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Effect of *n*–3 and *n* − 6 eicosanoids on intestinal Caco-2 cell growth

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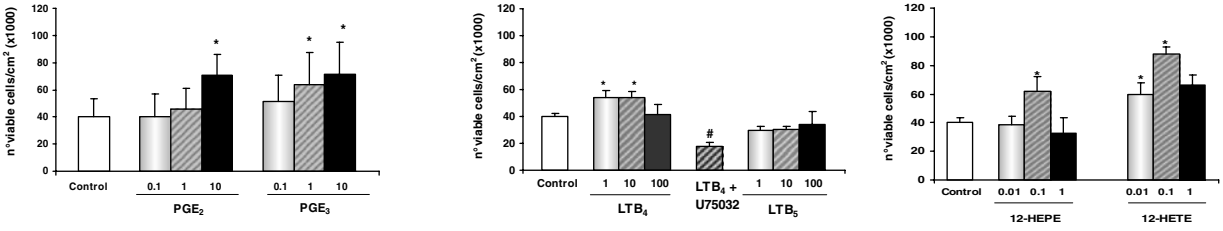
It is now recognized that epithelial cells are critical cell population in the initiation, regulation and resolution of innate and adaptive immune responses at mucosal sites. Thus, the intestinal epithelium forms a regulated and selectively permeable barrier that allows passage of nutrients, but restricts the access of potential harmful substances. These events are consequence, at least in part, of a highly dynamic continuously renewed/repair processes involving cell proliferation and migration.

Arachidonic acid (AA), a common *n* − 6 polyunsaturated fatty acid (PUFA), is found esterified at the sn-2 position of membrane phospholipids. When AA is released, it is oxidized by cyclooxygenases (COX) to produce prostaglandins (PG) such as PGE_2. Moreover, AA is also metabolized by lipoxygenases (LOX) producing leukotrienes (LT) such as LTB_4 and hydroxyeicosatetraenoic acids (HETEs). Eicosapentaenoic acid (EPA), an *n*–3 PUFA found mainly in fish oil, can also function as a substrate for COX-2 and LOXs resulting in the synthesis of 3-series PG, 5-series LT and hydroxyeicosapentaenoic acids (HEPEs)[1,2]. Recently, we observed the role of AA metabolites produced by COX on Caco-2 cell growth[3,4]. Moreover, AA metabolites of LOX pathway are also involved in epithelial cell proliferation[5]. Taking into account the above-mentioned facts, we sought to investigate the effect of *n*–3 and *n* − 6 eicosanoids on Caco-2 cell proliferation.

Cell growth was determined by microscopic assay using ethidium bromide/acridine orange staining in preconfluent Caco-2 cell cultures in the presence of eicosanoids (48 h). The data ($n = 6$–9 for each condition) were compared by Student's *t* test and in all cases, $^*P < 0.05$ was considered to denote significance.

Our results show that PGE_2 and PGE_3 (0.1–10 nM) significantly induce Caco-2 growth in a concentration-dependent manner, reaching an enhancement of almost 100% respect to control condition (Fig. 1). Interestingly, the effect of PGE_3 was slight higher than PGE_2 and both were blocked by EP_1 (SC19220, 60 nM) and EP_4 (AH23848, 20 nM) antagonist, but not by EP_2 (ONO240, 2 nM) antagonist. LTB_4 (1–100 nM) was also able to significantly increase Caco-2 proliferation (50%), whereas LTB_5 was without effect (Figure 2). This mitogenic effect of LTB_4 (10 nM) was completely reverted by a BLT1 antagonist (U75032, 1 μM). Finally, we observed that 12-HETE and 12-HEPE (0.1 μM) present a significant proliferative action on intestinal epithelial cells (Fig. 3). Thus, *n*–3 and *n* − 6 eicosanoids synthetised by COX-2 and 12-LOX might be involved in the control of renewed/repair processes in the intestinal epithelium, whereas *n*–3 but not *n* − 6 metabolites from 5-LOX could also participate in these events.



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