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Regulatory T Cells and Viral Disease

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1. Introduction

The mammalian immune system has the ability to distinguish self from non-self-antigens, a phenomenon which begins in the thymus during T cell development. T cells that express a fully rearranged T cell receptor (TCR) with a high affinity for self-antigens presented in the thymus are deleted or undergo anergy in a process known as negative selection. Because of this mechanism, T cells in the periphery are primarily specific for non-self-antigens. However, this process is somewhat inefficient, because some self-reactive cells escape deletion therefore additional mechanisms are required to maintain peripheral immune tolerance. Regulatory T cells (T_{regs}) are a distinct subset of T cells that are critical for maintaining both immune homeostasis and peripheral immune tolerance. T_{regs} are typically identified by expression of the forkhead box 3 (FoxP3) transcription factor. The majority of FoxP3+ cells also express CD4 and express high levels of the IL-2 receptor (CD25). Additional subsets of T_{regs} that have been described in humans and mice include Tr1 cells, T helper 3 cells (Th3), NK cells, and CD8+ T_{regs} (Beissert S, 2006). CD4+ T cells that express high levels the IL-2α receptor ($CD25^{high}$) do not respond to T cell receptor (TCR) activation or mitogen stimulation, and inhibit IL-2 transcription in CD25- cells. Suppression of CD25- cells is contact dependent, and requires activation of the T_{regs} through the TCR; however, once activated, the suppressor effector function is nonspecific (Thornton AM, 2000). In mice and humans, FoxP3+ cells also express high levels of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and glucocorticoid-induced tumor necrosis factor receptor (GITR) on the surface (Bacchetta R, 2005). CD4+CD25+ T cells suppress the immune response to some viruses, protozoa, and bacteria, and aid in the survival of intracellular pathogens (Sakaguchi, 2003) most likely by potent suppression of proliferation and IFN-γ production of both CD4+ and CD8+ T lymphocytes (Bacchetta R, 2005). Tr1 cells secrete high amounts of IL-10 and moderate amounts of TGF-β. Inhibiting IL-10 with neutralizing antibody blocks the suppressor effects of Tr1 cells (Beissert S, 2006). Th3 cells produce high concentrations of TGF-β and moderate amounts of IL-10, and the suppressor effects are not antigen specific (Beissert S, 2006). Interestingly, Th3 cells suppress the activation of both Th1 and Th2 cell clones while other subsets primarily inhibit Th1 cells and have no effect on Th2 cells (Beissert S, 2006). A number of studies have shown that T_{regs} affect the magnitude of immunity and outcome of viral infections, especially with persistent viruses that give rise to chronic lesions (Rouse BT, 2006). Depletion of T_{regs} prior to infection using a monoclonal antibody against the IL-2α receptor results in enhanced in vivo CD8+ and CD4+ T lymphocyte proliferation, and increased mucosal antibody levels in response to herpes

simplex viral infection in mice (Rouse BT, 2006). Humans with chronic hepatitis C virus have IL-10-producing Tr1 cells, while those who control infection do not. The IL-10 - producing cells were shown to modulate the activity of protective IFN-γ producing T lymphocytes, and both the Th1 and regulatory T cells were induced against the same epitopes (MacDonald AJ, 2002). Additionally, immunosuppression induced by chronic retroviral infection in the absence of T cell depletion was shown to be mediated by CD4+ regulatory T lymphocytes in mice (Iwashiro M, 2001). Importantly, these regulatory T lymphocytes suppressed IFN-γ production by CD8+ T lymphocytes, contributing to virus persistence (Dittmer U, 2004). The ability of viruses to induce proliferation and activation of regulatory T cells likely contributes to delayed clearance and persistence in the host.

2. Regulatory T cell biology and development

Following infection, naïve CD4+ T cells recognize antigen presented on antigen presenting cells, bound to class II major histocompatibility complexes (MHC class II). These CD4+ T cells expand and differentiate into effector T cells that can become polarized into distinct subsets depending on the cytokine environment (McKinstry KK, 2010). The best characterized are Th1 and Th2 subsets that have been associated with cell-mediated (Th1) and humoral (Th2) immunity (reviewed in (Sakaguchi S, 2010). In addition to T cells, B cells, and plasma cells are vital in development of humoral immunity. The role of plasma cells in antibody development is beyond the scope of this discussion. Recently, additional subsets have been described, including Th9, Th17, Th22, T-follicular helper cells (Tfh), and regulatory T cells. Recent studies have shown that multiple CD4+ T cells are actually generated *in vivo*, rather than distinct subsets as previously thought. The effector cells secrete large amounts of cytokines, chemokines, and other proteins that can produce cytotoxicity to host tissues, or induce autoimmunity. Until recently, control of T_{reg} function was believed to have primarily been through cytokine signaling. However, there is evidence that T_{regs} can also sense pathogens through toll-like receptors (TLRs) which modifies their behavior (Sutmuller RPM, 2006). The role of cytokines and TLRs in controlling T_{reg} function will be discussed separately.

Th subset	Selected Key Transcription factors	Cytokines produced
Th1	T-bet	IFN-γ, TNF, IL-2
Th2	GATA-3	IL-4, IL-5, IL-13
Th17	ROR-γt	IL-17, IL-22
Tfh	Bcl-6	IL-4, IL-21
Treg	Foxp3	IL-10

Table 1. CD4+ T cell subsets (modified from (McKinstry KK, 2010))

Regulatory T cells function to provide a balance between combating pathogens and the risk of developing autoimmunity or overwhelming inflammation. Regulatory T cells can be divided into two groups – natural T_{regs} develop in the thymus, while inducible T_{regs} are generated in the periphery from conventional T cells in response to different stimuli. The natural T_{regs} are the best characterized of the two groups and make up approximately 5-10% of circulating T lymphocytes in mice and humans (Gückel E, 2011). Regulatory T cells are primarily characterized by the expression of the transcription factor FoxP3. FoxP3 maintains

T_{reg} gene expression induced by other transcription factors rather than actually driving T_{reg} development. However, FoxP3 is essential for T_{reg} function since loss of FoxP3 function results in severe lymphoproliferative disease and autoimmunity in humans and mice (Bennett CL, 2001). The role of FoxP3 in maintaining self-tolerance was first identified in scurfy mice, and then in humans with immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, both of which have a FoxP3 mutation as the underlying genetic defect. Humans express two isoforms of FoxP3 (A and B), either of which has regulatory function. FoxP3B contains a deletion of the proline-rich exon 2 which is required to bind to the retinoic acid receptor-related orphan receptor-α (RORα). In addition, FoxP3B lacks the amino-terminal residues that interact with nuclear factor of activated T cells (NFAT) (Sakaguchi S, 2010). In humans, FoxP3 expression on T_{regs} is transient, and downregulation of FoxP3 expression decreases the ability of these cells to suppress. In contrast, this transient expression has not been found in mice; however, mouse conventional T cells can be converted to FoxP3+ T regs following stimulation with TFGβ or retinoic acid. These adaptive T_{reg} cells also express FoxP3, CD25, and CTLA4 (Sakaguchi S, 2010). In humans, FoxP3+ T cells stimulated with TGFβ do not have suppressive activity and may require other factors to develop T_{reg} function. Both natural and induced T_{reg} cells have unique surface markers that differentiate them from conventional T cells. The surface marker expression is summarized in Figure 1.

