NEW ROLES FOR CYSTEINYL LEUKOTRIENE IN ASTHMA: FROM AIRWAY REMODELLING TO β2-DRENORECEPTOR DYSFUNCTION

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Cysteine-containing leukotrienes (cys-LTs) LTC_4, LTD_4 and LTE_4, are widely recognized to be involved in a number of inflammatory diseases, particularly in asthma, participating both to the early bronchoconstriction but also to the late chronic inflammatory component of the disease. β_2-Adrenoceptors (β_2-AR) relax airway smooth muscle by activation of the Gs-protein and stimulation of the adenylyl-cyclase (AC). **Results** - First, we demonstrate that in human airway smooth muscle cells (HASMCs) LTD_4-stimulated thymidine incorporation and potentiation of EGF-induced mitogenic signaling mostly depends upon EGF-R transactivation through the stimulation of $CysLT_1$-R. Accordingly, we found that LTD_4 stimulation was able to trigger the increase of Ras-GTP and, in turn, to activate ERK1/2. We also showed that EGF-R transactivation was sensitive to pertussis toxin (PTX) and phosphoinositide 3-kinase (PI3K) inhibitors and that it occurred independently from Src activity, despite a strong impairment of LTD_4-induced DNA synthesis following Src inhibition. More interestingly, $CysLT_1$-R stimulation increased the production of ROS and *N*-acetylcysteine (NAC) abolished LTD_4-induced EGF-R phosphorylation and thymidine incorporation. Second, in HASMCs in cultures, both LTD_4 and phorbol-12-myristate-13-acetate caused significant reductions of maximal isoproterenol-induced cAMP accumulation, which were fully prevented by montelukast and GF109203X, respectively. More importantly, GF109203X also prevented the attenuating effect of LTD_4 on isoproterenol-induced cAMP accumulation. In human bronchial rings, both montelukast and GF109203X prevented the rightward displacement of the concentration-response curves to salbutamol induced by allergen challenge. **Conclusions** - Our data demonstrate that in HASMC LTD_4 stimulation of a $G_{i/o}$ coupled $CysLT_1$-R triggers the transactivation of the EGF-R through the intervention of PI3K and ROS. While PI3K and ROS involvement is an early event, the activation of Src occurs downstream of EGF-R activation and is followed by the classical Ras-ERK1/2 signaling pathway to control G1 progression and cell proliferation. Furthermore, LTD_4 induces β_2-adrenoceptor desensitization in HASMCs, which is mediated through the activation of PKC. Allergen exposure of sensitized human bronchi may also cause a β_2-adrenoceptor desensitization through the involvement of the $CysLT_1$R-PKC pathway. Collectively, these data demonstrate a new network of receptor cross-talk in HASMCs and suggest more evidences for the use of leukotriene modifiers in concurrent administration with β2-agonists in asthma therapy.