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The Role of T Cells in Type 1 Diabetes

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1. Introduction

The role of T cells as pathogenic effector cells in type 1 diabetes (T1D) is well established. Both $CD4^+$ and $CD8^+$ cells can play distinct and highly pathogenic roles mediating diabetogenesis. Other cell types including NK, B cells, macrophages and dendritic cells also play coordinate roles. Ultimately auto-aggressive T cells invade pancreatic islets focusing destructive force on the beta cells that produce insulin. The initial insult may be solely inflammation but nonetheless results in loss of insulin production. This chapter will focus on the different T cell subtypes including a newly described helper T cell subtype, Th40, which is highly pathogenic in T1D. Discussion will include how auto-aggressive T cells can arise and suggest alternative means to control auto-aggressive T cells. The ultimate goal for a successful treatment is to control pathogenic effector cells without causing immune suppression, a feat that has yet to be achieved. Considering new paradigms about diabetogenesis may provide substantive clues towards effectively curing this ravaging disease.

2. $CD4^+$ T cells and inflammation

$CD4^+$ T cells differentiate and based on immunologic functions and cytokine production are grouped into different sub types of T "helper" (Th) cells. Help is provided to CD8 cells in the form of IL-2 to drive viral protection or to B cells in the form of IL-4/IL-5 to promote the humoral immune arm. Other forms of help include IFNγ (1, 2) to create activated macrophages that aid innate immunity. Naive T cells are polarized by IL-12 to a Th1 phenotype producing IFNγ, TNFα, IL-2, IL-1β *etc.*, (Fig. 1) leading to localized inflammation (3, 4). IL-4 polarizes Th2 cells to produce IL-4, IL-5, IL-10, IL-13 etc., and is associated with an anti-inflammatory response. Of further interest is IL-6, which is categorized as a Th2 cytokine, but atypical of that family IL-6 is pro-inflammatory; suggesting that IL-6 would have better fit with Th1 cytokines.

T cell subsets impact each other's functional capabilities; IFNγ inhibits Th2 cells while promoting Th1 cells and IL-4 inhibits the Th1 response (5). These T helper subtypes provide an interesting back drop for T1D. Th1 cytokines like IFNγ and TNFα have been shown to be prominent in driving disease (6). However, $IFN\gamma^{-/-}$ mice still develop T1D and when IFNγ is blocked with a neutralizing antibody early in diabetogenesis, disease is exacerbated (7). An additional complication is that T cells isolated from $IFN\gamma^{-/-}$ mice transfer disease very effectively, suggesting that IFNγ is important for trafficking rather than islet destruction (8). When IFNγ is not available Th17 cells drastically increase in number (7), suggesting a role for Th17 cells in T1D development.