2.1 Natural regulatory T cells

Natural regulatory T cells were first discovered in two animal models of autoimmunity. In the first, neonatal mice were thymectomized at 2-4 days of life. These mice developed autoimmune disease that could be abrogated by adoptive transfer of CD4+ T cells from normal mice. In the second, adult rats were thymectomized and subjected to X-ray irradiation. Adoptive transfer of CD4+ T cells from normal rats similarly abrogated the autoimmune disease, suggesting that CD4+ T cells within the thymus suppressed the development of autoimmunity. Later experiments showed that adoptive transfer of thymocytes depleted of CD4+CD25+ cells resulted in the development of autoimmune disease in syngeneic T cell deficient mice (reviewed in (Sakaguchi S, 2010)). Thymic stromal cells and dendritic cells are critical for nT_{reg} development. Natural regulatory T cells develop in the thymus through interactions between the high-affinity T cell receptor and cognate antigens on thymic epithelial cells. Co-stimulation through CD28 and common gamma (cγ) chain cytokines, especially IL-2 and IL-7 have also been shown to be necessary for nT_{reg} development. Signal transducer and activation of transcription 5 (STAT5) signaling through the cγ chain is also required. Thymic development of nT_{reg} cells follows a two-step process: 1), thymocytes upregulate CD25 and other IL-2 signaling molecules in response to TCR/CD28 co-stimulation and 2), $CD4+CD25^{high}FoxP3-$ T_{regs} respond to IL-2 independent of the TCR, and induce FoxP3 expression in response to STAT5 activation (Gückel E, 2011). T_{reg} cell-intrinsic NF-κB activation is essential for thymic T_{reg} development (Gückel E, 2011). Naturally occurring T_{regs} cannot produce IL-2 and therefore rely on paracrine IL-2 production from conventional T cells. Mice deficient in IL-2 or CD25 have reduced numbers of FoxP3+ T cells and a dramatic reduction in peripheral and thymic T_{regs}. In humans, Hassall's corpuscles in the thymic medulla secrete thymic stroma lymphopoietin (TSLP) which activates immature dendritic cells and upregulates the expression of co-stimulatory molecules. The activated DCs induce FoxP3 expression in CD4+CD8-CD25- thymocytes (Sakaguchi S, 2010).

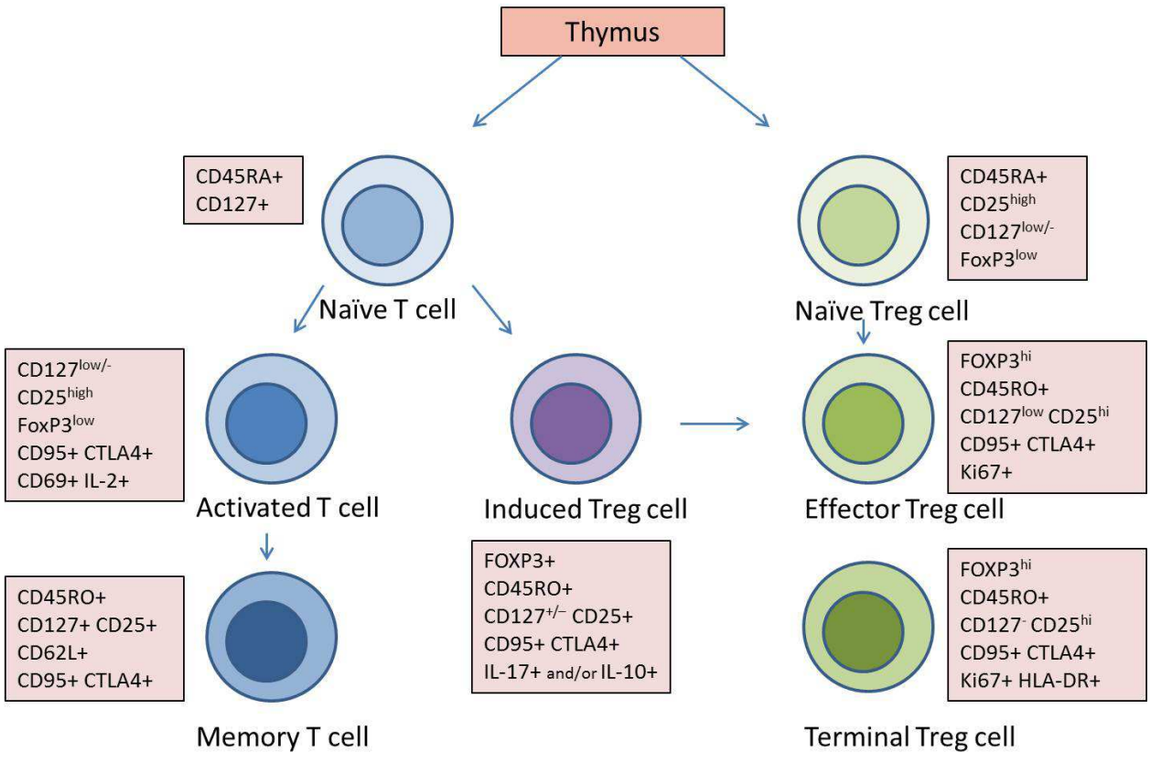

Fig. 1. Regulatory T cell development. The phenotype of different stages of CD4+ T cell differentiation into the conventional T cell and regulatory T cells are shown. The T cells originate in the thymus and emigrate as naïve CD45RA+ T cells to the periphery where they are activation. Activation induces differentiation into either conventional or regulatory T cells. Conventional T cells can then differentiate into memory T cells. Treg cells have not yet been shown to produce memory cells, but they do differentiate into terminal effector Tregs. Treg-like cells are induced from conventional T cells depending on cytokine stimulation. These converted Treg-like cells have cell surface markers similar to those expressed by natural Tregs. CTLA4, cytotoxic T lymphocyte antigen 4; FOXP3, forkhead box P3 (Modified from (Sakaguchi S, 2010)).

2.2 Inducible regulatory T cells

A less well-characterized subset of regulatory T cells is the inducible T_{regs} that develop from conventional T cells under certain conditions. iT_{regs} are induced by prolonged exposure to circulating antigen or weak co-stimulation in the periphery. Additionally, soluble factors such as the cytokines IL-4, IL-10 and TGF-β, retinoic acid or neuropeptides can enhance Foxp3 upregulation and iT_{reg} generation in the periphery. FoxP3 expression induces upregulation of other T_{reg} molecules including CTLA-4, GITR, and CD127. Tr1 cells secrete IL-10, while Th3 cells secrete TGF-β. Other cells with adaptive regulatory function include some CD4-CD8- and CD8+CD28- T cells (Sakaguchi S, 2010). Early after iT_{regs} are stimulated, they express high levels of cell-cycle progression and T cell activation-associated genes (Prots I, 2011), mimicking genes that are upregulated in activated effector T cells. As iTregs mature, expression of these genes diminishes while they remain high in mature effector T cells. By 10 days after differentiation into iT_{regs}, most cell cycle progression and T

cell activation genes are expressed at levels approximately 3 times lower than in effector T cells. In addition, genes in the FoxO family of transcription factors are over-expressed in iT_{regs} compared to overexpression of the FoxM1 family in effector cells (Prots I, 2011).

