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Lymphocyte-Mediated Immune Regulation in Health and Disease: The Treg and γδ T Cell Co-Conspiracy

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Abstract

The significance of lymphocytes functioning to mediate immunological tolerance has garnered increasing appreciation during the last several decades. CD4+ CD25+ α/β T cells have arguably been the most extensively studied regulatory lymphocyte to date, perhaps owing to the dramatic phenotype observed mice and humans with mutated Foxp3. However, emerging studies suggest that the lineage of regulatory lymphocytes is quite robust. Most notably, while γδ T cells are more traditionally regarded as mediators of cytotoxic function, they are beginning to be regarded as potential negative regulators of immunity. While regulatory γ/δ T cells may possess a degree of transcriptional overlap with 'classical Tregs', there remains less clarity in regards to the mechanisms driving the suppressive potential of these cells. In this review, I will discuss the role of Tregs in establishing tolerance in the steady state as well as disease, and how their accumulation and function may be modulated by myeloid cells in the local microenvironment. I will also discuss the necessity to extend our understanding of the regulatory nature of γδ T cells, which may lead to the unearthing of novel paradigms of immunity, perhaps most notably with respect to cancer.

Introduction

Studies of regulatory immune cells of lymphoid origin over the several decades have focused on regulatory T cells (Tregs), T cells which are classically defined by their expression of CD4, CD25, and the transcription factor Fork head box P3 (Foxp3) in concert with their ability to exert immunological suppressive function. These suppressive lymphocytes were initially discovered upon the observation that mutation of the *Foxp3* gene leads to dysregulated lymphoproliferation, mulitorgan leukocyte infiltration, and autoimmunity in mice and humans (Brunkow et al. 2001, Godfrey et al. 1991, Godfrey, Wilkinson & Russell 1991). Over the years, the significance of these cells in modulating anti-viral immune responses as well as their ability to drive malignant progression through a variety of mechanisms has become apparent (Chevalier, Weiss 2013, Khaitan et al. 2016, Curiel et al. 2004). In addition to the direct cell-to-cell suppressive properties of Tregs, mediated by IL-10, TGF-β, and others (Vignali 2008), emerging evidence suggests these cells may

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function in complex with cells of myeloid lineage to function in a global immune suppressive network.

In addition to classical Tregs, the lymphoid lineage contains additional T lymphocytes which may function as regulatory cells in the appropriate stimulatory context. Developing studies in tumor immunology have identified gamma-delta (γδ) T cells as functioning under a suppressive program in order to dampen anti-tumor immunity and facilitate malignant progression. γδ T cells outnumber conventional αβ CD4+ Tregs in many solid tumors such as breast and ovarian cancers, yet they remain underinvestigated (Rabinovich, Conejo-Garcia 2016). Therefore, extending our understanding of the mechanistic properties driving the suppressive nature of such cells may lead to enhanced prognostic and therapeutic benefit.

‘Classical’ regulatory T cells

Tregs are a heterogeneous population, composed of CD4+ thymic-derived (nTreg) and peripherally induced Treg (iTreg). Differentiation of nTreg occurs in the thymus, while iTreg are generated from conventional naïve $CD4^+$ T cells due to the composition of their local microenvironment in peripheral tissue. The Treg-dependent transcriptional program has yet to be fully elucidated; it is, however, known that the suppressive function of murine Tregs is dependent on the activity of Foxp3 (Fontenot, Gavin & Rudensky 2003, Hori, Nomura & Sakaguchi 2003)While human Tregs do express Foxp3, its expression is not necessarily indicative of suppressive activity of $CD4^+$ T cells (Wang et al. 2007, Miyara et al. 2009, Hori, Nomura & Sakaguchi 2003). Foxp3 binds DNA through a winged helix-forkhead DNA binding domain and functions as a transcriptional repressor via a histone acetyltransferase-deacetylase complex (Li et al. 2007). Moreover, Foxp3 has been identified to interact with, and requires finely tuned expression of the NFATs, as well as NF-kB, and Runx1/AML1 for nTreg and iTreg development and function (Vaeth et al. 2012, Sumpter, Payne & Wilkes 2008, Ono et al. 2007, Bettelli, Dastrange & Oukka 2005).

