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T HELPER CELLS IN PERIODONTAL PATHOGENESIS – A REVIEW

Periodontology

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ABSTRACT

Effector CD4 T cells provide host defensive mechanisms against pathogens through the production of effector cytokines, which activate other immune cells such as macrophages and CD8 T cells in killing infected cells and help B cells in producing antibodies to mediate humoral immune responses Upon TCR activation in a particular cytokine milieu, naïve CD4 T cells can differentiate into Th1 cells. IL-12 secreted by APCs activates the transcription factor STAT4, and IFN-γ produced by NK cells and/or T cells themselves activates another transcription factor, STAT1. Th1 polarization is induced by the cytokines interleukin (IL)-12 and IFN-α, both of which are present in the inflammatory milieu.. Stable periodontal lesions resemble a delayed type hypersensitivity lesion and progressive lesion involves large number of B cells, these lesions may be mediated by Th1 and Th2 cells, respectively. Th17 cells have been identified in the periodontal tissues. Th17 has been proposed to exert both proinflammatory and anti-inflammatory functions. Tregs levels were upregulated in chronic periodontitis lesions as protection against self-antigens . Th cell lineages have been proposed to exist, with widely differing functions.Further investigations are required to fully appreciate the role of The cells in periodontal disease.

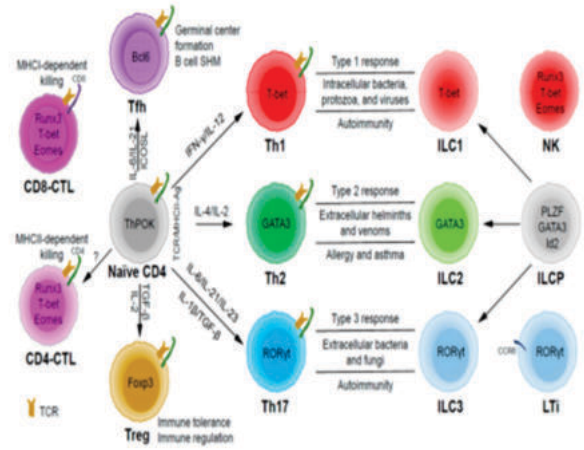
KEYWORDS

T Helper Cells, Immune Response, Transcription factor , Periodontitis

INTRODUCTION

CD4 T helper cells, as a key component of this system, play a critical role in defending infections throughout life by coordinating the actions of other immune cells as well as non-immune cells. CD4 T cells originate from common lymphoid progenitors in the bone marrow, develop in the thymus, and execute their functions mainly in peripheral tissues and various lymphoid organs [19].CD4 T cells first need to be activated when receiving pathogen signals delivered by antigen-presenting cells (APCs), such as dendritic cells (DCs), and then differentiate into distinct T effector (Teff) populations based on the nature of infections.

Effector CD4 T cells provide host defensive mechanisms against pathogens through the production of effector cytokines, which activate other immune cells such as macrophages and CD8 T cells in killing infected cells and help B cells in producing antibodies to mediate humoral immune responses [25]Based on the expression of signature cytokines and lineage-specific master transcription factors, CD4 T helper (Th) cells are typically categorized into five major subsets Th1 (interferon (IFN)-γ and T-bet), Th2 (interleukin (IL)-4/IL-5/IL-13 and GATA3), Th17 (IL-17/IL-22 and RORγt), Tfh (IL-21 and Bcl6) and Treg (T regulatory) (IL-10/transforming growth factor (TGF)-β/IL-35 and Foxp3)



TH1 CELLS

The Th1/Th2 dichotomy was first proposed by Robert Coffman and Tim Mosmann in 1986 when they reported that CD4 T helper cell clones from mice can be divided into two distinct types based on their cytokine production profile [21]Upon TCR activation in a particular cytokine milieu, naïve CD4 T cells can differentiate into Th1 cells. IL-12 secreted by APCs activates the transcription factor STAT4, and IFN-γ produced by NK cells and/or T cells themselves activates another transcription factor, STAT1; both STAT1 and STAT4 activation are capable of inducing the expression of the Th1-inducing master transcription factor T-bet . T-bet, by cooperating with Hlx [22], Runx3 , Ets-1 , and Bhlhe40 , promotes IFN-γ production.

Th1 polarization is induced by the cytokines interleukin (IL)-12 and IFN-α, both of which are present in the inflammatory milieu. These cytokines are normally produced by the DCs or the natural killer (NK) cells.[20] In the periodontal environment, DC infiltration has been stronglyassociated with gingival inflammation.[15] These cells have toll-like receptors (TLR) on their surface that enable them to respond to the pathogen-associated molecular patternslipopolysaccharide, fimbriae of the periodontal pathogens.

