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Review Article

Regulatory T Cells in Avian Species

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ABSTRACT

The immune system protects the host from foreign pathogens while avoiding damage towards self–antigens. T regulatory cells (Tregs), a subset of T cells, specialize in immune suppression. A host immune response is a result of interplay between different components of the immune system. Interplay between Tregs and other components of the immune system will determine whether the outcome will be a persistent infection or successful pathogen clearance. Avian Tregs are characterized by the presence of both CD4 and CD25. Avian $CD4^+$ and $CD25^+$ cells produce high amounts of IL–10 and lack IL–2 mRNA; and suppress T cell proliferation *in vitro* through both contact–dependent and independent pathways. Avian Treg properties and numbers are influenced by infections and inflammatory status of the bird. Compared to mammals, avian Treg research is still in early stages of reseearch and, thus, extensive characterization of avian Tregs is required. In mammals, Treg–targeted therapy is applied for numerous situations, e.g. infections, tumors, autoimmune diseases, sepsis, shock, and vaccine. Similar to mammals, avian diseases will benefit from Treg–targeted therapy.

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INTRODUCTION

The immune system protects the host from foreign pathogens while avoiding damage towards self–antigens. T regulatory cells (Tregs), a subset of T cells, specialize in immune suppression. An adaptive immune response involves recruitment of effector (T and B) cells and Tregs. Activated immune cells, although essential for pathogen elimination, produce inflammatory cytokines and reactive oxygen species and can cause undesirable host damage (Belkaid and Rouse, 2005). Tregs protect the host from an excessive immune response and maintain self tolerance and mucosal tolerance (Workman et al., 2009). The balance between the effector cells and Tregs is important for optimal immune responses, the proper control of immune responses, and for establishing tolerance to self–antigens. Disruption in function of Tregs is a primary cause of autoimmune and inflammatory diseases. On the other hand, hyperactive Tregs can impair T cell, B cell, and other immune cell functions and, therefore, are implicated in impaired microbial defenses, pathogen persistence (Li et al., 2008), and impaired vaccine responses (Stober et al., 2005).

LACK OF UNIQUE MARKERS FOR TREGS

Among the different species in which Tregs have been characterized, human and mice Tregs have been extensively studied. Tregs constitutively express surface proteins like CD25, CD45, CTLA–4, HLA–DR, or GITR (Jonuleit and Schmitt, 2003), but these markers are not present in Tregs of all species or exclusive to Tregs in any particular species. Among the markers that can be defined to be unique to Tregs, the most commonly used marker is FoxP3 (Hori et al., 2003). FoxP3, a transcription factor, is essential for development and function of mammalian Tregs (Belkaid and Rouse, 2005). FoxP3 transcriptionally represses IL–2 and maintains suppressor functions of Tregs (Raimondi et al., 2007). Mutations in the FoxP3 gene cause autoimmune disease in scurfy mice (Brunkow et al., 2001) and such mice succumb to autoimmune pathology (Huter et al., 2008). Though absence or mutations in FoxP3 gene results in impaired Treg functions, presence of FoxP3 genes does not necessarily confer suppressive properties. Human T cells transiently express FoxP3, without expressing the suppressive properties or cytokines characteristics of Tregs (Gavin et al., 2006; Wang et al., 2007), though such T cells with transient FoxP3 expression with no suppressive properties are yet to be reported in other species. Our group reported that in chickens, $CD4^+CD25^+$ cells express suppressive properties even though *in silico* analysis failed to identify FoxP3 gene in the chicken genome (Selvaraj, 2013).

PROPERTIES OF TREGS

There are several different categories of suppressive cells, namely T regulatory–1 cells (Tr1) (Roncarolo et al., 2006), T helper 3 cells (Th3) (Carrier et al., 2007), $CD8^+FoxP3^+$ (Lu and Cantor, 2008), γδ T cells (Wildner et al., 1997; Wildner et al., 2004; Hoffmann et al., 2008), natural killer T cells (Smyth and Godfrey, 2000), and $CD4^-8^-TCR\alpha\beta^+$ (Zhang et al., 2000). The hall mark characteristics of $CD4^+25^+$ Tregs that differentiate $CD4^+25^+$ Tregs from the above mentioned suppressive populations are:

1. $CD4^+25^+$ Tregs originate as a separate lineage of cells in the thymus (Apostolou et al., 2002).
2. $CD4^+25^+$ Tregs are anergic (meaning they don't proliferate) *in vitro* (Thornton and Shevach, 1998).
3. $CD4^+25^+$ Tregs *in vitro* anergy and suppressive properties are reversed by exogenous IL–2 (Thornton and Shevach, 1998).
4. $CD4^+25^+$ Tregs express CTLA–4, LAG–3 and PD–1 (Yi et al., 2006).

