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T Regulatory Cell and Body Tolerance

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ABSTRACT

Humans are always exposed to environmental microbes, the micro biome studies that have under scored the trust of mammalian systems on appropriate microbial colonization to support metabolic and immune homeostasis. Chronic inflammatory disease including allergy, have increased dramatically over the past decades. The role of the Treg in defining both the local and systemic immune response, also in GI response to pathogenic microbes is important. In this review, we examined the role of regulatory T cells in Gut and whole body homeostasis.

Keywords: T Regulatory Cell, Body Tolerance, Chronic inflammatory disease, homeostasis.

INTRODUCTION

To maintain homeostasis in gut immune response to food antigen should be inhibited [1,2]. Tolerance has complications systemic immune responses including delayed type hypersensitivity reactions, antibody formation and lymphocyte proliferation [3]. However oral tolerance acts locally in the gut. Dendritic cells (DCs) in the mesenteric lymph nodes present the food protein to the T cells [4]. DCs in the lamina take up antigen and in a chemokine (C-C motif) receptor 7-dependent process and migrate to the mesenteric lymph nodes to activate naive T cells [5,6]. Normal Treg response and flora bacterial cell are required for the maintenance of gut immune homeostasis [7]. The gut is an immunologically unique organ with ability to mount an adaptive immune response to pathogens while maintaining tolerance to commensal bacteria and dietary antigens [8]. Treg and their marker as a fork head/winged helix transcription factor called FoxP3[9] mediate the peripheral tolerance by suppressing the auto reactive T cells activity [10]. Treg cells expressing FOXP3 marker and present interleukin (IL)-10 have a major role in maintaining gut immune homeostasis [11]. Transfer of naive CD4+ T-cells into immune deficient mice in the absence of T regulatory cells resulted inflammation [12]. However, transfer of Treg cells prevents immune disease, through acting through both IL-10 and transforming growth factor- β (TGF- β)-dependent and independent mechanisms, stop the progression of disease and reverses pathology [13]. T regulatory cell T regulatory cells are classified in two groups: natural (nTreg) and adaptive (induced) [14]. nTreg are CD4+CD25+ T cells which develop and migrate from the thymus to perform their role in immune homeostasis.

Induced Tregs are non-regulatory CD4+ T cells which acquire CD25 (IL-2R α) outside of the thymus and are typically induced by disease and inflammation [15]. Gut homing in murine model requires the interaction of ITGB7 (integrin, beta 7 is a protein-coding gene) expressed by immune cells with MADCAM1 (mucosal vascular address in cell adhesion molecule 1) present on intestinal venules [16]. ITGB7 gene encodes a protein that is a member of the integrin superfamily (heterodimer protein). Members of this family induced by ligand that cause signaling from the extracellular matrix to inside the cell. Role of p38 α in Treg regulation p38 α in intestinal epithelial cells play a major role in protection against pathogen and non-pathogen bacterial cell by regulating T cell recruitment [17].

P38 α is a member of the serine-threonine MAPK (Mitogen-activated protein kinases) family and regulates numerous processes, including inflammation and immune responses [18,19]. P38 α mediated expression of proinflammatory cytokines and chemokine's that initiated by TLR responses in innate immune cells [20]. P38 α have a three role (A): regulates the development of T cells in thymus (B) differentiation of naive T cells into effector cells and (C) production of cytokine that contribute to inflammation [21]. Abrogation of p38 α T cells resulted in impaired pathogen deletion from colon tissues due to the reduced production of proinflammatory cytokines by T cells [22].

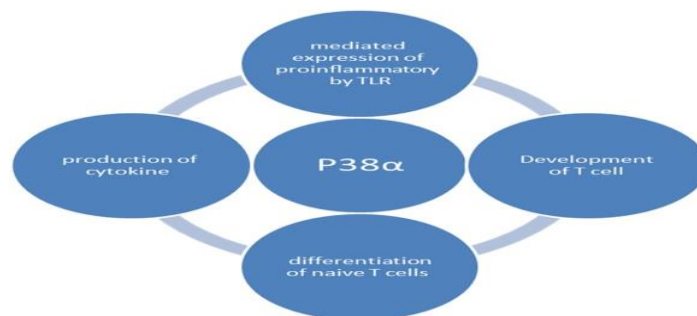


Figure-1: Mechanism of p38 α in body homeostasis

mechanism of the cytokine expression by p38a is unknown. Stat (Signal transducers and activators of transcription) is a complex proteins that after activation cause expression of many genes [23]. However, activation of STAT1 is involved in IFN- α Production. The phosphorylation of STATs by p38a may regulate the cytokine production [17].

