

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_H-cell polarization.

The requirements for T_H2 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 α (TNF α).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 α 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 α -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_R1-like regulatory T-cell phenotype.⁶ These observations support the concept that TNF α -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 α , 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 α 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 α , 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

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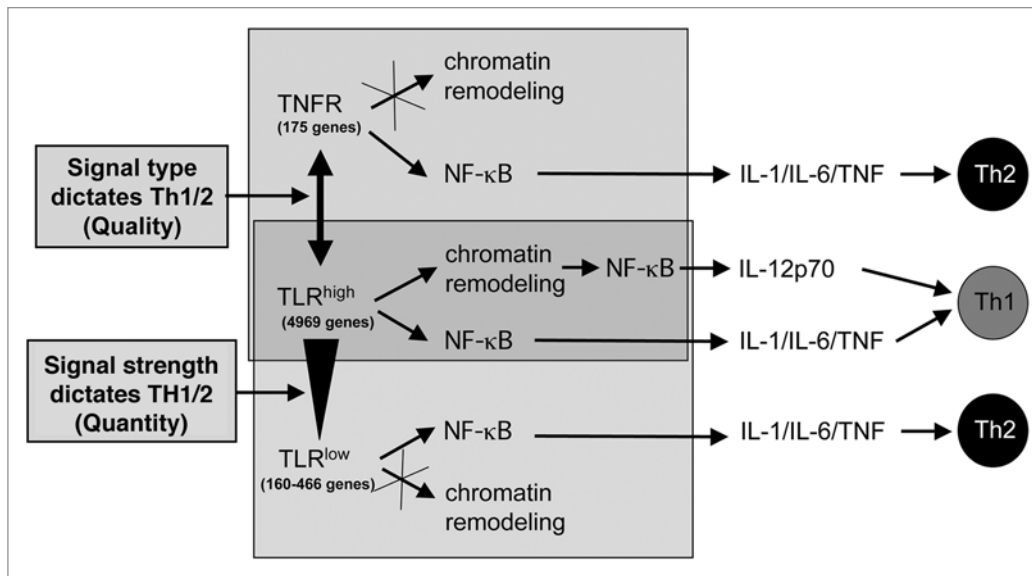


Figure 1. Qualitative and quantitative differences in dendritic cell maturation affect T_H1/T_H2 polarization. Dendritic cell (DC) maturation can be initiated by various types of pattern recognition receptors, such as Toll-like receptors (TLRs), or by the receptors for various pro-inflammatory cytokines, such as the $TNF\alpha$ 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 $NF\kappa B$ can rapidly bind to the promoter region of genes coding for interleukin (IL)-1, IL-6 and $TNF\alpha$. 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 $NF\kappa B$. 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 $NF\kappa B$, 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.

genes, including the 24 pro-inflammatory genes linked to the T_H2 program as well as additional genes like those coding for the typical T_H1 -inducing cytokine IL-12p35 (constituting part of IL-12p70) and the Notch ligand Delta-4.⁴ Only a moderate shift of Jagged-2 could be observed in T_H2 cell-polarizing DCs and no difference was observed in Jagged-1 expression in both T_H1 - or T_H2 -inducing DC.¹ Taken together, these data indicate that relatively small pro-inflammatory gene signature characterizes T_H2 -inducing DCs, while many additional factors are required for the development of a T_H1 -inducing DC. Thus, our findings support the default theory of T_H2 cell induction. In addition, our data support previous findings indicating that a low peptide dose favors T_H2 polarization.³ In our experimental, the low peptide dose was mimicked by the partial maturation of DCs, leading to a comparatively less efficient antigen presentation that may allow for T_H2 induction. In line with our observation, quantitative aspects about T_H polarization have just been revisited.⁷

How can the strength of DC maturation signals mediate a T_H2 to T_H1 shift? Both $TNF\alpha$ and LPS are well-known inducers of the transcription factor $NF\kappa B$. However, the accessibility of genes for $NF\kappa B$ 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 $NF\kappa B$ activity at different cytokine-encoding genetic loci. Indeed, the accessibility of the IL-12p35-coding locus in DCs requires nucleosome remodeling.⁸ In line with this notion, the release of $TNF\alpha$, 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 (IFN β) was highly susceptible to HDAC inhibitors.⁹ In addition, the recruitment of the $NF\kappa B$ subunit RelA to the promoter region of the $TNF\alpha$ -coding gene was rapid, while it was delayed for the IL-12-coding locus.¹⁰

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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