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5. $CD4^+25^+$ Tregs produce high amounts of IL–10 (Dieckmann et al., 2001) and low amounts of IL–2 (Jonuleit et al., 2001; Takahashi et al., 1998).

TREGS DYSREGULATION DURING INFECTIONS

Tregs are a central player in immune suppression. Tregs are the only cells that can directly suppress every other component of the immune system. Tregs can suppress T effector cells, dendritic cells (Sakaguchi et al., 2008), B cells (Lim et al., 2005), macrophages (Tiemessen et al., 2007), NK cell (Frimpong–Boateng et al., 2010), mast cells (Gri et al., 2008), neutrophils and eosinophils (Thorburn and Hansbro, 2010). Given this "universal" action of Tregs, it is reasonable to assume that though Treg activity could be beneficial to the host, Tregs simultaneously inhibit host immunity and cause persistent infections. Treg dysregulation during persistent viral infections has been reviewed elegantly (Belkaid, 2007; Li et al., 2008). During viral infections, T cell response leads to viral clearance. However, many viruses induce persistent infections despite continuous measurable T cell responses (Rehermann et al., 1996), a situation in which Tregs may be involved (Ward et al., 2007).

Tregs suppress the functions of $CD4^+$ and $CD8^+$ cells in the host and cause persistent infections of Friends virus (Robertson et al., 2006; Zelinskyy et al., 2006), Vaccinia virus (Haeryfar et al., 2005), Human Immunodeficiency virus (Epple et al., 2006; Nilsson et al., 2006), Hepatitis C virus (Boettler et al., 2005; Bolacchi et al., 2006), Hepatitis B virus (Stoop et al., 2007; Xu et al., 2006), Human T Lymphotropic virus (Yamano et al., 2005; Oh et al., 2006), Cytomegalovirus (Aandahl et al., 2004), and Feline Immunodeficiency virus (Mikkelsen et al., 2010). The influenza virus might have evolved to induce Tregs. Influenza–specific–Tregs suppress cytotoxic T lymphocytes by blocking $CD8^+$ cell expansion. Tregs, stimulated with hemagglutinin antigen, expand more rapidly than $CD8^+$ T cells and are highly suppressive in mice (Chappert et al., 2010). In humans, Treg numbers increase while $CD4^+$ cell numbers, B–lymphocytes numbers, and macrophage IFNγ and TNFα production decrease post H1N1 infection (Giamarellos–Bourboulis et al., 2009). Tregs inhibit proliferation and IFNγ production of influenza–specific CD8 in the local environment (Lund et al., 2008; Khatri et al., 2010). Treg dysregulation is present during influenza A infection in mice (Haeryfar et al., 2005). In chickens, $CD4^+CD25^+$ (Tregs) numbers increased following H9N2 avian influenza virus infection, but the authors could not explain the upregulated roles of Tregs during viral infection (Teng et al., 2006). The above studies strongly suggest the involvement of Tregs in augmenting the pathogenesis of avian influenza infections. Treg research with mammals suggests that the increase in Tregs percentage post–influenza infection might be a local effect rather than a systemic effect (Lund et al., 2008; Khatri et al., 2010). Tregs reduce accumulation of macrophages in the lungs of influenza A virus–infected mice (Antunes and Kassiotis, 2010).

Tregs express several toll–like receptors (TLR), which recognize pathogen–associated molecular patterns (Caramalho et al., 2003). Tregs express TLR3, which recognizes double stranded RNA present during viral infections (Qian et al., 2007). TLR3–mediated activation amplifies the suppressive properties of Tregs (Qian et al., 2007). In addition, the host damage that occurs during infection and inflammation activates Tregs (Belkaid and Rouse, 2005). Some pathogens have evolved to selectively induce Tregs (Wilson et al., 2005; Lysaght et al., 2007) and thereby impede host immune responses. Treg–mediated suppression of host immune cells prevents an effective immune response against pathogens. IL–10 and TGFβ produced by Tregs suppress $CD8^+$ effector cells against viral pathogens (Kinter et al., 2004). Tregs suppress IFNγ production by the host during an anti–viral response and thereby effectively impair the host defense against viral infections (Bolacchi et al., 2006). The role of Tregs in depressing a host immune response during viral infections has been confirmed by experiments that selectively target or deplete Tregs during viral infections.

ENHANCED ANTI–VIRAL IMMUNE RESPONSE FOLLOWING TREG DEPLETION/ABLATION

Depletion of Tregs using anti–CD25 neutralizing antibody relieves the *in vivo* suppression of an antiviral immune response and contributes to faster oncolytic viral clearance (Kottke et al., 2008). Depletion of Tregs enhances the activity of natural killer cells, activity of lymphokine–activated killer cells, and production of IFN (Kottke et al., 2008). Treg ablation enhances the virus–specific $CD8^+$ T cell numbers and production of IFN in the spleen of infected animal (Zelinskyy et al., 2009). Treg depletion results in reactivation of virus–specific T cells in chronically infected mice (Dietze et al., 2011). *In vitro*, anti–IL–10 antibodies, which are expected to abrogate Treg functions (Sun et al., 2010), increase viral antigen–specific T cell proliferation (Landay et al., 1996).

