation led to the activation of the non-canonical nuclear factor-κB (NF-κB) pathway (which involves RELB) as well as the canonical NF-κB pathway (which involves p65 and REL). As was shown in earlier studies, this occurred through spleen tyrosine kinase (SYK), which associates with the cytoplasmic domain of dectin 1. However, the authors also showed that a second, SYK-independent pathway was activated following dectin 1 ligation through the activation of another kinase known as RAF1. Inhibiting the expression of either SYK or RAF1 by RNA interference markedly altered the cytokine profile of DCs that had been stimulated with dectin 1 ligands, suggesting that both of these pathways are required for the production of specific cytokines by DCs during an immune response to a fungal pathogen.

Interestingly, although these two signalling pathways downstream of dectin 1 were activated independently, they were found to integrate at the level of NF-κB activation. More specifically, the non-canonical NF-κB subunit RELB that is activated by the SYK pathway was found to be negatively regulated by the RAF1 pathway through RAF1-mediated sequestration of RELB into inactive p65–RELB dimers. This inhibition, in turn, caused an induction of interleukin-1β (IL-1β) and IL-12p40 expression. Activation of RAF1 following dectin 1 ligation was also found to increase the expression of several other cytokines (including IL-6, IL-10 and IL-12p35) by phosphorylating and thereby promoting the acetylation of the canonical NF-κB subunit p65, which activates the transcription of many cytokine genes.



So, the production of cytokines by DCs following dectin 1 ligation requires both SYK- and RAF1-mediated signalling pathways, but what does this mean in the context of an adaptive immune response to a fungal pathogen? In line with the finding that RAF1 was required for optimal expression of IL-12p40 and IL-12p35 (which are important for T_H1-cell responses), inhibition of RAF1 in DCs that were stimulated with *C. albicans* caused impaired T_H1-cell polarization *in vitro*. As SYK and RAF1 were also found to be essential for the optimal production of T_H17-cell-polarizing cytokines (including IL-1β and IL-6) by DCs in response to dectin 1 ligands, these signalling pathways may also be important for the induction of T_H17 cells during a fungal infection. Therefore, the authors propose that RAF1 might be an ideal therapeutic target by which to 'steer' the immune response to clear infections in which T_H1 and T_H17 cells have a central role in host defence.

Sarah Allan

ORIGINAL RESEARCH PAPER Gringhuis, S. I. *et al.* Dectin-1 directs T helper cell differentiation by controlling noncanonical NF-κB activation through Raf-1 and Syk. *Nature Immunol.* 4 Jan 2009 (doi:10.1038/ni.1692)