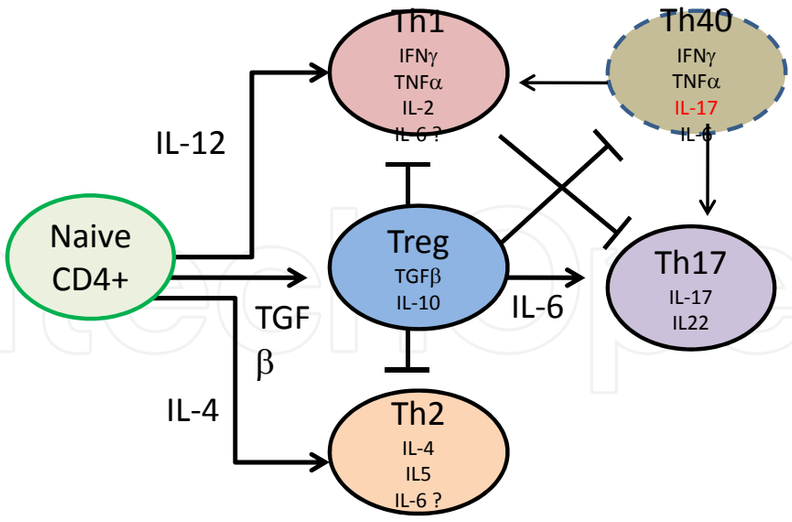


Fig. 1. Stages of helper T cells

Th17 cells have been postulated as a distinct T helper subtype that produces IL-17 and IL-22 (9). Th17 cells are linked to microbial immunity (10, 11) and to autoimmune diseases including multiple sclerosis and the experimental autoimmune encephalitis (EAE) mouse model of that disease. Studies further link Th17 cells to experimental autoimmune uveitis (EAU) (12-14), rheumatoid arthritis (15), systemic lupus erythematosus (16) and to delayed airway hypersensitivity (17). Th1 or Th17 cells are capable of becoming pathogenic effector cells, however distinguishing surface biomarkers that identify predominantly auto-aggressive T cells rarely have been forthcoming. The role of Th17 cells as pathogenic effector cells in T1D is still debated. Th17 and diabetes was further explored using a T cell receptor (TCR) transgenic model. Cells were isolated from BDC2.5.TCR transgenic mice and polarized to a Th1 or Th17 phenotype (18), then transferred to NOD.scid recipients. Th1 recipients became diabetic more quickly than Th17 recipients (18). When Th17 cells were removed and analyzed it was determined that a majority of those cells produced IFNγ. The interpretation was that Th17 cells could convert to Th1 phenotype and the Th1 phenotype alone was responsible for disease. However, given that the BDC2.5 TCR recognizes an islet antigen, recently determined to be Chromogranin-A and that antigen is always present, the T cells from BDC2.5.TCR.Tg mice could never be considered truly naïve. This therefore could impact the polarization process.

Another T helper produced cytokine with high potential in diabetogenesis is IL-6. IL-6 levels were reported generally increased in T1D subjects, including long – term diabetics (19) . However it also was reported that IL-6 levels are not predictive of outcome or disease progression (20). In another demonstration of discordance between human and mouse transitional studies, it was shown that blocking IL-6 in young NOD mice prevents disease onset (6, 21). While not examined in that study, the inhibition of IL-6 may have impeded the generation of Th17 cells. Administration of IL-12 to young NOD mice induces increases in IFNγ producing cells, but interestingly also induces diabetes in IFNγ receptor knockout mice (21). This suggests that control of IFNγ producing cells alone is inadequate for controlling diabetogenesis. These studies indicate a complicated picture with no tightly characterized cell type dominating the disease process.

3. Tregs and T1D

A critical player in the T cell dyad of the inflammatory/anti-inflammatory milieu is the regulatory T cell subset (Tregs). Tregs function to control effector cells and to diminish the inflammatory response. Tregs are generally classified by expression of CD4, $CD25^{hi}$ (the alpha chain of the IL-2 receptor) and the transcription factor FoxP3 (22). Other molecules are associated with Tregs including GITR, CTLA-4, CD103, $CD127^{lo}$, and CD62L. Tregs can arise naturally or be induced in the periphery. Naturally arising Tregs develop in the thymus and require self-antigen recognition for development. This was demonstrated using recombination activating gene, (RAG1 and RAG2) knockout mice that do not develop Tregs (23, 24). In a TCR transgenic mouse model it was shown that Tregs develop in the thymus as long as RAG1 and RAG2 are available (24). In the TCR transgenic mice that are $RAG^{-/-}$ and therefore do not express endogenous TCR molecules, Tregs do not develop (25, 26). This poses an interesting scenario that a set of self – antigen reactive T cells are able to preferentially escape negative selection. That possibility poses the central question of whether those cells ultimately become pathogenic.

The other type of Treg is induced in the periphery requiring interactions with antigen and polarizing exposure to TGFβ (Fig. 1). An interesting aspect is that Th17 effector cells can arise directly from Tregs (Fig. 1). Polarization studies show that treating Tregs with IL-6 promotes a Th17 phenotype (27). Given that Tregs from the thymus are auto-antigen reactive and that a later burst of IL-6 promotes Th17 cells, this could constitute a mechanism for central tolerance escape.

Studies in mouse autoimmune models have shown that knocking out Tregs favors autoimmunity. In T1D studies there remains disparity as to the role of Tregs in controlling disease. It has been reported in mouse (28) and in human (29) T1D subjects that the actual number and function of Tregs is normal. An interesting observation was made however that Tregs from pancreatic lymph nodes of T1D subjects are dysregulated in function (30), when compared to Tregs from peripheral blood. Another study has shown that regulatory CD8+ T cells that recognize the atypical HLA-E presenting the self – antigen Hsp60 are defective in T1D (31). This suggests that the disparity in Treg number and function in autoimmune disease may relate to the location and classification of the Tregs.

