Butyrate as pro-resolving factor reduces inflammation and induces chemotaxis via GPR43 receptor in murine chondrocyte cell line

C. Pirozzi[1], A. Lama[1], F. Di Guida[1], A. Calignano[1], G. Mattace Raso[1], O. Gualillo[2] and R. Meli[1].

[1] Department of Pharmacy, University of Naples Federico II, Naples, Italy; [2] SERGAS (Servizo Galego de Saude) and IDIS (Instituto de Investigación Sanitaria de Santiago), the NEIRID Lab (Neuroendocrine Interactions in Rheumatology and Inflammatory Diseases), Research Laboratory 9, Santiago University Clinical Hospital, Santiago de Compostela, Spain.

Osteoarthritis (OA) is mainly characterized by a progressive degeneration of cartilage, in which chondrocytes are the predominant and pivotal cells. In this pathology chondrocyte phenotype changes and apoptosis and extracellular matrix degradation occur, involving the whole synovial joint organ [1-4]. The alteration of cartilage homeostasis is mediated by several factors, such as nitric oxide (NO) [5], an important mediator induced by pro-inflammatory cytokines, i.e. IL-1. Butyrate is a short chain fatty acid derived from the degradation of dietary fiber by bacteria under anaerobic conditions in the colon, where represents the main energy source for colonocytes. Among its many intestinal and extra-intestinal activities, butyrate plays an important role as inhibitor of class I and II histone deacetylases (HDACs). In particular, it has been demonstrated that HDAC inhibitors suppress IL-1β-induced nitric oxide and prostaglandin E2 production in human chondrocytes [6].

The aim of this study was to evaluate the mechanisms of action underlined to butyrate anti-inflammatory effects and more interestingly the closed-association to its receptor-mediated chemoattractant activity in IL-1-stimulated ATDC5 chondrogenic cells.

In our experiments, the anti-inflammatory effect of butyrate (250 μM) in chondrocyte cells was shown (on nitrite formation, iNOS, COX-2, IL-6, VCAM-1 and ICAM-1 expression). Interestingly, butyrate modulated inflammatory adipokine production reducing lipocalin-2 (LCN2), highly expressed in hypertrophic chondrocytes, and nesfatin-1 (or NUCB2) involved in rheumatic disorders, such as OA and associated inflammation.

After 15 and 30 min cell stimulation by IL-1, the activation of p65 subunit and consequently IκB-Î± degradation were evaluated in nucleus and cytoplasm lysates, respectively. Butyrate significantly reduced NFκB p65 expression and consistently increased IκB-Î±. Moreover, butyrate effect involved MAP-kinase cascade signaling, reducing the phosphorylation of p44/42 MAPK (or 44/42 ERK) and p38.

Butyrate counteracted the increase of MMP13 and the reduction of type II collagen induced by IL-1, underlying its important role in limiting extracellular matrix disruption and the loss of collagen, important structural protein in healthy cartilage. Butyrate activity was confirmed in mature chondrocytes after cell differentiation.

Interestingly, butyrate showed a chemoattractant effect, inducing the expression of important chemokines involved in inflammation and in leucocyte recruitment (Ccl3 and Cx3cl1), and the activation of pro-resolving annexin-1. To demonstrate that the chemoattractant and pro-resolving effect of butyrate was independent by the type of inflammatory challenge, we confirmed its activity after LPS and TNF-Î± stimulation.

A further novelty of our data is the direct involvement of GPR43 in chemoattractant activity of butyrate in chondrocytes, demonstrating the inability of butyrate to induce Cx3cl1 and AnxA1 expression, after GPR43 silencing.

The capability of sodium butyrate in reducing inflammation in chondrocytes can suggest its clinical application as pro-resolving factor of cartilage inflammation and disruption for the treatment of OA and its related complications.

References

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