How quantitative differences in dendritic cell maturation can direct \( T_{H1} / T_{H2} \)-cell polarization

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Abbreviations: EAE, experimental autoimmune encephalomyelitis; DC, dendritic cell; HDAC, histone deacetylase; IL, interleukin; IFN, interferon; LPS, lipopolysaccharide; MYD88, myeloid differentiation primary response gene 88; TLR, Toll-like receptor; TNF, tumor necrosis factor; VSG, variant surface glycoproteins

The polarization of \( T_{H1} \) or \( T_{H2} \) responses by dendritic cells (DCs) requires distinct maturation conditions. Our data indicate that quantitative differences in DC maturation dictate a \( T_{H1} \) or \( T_{H2} \)-cell polarization outcome. We discuss how chromatin remodeling at DC loci coding for pro-inflammatory vs. polarizing cytokines may explain differential \( T_{H2} \)-cell polarization.

The requirements for \( T_{H2} \)-2 polarization in terms of nature and activation state of antigen-presenting cells, and more specifically the dendritic cell (DC) subset and maturation stimuli, are not fully understood. In fact, \( T_{H2} \) cells may be generated under different conditions. Here, we discuss our recent findings about the common features of different murine \( T_{H2} \)-polarizing DCs.\(^1\) Our data indicate that quantitative differences in DC maturation dictate \( T_{H1} \) vs. \( T_{H2} \) cell-polarization. While strong DC maturation signals activate up to 5,000 genes and lead to a \( T_{H1} \) shift, a weaker DC maturation stimulus induces 10- to 20-fold fewer genes and hence promotes the development of \( T_{H2} \) cells.

Reports on the requirements for \( T_{H2} \)-cell polarization differ to considerable extents. Some authors report that \( T_{H2} \) responses can develop via a default pathway, i.e., that the absence of interleukin (IL)-12p70 production is sufficient for the maturation of \( T_{H2} \) cells.\(^2\) Other groups found that the differentiation of \( T_{H1} \) vs. \( T_{H2} \) effector cells depend on a peptide dose and/or binding affinity.\(^3\) Finally, differential expression of the Notch ligands Jagged-1 and -2 on antigen-presenting cells has been proposed as a decisive element for the development of \( T_{H2} \) responses.\(^4\) These observations suggest that the absence of an active polarizing signal, especially under weak T-cell stimulatory conditions, is sufficient to promote \( T_{H2} \) immunity, although specific ligands may exist that promote \( T_{H2} \)-cell polarization by DCs.

It appears that helminth-derived products evoke only mild transcriptional alterations in DCs, resulting in a immature/partially mature DC phenotype,\(^5\) similar to that we observed when DCs were exposed to endogenous pro-inflammatory factors such as tumor necrosis factor \( \alpha \) (TNF\( \alpha \)).\(^6\) Partially mature DCs exert tolerizing but also \( T_{H2} \)-cell polarizing functions. Partial DC maturation is characterized by the upregulation of MHC Class II and co-stimulatory molecules along with the absent production of cytokines. Partially mature DCs as elicited by TNF\( \alpha \) induce the differentiation of IL-4+ \( T_{H2} \) cells after a single round of T-cell stimulation in vitro and in vivo.\(^1\) Repetitive injections of TNF\( \alpha \)-matured DCs prevented the induction of experimental autoimmune encephalomyelitis (EAE) by the shift from \( T_{H2} \) toward IL-10+ IL-13+ CD4+ T cells, compatible with a \( T_{H2} \)-like regulatory T-cell phenotype.\(^6\) These observations support the concept that TNF\( \alpha \)-induced partially mature DCs exhibit tolerogenic features. Although the scientific literature indicated that DC maturation profiles induced by helminths or parasites can be similar to those obtained with TNF\( \alpha \), a direct comparison had not yet been performed.

