Human Langerhans cells selectively activated via Toll-like receptor 2 agonists acquire migratory and CD4+ T cell stimulatory capacity.

Abstract:
In epidermal Langerhans cells (LCs), the expression pattern and the functions of TLRs have been poorly characterized. By using mAb, we show that LCs from human skin express TLR1, -2, -5, -6, and -9, the cognate receptors for detection of specific bacteria-derived molecules. As compared with other TLR agonists, LCs acquired a more matured phenotype when activated by specific bacterial or synthetic TLR2 agonists. In addition, monocyte-derived Langerin(+)CD1c(+)LCs (CD1c(+)MoLCs) secreted higher amounts of IL-6 and TNF-alpha by stimulation via TLR2 than by stimulation via TLR3, -4, -5, -8, and -9. In contrast to MoLCs, dendritic cells, generated from the same donor monocytes, were activated by agonists of TLRs other than TLR2 as well. Lipopeptides triggering TLR2 induced IL-1R-associated kinase-1 phosphorylation and migration toward the chemokines CCL19 and CCL21 in epidermal LCs and CD1c(+)MoLCs. Up-regulation of CD86, CD83, and CCR7, TNF-alpha and IL-6, and NF-kappaB activation and proliferation of CD4(+) T cells could be inhibited TLR2-specific blockage using antibodies prior to TLR2 activation. Application of anti-TLR1, anti-TLR6, and anti-TLR2 indicated an exclusive role of TLR2 in IL-6 induction in human LCs. Collectively, our results show that TLR2 expressed by LCs mediates inflammatory responses to lipopeptides, which implicates a
central role in sensing pathogens in human skin.