IFN-α/IFN-γ in conjunction with IL-12 activates signal transducer and activator of transcription-1 (STAT-1) in the naive CD4 T cells. Activated STAT-1 upregulates the master regulator of Th1 differentiation-T box expressed in T cell (T-bet). Activation of T-bet leads to induction of the receptor IL-12Rβ2 , making these cells more responsive to IL-12. This in turn, causes activation of STAT-4, which then upregulates IFN-γ production by the Th1 cells.

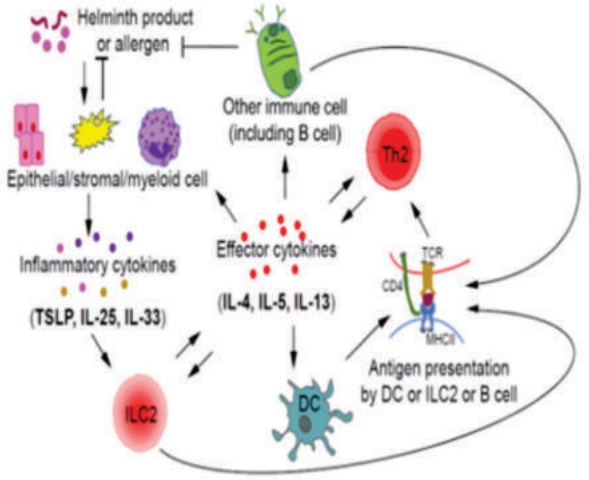
TH 2 CELLS

Naïve CD4 T cells after receiving signals from DCs may differentiate into Th2 cells after their activation . IL-2 and IL-4 are two important cytokines during Th2 cell differentiation, particularly in vitro. IL-2 and IL-4 activate STAT5 and STAT6, respectively, and the latter induce the expression of the Th2 master transcription factor GATA3 in activated CD4 T cells . These cells produce IL-4 in addition to IL-5 and IL-13; cytokines that are involved in immunoglobulin (Ig) class switching in B cells.[26,31]

Th2 development is induced by production of IL-4, which in turn is produced by the naive T cells or the mast cells/ macrophages. [1,23] In the periodontal milieu, naive T cells constitute only a small proportion of T-cell infiltration within the tissues; it is comprised predominantly of the memory or the effector cells.Both macrophages and mast cells have been identified in the periodontal environment and as early responders, they are the likely source of IL-4 production.[9],IL-4 signaling results in activation of STAT-6 which then upregulates the master switch of Th2 differentiation, GATAbinding protein-3 (GATA-3).[33] In addition to GATA-3, STAT- 5 signaling is also required for complete Th2 differentiation.[33]

Stable periodontal lesions resemble a delayed type hypersensitivity lesion and progressive lesion involves large number of B cells, these lesions may be mediated by Th1 and Th2 cells, respectively. It has been shown that a strong innate response leads to a Th1 response under the influence of IL-12, IL-2 and IFN-γ while a weak innate response leads to a Th2 response under the influence of IL-4 cytokines. In a stable lesion, IFN-γ enhances the phagocytic activity of both neutrophils and

macrophages and hence contains the infection.[10] In case of a poor innate immune response and minimal Il-12 production, a weak Th1 response may not contain infection. Mast cell stimulation and the subsequent production of IL-4 would encourage a Th2 response, B-cell activation and antibody production.



TH 17 CELLS

Th17 cells are important for type 3 immune responses in defending extracellular bacteria and fungi invasion; they are also found to be involved in many autoimmune diseases, such as multiple sclerosis, because of their pathogenic effects [4]Products of extracellular bacteria and fungi can activate antigen-presenting cells to produce pro-inflammatory cytokines IL-1β, IL-6, and IL-23, which in turn direct naïve CD4 T cells to differentiate into Th17 cells . IL-6 and IL-23 activate STAT3 to induce the expression of Th17 master transcription factor RORγt [5]

TCR signaling can induce RORγt expression through the NFAT/NF-κB/AP-1 pathway . RORγt, by collaborating with other transcription factors such as IRF4, BATF, and Runx1, promotes the expression of Th17 lineage-specific genes [6]. Differentiated Th17 cells are capable of secreting effector cytokines, such as IL-17A, IL-17F, and IL-22, to activate nonimmune and immune cells to produce matrix metalloproteinases (MMPs), nitric oxide (NO), cytokines, and antimicrobial peptides to clear extracellular pathogens [24]. Th17 cells express a signature chemokine receptor CCR6 (inflamed tissues homing receptor and essential for homeostasis) [16], which is also considered as a unique marker in identifying human Th17 cells.

