IL-1β INDUCES DNA DEMETHYLATION, AT GENOME LEVEL AND IN SPECIFIC CpG SITES OF IL-6 AND IL-8 GENES IN HUMAN INTESTINAL EPITHELIAL CELLS

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Inflammation is a complex physiological response that requires the activity of a sophisticated regulatory network involving the activation of specific genes for defense, tissue repair and remodeling.
Although transcriptional activation has been shown to be critical in the regulation of inflammatory genes (1) the role of epigenetic phenomena in the modulation of the inflammatory response is now emerging (2). Specifically, it has been recently reported that proinflammatory stimuli induce DNA demethylation in the interleukin IL-1β promoter of human articular chondrocytes (3). IL-1β cytokine, among several proinflammatory agents, represents an essential player in the inflammatory conditions of the gut (4): functioning as the strongest signal transduction to NF-kB, IL-1β increases in intestinal paracellular permeability and over-expression of proinflammatory genes (5). In this tissue, moreover, inflammatory response is crucial to maintain its structural integrity and function, thus, alteration and deregulation of inflammatory pathways contribute to tissue damage and ulceration, and are pivotal factors in the pathogenesis of several inflammatory gut diseases.
In the present study we evaluate both wide-ranging and gene-specific epigenetic changes in the inflammatory response of Caco-2 cells differentiated into intestinal epithelial cells and exposed to the inflammatory actions of IL-1β. Our results clearly show that IL-1β induces changes in the DNA methylation either at genome and gene level and that the local methylation changes are induced in two pro-inflammatory genes that are IL-1β-regulated. In particular, we show that a cell exposure to IL-1β for 24 h induces, in a dose-dependent manner, hypomethylation of genomic DNA in respect to untreated cells. We also observe a reduced DNA methyltransferases activity of cell lysates obtained from IL-1β treated cells. Finally our data show that IL-1β is able to induce hypomethylation of specific CpG sites in IL-6 and IL-8 genes.
These preliminary results suggest that IL-1β in intestinal epithelial cells is able to act as an epigenetic modulator towards the entire genome and specific genes.
Modulation of epigenetic changes in inflammation may provide a new "reading frame" of the inflammatory diseases molecular basis. Since epigenetic modifications are potentially reversible, a thorough understanding of these changes during inflammatory response opens opportunities to develop efficient agents for specific targets.

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