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Title: Role of 15-lipoxygenase in the polarization of human lung macrophages

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Body: Introduction: Metabolites from the 15-lipoxygenase (15-LO) pathway have been involved in the pathogenesis of airway allergic inflammation. 15-LO expression is up-regulated by IL-4/IL-13 in human monocytes-derived macrophages and overexpression of 15-LO increases the production of proinflammatory cytokines by human lung epithelial cells or murine macrophages. Our aims were to investigate the role of 15-LO in the M1/M2 polarization of human lung macrophages (LM). Methods: LM were isolated from patients undergoing surgery for carcinoma and challenged with LPS (to obtain M1 LM), IL-13 or IL-4 (to obtain M2 LM), treated or not with the dual 12-/15- or the specific 15-LO inhibitors (nordihydroguaiaretic acid (NDGA (10µM)) and PD146171 (10 µM), respectively). Expression of 15-LO, type 2 cyclooxygenase (COX2), and prostaglandin E synthase (PGES) was determined with RT-qPCR; M1-(TNF-α, CCL2, 3, CXCL8) and M2-(CCL13, 18 and 22) cytokines were quantified with ELISA; 15(S)-HETE and PGE2 with EIA. Results: LPS induced an increase in the expression of COX2 and PGES transcripts and in the production of 15(S)-HETE (15-LO metabolite) and PGE2. LPS also induced the production of TNF-α, CCL2, 3 and CXCL8 which was inhibited by the 15-LO inhibitors. IL-13/IL-4 induced an increase of 15-LO transcript and the production of M2-cytokines, which was inhibited by the 15-LO inhibitors. In contrast, the non selective COX inhibitor indomethacin did not alter either the LPS- or the IL-4/IL-13-induced production of M1/M2 cytokines. Conclusion: The 15-LO pathway appears to be involved in the regulation of the in vitro M1/M2 polarization of human lung macrophages. The eicosanoids involved in this pathway remain to be identified.