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The capacity to develop protective immunity against mycobacteria is heterogeneously distributed among human beings, and it is currently unknown why the initial immune response induced against Mycobacterium tuberculosis (Mtb) does not provide proper clearance of this pathogen. Dendritic cells (DCs) are some of the first cells to interact with Mtb and they play an essential role in development of protective immunity against Mtb. Given that Mtb-infected macrophages have difficulties in degrading Mtb, they need help from IFN-γ-producing CD4+ T cells propagated via IL-12p70-producing DCs. Here we report that Mtb modifies human DC plasticity by expanding a CD14+ DC subset with weak IL-12p70-producing capacity. The CD14+ Mtb-promoted subset was furthermore poor inducers of IFN-γ by naive CD4+ T cells, but instead prompted IL-17A-producing RORγT+ CD4+ T cells. Mtb-derived peptidoglycan and mannosylated lipoarabinomannan partly recapitulated the subset partition induced by Mtb. Addition of IFN-γ, but neither IL-17A nor IL-22, which are potentially produced by Mtb-exposed γ/δ-T cells in mucosal linings, inhibited the differentiation toward CD14+ DCs and promoted high-level IL-12p70 in Mtb-challenged DCs. We conclude that Mtb exploits DC plasticity to reduce production of IL-12p70, and that this process is entirely divertible by exogenous IFN-γ. These data suggest that strategies to increase local IFN-γ production in the lungs of tuberculosis patients may boost host immunity toward Mtb.

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