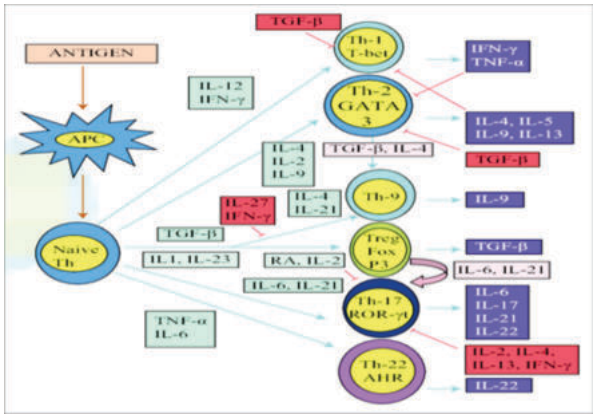
Th17 cells have been identified in the periodontal tissues.[2]. Th17 has been proposed to exert both proinflammatory and anti-inflammatory functions. It was demonstrated that Porphyromonasgingivalis outer membrane protein induced a significant increase in the production of IL-17. IL-17 has been shown to stimulate epithelial, endothelial and fibroblastic cells to produce IL-6, IL-8 and PGE2.[13] In addition, IL-17 induces receptor activator of nuclear factor-κ B ligand (RANKL) production by osteoblasts[17,29] and thus influence osteoclastic bone resorption. Th17 cells may be involved in Th1 modulation and enhanced inflammatory mediators' production by gingival fibroblasts in periodontal disease. Th17 cells may be primary source of RANKL production in periodontal disease.It could thus, be hypothesized that in a progressive periodontallesion that is dominated by excessive proinflammatory cytokineproduction, Th17 cell would predominate.

T REG CELLS

Regulatory T cells can develop in the thymus during negative selection, and these Treg cells are called thymic-derived Treg cells . Treg cells, by recognizing self-antigens, mainly control self-reactive effector T cells that escaped negative selection to maintain immune tolerance [27].Regulatory T cells are classified into natural (Treg) and adaptive cells (Tr1, Th3). While, Treg cells have evolved to provide protection against autoantigens, Tr1 cells are required for tolerogenecity. Treg cells are thought to develop in the presence of TGF-β, but in the absence of IL-6, IL-1 and this process is favored by IL-2 and retinoic acid.

Treg cells exert their regulatory functionby secreting regulatory cytokines (such as IL-10, TGFβ, and IL-35) [28]; by consuming IL-2, which is important for effective CD4 T cell survival and proliferation ; by expressing cell surface receptors that transmit negative signals (such as CTLA-4, CD39, CD73) ; and by inducing trogocytosis to strip off the antigen-MHCII complexes from APCs in an antigen-specific manner .

Tregs levels were upregulated in chronic periodontitis lesions as protection against self-antigens such as collagen-1. Ernst[8] demonstrated that Treg cells downregulated RANKL expression in periodontal disease.In the presence of proinflammatory cytokines such as IL-1, IL-6 and low concentration of TGF-β, RORγt is further unregulated, whereas Foxp3 expression is inhibited. On the other hand, in the absence of these proinflammatory cytokines,high concentration of TGF-β favor Foxp3 expression and result in Treg-cell differentiation. In inflammatory states, retinoic acid levels are suppressed, as a result of which Treg differentiation is downregulated, thus tipping thebalance in favor of a Th17 response.Inastable lesion, characterized by matrix formation and TGF-βproduction, would be predominantly associated with Treg cells.



Diversification Of Cd4 T Cell Lineages

CONCLUSION

Different types of adaptive immune responses are executed by Th1/Th2/Th17 cells, respectively, with each subset of T helper cells possessing their unique properties in producing their signature cytokines. The heterogeneity and plasticity of CD4 T cell subsets are largely determined by the temporal and quantitative co-expression of multiple master transcription factors during the differentiation of these cell subsets [12]. The pathogenic mechanisms governing periodontal disease is complex and results from disruption of a delicatebalance that exists between the various Th cells and their effect or cytokines. Th cell lineages have been proposed to exist, with widely differing functions. Further investigations are required to fully appreciate the role of The cells in periodontal disease.With exciting new findings in basic immunology, our better and deeper understanding of this powerful The cell system will help us uncover innovative measures for periodontal disease management.

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