Therefore, we investigated how the genetic maturation signature and the corresponding \( T_{H2} \)-cell differentiation potential may differ between DC exposed to TNF\( \alpha \) and pathogens. To this aim, we selected two variant surface glycoproteins (VSGs) purified from Trypanosoma brucei that had previously been characterized for their immunomodulatory potential. Surprisingly, low concentrations of VSG elicited a weak Toll-like receptor (TLR)/myeloid differentiation primary response gene 88 (MYD88)-transduced signal, promoted a genetic program that is highly similar to that triggered by TNF\( \alpha \), and lead to a semi-mature DC phenotype.\(^1\) VSG-matured DCs were able to instruct \( T_{H2} \) priming in vitro and in vivo. A common signature including 24 pro-inflammatory genes was identified among three distinct types of \( T_{H2} \)-cell polarizing DC populations analyzed in this study. Of note, DC maturation by lipopolysaccharide polarized \( T_{H1} \) responses while inducing almost 5,000
These data indicate that genes coding for prototypic pro-inflammatory cytokines can be activated easily and rapidly in DCs, while genes coding for polarizing cytokines may require stronger and/or prolonged stimuli that allow for chromatin modifications. In this setting, a mild maturation signal would give rise to TH2-inducing DCs, while stronger and extended stimuli would allow for the development of TH1-inducing DCs, most likely as a result of the differential accessibility of the IL-12-coding gene. Taken together, these findings support a model in which not only the quality of DC maturation signals, as determined by the activation of either pattern recognition receptors or cytokine receptors, but also quantitative differences in maturation signals that are conveyed by the same pattern recognition receptors can critically influence TH1/TH2 polarization (Fig. 1).

Figure 1. Qualitative and quantitative differences in dendritic cell maturation affect T_{h1}/T_{h2} polarization. Dendritic cell (DC) maturation can be initiated by various types of pattern recognition receptors, such as Toll-like receptors (TLRs), or by the receptors for various pro-inflammatory cytokines, such as the TNFα receptor TNFR. The genetic signatures resulting from TNFR-conveyed and weak TLR-conveyed signals are remarkably small and highly similar to each other, sharing a common pro-inflammatory component. When DC maturation is triggered by TNFR or weak TLR signals (TLR^{low}), the transcription factor NFκB can rapidly bind to the promoter region of genes coding for interleukin (IL)-1, IL-6 and TNFα. This type of DC maturation promotes T_{h2}-cell polarization. In response to these signals, no chromatin remodeling at the IL-12-coding gene promoter occurs to allow for the binding of NFκB. In contrast, strong and prolonged TLR (TLR^{high}) signals are required to allow for chromatin remodeling at promoter region of the IL-12-coding gene and hence for the (delayed) binding of NFκB, resulting in the maturation of T_{h1}-polarizing DCs. This model integrates findings indicating that both DC maturation signal type (quality) and intensity (quantity) influence can T_{h1} vs. T_{h2}-cell polarization.

How can the strength of DC maturation signals mediate a T_{h2} to T_{h1} shift? Both TNFα and LPS are well-known inducers of the transcription factor NFκB. However, the accessibility of genes for NFκB binding may differ, resulting in completely distinct functional outcomes. In particular, the post-translational opening of chromatin following the activation of histone acetyltransferases or the inhibition of histone deacetylases (HDACs) can influence NFκB activity at different cytokine-encoding genetic loci. Indeed, the accessibility of the IL-12p35-coding locus in DCs requires nucleosome remodeling. In line with this notion, the release of TNFα, IL-1 and IL-6 by DCs was not influenced by HDAC inhibitors (or needed prolonged inhibition), while the secretion of IL-12p35, IL-12p40 and interferon β (IFNβ) was highly susceptible to HDAC inhibitors. In addition, the recruitment of the NFκB subunit RelA to the promoter region of the TNFα-coding gene was rapid, while it was delayed for the IL-12-coding locus.

These data indicate that genes coding for prototypic pro-inflammatory cytokines can be activated easily and rapidly in DCs, while genes coding for polarizing cytokines may require stronger and/or prolonged stimuli that allow for chromatin modifications. In this setting, a mild maturation signal would give rise to T_{h2}-inducing DCs, while stronger and extended stimuli would allow for the development of T_{h1}-inducing DCs, most likely as a result of the differential accessibility of the IL-12-coding gene. Taken together, these findings support a model in which not only the quality of DC maturation signals, as determined by the activation of either pattern recognition receptors or cytokine receptors, but also quantitative differences in maturation signals that are conveyed by the same pattern recognition receptors can critically influence T_{h1}/T_{h2} polarization (Fig. 1).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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