2.3 Toll-like receptors

At the center of the balance between protective immunity and autoimmunity are the pattern recognition receptors on antigen presenting cells that activate innate immunity and provide the bridge between innate and adaptive immunity. Pattern recognition receptors include Toll-like receptor molecules (TLRs), Nod and Nod-like receptors, RIG-I-like receptors (RLRs), and C-type lectin receptors (Dai J., 2009). TLRs are critical for sensing pattern associated molecular patterns (PAMPs) such as those from bacteria, viruses, protozoa, and fungi, and act to bridge innate and acquired immunity. Stimulation of TLRs by PAMPs alerts the immune system to the presence of microbial infections, triggers maturation in dendritic cells, and allows them to initiate adaptive immunity. TLRs have recently been found to be expressed on T_{regs} as well, and may act to curtail excessive inflammation, autoimmunity, and sepsis (Sutmuller RPM, 2006). However, TLR signaling has also been shown to block T_{reg} activity, leading to an enhanced immune response. Therefore, the function of T_{regs} can be attenuated or enhanced depending on TLR activity in response to certain pathogens (Dai J., 2009). Of the thirteen TLRs that have been identified in mice and humans, T_{regs} express TLRs 7, 8, and 9 intracellularly, and 1, 2, 4, 5, 6, and 10 on the surface. Additionally, T_{reg} subsets express significantly more TLR4, TLR5, TLR7, and TLR8 than conventional T cells. TLR4 recognizes lipopolysaccharide (LPS), which is produced by gram negative bacteria, while TLR2 is activated by lipoteichoic acid (LTA) and bacterial lipoproteins. TLR7 and TLR8 recognize single stranded RNA, and TLR9 recognizes unmethylated CpG DNA motifs found primarily in DNA viruses and some prokaryotic genomes (Sutmuller RPM, 2006). Interestingly, bacterial product signaling through TLR 2, 4, and 5 results in increased T_{reg} function in a MyD88 and phosphatidylinositol 3-kinase (PI-3 kinase)-dependent fashion; while signaling through intracellular TLRs 7, 8, and 9 decreases T_{reg} function (Dai J., 2009). The reason for the dual function of T_{regs} in infection is unclear; however Dai et. al suggest that the dual response is a necessary pathogen-specific response. On the one hand, bacterial and fungal products are responsible for acute sepsis, and these products are recognized by cell surface TLRs 2, 4, and 5. A robust anti-inflammatory response is necessary to prevent overwhelming inflammation in septic individuals. On the other hand, viruses do not cause sepsis, and an adaptive immune response is necessary for protective immunity. Recognition of viruses through intracellular TLRs 7, 8, and 9 ensures a robust effector T cell response by inhibiting the function of T_{regs} (Dai J., 2009). Alternatively, changes in T_{reg} function may be a result of the expression levels, the density, or the subcellular localization of TLRs, or of differential expression of co-stimulatory or accessory molecules, or the cytokine milieu. Importantly, TLR2 seems to be crucial in expanding and regulating T_{reg} function. TLR-2 deficient mice have significantly fewer T_{reg} cells than control mice, and administering TLR2 ligands to wild-type mice increases T_{reg} numbers. TLR2 triggering, IL-2 treatment, and TCR ligation can overcome T_{reg} anergy *in vitro* and *in vivo*. Additionally, Foxp3 expression was decreased following TLR2 stimulation of T_{reg} cells. How TLR-signaling affects Foxp3 expression is still unknown. TLR2 ligand also increases IL-2 receptor expression on T_{regs} and induces IL-2 production by conventional T cells resulting in IL-2 mediated abrogation of suppression (Sutmuller RPM, 2006).

2.4 Cytokines

Recently, the Th1/Th2 paradigm has shifted to focus on other subsets of T cells. The focus has been on the relationship between regulatory T cells and CD4+ T cells that secrete IL-17 (Th17 cells). These cells are derived from a common progenitor cell, and develop in response to the cytokine milieu. T_{regs} and Th17 cells even share common chemokine receptors and homing properties (Kanwar B, 2010). The balance between these subsets is important in many immune disorders related to host-pathogen interaction, inflammatory syndromes, autoimmune disease, and immunodeficiency. T_{reg} cell development is dependent on cytokine production: the presence of TGF-β favors T_{reg} differentiation (Fig 2), while the addition of IL-6 favors Th17 development, and IL-4 and TGF-β favors Th9 development (Jutel M, 2011). TGF-β upregulates the retinoic acid receptor-related orphan receptor-γt (ROR-γt), which is a master transcription factor of Th17 differentiation. TGF-β also induces FoxP3 upregulation when IL-6 is not present. The presence of IL-6 inhibits T_{reg} development and induces development of Th17 cells. One of the first ways found to modify T_{reg} function was using high concentrations of IL-2. Adding extra IL-2 to *in vitro* suppression assays resulted in abrogation of suppression. It was then found that IL-2 can both overcome T_{reg}-mediated suppression, as well as enhance T_{reg} function by upregulating IL-10, FoxP3, and CTLA-4. IL-2 - deficient mice fail to generate functional regulatory T cells in the periphery, lose CD4+ T cell homeostasis, and suffer from lethal lymphoid hyperplasia,

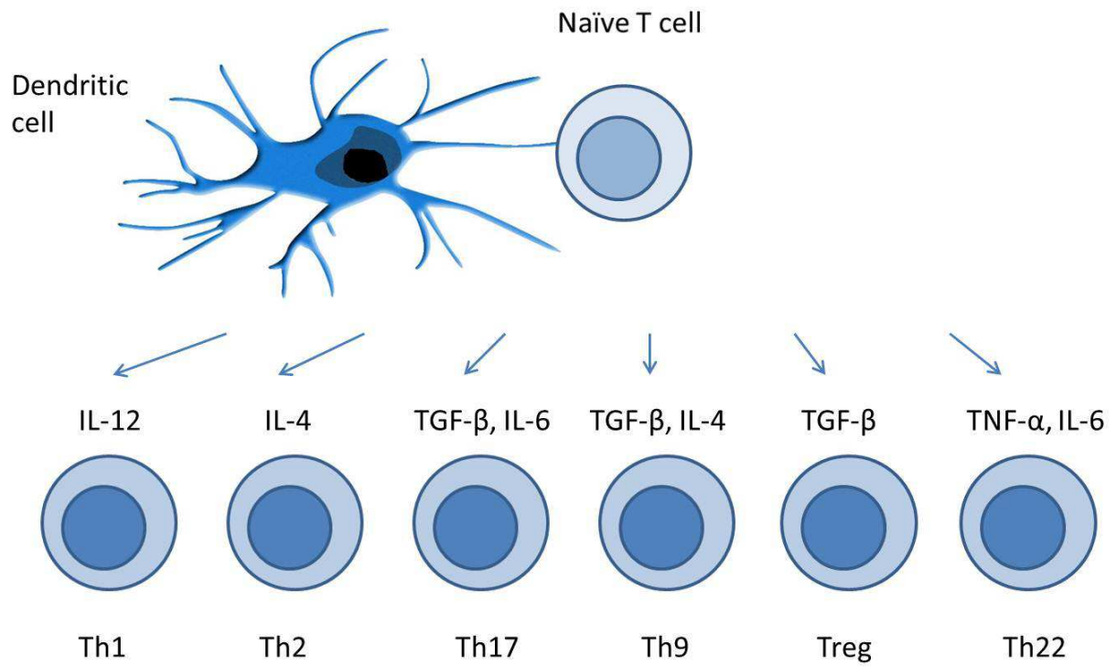

Fig. 2. The differentiation of naïve T cells into effector T cells is mediated by cytokines in the microenviroment. The resulting cytokine profiles, responses to chemokines, and interactions with other cells promote different types of inflammatory responses. In the presence of TGFβ alone, naïve T cells differentiate into regulatory T cells. However, if IL-4 or IL-6 is present, the naïve T cells differentiation into proinflammatory Th9 or Th17 cells. IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor (modified from (Jutel M, 2011))

underscoring the significance of IL-2 in T_{reg} development (Sutmuller RPM, 2006). Studies have shown that IL-2 production by effector T cells is not affected; however, T_{regs} act as an IL-2 sink, and sequester IL-2 from the supernatant. Therefore IL-2 likely plays a dual role in boosting T_{reg} function while allowing effector T cells to escape T_{reg}-mediated suppression (Walker, 2009). Interestingly, IL-15 can take over many of IL-2's functions as a growth factor *in vitro*, a phenomenon that may be related to the fact that IL-15 signals through the common IL-2 receptor β and γ chains. However, IL-15 deficient mice do not develop lymphoid hyperplasia, suggesting that IL-2 is more important in T_{reg} development (reviewed in (Sutmuller RPM, 2006)).

