Proceedings of the Nutrition Society (2013), **72 (OCE1)**, E52 doi:10.1017/S0029665113000542

6th International Workshop on Immunonutrition, 15th–17th October 2012, Palma de Mallorca

LTD_4 is involved in the control of non-differentiated intestinal epithelial cell growth

M. Cabral, J. J. Moreno and R. Martín-Venegas
Departament de Fisiologia, Facultat de Farmàcia, Universitat de Barcelona

Leukotriene D_4 (LTD_4) is a powerful pro-inflammatory mediator, which is formed from arachidonic acid through 5-lipoxygenase (5-LOX). LTD_4 mediates its effects through two specific cell surface receptors, $CysLT_1R$ and $CysLT_2R$[1]. Colon tumours have an increased expression of $CysLT_1R$ and it has recently been observed that colon cancer patients with high expression levels of this receptor have poor prognosis[2].

The aim of this study was to investigate the potential role of LTD_4 on the control of non-differentiated intestinal epithelial cell growth using intestinal human Caco-2 cells (HTB37, ATCC) in culture.

We observed that LTD_4 (1–100 nM) induces Caco-2 cell proliferation in a concentration dependent manner. Moreover, cell growth and DNA synthesis induced by LTD_4 were reverted by specific $CysLT_1R$ antagonists, such as MK571 and LY171883, thus indicating the involvement of this receptor in these events.

Considering that LTD_4 up-regulates 5-LOX, cyclooxigenase 2 (COX-2) and $CysLT_1R$ levels in intestinal epithelial cells[3], we study the role of COX pathway on the effect of LTD_4 on Caco-2 cell growth. Our findings show that LTD_4 induces PGE_2 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 LTD_4. Furthermore, similar effects were obtained using antagonists of PGE_2 receptor, such as SC19220, a specific EP_1 antagonist, and AH23838, a specific EP_4 antagonist.

These data suggest that the proliferative effect of LTD_4 is dependent on PGE_2 synthetized by both COXs and on PGE_2 interaction with EP_1 and EP_4 receptors. Finally, we provide evidence that LTD_4 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 LTD_4 is involved in the regulation of Caco-2 cell growth through the interaction of $CysLT_1R$ and the subsequent PGE_2 synthesis and cell signaling pathways activation. It is hoped that these findings show novel mechanisms by which the effect of LTD_4 on intestinal epithelial cell growth may be mediated.

Supported by *Ministerio de Ciencia e Innovación* (BFU2007–61727/BFI) and *Generalitat de Catalunya* (2009SGR0438).

1. Heise CE, O'Dowd BF, Figueroa DJ *et al*. (2000) *J Biol Chem* **275**, 30531–30536.
2. Magnusson C, Mezhybovska M, Lörinc E *et al*. (2010) *Eur J Cancer* **46**, 826–835.
3. Yudina Y, Parhamifar L, Bengtsson AM, Juhas M, Sjölander A. (2008) *Prostaglandins Leukot Essent Fatty Acids* **79**, 223–231.