4. Th40 cells: a biomarker for pathogenic effector T cells

In numerous studies CD40 has been identified as a biomarker for auto-aggressive T cells (19, 28, 32-36). A panel of highly pathogenic, auto-aggressive T cell clones, including the well described BDC2.5 clone express CD40 (34-36). Although CD40 has been typically associated with antigen presenting cells, it was demonstrated on primary T cells in NOD mice, the type 1 diabetes model, and in the process identified a unique effector $CD4^+$ T cell population, characterized as $CD4^+CD40^+$ [Th40] (19, 28, 32-37). Importantly, Th40 cells were detected in both autoimmune and non-autoimmune mouse strains but occurring at a significantly greater percentage and cell number in autoimmunity (19, 28, 32-35). In fact, the percentage of Th40 cells increased proportionately with increasing insulitis leading to eventual diabetes in NOD mice (34). Primary Th40 cells isolated directly from the pancreata of pre-diabetic and diabetic NOD mice transferred progressive insulitis and diabetes to NOD.*scid* recipients (34, 36), demonstrating pathogenicity of these T cells. In other studies it was shown that Th40 cells are sufficient and necessary for T1D transfer (28, 36, 38, 39). CD40 depleted and

Treg depleted T cells are incapable of disease transfer, even when those cells are pre-activated (28).

Extending these studies, Th40 cells are highly significantly expanded in human T1D, but not in T2D or control subjects (19). Th40 cells from T1D subjects were responsive to diabetes associated antigens including insulin peptides, GAD peptides and whole islets. Th40 cells from T1D subjects but not from controls proliferate when exposed to self-antigens and are induced to produce and secrete cytokines. Typically Th1 cytokines are favored (19). However it was further demonstrated that Th40 cells also can produce IL-17 and furthermore that a subset of Th40 cells produce IL-17 and IFNγ at the same time (40). As such, Th40 cells can be categorized between Th1 and Th17 phenotypes having characteristics of both (Fig. 1). Another interesting feature is that Th40 cells from human T1D subjects produce a substantially elevated level of IL-6; but unlike the other cytokines produced by these T cells, IL-6 production is not dependent upon antigen recognition (19). This could align with the notion that autoimmune diabetes favors a loss of Tregs by providing a mechanism to convert Tregs to Th17 cells (Fig. 1). This process may proceed through the Th40 subset, which as mentioned are greatly expanded in number in T1D (19, 28, 32, 35-41).

Blocking CD40 interaction with its natural ligand CD154 provides a useful treatment strategy in autoimmunity and T1D in particular. CD40 – CD154 interactions have proven crucial in several autoimmune diseases including T1D (42-44). Blocking CD40 – CD154 interactions at 3-weeks of age in NOD mice prevents T1D onset (44). Taken further, blocking CD40 – CD154 interactions in NOD prevented the expansion of auto-aggressive T cells while allowing expansion of innate regulatory, $CD4^+CD25^+$ T cells (34). Thus, blocking CD40 – CD154 interaction restores T cell homeostasis. CD154 is temporally induced on activated T cells (45, 46), is found on platelets (47-49), smooth muscle, vascular endothelial cells and antigen presenting cells (50). CD154 is a member of the TNF super-family, demonstrating high protein sequence homology with TNF (51). Like TNF, CD154 occurs in a soluble form and may behave as a cytokine (52, 53). Interestingly, CD154 including the soluble form is hyper-expressed in T1D (54).

5. T cell co-stimulation and disease

A primary paradigm of immunology states that T cells require two signals to achieve effector status; an antigen specific recognition signal and a second co-stimulus (55). The classic T cell co-stimulus is CD28 on T cells interacting with B7 on APC. However $CD28^{-/-}$ mice that did not develop disease after initial injections, developed fulminant EAE after a second round of induction (56) . In that model a faster, more severe EAE occurred in the absence of the CD28 T cell co-stimulatory pathway. It has been repeatedly shown that TCR engagement alone is insufficient for effector functions. Given that T cells require a co-stimulus for activation the above study suggests a second, perhaps more pernicious T cell co-stimulatory mechanism. Interestingly in that study, blocking CD40 – CD154 through administration of an anti-CD154 resulted in significant long-term inhibition of clinical EAE relapse (56). While CD40 signaling directly impacts antigen presenting cells, in contrast to established paradigms, CD40 has been shown to function effectively as a T cell co-stimulus (57, 58). In fact, CD40 engagement of T cells proved as effective as CD28 co-stimulus (40, 58, 59).