2.5 The suppressive activity of regulatory T cells

Currently, human T_{reg}-mediated suppression has only been studied *in vitro* and it is not yet clear if *in vitro* suppression translates to what occurs *in vivo*. Additionally, the exact molecular mechanism of suppression is not yet known. However; the mechanism of suppression has been studied both *in vivo* and *in vitro* in mice and may provide clues as to what occurs in humans. Even though conventional T cells in mice can be induced to express high levels of FoxP3 and have suppressive activity (unlike humans), mice nevertheless provide a valuable animal model to study the overall mechanism of T_{reg}-mediated immune suppression. From mouse studies, we know that several mechanisms may be involved, including cytokine expression, metabolic disruption of the target cell, the alteration of the ability of dendritic cell to activate conventional T cells, and cytolysis (Sakaguchi S, 2010). For example, CTLA4 expressed by T_{regs} can alter expression of CD80 and CD86 on dendritic cells and prevent activation of effector T cells (Wing K, 2008). T_{reg}-mediated suppression requires initial activation through the T cell receptor (Thornton AM, 2000). However, once activated, they do not require antigen-specific TCR activation. In fact, following TCR activation, T_{regs} typically undergo apoptosis yet remain suppressive. Surprisingly, even paraformaldehyde-fixed T_{regs} retain their suppressive function. Suppression also depends on the level of effector T cell activation. Those effector T cells that receive strong co-stimulatory signals remain refractory to T_{reg}-mediated suppression. Additionally, growth-promoting cytokines can overcome T_{reg} function. This suggests that inflammatory responses cannot be modulated in conditions where strong pro-inflammatory signals predominate (Sakaguchi S, 2010). The direct interaction between DCs and T_{reg} can also influence T_{reg} function. T_{reg} cells can downregulate co-stimulatory molecules on immature DCs; however, mature DCs are resistant to T_{reg} effects. Mature DCs express high levels of CD80, CD86, and CD40 which can increase T_{reg} numbers. DCs can also overcome T_{reg}-mediated suppression through the tumor necrosis factor receptor superfamily. Glucocorticoid-induced TNF receptor family-related gene (GITR), OX40, 4-1BB, and RANK can all block T_{reg} -mediated suppression. GITR is expressed at high levels on T_{regs}, and the ligand is expressed primarily on DCs and macrophages. Triggering through GITR induces T_{reg} proliferation but can also block suppression (Sutmuller RPM, 2006).

3. Regulatory T cells in cancer

T_{regs} play a dual role in preventing and enhancing disease in cancer. On one hand, T_{regs} have been shown to inhibit the activation of both CD4+ and CD8+ tumor-suppressor T lymphocytes, and suppress anti-tumor immunity (Zamarron BF, 2011). A correlation between greater numbers of FoxP3+ T cells and larger invasive breast ductal carcinomas

was found in sentinel lymph nodes of patients (Gupta R, 2011). Similarly, depletion of FoxP3+ T cells enhances tumor rejection in mice (Zamarron BF, 2011). In these examples, strategies to prevent T_{reg} activation would be needed to enhance anti-tumor immunity. On the other hand, chronic inflammation can promote the development of cancers such as feline vaccine associated sarcomas, feline post-traumatic ocular sarcomas, and colon and hepatocellular carcinomas in humans. In these cases, activating T_{regs} may be necessary to prevent the progression to cancer. Anti-tumor immunity or immunosurveillance is necessary to prevent the development and progression of cancers, through the recognition and elimination of tumor cells. Elimination of tumor cells is primarily dependent on Th1 and CD8+ T cells, and pro-inflammatory cytokines like IFN-γ. It is well established that immunosuppression results in an increase in viral-associated neoplasia. CD4+ T_{regs} initially respond to limit chronic inflammation; however, once tumors are established, their immunosuppressive effect limits anti-tumor immunity and promotes tumor cell growth. Higher numbers of T_{regs} are associated with a shorter time to treatment in patients with chronic lymphocytic leukemia (Weiss L, 2011). Increased expression of FoxP3 and higher numbers of FoxP3+ T cells is associated with a poorer prognosis and shorter time to recurrence in ovarian cancer (Wolf D, 2005), metastatic melanoma (Knol AC, 2011), and gastric cancer (Shen Z, 2010). Paradoxically, in humans, hepatocellular carcinoma is often associated with chronic hepatitis B or C infection. The proposed mechanism is that chronic, unresolved inflammation triggers tumor growth, angiogenesis, and tumor survival (Grivennikov SI, 2010). Additionally, autoimmune diseases are associated with the development of lymphoma, and colon cancer is associated with chronic intestinal inflammation and ulcerative colitis (Grivennikov SI, 2010). Interestingly, T_{regs} within the tumor microenvironment of most cancers are associated with a poor prognosis; however, high T_{reg} infiltration in colon cancer is associated with a favorable prognosis (Ladoire S, 2011). Importantly, this favorable prognosis is not associated with inactivation or loss of function of mismatch repair genes (reviewed in Ladoire, et al, 2011 (Ladoire S, 2011)). While TGFβ is required for activation of FoxP3, the addition of IL-6 results in activation of Th17 cells through the transcription factor RORC. Th17 cells produce IL-17 in the tumor microenvironment. IL-17 has an angiogenic effect, promoting cancer growth and survival, which is necessary for tumor progression. In conditions of excessive inflammation, IL-6 and TGF-β may inhibit T_{reg} function and promote the development of Th17 cells. A recent study by Tosolini et. al demonstrated that colorectal cancers with high numbers of Th17 have a significantly worse prognosis than those with high numbers of T_{reg} cells (Tosolini M, 2011). Although strategies to block T_{reg} function in the treatment of cancer to enhance tumor immunity may be effective for some cancers, they cannot be used as widespread treatments because of the dual role of T_{regs} in the development and progression of cancer.

4. Viral-mediated regulatory T cell induction

Regulatory T cells typically increase late in chronic viral disease to prevent a persistent inflammatory response and viral-mediated immunopathology. In fact, tissue-protective effects of T_{reg} were shown in models of respiratory syncytial virus, Friend virus, and West Nile Virus infection. Additionally, T_{reg} responses to viruses (and bacteria) form the basis of the "hygiene hypothesis." Infection with influenza A in suckling mice protected these mice as adults against allergy induced airway hyperactivity due to the expansion of allergen-specific regulatory T cells (Chang YJ, 2011). Additionally, regulatory T cells responses to