Tregs OF AVIANS

Tregs have been extensively characterized in several animals like baboons (Porter et al., 2007), cows (Seo et al., 2007; de Almeida et al., 2008), pigs (Kaser et al., 2008), cats (Lankford et al., 2008), and rabbits (Nesburn et al., 2007). We earlier identified and characterized chicken $CD4^+CD25^+$ cells as Tregs in chickens (Shanmugasundaram and Selvaraj, 2011b). Similar to the CD25 expression in mammals (Baecher–Allan et al., 2001), CD25 expression in chicken thymic $CD4^+$ cells was continuous in that cells express high, intermediate, or low levels of CD25, and the boundary between $CD25^{high}$, $CD25^{intermediate}$, and $CD25^{low}$ population is not clear (Shanmugasundaram and Selvaraj, 2011b). Chicken Tregs produce 29–fold higher IL–10 mRNA than non–Tregs. IL–10, an immunosuppressive cytokine, inhibits macrophages and dendritic cell functions (Fujio et al., 2010) and is a critical cytokine responsible for the suppressive properties of Tregs (Gangi et al., 2005). Similar to chicken Tregs, ducks (Shanmugasundaram and Selvaraj, 2012d) and turkey (Shanmugasundaram and Selvaraj, 2012e) $CD4^+CD25^+$ cells had higher IL–10, TGF–β, CTLA–4, and LAG–3 mRNA amounts than $CD4^+CD25^-$ cells from the respective species.

In chickens, Tregs initially appear at 16 d of embryonic development, and the first wave of Tregs preferentially migrates to the intestine (Shanmugasundaram and Selvaraj, 2012a). We identified that a single peritoneal injection of anti–chicken CD25 mAb decreases IL–10–producing Tregs in the intestine of chickens by approximately 80% (Shanmugasundaram and Selvaraj, 2012b). The depletion is temporary as Tregs return to their baseline levels at approximately 20 d post–CD25 injection. In ovo injection of 0.5 mg/egg of anti–chicken CD25 mAb at 16 d of embryonic development almost completely depleted circulating Tregs at hatch and that the birds remained depleted of Tregs until 25 d post–hatch. Chicks hatched from anti–chicken CD25–mAb–injected eggs had ~75% decrease in Tregs in the cecal tonsils at 16 d post–hatch (Shanmugasundaram and Selvaraj, 2013). Chicks hatched from anti–chicken CD25 mAb injected eggs also had no detectable amount of Tregs in cecal tonsils at 0, 3, and 5 d post–hatch (unpublished observations).

We have also characterized chicken Tregs during Salmonella (a gut pathogen like coccidia) lipopolysaccharide–induced inflammation (Shanmugasundaram and Selvaraj, 2011a; 2012c). The LPS injection increases $CD4^+CD25^+$ cell percentage

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approximately 2.5–fold in the spleen at 2 d post–LPS injection compared to the no–LPS–injected group, though the Treg numbers came back to normal levels at 5 d post–LPS injection (Shanmugasundaram and Selvaraj, 2012c). We evaluated the suppressive properties of chicken $CD25^+$ cells from LPS injected or control groups. At a Treg: T responder cell ratio of 1:1, $CD25^+$ cells only from 5 and 12d post–LPS injection were suppressive while $CD25^+$ cells from 2 d post–LPs injection were not suppressive. Chicken non–Tregs appear, therefore, to up-regulate CD25 transiently, with no suppressive properties, post–LPS treatment. The other possibility is Tregs undergoes extensive proliferation and lose suppressive properties post–LPS treatment. Because chicken Treg specific markers are not available, we cannot exclude either of the above possibility.

Compared to mammalian Tregs, research in avian Tregs are in earlier stages. Further characterization of avian Tregs will benefit poultry production. For example, avian Tregs, with anti–inflammatory potential, can be targeted to decrease inflammation and mortality during an immune response in commercial settings. In mammals, Treg–targeted therapy [anti–CTLA–4 (Gabriel and Lattime, 2007), anti–IL–2 (Kottke et al., 2008), anti–CD25 (Bielekova et al., 2004)] is applied for numerous situations, e.g. infections, tumors, autoimmune diseases, sepsis, shock, and vaccine. Similar to mammals, avian diseases will benefit from Treg–targeted therapy. A host immune response is a result of interplay between different components of the immune system. Interplay between Tregs and other components of the immune system will determine whether the outcome will be a persistent infection or successful pathogen clearance.

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