6. Th40 cells and TCR revision

Another paradigm of immunology holds that TCR molecules are generated in the thymus without further alteration. However, it has been demonstrated that RAG1 and RAG2, the recombinase proteins that are responsible for TCR generation, are inducible in peripheral T cells (35, 60-70). Following induction of RAGs, altered expression of TCRα (34, 35) and TCRβ (64, 65, 71) molecules on peripheral T cells, (TCR revision) was demonstrated. This has serious implications for T cell function and autoimmune potential. TCR revision could directly create auto-aggressive T cells that would not be negatively selected. Regardless of whether auto-aggressive T cells are thymic escapees or generated in the periphery, they accumulate under autoimmune conditions (72). Another intriguing finding is that IL-17 producing T cells are more likely to undergo TCR revisions (60). Cumulatively, these findings have direct implications for T1D and other autoimmune diseases. Eventual TCR revision of the initial auto-aggressive T cells could promote tolerance by altering antigen specificity of pathogenic T cells; thus resulting in remission. Alternatively, TCR revision by necessity dictates that T cells with TCR that were never exposed to thymic selection conditions are found in the periphery and therefore may have initiated the autoimmune insult.

7. Conclusions

T cells play a critical role in diabetogenesis as do other cells. Different categories of T cells, Th1, Th17 and now Th40 are being identified in this disease, yet a major concern for understanding and ultimately treating the disease requires a global outlook. How is it that each of these cell types contribute to the overall disease and how do they work in concert to establish and maintain debilitating inflammation. Controlling the inflammatory process without inducing unwanted immune suppression will require surgical precision. It is likely that no one treatment option will prove completely successful, and focusing on any one cell type will diminish the ability to comprehend the overall picture of the disease process. Creating a comprehensive framework of study will be essential for successful treatment.

8. References

[1] Stout, R. D., S. K. Watkins, and J. Suttles. 2009. Functional plasticity of macrophages: in situ reprogramming of tumor-associated macrophages. *J Leukoc Biol* 86:1105-1109.

[2] Suttles, J., and R. Stout. 1997. The many roles of CD40 in cell-mediated inflammatory responses. *Immunol. Today* 17:487-492.

[3] Crane, I. J., and J. V. Forrester. 2005. Th1 and th2 lymphocytes in autoimmune disease. *Crit Rev Immunol* 25:75-102.

[4] Lafaille, J. J. 1998. The role of helper T cell subsets in autoimmune diseases. *Cytokine Growth Factor Rev* 9:139-151.

[5] Romagnani, S. 2000. T-cell subsets (Th1 versus Th2). *Ann Allergy Asthma Immunol* 85:9-18; quiz 18, 21.

[6] Campbell, I. L., T. W. Kay, L. Oxbrow, and L. C. Harrison. 1991. Essential role for interferon-gamma and interleukin-6 in autoimmune insulin-dependent diabetes in NOD/Wehi mice. *J Clin Invest* 87:739-742.

[7] Jain, R., D. M. Tartar, R. K. Gregg, R. D. Divekar, J. J. Bell, H. H. Lee, P. Yu, J. S. Ellis, C. M. Hoeman, C. L. Franklin, and H. Zaghouani. 2008. Innocuous IFNgamma induced by adjuvant-free antigen restores normoglycemia in NOD mice through inhibition of IL-17 production. *J Exp Med* 205:207-218.

[8] Savinov, A. Y., F. S. Wong, and A. V. Chervonsky. 2001. IFN-gamma affects homing of diabetogenic T cells. *J Immunol* 167:6637-6643.

[9] Korn, T., E. Bettelli, M. Oukka, and V. K. Kuchroo. 2009. IL-17 and Th17 Cells. *Annu Rev Immunol* 27:485-517.

[10] Schulz, S. M., G. Kohler, C. Holscher, Y. Iwakura, and G. Alber. 2008. IL-17A is produced by Th17, gammadelta T cells and other CD4- lymphocytes during infection with Salmonella enterica serovar Enteritidis and has a mild effect in bacterial clearance. *Int Immunol* 20:1129-1138.