Mycobacterium spp. may provide the explanation for the decreased incidence of asthma and autoimmune diseases in developing countries. However, some viruses have exploited the regulatory immune response, and trigger T_{reg} activation early in the course of disease, leading to immune suppression and viral persistence. Viruses activate endosomal TLRs 3, 7, 8, and 9 (Rouse BT, 2010). Of those, only TLR 7, 8, and 9 are expressed in T_{regs} (Dai J., 2009). Rather than triggering pro-inflammatory cytokines like IFN-α or IFN-γ, persistent viruses often trigger production of IL-10 and TGF-β. For example, dendritic cells infected with Japanese encephalitis virus have increased production of IL-10 and decreased production of IFN-α and TNF-α. In addition, when these infected DCs are cultured with allogenic T cells, they also expanded the population of regulatory T cells (Cao S, 2011). Dendritic cells from lymphocytic choriomeningitis virus-infected mice and monocytes from people infected with hepatitis B, hepatitis C, and human immunodeficiency virus similarly produce increased levels of IL-10 (reviewed in (Rouse BT, 2010)). IL-10 blocks production of pro-inflammatory cytokines and chemokines, and down-regulates MHC class II expression. IL-10 can also inhibit pro-inflammatory cytokine signaling pathways such as NF-κB. In addition, IL-10 suppresses phosphorylation of STAT1 and induces suppressor of cytokine signaling 3 (SOCS3) expression by neutrophils and macrophages (Rouse BT, 2010). Protective immunity against hepatitis C virus is associated with a robust Th1 response and production of IFN-γ. However, approximately 85% of patients respond with IL-10-producing CD8+ and CD4+ T cells, and occasionally FoxP3+ T_{regs} (Wang J-P, 2010). These patients develop chronic HCV infection, while those that respond with a Th1 response clear the virus (Rouse BT, 2010). Hall et al showed that HCV-infected hepatocytes are capable of inducing T_{regs}. HCV-infected hepatoma cell lines were co-cultured with activated CD4+ T cells resulting in decreased production of IFN-γ and increased expression of CD25, CTLA-4, FoxP3, and LAP. These T_{regs} were able to suppress effector T cells and upregulate production of TGF-β. T_{reg} function and phenotype was inhibited by blocking TGF-β, suggesting that this phenomenon is also TGF-β dependent (Hall CHT, 2010). Early in disease, T_{regs}, TGF-β, and IL-10 production in HCV infection are associated with development of chronic infection. On the other hand, in patients already chronically infected with HCV, IL-10 production does appear to have a protective effect since patients with the highest level of IL-10 tend to have a better prognosis. Disease progression in human and simian immunodeficiency virus infection is associated with the loss of Th17 cells, and an increase in CD4+FoxP3+ T_{regs}. Surprisingly, the loss of Th17 cells was associated with increased immune activation. Investigators found that because Th17 cells were responsible for maintaining the integrity of the mucosal barrier in the intestine, loss of Th17 cells resulted in increased microbial translocation across the gut (reviewed in (Kanwar B, 2010). Both HIV and SIV infection trigger an increase in regulatory T cells that produce TGF-β1. This in turn triggers TGF-β1 signaling in fibroblasts resulting in production of chitinase 3-like1 (CHI3L1) and pro-collagen. CHI3L1 enhances maturation of the procollagen into collagen in lymphoid tissue fibroblasts resulting in lymphoid tissue fibrosis. Lymphoid tissue fibrosis limits access of lymphocytes to reticular cells and IL-7 which depletes naïve CD4+ T cells. This may be one mechanism of CD4 depletion in HIV (Zeng M, 2011).

Further evidence of the role of T_{regs} in chronic viral infections is seen in the mouse model of infection with lymphocytic choriomeningitis virus (LCMV). Infections with different strains of LCMV can either cause acute infection that is cleared within a week (Armstrong strain), or chronic infection in which the mice are infected for life (variant clone 13). In variant clone 13-infected mice, mice with a specific TCR (Vβ5) have more prominent activation and

expansion of T_{regs}. These T_{regs} expand from an existing T_{reg} -population and expansion is dependent on retrovirus-encoded superantigens in the mouse genome (Punkosdy GA, 2011). However, it is not known if the T_{reg} expansion is involved in establishing chronic infection in this model. These viruses and others have exploited the phenomenon of activation of T_{regs} in response to infection by triggering T_{reg} proliferation early in disease progression. T_{reg} activation allows them to evade the host immune response and persist in the host. Using animal models to understand the mechanism of T_{reg} activation and expansion is vital to developing strategies to combat some of the persistent viral diseases that are not controlled well by vaccination.

5. The pig as an immunological model

Pigs provide a powerful tool in viral immunology studies, including the study of both innate and adaptive immunity. Germ free and gnotobiotic pigs can be relatively easily derived by cesarean section, and since pigs have epitheliochorial placentation, there is no interference by maternal antibody if the pigs are removed from the dam before suckling (Butler JE, 2009),(Butler JE, 2007). Although outbred, the pig is large enough that all *in vitro* tests can be done using cells from the same animal. Additionally, litter sizes are very large, decreasing genetic diversity of individual animals. Like humans, each individual can be treated as a biological unit (Butler JE, 2009), and using isolator piglets can decrease environmental variables. Pigs have digestive and respiratory systems, as well as T cell receptor and light chain repertoires that are similar to humans (reviewed in Butler, et al., 2009(Butler JE, 2009)). Importantly, porcine dendritic cells (DC) resemble human DCs, making them ideal to study pathogen responses relevant to humans (Paillot R, 2001; Raymond CR, 2005; Summerfield A, 2009). Additionally, porcine regulatory T cells function similarly to humans.

6. Porcine regulatory T cells

While regulatory T cells had been described and characterized in humans and mice since 1995 (Sakaguchi S, 1995), they were not demonstrated in pigs until 2008 (Käser T, 2008a, b). Although FoxP3 expression has been found in cells without suppressive activity in mice (Chen X, 2011), FoxP3 remains the most relevant phenotypic marker for T_{regs} in pigs. Identification and characterization of these cells was made possible by the fact that the anti-mouse monoclonal antibody FJK-16s (eBiosciences, San Diego, CA) cross-reacts with porcine regulatory T cells (Käser T, 2008b). The majority of FoxP3+ cells are also CD25+; however, in contrast to the findings of Käser et. al, we identified a small percentage of porcine FoxP3+ cells that do not express CD25. Besides CD4+ T_{regs}, FoxP3 expression was also found on CD4-CD8α+ T cells, as well as CD4+ T_{regs} that also expressed CD45RC (Käser T, 2008a), CD8α, and MHC-II (Käser T, 2008b). Our understanding the mechanism of porcine T_{reg} suppression is still in its infancy. A recent publication by Käser et al demonstrated that T_{reg} suppression can occur in any one of three ways: 1) cell-contact dependent, 2) production of IL-10 or TGF-β, or 3) by competing for IL-2 (Käser T, 2011). Interestingly, the authors showed that IL-10 was produced by $CD4+CD25^{dim}$ cells, which have lower suppressive activity in swine (Käser T, 2008a). This suggests that IL-10 is likely produced by activated Th2 cells rather than regulatory T cells.