In addition to their vital role in maintaining lymphocyte homeostasis, Tregs have been shown to contribute to the pathogenicity of chronic viral infections, such as hepatitis C virus (HCV). Ren et al. have recently demonstrated that NF-kB-mediated induction of miR146a, resulting in a Th2 response in the setting of chronic HCV infection, thus driving immune tolerance and viral persistence (Ren et al. 2016).

Interestingly, in the setting of human immunodeficiency virus (HIV) infection chronic immune activation is a key factor of disease progression (Hearps et al. 2014). It has therefore been hypothesized that increasing viral load may result in such comorbidity due to a deleterious effect on Tregs. However, clarifying the role of Tregs in HIV progression has been difficult due to conflicting studies of their suppressive function, and the unreliability of the phenotypic markers used to identify these cells in HIV infection (Chevalier, Weiss 2013). It has recently been demonstrated, however, that functionally suppressive Tregs, which coexpress the transcription factors Foxp3 and Helios, have been shown to selectively increase in HIV positive patients suppressed with antiretroviral therapy, while Foxp3+ Helios-Tregs remained similar to healthy adults (Mercer et al. 2014). In a corroborating study, it was shown that T cells coexpressing Foxp3 and Helios are bona fide memory Tregs

in perinatally infected children with HIV, and are positively correlated with falling percentages of CD4+ T cells and increasing HIV plasma viremia and systemic immune activation (Khaitan et al. 2016). The identification of such functionally suppressive Tregs should now drive studies to identify the role of these cells in protecting or impairing the host's clinical state during HIV infection.

The role of Tregs in Cancer

Growing interest in the immunobiology of cancer, coupled with the recent clinical advances in the treatment of several distinct cancers using immunotherapy has promoted an interest in elucidating the functional role of Tregs in cancer. The accumulation of Tregs has been correlated with a poor prognosis in patients with a variety of solid cancers, such as ovarian, breast, and hepatocellular carcinoma, among others (Curiel et al. 2004, Bates et al. 2006, Petersen et al. 2006, Gao et al. 2007, Griffiths et al. 2007, Hiraoka et al. 2006, Perrone et al. 2008), in which their cell intrinsic suppressive mechanisms generally utilize TGF-β and IL-10, as has been discussed elsewhere (Mougiakakos et al. 2010). Additionally, Foxp3+ CD4+ regulatory T cells have been identified within the microenvironment of cutaneous squamous cell carcinoma (cSSC) (Schipmann et al. 2014, Lai et al. 2016). cSSC is an interesting tumor from an immunological point-of-view, as these tumors are generally well infiltrated by lymphocytes, yet such lymphocytes appear incapable of rejecting this neoplasm. Indeed, it has recently been demonstrated that Foxp3 expressing T cells are responsible for mediating immune suppression within this microenvironment, and are associated with tumor cell metastatic potential (Lai et al. 2016).

Myeloid cells, in addition to Tregs, are also now well appreciated to polarize to a suppressive phenotype and to blunt immunity in cancer-bearing hosts. In fact, the cell intrinsic role of alternatively activated macrophages (M2), dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs) have been well characterized as suppressing type I immunity in cancer (Manjili 2012, Marvel, Gabrilovich 2015). However, the crosstalk between myeloid and lymphoid regulatory networks is less well characterized; the major contribution of Tregs to anti-tumor immune suppression and tumor escape may be the result of their function within a larger immunosuppressive network. Huang et al. initially described the role of immature immunosuppressive myeloid cells (now commonly regarded as MDSCs) to induce the development of Foxp3+ regulatory T cells in vitro, as well as in the MCA26 murine model of colon carcinoma (Huang et al. 2006). Such MDSCs mediated development of Tregs was shown to be dependent on IL-10 and IFN-γ, but not IL-13. Subsequent studies in cancer have also outlined the significance of CD40 expressing MDSCs functioning to activate Tregs (Pan et al. 2010), the ability of MDSCs to promote tolerance in B-cell lymphoma by expanding Tregs (Serafini et al. 2008), and the role of monocytic MDSCs ($CD11b^{+}$, $Ly6G^{lo}$, $Ly6C^{+}$) in recruiting Tregs in a CCR5-dependent manner in the murine B16 melanoma model (Schlecker et al. 2012).