[11] Steinman, L. 2008. A rush to judgment on Th17. *J Exp Med* 205:1517-1522.

[12] Weaver, C. T., L. E. Harrington, P. R. Mangan, M. Gavrieli, and K. M. Murphy. 2006. Th17: an effector CD4 T cell lineage with regulatory T cell ties. *Immunity* 24:677-688.

[13] Bettelli, E., M. Oukka, and V. K. Kuchroo. 2007. T(H)-17 cells in the circle of immunity and autoimmunity. *Nat Immunol* 8:345-350.

[14] Luger, D., P. B. Silver, J. Tang, D. Cua, Z. Chen, Y. Iwakura, E. P. Bowman, N. M. Sgambellone, C. C. Chan, and R. R. Caspi. 2008. Either a Th17 or a Th1 effector response can drive autoimmunity: conditions of disease induction affect dominant effector category. *J Exp Med* 205:799-810.

[15] Wong, P. K., J. M. Quinn, N. A. Sims, A. van Nieuwenhuijze, I. K. Campbell, and I. P. Wicks. 2006. Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis. *Arthritis Rheum* 54:158-168.

[16] Garrett-Sinha, L. A., S. John, and S. L. Gaffen. 2008. IL-17 and the Th17 lineage in systemic lupus erythematosus. *Curr Opin Rheumatol* 20:519-525.

[17] Komiyama, Y., S. Nakae, T. Matsuki, A. Nambu, H. Ishigame, S. Kakuta, K. Sudo, and Y. Iwakura. 2006. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *J Immunol* 177:566-573.

[18] Bending, D., H. De La Pena, M. Veldhoen, J. M. Phillips, C. Uyttenhove, B. Stockinger, and A. Cooke. 2009. Highly purified Th17 cells from BDC2.5NOD mice convert into Th1-like cells in NOD/SCID recipient mice. *J Clin Invest*.

[19] Waid, D. M., R. J. Wagner, A. Putnam, G. M. Vaitaitis, N. D. Pennock, D. C. Calverley, P. Gottlieb, and D. H. Wagner, Jr. 2007. A unique T cell subset described as CD4loCD40+ T cells (TCD40) in human type 1 diabetes. *Clin Immunol* 124:138-148.

[20] Kaas, A., C. Pfleger, L. Hansen, K. Buschard, N. C. Schloot, B. O. Roep, and H. B. Mortensen. Association of adiponectin, interleukin (IL)-1ra, inducible protein 10, IL-6 and number of islet autoantibodies with progression patterns of type 1 diabetes the first year after diagnosis. *Clin Exp Immunol* 161:444-452.

[21] Trembleau, S., G. Penna, S. Gregori, N. Giarratana, and L. Adorini. 2003. IL-12 administration accelerates autoimmune diabetes in both wild-type and IFN-gamma-deficient nonobese diabetic mice, revealing pathogenic and protective effects of IL-12-induced IFN-gamma. *J Immunol* 170:5491-5501.

[22] Sakaguchi, S., M. Ono, R. Setoguchi, H. Yagi, S. Hori, Z. Fehervari, J. Shimizu, T. Takahashi, and T. Nomura. 2006. Foxp3+ CD25+ CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. *Immunol Rev* 212:8-27.

[23] Sakaguchi, S., T. Yamaguchi, T. Nomura, and M. Ono. 2008. Regulatory T cells and immune tolerance. *Cell* 133:775-787.

[24] Yamaguchi, T., K. Hirota, K. Nagahama, K. Ohkawa, T. Takahashi, T. Nomura, and S. Sakaguchi. 2007. Control of immune responses by antigen-specific regulatory T cells expressing the folate receptor. *Immunity* 27:145-159.

[25] Kersh, G. J., D. L. Donermeyer, K. E. Frederick, J. M. White, B. L. Hsu, and P. M. Allen. 1998. TCR transgenic mice in which usage of transgenic alpha- and beta-chains is highly dependent on the level of selecting ligand. *J Immunol* 161:585-593.

[26] Koh, W. P., E. Chan, K. Scott, G. McCaughan, M. France, and B. Fazekas de St Groth. 1999. TCR-mediated involvement of CD4+ transgenic T cells in spontaneous inflammatory bowel disease in lymphopenic mice. *J Immunol* 162:7208-7216.