Role of cytokines in hemostasis

Disorder in control of homeostasis an intestinal cause inflammatory bowel disease (IBD) [24]. IL-23 is essential for several pathological reactions, including the autoimmune response [25]. IL-23 also has ability to support of development of a subset of TCD4+ inflammatory cell known as Th17 cells [26]. Th17 cells are characterized by their production of IL-6, IL-17 and TNF- α and have been associated with the induction of inflammation [27, 28]. Treg and Th17 develop programs are equally interconnected, following TCR stimulation a naive T cell can express FoxP3 and become a Treg cell in the presence of TGF- β while in the presence of TGF- β and IL-6 or IL-21 and IL-23, the Treg pathway is abrogated, and T cells developed into Th17 cells [10].



Figure-2: A: in the present of only TGF- β naïve T-cell become Treg. B: combination of TGF- β with IL-6 or IL-21 or IL-23 naïve T-cell become TH-17.

IL-23 has an ability to expand or maintain effector Th17 cell populations [29,30]. Tomohide Yamazaki et al. founding that the expression of CCR6 was elevated in Th17 cells compared with Th2 or Th1 cells [31]. TGF- β has a major role to induced CCR6 mRNA in T cells. IL-6 or IL-21 did not further enhance this induction by TGF- β . TGF- β induces Foxp3 expression in T cells and express CCR6 in Treg cells [31]. CCL20 is the only ligand for CCR6 and Th17 cells can produce CCL20 to attract other Th17 and Treg cells through CCR6 [31]. In the mice with CCR6-deficient, population of Treg and TH17 cells was significantly reduced in lung and mesenteric LN. Treg cells and TH17 cells migrated in response to CCL20, indicating that CCR6 on both cells are functional. CCL20 also induced in non-hemopoietin cells by IL-17 [32]. First Th17 entered into the target tissues and induced by local APCs, will express CCL20 and IL-17, Production of CCL20 causes further recruitment of other CCR6-expressing Th17 cells that lead to chronic inflammation.

Intestinal hemostasis

In study by Josefowicz et al. Indicated that MHCII dependent, commensal or food- specific iTregs comprise a majority of the lamina propria (LP) Treg [33]. Tregs in lamina propria are exposed to additional microbial and dietary metabolite signals that in hence their development and expansion [34, 35]. IL-2 is required for Treg proliferation even in the absence of direct TCR-MHCII interactions [36]. Smigiel et al. Described IL-2-dependent Tregs preferentially found in secondary lymphoid tissues and IL-2-

independent Tregs, which expressed lower levels of the CD25 were enriched in the LP [37]. However, comprise these Treg shown the IL-2 would have an increased role in maintenance of IL-2 dependent Treg in LP but maintenance of IL-2 independent Treg depends on continued signaling through the co-stimulatory receptor ICOS [37].

T reg cell affluence is tightly linked to the number and activity of antigen-presenting DCs and co-receptor CD28 and ICOS [38-40]. Treg cells were highly enriched for the expression of adhesion and chemo-attractant receptors such as CXCR3, CD103, P-selection ligand and for surface markers associated with cellular activation such as KLRG1, CD69 and ICOS that required for migration to non-lymphoid tissues [37]. Expression of CCR7 by Treg in lymph node is higher in contrast to Treg in periphery.

The treatment of murine with CTLA4 Immunoglobulin fusion protein results in a rapid reduction of Tregs in lymph node [41]. Tested all mouse strains (BALB/c, B6 and NOD) with anti-B7 Abs has same results [37]. Moreover, unlike CD28^{-/-} in young mice, CTLA4^{-/-} have normal level of Treg in the periphery suggesting that CD28 has a major function both for the development of Tregs in the thymus and for their maintenance in the periphery. CD28 has a major role in IL-2 production by activation T cells [42]. Mice with deficient in IL-2 or IL-2 receptor have very low numbers of Tregs in the periphery [43] and developed systemic autoimmune diseases [44].

After 2 week	DAY 1
Treg were barely detectable	IL-2 in mouse with CD28 ^{-/-}
Treg proliferation	IL-2 with present CD28

Figure-3: in the present of IL-2 alone hemostasis of Treg failed, but in the present of IL-2 with CD28 have sufficient for supporting Treg survival.

CONCLUSION

T regulatory has a major role in body hemostasis. Lack of regulatory T cells control cause autoimmune response, in contrast complete inhibition of T CD4⁺ cell can result in cancer progression. However, regulatory Treg at any time based on the amount of cytokine performs its function. In the early immune response, T reg allowed T cell to activity, the end of response T cells are restrained to prevent tissue damage. Treg itself have a CXCR5 marker in germinal center, after leave the lymph node with present different marker can adopted to other organ allows Treg to transfer to immune response place.

Regulates	Gut	Germinal center	Skin
Transcription factor	STAT3	BCL-6	T-bet
Hemostatic mediator	IL-10,IL-6	-	INF-γ
Chemokine receptor	CCR6	CXCR5	CCR3,CCR4

Figure-4: role of different transcription factor and chemokine receptor in migration of Treg cell.

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