Furthermore, while the role of tumor-associated neutrophils (TANs) within the tumor microenvironment remains controversial and is likely context dependent (Deryugina et al. 2014, Eruslanov et al. 2014, Fridlender, Albelda 2012, Uribe-Querol, Rosales 2015), however, recent studies have outlined a role for TANs in the promotion of Treg infiltration

into tumor beds. In a study by Mishalian et al. utilizing a murine model of malignant mesothelioma, it was demonstrated that 'N2' TANs were the major mediators in the production of CCL17 (Mishalian et al. 2014). The generation of this chemokine gradient was directly associated with an increase in the frequency of infiltrating Foxp3+ Tregs. This was recently corroborated in work by Zhou et al. in which TANs derived from human hepatocellular carcinoma patients were determined to produce CCL2, in addition to CCL17, to promote Treg infiltration into the tumor bed (Zhou et al. 2016). Such studies outline the role of myeloid cells, particularly MDSCs and neutrophils, in framing the immunosuppressive network in cancer.

The paradox of tumor-associated Tregs

While the accumulation of Foxp3 expressing CD4+ T cells is generally associated with poor prognosis in cancer patients due to their ability to suppress antitumor immunity, it has paradoxically been demonstrated that the presence of Tregs in some tumors may promote a beneficial response for the host in human colorectal cancer (Ladoire, Martin & Ghiringhelli 2011, Salama et al. 2009). As proposed by Ladoire et al. (Ladoire, Martin & Ghiringhelli 2011), the prognostic value of Foxp3+ tumor-infiltrating may be due to the unique microenvironment of colorectal cancer. Wherein inflammation driven by Th17 cells responding to the local gut flora may facilitate malignant progression, a higher frequency of Tregs may function to suppress Th17-specific inflammatory responses and thus delay malignant progression and result in a better prognosis. In recent years, the contribution of the gut microbiota to the modulation of anti-tumor responses has become increasingly clear (Rutkowski et al. 2015, Viaud et al. 2013, Iida et al. 2013). Thus, while a plethora of evidence correlates the infiltration of Tregs into the tumor bed with poor prognosis, the functional outcome of tumor-infiltrating Tregs appears to be highly dependent on the nature of the tumor microenvironment, and warrants intensive study. Therefore a degree of caution should be utilized in strategies invoking depletion of Tregs to improve patient responses.

γδ T cells: atypical regulatory T cells

In addition to classical regulatory T cells, i.e. CD4+ αβ T cells expressing Foxp3, the emergence of additional regulatory T cell subsets has deepened our understanding of the role of lymphocytes in the maintenance of tolerance. As early as 1989 it has been suggested that non-αβ T cells may function as immune suppressors (Patel et al. 1989), and the direct suppressive function of murine and human γδ T cells has subsequently been demonstrated (Kuhl et al. 2009, Rutkowski et al. 2015, Casetti et al. 2009, Hua et al. 2013). Such suppressive potential of Vδ1 and Vδ2 regulatory γδ T cells has been linked with the expression of Foxp3 (Hua et al. 2013, Casetti et al. 2009), which appears to occur under the influence of TGF-β-dependent signaling (Kang et al. 2009).

γδ T cells account for 5% of circulating T cells, and are mainly composed of the Vδ9Vγ2 subset. Phosphorylated metabolites have been recognized to potently activate γδ T cells in humans, and recently it was discovered that a member of the butyrophilin family, butyrophilin-3A1 (BTN3A1), effectively presents phosphorylated metabolites resulting in γδ T cell activation (Vavassori et al. 2013, Harly et al. 2012). Intriguingly γδ T cells have

been shown to display both cytotoxic and regulatory functions, most notably in the setting of cancer.