[27] Suto, A., D. Kashiwakuma, S. Kagami, K. Hirose, N. Watanabe, K. Yokote, Y. Saito, T. Nakayama, M. J. Grusby, I. Iwamoto, and H. Nakajima. 2008. Development and characterization of IL-21-producing CD4+ T cells. *J Exp Med* 205:1369-1379.

[28] Waid, D. M., G. M. Vaitaitis, N. D. Pennock, and D. H. Wagner, Jr. 2008. Disruption of the homeostatic balance between autoaggressive (CD4+CD40+) and regulatory (CD4+CD25+FoxP3+) T cells promotes diabetes. *J Leukoc Biol* 84:431-439.

[29] Schneider, A., M. Rieck, S. Sanda, C. Pihoker, C. Greenbaum, and J. H. Buckner. 2008. The effector T cells of diabetic subjects are resistant to regulation via CD4+ FOXP3+ regulatory T cells. *J Immunol* 181:7350-7355.

[30] Gagliani, N., A. Ferraro, M. G. Roncarolo, and M. Battaglia. 2009. Autoimmune diabetic patients undergoing allogeneic islet transplantation: are we ready for a regulatory T-cell therapy? *Immunol Lett* 127:1-7.

[31] Jiang, H., S. M. Canfield, M. P. Gallagher, H. H. Jiang, Y. Jiang, Z. Zheng, and L. Chess. HLA-E-restricted regulatory CD8(+) T cells are involved in development and control of human autoimmune type 1 diabetes. *J Clin Invest* 120:3641-3650.

[32] Vaitaitis, G. M., and D. H. Wagner, Jr. 2008. High distribution of CD40 and TRAF2 in Th40 T cell rafts leads to preferential survival of this auto-aggressive population in autoimmunity. *PLoS One* 3:e2076.

[33] Siebert, J. C., M. Inokuma, D. M. Waid, N. D. Pennock, G. M. Vaitaitis, M. L. Disis, J. F. Dunne, D. H. Wagner, Jr., and H. T. Maecker. 2008. An analytical workflow for investigating cytokine profiles. *Cytometry A* 73:289-298.

[34] Waid, D. M., G. M. Vaitaitis, and J. Wagner, D.H. 2004. Peripheral Expansion of $CD4^{lo}CD40^{+}$ Auto-Aggressive T Cells During Insulin-Dependent Diabetes Mellitus. *European Journal of Immunology 34*:1488-1497.

[35] Vaitaitis, G. M., M. Poulin, R. J. Sanderson, K. J. Haskins, and D. H. Wagner Jr. 2003. CD40-Induced Expression of Recombination Activating Gene (RAG) 1 and RAG2: A Mechanism for the Generation of Autoaggressive T Cells in the Periphery. *Cutting Edge, J. Immunol.* 170:3455-3459.

[36] Wagner, D. H., Jr., G. Vaitaitis, R. Sanderson, M. Poulin, C. Dobbs, and K. Haskins. 2002. Expression of CD40 identifies a unique pathogenic T cell population in type 1 diabetes. *Proc Natl Acad Sci U S A* 99:3782-3787.

[37] Vaitaitis, G., and D. H. Wagner Jr. 2010. CD40 Glycoforms and TNF-Receptors 1 and 2 in the Formation of CD40 Receptor(s) in Autoimmunity. *Mol. Immunol.* 47:2303-2313.

[38] Waid, D. M., G. M. Vaitaitis, and D. H. Wagner, Jr. 2004. Peripheral CD4loCD40+ auto-aggressive T cell expansion during insulin-dependent diabetes mellitus. *Eur J Immunol* 34:1488-1497.

[39] Vaitaitis, G. M., M. Poulin, R. J. Sanderson, K. Haskins, and D. H. Wagner, Jr. 2003. Cutting edge: CD40-induced expression of recombination activating gene (RAG) 1 and RAG2: a mechanism for the generation of autoaggressive T cells in the periphery. *J Immunol* 170:3455-3459.

[40] Vaitaitis, G., D. M. Waid, and D. H. Wagner Jr. 2010. The expanding role of TNF-receptor super family member CD40 (tnfrsf5) in autoimmune disease: Focus on Th40 cells. *Curr Immunol Rev* 6:130-136.

