LTD₄ is involved in the control of non-differentiated intestinal epithelial cell growth

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Leukotriene D₄ (LTD₄) is a powerful pro-inflammatory mediator, which is formed from arachidonic acid through 5-lipoxygenase (5-LOX). LTD₄ mediates its effects through two specific cell surface receptors, CysLT₁R and CysLT₂R. Colon tumours have an increased expression of CysLT₁R and it has recently been observed that colon cancer patients with high expression levels of this receptor have poor prognosis.

The aim of this study was to investigate the potential role of LTD₄ on the control of non-differentiated intestinal epithelial cell growth using intestinal human Caco-2 cells (HTB37, ATCC) in culture.

We observed that LTD₄ (1–100 nM) induces Caco-2 cell proliferation in a concentration dependent manner. Moreover, cell growth and DNA synthesis induced by LTD₄ were reverted by specific CysLT₁R antagonists, such as MK571 and LY171883, thus indicating the involvement of this receptor in these events.

Considering that LTD₄ up-regulates 5-LOX, cyclooxigenase 2 (COX-2) and CysLT₁R levels in intestinal epithelial cells, we study the role of COX pathway on the effect of LTD₄ on Caco-2 cell growth. Our findings show that LTD₄ induces PGE₂ synthesis in Caco-2 cell cultures. Moreover, ketoprofen, a COX inhibitor, NS398, a specific COX-2 inhibitor, and SC560, a specific COX-1 inhibitor, were able to inhibit Caco-2 cell growth and DNA synthesis induced by LTD₄. Furthermore, similar effects were obtained using antagonists of PGE₂ receptor, such as SC19220, a specific EP₁ antagonist, and AH23838, a specific EP₄ antagonist.

These data suggest that the proliferative effect of LTD₄ is dependent on PGE₂ synthetized by both COXs and on PGE₂ interaction with EP₁ and EP₄ receptors. Finally, we provide evidence that LTD₄ stimulates several cell signalling pathways involved in cell growth, such as ERK, β-catenin, CREB, and p38α.

On the basis of our results we can conclude that LTD₄ is involved in the regulation of Caco-2 cell growth through the interaction of CysLT₁R and the subsequent PGE₂ synthesis and cell signaling pathways activation. It is hoped that these findings show novel mechanisms by which the effect of LTD₄ on intestinal epithelial cell growth may be mediated.

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