Pathogen recognition through TLR versus NOD receptors has opposite effects on monocyte fate decision

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Circulating monocytes are recruited to inflamed or mucosal tissues where they differentiate into monocyte-derived dendritic cells (mo-DC) and monocyte-derived macrophages (mo-mac). At these sites, monocytes can encounter a broad range of pathogens or commensal bacteria. How pathogen recognition impacts monocyte fate remains unknown. Using an in vitro model for human monocyte differentiation, we show that some bacteria such as Salmonella typhimurium promote mo-mac differentiation while Mycobacteria such as Mycobacterium butyricum favor mo-DC. To decipher the mechanisms involved, we analyzed individual Pathogen-Recognition Receptor ligands. We found that Toll-Like Receptor (TLR) and Nucleotide-binding Oligomerization Domain (NOD) receptor ligands have opposite effects on monocyte fate. NOD receptor ligands induce mo-DC differentiation via the secretion of TNFα. By contrast, TLR ligands promote mo-mac differentiation through a cell-intrinsic mechanism, even in the presence of TNFα. We further showed that TLR ligands selectively inhibit the expression of IRF4, but not of other regulators of mo-DC differentiation such as AHR and BLIMP-1. Finally, we examine the physiological relevance of these findings. These results shed new light on the mechanisms of monocyte fate decision when exposed to complex signals at mucosal surfaces or during infection.

Keywords : monocyte, différentiation, pathogens
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