[41] Vaitaitis, G. M., and D. H. Wagner, Jr. CD40 glycoforms and TNF-receptors 1 and 2 in the formation of CD40 receptor(s) in autoimmunity. *Mol Immunol* 47:2303-2313.

[42] Durie, F. H., R. A. Fava, T. M. Foy, A. Aruffo, J. A. Ledbetter, and R. J. Noelle. 1993. Prevention of collagen-induced arthritis with an antibody to gp30 the ligand for CD40. *Science* 281:1328-1330.

[43] Lutgens, E., L. Gorelik, M. J. Daemen, E. D. de Muinck, I. S. Grewal, V. E. Koteliansky, and R. A. Flavell. 1999. Requirement for CD154 in the progression of atherosclerosis. *Nat Med* 5:1313-1316.

[44] Balasa, B., T. Krahl, G. Patstone, J. Lee, R. Tisch, H. O. McDevitt, and N. Sarvetnick. 1997. CD40 Ligand-CD40 interactions are necessary for the initiation of insulitis and diabetes in nonobese diabetic mice. *Journal of Immunology* 159:4620-4627.

[45] Yellin, M. J., J. Sinning, L. R. Covey, W. Sherman, J. J. Lee, E. Glickman-Nir, K. C. Sippel, J. Rogers, A. M. Cleary, M. Parker, L. Chess, and S. Lederman. 1994. T Lymphocytes T cell-B cell activating molecule/ CD40-L molecules induce normal B cells or Chronic Lymphocytic Leukemia B cells to express CD80(B7/BB1) and enhance their costimulatory activity. *Journal of Immunology* 153:666-674.

[46] Noelle, R. 1995. The role of gp39 (CD40L) in immunity. *Clinical Immunology and Immunopathology* 76:5203-5207.

[47] Wang, C. L., Y. T. Wu, C. A. Liu, M. W. Lin, C. J. Lee, L. T. Huang, and K. D. Yang. 2003. Expression of CD40 ligand on CD4+ T-cells and platelets correlated to the coronary artery lesion and disease progress in Kawasaki disease. *Pediatrics* 111:E140-147.

[48] Andre, P., L. Nannizzi-Alaimo, S. K. Prasad, and D. R. Phillips. 2002. Platelet-derived CD40L: the switch-hitting player of cardiovascular disease. *Circulation* 106:896-899.

[49] Hermann, A., B. H. Rauch, M. Braun, K. Schror, and A. A. Weber. 2001. Platelet CD40 ligand (CD40L)--subcellular localization, regulation of expression, and inhibition by clopidogrel. *Platelets* 12:74-82.

[50] Mach, F., U. Schonbeck, G. K. Sukhova, T. Bourcier, J. Y. Bonnefoy, J. S. Pober, and P. Libby. 1997. Functional CD40 ligand is expressed on human vascular endothelial cells, smooth muscle cells, and macrophages: implications for CD40-CD40 ligand signaling in atherosclerosis. *Proc Natl Acad Sci U S A* 94:1931-1936.

[51] Stone, G. W., S. Barzee, V. Snarsky, K. Kee, C. A. Spina, X. F. Yu, and R. S. Kornbluth. 2006. Multimeric soluble CD40 ligand and GITR ligand as adjuvants for human immunodeficiency virus DNA vaccines. *J Virol* 80:1762-1772.

[52] Stumpf, C., C. Lehner, S. Eskafi, D. Raaz, A. Yilmaz, S. Ropers, A. Schmeisser, J. Ludwig, W. G. Daniel, and C. D. Garlichs. 2003. Enhanced levels of CD154 (CD40 ligand) on platelets in patients with chronic heart failure. *Eur J Heart Fail* 5:629-637.

[53] Toubi, E., and Y. Shoenfeld. 2004. The role of CD40-CD154 interactions in autoimmunity and the benefit of disrupting this pathway. *Autoimmunity* 37:457-464.

[54] Jinchuan, Y., W. Zonggui, C. Jinming, L. Li, and K. Xiantao. 2004. Upregulation of CD40--CD40 ligand system in patients with diabetes mellitus. *Clin Chim Acta* 339:85-90.

