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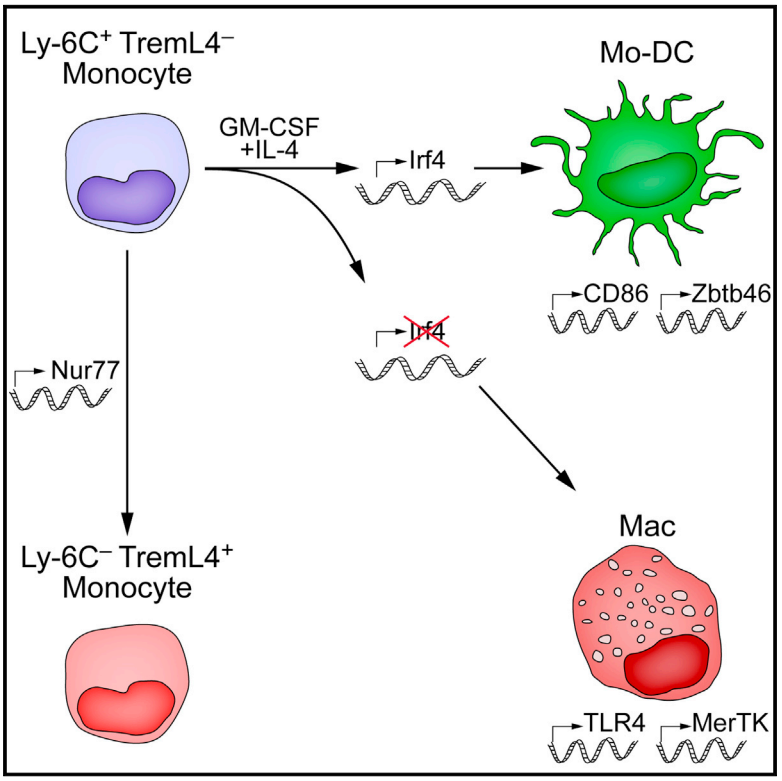
Distinct Transcriptional Programs Control Cross-Priming in Classical and Monocyte-Derived Dendritic Cells

Graphical Abstract



Highlights

- GM-CSF-derived Mo-DCs require IL-4 to cross-present cell-associated antigen
- Monocytes expressing TremL4 lose potential to differentiate into DCs
- Monocytes require IRF4, but not Batf3, to become APCs that can prime CD8+ T cells

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In Brief

The transcriptional programs required for differentiation of cross-priming APCs from various lineages are unknown. Briseño et al. show that Mo-DCs use a program distinct from that of cDCs, requiring IRF4 but not Batf3. These differences may impact the design of vaccines based on Mo-DCs that would require efficient cross-priming of T cells.

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Distinct Transcriptional Programs Control Cross-Priming in Classical and Monocyte-Derived Dendritic Cells

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SUMMARY

Both classical DCs (cDCs) and monocyte-derived DCs (Mo-DCs) are capable of cross-priming CD8$^+$ T cells in response to cell-associated antigens. We found that Ly-6C^{hi}TREML4$^-$ monocytes can differentiate into *Zbtb46*$^+$ Mo-DCs in response to granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4) but that Ly-6C^{hi} TREML4$^+$ monocytes were committed to differentiate into Ly-6C^{lo}TREML4$^+$ monocytes. Differentiation of *Zbtb46*$^+$ Mo-DCs capable of efficient cross-priming required both GM-CSF and IL-4 and was accompanied by the induction of *Batf3* and *Irf4*. However, monocytes require IRF4, but not BATF3, to differentiate into *Zbtb46*$^+$ Mo-DCs capable of cross-priming CD8$^+$ T cells. Instead, *Irf4*$^{-/-}$ monocytes differentiate into macrophages in response to GM-CSF and IL-4. Thus, cDCs and Mo-DCs require distinct transcriptional programs of differentiation in acquiring the capacity to prime CD8$^+$ T cells. These differences may be of consideration in the use of therapeutic DC vaccines based on Mo-DCs.

INTRODUCTION

Cross-presentation functions in initiating cytolytic CD8$^+$ T cell responses during viral infections (Joffre et al., 2012) and is mediated by classical dendritic cells (cDCs) derived from the common dendritic cell progenitor (Naik et al., 2007; Liu et al., 2007) and by monocyte-derived dendritic cells (Mo-DCs) (Nierkens et al., 2013). Efficient cross-presentation is carried out in vivo by a CD24$^+$ cDC subset requiring IRF8 and BATF3 (Briseño et al., 2014; Satpathy et al., 2012b), but the transcriptional requirements for Mo-DCs are undefined. In mice, monocytes can produce DCs under inflammatory conditions in vivo (Auffray et al., 2009; Cheong et al., 2010) or upon ex vivo treatment with granulocyte-macrophage colony-stimulating factor (GM-CSF) (Inaba et al., 1992, 1993; Caux et al., 1992). Human monocytes treated ex vivo with GM-CSF and interleukin-4 (IL-4) also acquire DC characteristics (Sallusto and Lanzavecchia, 1994; Romani et al., 1994). Mo-DCs express CD11c and major histocompatibility complex class II (MHC-II) (León et al., 2004), as well as the DC-specific transcription factors ZBTB46 and L-MYC (Satpathy et al., 2012a; KC et al., 2014). However, monocytes differentiated with GM-CSF alone generate a heterogeneous population of CD11c$^+$ cells (Helft et al., 2015), resembling either macrophages (GM-Macs, CD11b$^+$MHC-II^{lo}) or DCs (GM-DCs, CD11b$^+$MHC-II^{hi}). GM-DCs cross-present soluble antigen more efficiently than GM-Macs do (Helft et al., 2015).

Mo-DCs can promote T_H1 and CD8$^+$ T cell responses (León et al., 2007; Aldridge et al., 2009; Ji et al., 2013) but they differ from cDCs in the antigen processing pathways they use (Segura et al., 2009) and the phases of infection in which they are involved (Ballesteros-Tato et al., 2010). Mo-DCs react distinctly from cDCs in response to adjuvant (Langlet et al., 2012) and, unlike cDCs, act independently of GM-CSF signaling in vivo during steady state and immunization (Greter et al., 2012). Human Mo-DCs generated ex vivo with GM-CSF and IL-4 can elicit CD8$^+$ T cell responses against tumor antigens (Nestle et al., 1998; Höltl et al., 1999; Timmerman et al., 2002; Thurner et al., 1999) and subdominant neoantigens (Carreno et al., 2015) and they have been used in cancer vaccines (Palucka and Banchereau, 2013; Carreno et al., 2015). Although CDPs have been suggested as sources of DC vaccines (Guilliams and Malissen, 2015), the abundance and practical value of monocytes motivates understanding their cross-presentation capacity for use in future vaccine design.

How IL-4 regulates Mo-DC differentiation is still unclear. In macrophages, IL-4 signaling induces M2 polarization (El Chartouni et al., 2010) by STAT6 activation and induction of Jumonji-domain-containing-3 (*Jmjd3*). JMJD3 functions as a demethylase of histone 3 lysine 27 (Ishii et al., 2009) and promotes M2 polarization by regulating IRF4 expression (Satoh et al., 2010). Loss of either JMJD3 or IRF4 impairs expression of M2 macrophage genes such as *Arg1*, *IL13*, and *Fizz1* (Satoh et al.,