7. Regulatory T cells and pig viral diseases

7.1 The immune response to porcine reproductive and respiratory syndrome virus

Since the initial description of porcine reproductive and respiratory syndrome (PRRS) in the USA in 1987 (Collins JE, 1992; Keffaber, 1989), the disease has been shown to be endemic in many swine producing countries, and is now considered to be the most important disease of swine worldwide (www.prrs.org,(Xiao Z, 2004)). In the USA alone, economic losses caused by PRRS virus (PRRSV) infection are estimated to total $560 million (www.prrs.org). PRRSV is a single-stranded, positive sense RNA virus in the *Arteriviridae* family, order *Nidovirales* (Cavanaugh, 1997). Other *Arteriviridae* include lactate dehydrogenase-elevating virus, equine arteritis virus, and simian hemorrhagic fever virus (Cavanaugh, 1997). Within a susceptible herd, reproductive failure due to PRRSV infection can range from sporadic abortions to abortion storms that may persist within the herd for up to 6 months (Rossow, 1998). Third-trimester exposure may manifest as late-term abortion, or stillborn, partially autolyzed, or mummified fetuses (Rossow, 1998). Neonatal infection results in severe dyspnea and tachypnea, and mortality of up to 100%, while disease in weaned pigs is primarily due to pneumonia and secondary bacterial or viral infections (Rossow, 1998). In addition to clinical disease, PRRSV infection is associated with decreased local cellular immunity, resulting in increased susceptibility to secondary bacterial and viral infections, including *Streptococcus suis*, *Haemophilus parasuis*, *Mycoplasma hyopneumoniae*, *Salmonella choleraesuis*, and swine influenza virus (Riber U, 2004; Rossow KD, 1995; Zeman D, 1993). Piglets infected with PRRS in utero have a decreased innate immune response to bacterial pathogens (Riber U, 2004). Riber and colleagues showed that in utero infection with PRRSV inhibits the phagocytic ability of blood macrophages against *Salmonella* spp., and inhibits the oxidative burst capacity of alveolar macrophages (Riber U, 2004). Additionally, both PRRSV infection and vaccination decreases the efficiency of vaccines against *Mycoplasma hyopneumoniae* (Thacker EL, 2000) and porcine pestivirus (Suradhat S, 2006). Infection and vaccination with PRRSV induces a rapid, non-neutralizing antibody response, and an early, weak gamma interferon (IFN-γ) response (Meier WA, 2003; Wesley RD, 2006). The initial IFN-γ response is not PRRSV-specific and may be a result of activation of natural killer cells (Wesley RD, 2006). A PRRSV-specific T lymphocyte IFN-γ response does not appear until at least 2 weeks after infection (Xiao Z, 2004). The IFN-γ response gradually increases and plateaus at 6 months postinfection, and is associated with a slow increase in neutralizing antibody (Lopez OJ, 2004; Meier WA, 2003). Protective immunity is associated with both an IFN-γ and neutralizing antibody response; however, peak viremia and shedding occur before development of neutralizing antibody and IFN-γ (Lopez OJ, 2004). Acute infection is characterized by high viral load in alveolar and tissue macrophages, and may last up to one month. The acute infection is followed by persistence of lower levels of virus in lymphoid tissue and then clearance after several months (Lopez OJ, 2004). The cause of the delayed IFN-γ and neutralizing antibody response resulting in persistent infection is unknown. Meier et al. were unable to enhance the induction of PRRSV-specific IFN-γ secreting cells and generation of neutralizing antibody using an adjuvant that enhances the immune response to pseudorabies modified live vaccine (Meier WA, 2003). These data suggest that the virus somehow modulates the immune response to not only delay the response to the virus itself, but to also decrease the ability to mount a protective response against secondary infection. The ability to induce a rapid IFN-γ response is not only important for viral clearance, but also heterologous protection by vaccination (Díaz I, 2006; Martelli P, 2009).

Current vaccine strains do not provide adequate heterologous protection because of their inability to stimulate an adequate IFN-γ response. One reason for the inadequate IFN-γ may be due to the ability of PRRSV to stimulate regulatory T cells *in vitro* (Silva-Campa E, 2009). The mechanism of immune modulation by PRRSV is unknown. PRRSV infection results in a significant upregulation of IL-10 expression in peripheral blood mononuclear cells and pulmonary alveolar macrophages in vivo and in vitro, and the upregulation of IL-10 is increased significantly with concurrent *M. hyopneumoniae* infection (Suradhat S, 2003; Thanawongnuwech R, 2004). The increase in IL-10 expression correlates with an increased percentage of lymphocytes in bronchoalveolar lavage cells, suggesting that the lymphocytes are involved in cytokine production in the lungs (Suradhat S, 2003).

7.1.1 Immune modulation mediated by interleukin-10

Low levels of interleukin-10 (IL-10) stimulate the proliferation of B cells, and activate natural killer (NK) cells and CD8+ cytotoxic T cells (Vicari AP, 2004). However, the primary action of IL-10 is to inhibit inflammatory cytokines and antagonize the function of antigen presenting cells, including immature dendritic cells (DC) (Enk, 2005). In humans and mice, exposure of immature DCs to IL-10 in vitro results in decreased surface expression of MHC class I and II molecules, reduction of costimulatory molecules, and inhibition of pro-inflammatory cytokines including IL-1β, IL-6, TNFα, and IL-12 (Enk, 2005). Additionally, IL-10 inhibits the synthesis of pro-inflammatory cytokines, the production of nitric oxide, and MHC class II expression by macrophages (Fiorentino DF, 1991; Gazzinelli RT, 1992). Since IL-12-mediated production of IFN-γ by pulmonary alveolar macrophages reduces PRRS viral titers in the lungs and serum (Carter QL, 2005), inhibition of IL-12 synthesis by IL-10 likely enhances the occurrence of natural disease. IL-10 affects innate immunity by inhibiting the response to Toll-like receptors (TLR), including TLR7 and TLR8 that recognize single-stranded viral RNA (Vicari AP, 2004). IL-10 - treated DCs also induce the proliferation of regulatory T cells (T_{regs}) as well as antigen-specific anergy in CD4+ and CD8+ T lymphocytes (Enk, 2005). Importantly, IL-10 not only plays a role in the development of type 1 T_{regs} (Tr1), but is also one of the primary mechanisms by which T_{regs} inhibit effector T lymphocyte function (Vicari AP, 2004). In previous experiments, we have shown that PRRSV infection increases the number of CD4+CD25+FoxP3+ regulatory T cells in the lungs and PBMC of pigs (LeRoith, unpublished). Others have shown that the induced T_{regs} produce TGF-β, consistent with a Th3 phenotype,(Silva-Campa E, 2009) indicating that the cells are not only increased, but are also functional. Since intracellular viral ssRNA is recognized by TLR7 and 8, and TLR7- and 8-signalling downregulates T_{regs} (Dai J, 2009), it is unlikely that this increase in T_{reg} numbers is merely a result of infection.

Which components of the virus are responsible for T_{reg} proliferation are unknown, but are currently under investigation by our group. Importantly, we were able to demonstrate that T_{reg} induction by PRRSV results in increased susceptibility to natural *Mycoplasma hyopneumoniae* infection (LeRoith T, 2011). In this study, pigs were inoculated with a virulent strain of PRRSV and a modified live vaccine that was derived from the same strain. In attenuation of this virus to produce the vaccine strain, approximately 30% of the mutations were in the replicase region (ORF 1)(Yuan S, 2001) and the majority of the mutations in this region were silent. Another 35% of the mutations were in the structural proteins, and the majority of mutations resulted in conservative or non-conservative amino acid changes(Yuan S, 2001). We hypothesized that even with changes in the non-structural and

structural proteins that decrease the pathogenicity, the mutations did not alter the virus's ability to stimulate T_{regs}. Consistent with our hypothesis, we found that, although attenuated, the vaccine strain did not differ from the parent strain in its ability to activate T_{regs}. Although the animals were protected against PRRS challenge, animals in the attenuated vaccine group did not differ from animals in the virulent group in the severity of *M. hyopneumonia*-mediated disease (Table 2) (LeRoith T, 2011). Similar to previous findings that infection with wild type PRRSV or vaccination with PRRS MLV vaccines has been shown to decrease the efficacy of *M. hyopneumoniae* vaccines (Thacker EL, 2000), inoculation with all three PRRSV in this study resulted in activation regulatory T cells and likely decreased the ability of the pigs to mount an effective anti-bacterial immune.

