T lymphocyte cyclooxygenase isotypes and the role of T lymphocytes in modulating monocyte and synoviocyte cyclooxygenase expression

By

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TABLE OF CONTENTS

ABSTRACT

Rheumatoid arthritis is a common inflammatory condition associated with joint destruction and disability. T lymphocytes, monocytes, and synoviocytes present within the inflamed joint all contribute to the inflammatory response by production of lipid mediators (eicosanoids) and peptide mediators (cytokines).

Interleukin-17 is a relatively recently described pro-inflammatory T cell derived cytokine which has been shown to induce monocyte and synoviocyte cytokine production. In comparison to other T cell cytokines, such as interferon-γ, it is found in abundant levels in rheumatoid synovial tissue and fluid. T cells have also been shown to induce monocyte and synoviocyte cytokine production through direct cell-cell contact. Through these mechanisms T cells may contribute to the perpetuation of inflammation in rheumatoid arthritis.

The eicosanoids, prostaglandin E_2 and thromboxane A_2, which are formed via the cyclooxygenase pathway, also have a role in promoting inflammation. To date most work has concentrated on monocyte eicosanoid production and the effects of monocyte derived prostaglandin E_2 on T cell functions. Furthermore, there has been a view that T cells do not contain cyclooxygenase and are therefore unable to produce eicosanoids. The recognition that cyclooxygenase exists in both a constitutive form (cyclooxygenase-1) and an inducible form (cyclooxygenase-2) has renewed interest in cyclooxygenase in all cell types.

The aim of this thesis was to examine cyclooxygenase isotypes in T cells and to characterize eicosanoid production by each isotype. The ability of T cells to contribute to the inflammatory response via up-regulation of cyclooxygenase-2 in other cell types was also examined.

The data presented in this thesis indicate that T cells contain cyclooxygenase-1, which is able to produce small amounts of eicosanoids. Extensive analysis revealed no evidence for induction of cyclooxygenase-2 in T cells. Furthermore, activated T cells up-regulate expression of cyclooxygenase-2 in both monocytes and synoviocytes. Interleukin-17 was found to be an important mediator of cyclooxygenase-2 up-regulation both directly and through synergy with tumor necrosis factor-α and interleukin-1β. The therapeutic effects of tumor necrosis factor-α or interleukin-1β blockade may in part be mediated by inhibition of synergy with interleukin-17. Interleukin-17 should be considered as a therapeutic target in the management of rheumatoid arthritis.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

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