INTRODUCTION

Disc degeneration is a major cause of chronic low back pain (LBP) and a number of groups are currently investigating therapies targeted at repairing or regenerating the degenerated intervertebral disc (IVD). It is achieved by a balance between forces generated by two major structures within the IVD, the central nucleus pulposus (NP) and the outer annulus fibrosus (AF). The normal NP consists of type II collagen fibres and hydrophilic proteoglycans [1], which form a hydrophilic molecular complex that generates a swelling pressure sufficient to separate adjacent vertebrae, even under the loads operating within the spine. In degeneration of the IVD (DIVD), there is loss of hydrophilic matrix molecules from the NP. This leads to reduced vertebral separation and local spinal instability, which probably initiates the processes that lead to LBP through repetitive microtrauma [2], ingrowth of nociceptive nerves [3, 4] and disc bulging with encroachment of IVD tissue onto nerve roots. Inhibiting degenerative processes would be a novel approach to managing LBP and one in which modern molecular pathology should play a critical role through identifying key molecular targets.

Bovine lactoferricin (LfcinB) is a 25-amino acid cationic peptide with an amphipatic, anti-parallel β-sheet structure that is obtained by acid-pepsin hydrolysis of the N-terminal region of lactoferrin from cow’s milk. And it has a various biological activity such as anti-bacterial, anti-cancer, anti-viral, anti-fungal, and anti-oxidant activity.

The pro-inflammatory cytokines IL-1 are overexpressed in the degenerate IVD, and this has led to promoting formation of reactive oxygen species (ROS), which in turn, promote cartilage degeneration. Thus, we examined the biological capacity of lactoferricin to counteract the action mediated by these catabolic and/or anti-anabolic molecules in IVD.

METHODS

Chondrocyte were isolated from the nucleus pulposus of 15-18 months degenerate IVD, and this has led to promoting formation of reactive oxygen species (ROS), which in turn, promote cartilage degeneration. Thus, we examined the biological capacity of lactoferricin to counteract the action mediated by these catabolic and/or anti-anabolic molecules in IVD.

RESULTS

Lactoferricin inhibits the IL-1 α-induced MMPs & Aggrecanase; Stimulation of bovine disc chondrocyte with IL-1α induced the expression of MMPs (MMP-1, MMP-3, and MMP-13) and Aggrecanase (ADAMTS-4 and ADAMTS-5). The increase of MMPs and Aggrecanase by IL-1α was completely blocked by lactoferricin at the concentration of 100 μg (Fig. 1).

Lactoferricin increase the induction of aggrecan gene after stimulation with IL-1α; Pro-inflammatory cytokine, IL-1α, decrease the aggrecan gene induction in IVD. This aggrecan reduction by IL-1α was rescued by Lactoferricin dose dependently (Fig. 2A).

Lactoferricin decrease the decrease of iNOS by IL-1α; Overproduction of nitric oxide (NO) plays an important role in the pathogenesis of disc degeneration. Therefore, the suppression of iNOS is important for disc therapy. The iNOS is potentely induced by pro-inflammatory cytokine through activation of NFκB. Stimulation of bovine disc chondrocyte with IL-1α was decreased by Lactoferricin at the dose dependently.

PG production & Exclusion assay: Incubation chondrocyte with Lactoferricin for 21 days significantly increased PG production (Fig. 3A) And Lactoferricin blocked the inhibitory effect of IL-1α mediated PG reduction.

DISCUSSION

Here we reveal the antagonistic effect of lactoferricin on those catabolic mediators induced by IL-1, and thereby elucidating the physiological role of Lactoferricin in bovine IVD. IL-1 decreases synthesis and increases breakdown of matrix components affecting cartilage homeostasis. This action of IL-1 was completely inhibited by lactoferricin, and additionally lactoferricin increases aggrecan gene expression suggesting its dual role in bovine IVD as anti-catabolic and pro-anabolic. These findings provide evidence for possible therapeutic role of lactoferricin in reversing intervertebral disc degeneration.

REFERENCES


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