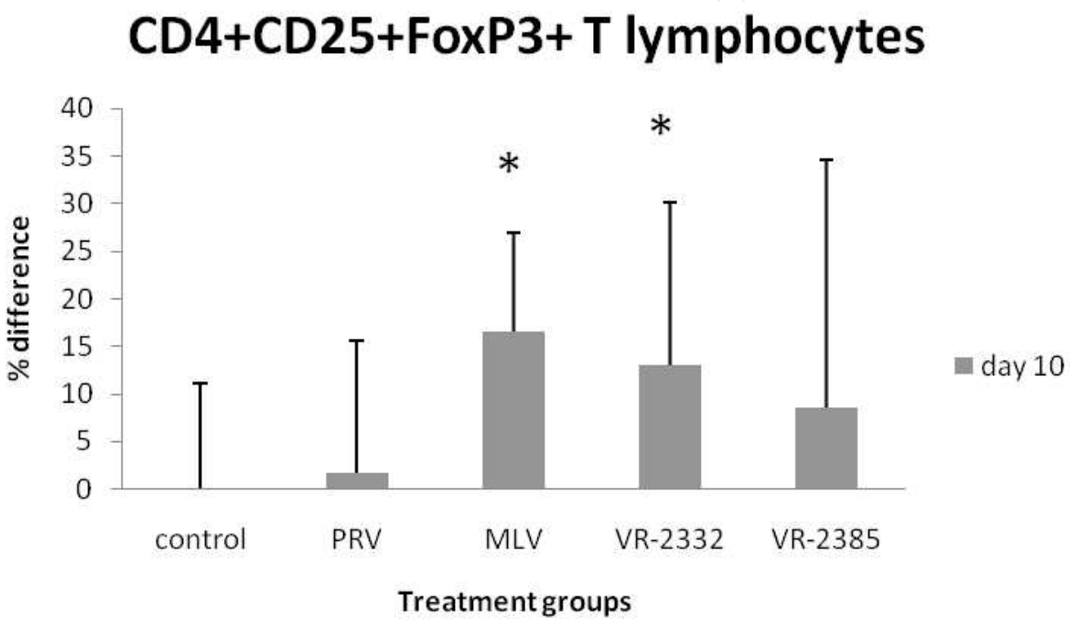

Fig. 3. Modified live virus vaccine and PRRSV infection significantly increases regulatory T cells 10 days post infection. The graph represents mean differences in regulatory T cells as determined by flow cytometry. Error bars represent standard errors. *= significantly different from the control ($p < 0.05$). PRV, pseudorabies virus; MLV, modified live virus vaccine; VR-2332, reference strain of porcine reproductive and respiratory syndrome virus; VR-2385, pathogenic strain of porcine reproductive and respiratory syndrome virus. (modified from (LeRoith T, 2011))

Importantly, vaccine efficacy appears to be related to the ability to stimulate IFN-γ production. Also, efficacy against heterologous virus challenge seems to correlate more with the ability to stimulate IFN-γ than homology of the vaccine strain to the infective strain. Current vaccines fail to protect against other strains (Mateu E, 2007), which may be due to their inability to stimulate IFN-γ production. Our study was the first to show the correlation between vaccine induction of T_{regs} and increased susceptibility to bacterial infection. Although T_{regs} that are induced by PRRS *in vitro* produce TGF-β (Silva-Campa E, 2009), the induction of T_{regs} may indirectly result in IL-10 production, a phenomenon that is well established in the PRRS literature (Feng WH, 2003; Suradhat S, 2003). Production of IL-10 instead of IFN-γ by the MLV vaccine strain would lead to a lack of heterologous protection,

and decreased efficacy of other vaccines, as seen by other authors (Thacker EL, 2000). Our results suggest that mutations in the vaccine strain that result in attenuation of the virus do not alter the virus's ability to stimulate T_{regs} (LeRoith T, 2011). This information can help us design vaccines in which the T_{reg}-stimulating epitopes can be mutated or deleted in order to stimulate a robust virus-specific IFN-γ response, and provide protection against heterologous strains (LeRoith T, 2011).

Treatment Group	Number of pigs with lung lesions	Lung lesion scores
Control	3/5	2.2 ± 0.96
PRV vaccine	5/7	2.67 ± 0.78
PRRSV MLV vaccine	7/8	3.14 ± 0.78**
PRRSV VR-2332	8/8	3.75 ± 1.06*
PRRSV VR-2385	5/8	3 ± 1.2

* Significantly different from the control (p = 0.024)
**Trend towards a significant difference from the control (p = 0.086)

Table 2. Incidence and severity of *Mycoplasma hyopneumoniae* microscopic lung lesions ((LeRoith T, 2011))

7.2 Small single-stranded circular DNA viruses

Porcine circovirus 2 (PCV2) is a small, single stranded, non-enveloped, circular DNA virus in the family *Circoviridae*. PCV2-associated diseases are of the most economically important diseases in swine, and include post-weaning multisystemic wasting syndrome (PMWS) and porcine dermatitis and nephropathy syndrome (PDNS) (Allan GM, 2000). Porcine circoviruses are widespread in the United States pork industry, and can often be isolated from both pork products and human feces (Li L, 2009). The contamination of human rotavirus vaccines by porcine circovirus type 1 and type 2 led to the temporarily suspension of the licensed rotavirus vaccines [http://www.virology.ws/2010/03/22/porcine-circovirus-dna-in-rotavirus-vaccine/]. Although PCV2 has been recognized as necessary to produce PCVAD, it is difficult to experimentally reproduce the disease with PCV2 alone (Magar R, 2000),(Allan GM, 2003). Typically infection by other viruses, immune stimulation, or vaccination is required to reproduce clinical disease (Krakowka S, 2001). Other small, single stranded, circular DNA viruses infecting both humans and other animals are of the genus Anellovirus, including Torque teno virus (TTV) and TTV-like mini virus (TLMV) (Biagini, 2004). TTV is ubiquitous in the human population; however no specific disease has been linked to TTV infection. Interestingly, TTVs are more frequently reported in malignant biopsies from human compared to controls (zur Hausen H, 2009) and are associated, at least epidemiologically with liver disease, respiratory disease, cancer, and blood disorders (Okamoto, 2009). Additionally, higher TTV viral loads are found in patients with systemic lupus erythematosis (SLE) and idiopathic inflammatory myopathies (Gergely P Jr, 2006). Swine TTV in conjunction with a respiratory virus has also been shown to produce PDNS without PCV2 in gnotobiotic pigs (Krakowka S, 2008), producing lesions not seen with the respiratory virus alone. How TTV and other circoviruses contribute to disease is unknown, but there is evidence that anelloviruses affect both innate and adaptive immunity and can impact how the infected