[55] Bachmaier, K., C. Pummerer, A. Shahinian, J. Ionescu, N. Neu, T. W. Mak, and J. M. Penninger. 1996. Induction of autoimmunity in the absence of CD28 costimulation. *J Immunol* 157:1752-1757.

[56] Girvin, A. M., M. C. Dal Canto, and S. D. Miller. 2002. CD40/CD40L interaction is essential for the induction of EAE in the absence of CD28-mediated co-stimulation. *J Autoimmun* 18:83-94.

[57] Munroe, M. E., and G. A. Bishop. 2007. A costimulatory function for T cell CD40. *Journal of Immunology* 178:671-682.

[58] Baker, R. L., D. H. Wagner, Jr., and K. Haskins. 2008. CD40 on NOD CD4 T cells contributes to their activation and pathogenicity. *J Autoimmun* 31:385-392.

[59] Munroe, M. E., and G. A. Bishop. 2007. A costimulatory function for T cell CD40. *J Immunol* 178:671-682.

[60] Zehn, D., M. J. Bevan, and P. J. Fink. 2007. Cutting edge: TCR revision affects predominantly Foxp3 cells and skews them toward the Th17 lineage. *J Immunol* 179:5653-5657.

[61] Cooper, C. J., G. L. Turk, M. Sun, A. G. Farr, and P. J. Fink. 2004. Cutting edge: TCR revision occurs in germinal centers. *J Immunol* 173:6532-6536.

[62] Cooper, C. J., M. T. Orr, C. J. McMahan, and P. J. Fink. 2003. T cell receptor revision does not solely target recent thymic emigrants. *J Immunol* 171:226-233.

[63] Ali, M., M. Weinreich, S. Balcaitis, C. J. Cooper, and P. J. Fink. 2003. Differential regulation of peripheral CD4+ T cell tolerance induced by deletion and TCR revision. *J Immunol* 171:6290-6296.

[64] McMahan, C., and P. Fink. 2000. Receptor revision in peripheral T cells creates a diverse V beta repertoire. *J Immunol* 165:690206907.

[65] Fink, P. J., and C. J. McMahan. 2000. Lymphocytes rearrange, edit and revise their antigen receptors to be useful yet safe. *Immunol Today* 21:561-566.

[66] McMahan, C. J., and P. J. Fink. 1998. RAG reexpression and DNA recombination at T cell receptor loci in peripheral CD4+ T cells. *Immunity* 9:637-647.

[67] Takase, M., E. M. Kanagawa, and O. Kanagawa. 2007. Age-dependent TCR revision mediated by interaction between alphabeta TCR and self-antigens. *J Immunol* 179:2163-2169.

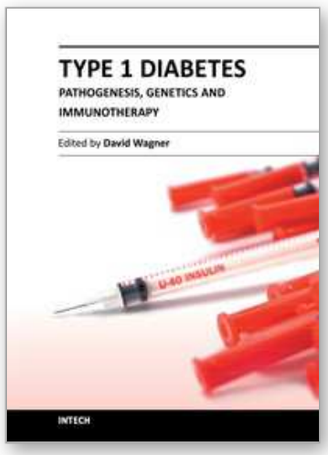
[68] Huang, C. Y., B. P. Sleckman, and O. Kanagawa. 2005. Revision of T cell receptor {alpha} chain genes is required for normal T lymphocyte development. *Proc Natl Acad Sci U S A* 102:14356-14361.

[69] Nagafuchi, H., H. Yoshikawa, Y. Takeba, K. Nara, K. Miura, M. S. Kurokawa, and N. Suzuki. 2004. Recombination activating genes (RAG) induce secondary Ig gene rearrangement in and subsequent apoptosis of human peripheral blood circulating B lymphocytes. *Clin Exp Immunol* 136:76-84.

[70] Huang, C. Y., R. Golub, G. E. Wu, and O. Kanagawa. 2002. Superantigen-induced TCR alpha locus secondary rearrangement: role in tolerance induction. *J Immunol* 168:3259-3265.

[71] Blish, C., B. Gallay, G. Turk, K. Kline, W. Wheat, and P. Fink. 1999. Chronic modulation of the TCR repertoire in the lymphoid periphery. *J Immunol* 162:3131-3140.

[72] Wagner, J., D.H. 2007. Reshaping the T cell repertoire: TCR editing and TCR revision for Good and for Bad. *Clin Immunol* I123:1-6.



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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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