host can respond to other pathogens (Maggi F, 2009). Some authors suggest that the role of TTV in carcinogenesis may be due to its effect on antitumoral immunity (zur Hausen H, 2009). Other small, single-stranded DNA viruses include human bocavirus, human parvovirus 4, and parvovirus B19 (B19). B19, the causative agent of Fifth disease in children, typically causes self-limiting disease in immunocompetent individuals; however, virus has been shown to persist in the bone marrow several years after primary infection (Servant-Delmas A, 2010). The mechanism of persistence is unknown. PCV2 is ubiquitous in the swine industry, and genetically similar strains have been isolated from both diseased and healthy pigs. There is overwhelming evidence that PCV2 has an immunomodulatory effect by infecting macrophages and dendritic cells (DC's) and inducing DC maturation (Vincent IE, 2005). Pigs with PMWS have higher viral loads of PCV2 (Rosell C, 1999),(Rovira A, 2002),(Liu Q, 2000), suggesting that disease is associated with enhanced PCV2 replication. One of the major contributors to the development of PMWS is co-infection with porcine reproductive and respiratory syndrome virus (PRRSV). Pigs with PMWS have an increase in monocytes, the presence of low-density immature granulocytes in peripheral blood; and a decrease in CD4+ and CD4+CD8+ T lymphocytes and B lymphocytes (Darwich L, 2002), (Segalés J AF, 2001). Pigs co-infected with PCV2 and PRRSV have more severe lymphoid depletion and enhanced PCV2 replication and tissue distribution (Allan GM, 2000; Harms PA SS, 2001; Rovira A, 2002), suggesting that the interaction between the two viruses is important in the pathogenesis of clinical disease. The effect of the interaction between the two viruses on the immune system is not well understood. It has been suggested that immune stimulation by PRRSV enhances PCV2-mediated disease (Krakowka S, 2001). However; PRRSV, both infection and vaccination, has been shown to non-specifically dampen the immune response to other infectious agents (Suradhat S, 2003; Thacker EL, 2000). Additionally, a protective effect of porcine parvovirus and erysipelas vaccination against PMWS was shown in piglets born to PCV2 infected sows, further supporting the idea that factors other than immune stimulation may be involved in clinical disease. Importantly, when PMWS is produced by a combination of PCV2 and PRRSV, although current vaccines against PCV2 are able to decrease the severity of PMWS-associated lesions, the vaccines alone are ineffective at completely diminishing the lesions to those of PRRSV infection alone (Opriessnig T MD, 2008). The contribution of the immune effects of each virus in producing clinical PMWS is unknown. PRRSV infects and replicates in alveolar macrophages and dendritic cells, resulting in IL-10 production and proliferation of regulatory T cells. PCV2 is taken up by DCs and alveolar macrophages but does not replicate in these cells and has no effect on them other than to increase differentiation of DCs. Importantly, generally co-infection by both viruses is needed to produce PMWS. Presumably, PCV2 may enhance differentiation of DCs, thereby increasing the number of cells available for PRRSV infection, resulting in increased IL-10 production, and regulatory T cell activation. Since T_{reg} activation is associated with a decreased IFN-γ response, and IFN-γ is necessary for protective immunity against PCV2, PRRSV-mediated activation of regulatory T cells may then dampen the immune response to PCV2, resulting in increased virus replication and clinical disease. We are interested in determining if the effects of PCV2 on DC maturation and PRRSV-mediated activation of T_{regs} is enhanced in pigs with endemic PCV2 infection, or if PCV2 infection at the time of PRRSV infection is necessary for developing PMWS. Our data shows that PCV2 is able to induce regulatory T cells (T_{regs}) *in vitro* (Fig 4), and this effect is enhanced by the addition of a second virus, PRRSV (Cecere T, manuscript under review).

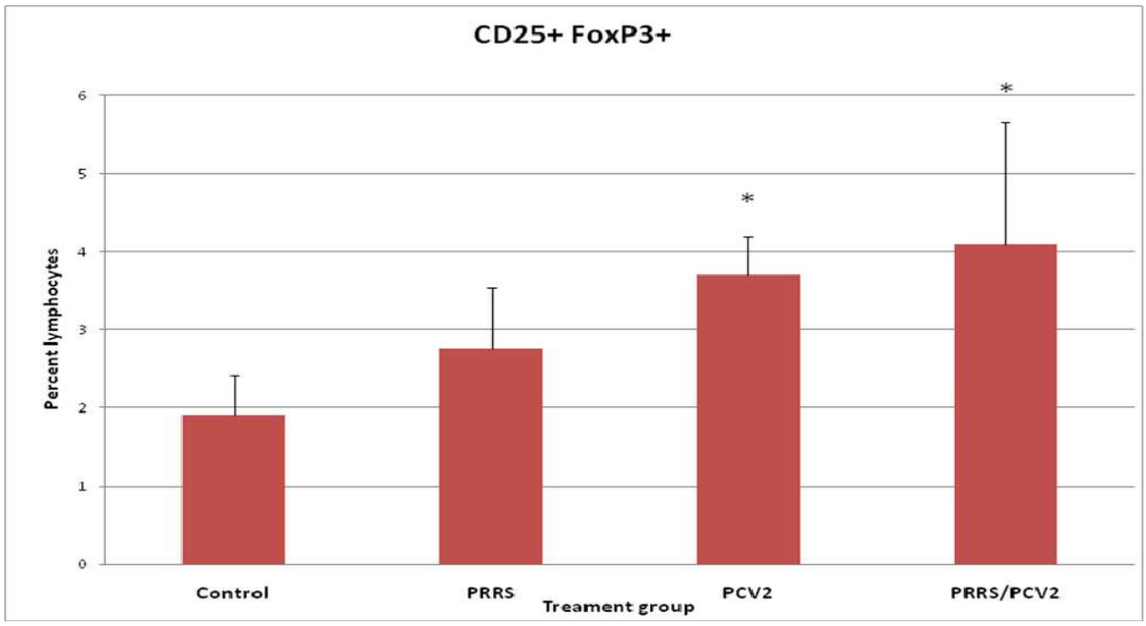

Fig. 4. PCV2 and PCV2/PRRSV co-infection of porcine dendritic cells results inactivation of CD25+FoxP3+ T lymphocytes *in vitro* compared to the control ($p < 0.05$).

What is unknown is whether or not chronic or persistent PCV2 or acute infection is associated with more severe pulmonary immunosuppression (as defined by T_{reg} activation and suppression of effector T cell function, IL-10 production, and suppression of IFN-γ production), leading to more severe manifestation of PMWS. It is also not yet clear if pigs persistently infected with PCV2 are at a higher risk of developing PMWS when infected with PRRSV than pigs acutely infected with PCV2 and PRRSV. Additionally, it is not known if acute PCV2 infection in pigs already persistenly infected with a different PCV2 genotype is associated with a higher incidence of PMWS when infected with PRRSV.

8. Conclusion

Regulatory T cells are critical for maintaining immune tolerance and immune homeostasis by protecting against devastating autoimmune disease and overwhelming inflammation. Without these subsets of T cells, animals quickly succumb to inflammatory or autoimmune diseases. The dual role of Tregs fits well into the perspectives proposed by Khatami that unresolved inflammation is the loss of balance between the "Yin" or tumoricidal and "Yang" or tumorigenic arms of acute inflammation (Khatami, 2008, 2009, 2011). Tregs play a vital role in preventing what Khatami terms "pathogen-induced immunological chaos," the "immune tsunami," or cytokine storm can then lead to inflammatory disease and cancer (Khatami, 2011). Immunologists are currently trying to identify strategies to enhance regulatory T cell activation to protect against inflammatory disease such as systemic lupus erythematosis and rheumatoid arthritis. However, some viruses, including PRRSV in pigs, have exploited these cells to enhance their survival and replication in the host. Activation of regulatory T cells by viruses dampens the immune response to the virus and allows them to replicate and persist in host tissues. Understanding the mechanism of T_{reg} activation by viruses is critical for identifying new strategies to prevent the effects on the host. In many

cases, activation of T_{regs} not only dampens the immune response to the virus, but non-specifically dampens the immune response to other pathogens. While the initial immune suppression likely plays a role in virus persistence, the non-specific immune suppression is one of the mechanisms by which secondary infection can occur. The complete effects of these viruses on the immune response of the host are still under investigation. The ability of certain viruses to stimulate regulatory provides valuable insight as to how viruses modulate the immune system. Understanding the mechanisms of T_{reg} induction is important in determining the contribution of RNA and small single-stranded circular DNA virus like PCV2, TTV, and parvovirus to the development of disease. Understanding the contribution of the immune response to viruses is also essential for vaccine development. PRRSV and PCV2 infection in swine provide a valuable animal model to study the immune effects of viruses because pigs are outbred and are immunologically similar to humans. Additionally, germ-free and colostrum deprived pigs are relatively easy to derive and function well in the experimental environment. With these models, we may be able to uncover some of the mysteries of the contribution of T_{regs} in chronic infectious and inflammatory disease.

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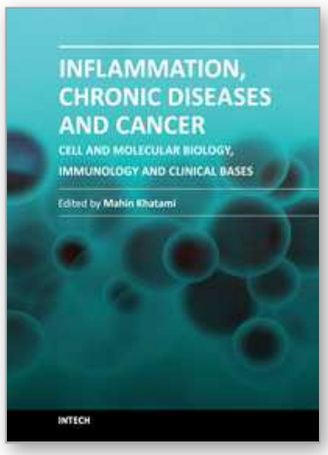

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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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