More recently it has been demonstrated that γδ T cells may function in a tertiary manner to promote immune suppression. Rezende et al. have described the migration of thymic γδ T cells to the periphery, where they upregulate membrane-bound TGF-β1 and acquire a regulatory phenotype (Rezende et al. 2015). The regulatory function of such cells manifests via their ability to function as antigen presenting cells, which then induce classical CD4+ Foxp3+ regulatory T cells.

Furthermore, the expression of the transcription factor, Helios, which is widely expressed in conventional CD4+ Tregs, is also expressed in a significant percentage of freshly isolated circulating γδ T cells; Peters et al. have demonstrated a direct role of Vδ2 γδ T cells to inhibit the proliferation of CD4+ αβ T cells in a contact-dependent manner, wherein ~33% of peripheral γδ T cells constitutively expressed the transcription factor Helios (Peters et al. 2014). These studies suggest a degree of transcriptional overlap amongst conventional CD4+ Tregs, and suppressive γδ T cells, however the transcriptional program regulating the suppressive function regarding both of these cell types has yet to be fully defined.

The role of γδ T cells in cancer

It has been suggested that γδ T cells may have potential applications for cancer immunotherapy (Legut, Cole & Sewell 2015), owing to their ability to target tumor antigens irrespective of HLA haplotype and thus potentiating their application as ‘off-the-shelf’ cellular immunotherapy. For instance, γδ T cells have demonstrated cytotoxic function against colon cancer and myeloma cells, (Wu et al. 2015, von Lilienfeld-Toal et al. 2006). Additionally, recent studies have suggested a cytotoxic role for Vδ9Vγ2 T cells in patients with melanoma; wherein an elevated frequency of circulating as well as tumor infiltrating Vδ9Vγ2 T cells in early stage tumors were correlated with decreased mortality and disease relapse (Toia et al. 2016). Interestingly, however, it was observed that melanoma patients with a poor prognosis possessed a dramatically increased frequency of tumor-infiltrating Vδ9Vγ2 T cells in late stage disease. While no functional studies were performed, such observations may represent the acquisition of a suppressive phenotype due to modulation of the tumor microenvironment (Toia et al. 2016).

Indeed, there is mounting evidence suggesting that tumor-associated γδ T cells function as drivers of malignancy. In fact, it has become increasingly clear that γδ T cells possess the potential to potently suppress anti-tumor immunity (Rutkowski et al. 2015). In fact, tumor-derived factors, such as IP-10, have been implicated in driving the accumulation of γδ T cells into the tumor bed in human breast cancer; conversely, inhibition of γδ trafficking to tumor beds has demonstrable enhancement of anti-tumor immunity (Ye et al. 2013). In addition, evidence presented by Rutkowski et al. implicates a role for galectin-1 secreting γδ T cells in dampening antitumor immunity, both in transplanted and autochthonous tumor models (Rutkowski et al. 2015).

Intriguingly, the study by Rutkowski et al. unveiled an immunosuppressive network in which microbially driven TLR-5-dependent IL-6 functioned to mobilize MDSCs; these MDSCs were found to drive γδ T cell-derived galectin-1 in order to facilitate malignant progression (Rutkowski et al. 2015). Likewise, a recent study by Coffelt et al., implicates a role for IL-17 producing γδ T cells in polarizing and expanding TANs in tumor-bearing mice (Coffelt et al. 2015). Such TANs were demonstrated to specifically suppress CD8+ T cells, thus promoting metastasis in a murine model of breast cancer. These studies therefore suggest that not only do γδ T cells have the ability to function as direct suppressors of anti-tumor immunity, but that they may also function in a broader suppressive network to drive malignant progression.

Concluding Remarks

The immunoregulatory axis required for maintaining immune tolerance in a variety of biological scenarios has been the subject of intense study which now serves as the backbone of immunology. While the study of regulatory lymphocytes has, in general, predominately focused on the cellular-intrinsic suppressive activity of classical CD4+ α/β T cells, emerging data suggests that these cells operate within a broad immunosuppressive network involving regulatory myeloid cells as well a regulatory γ/δ T cells. At least in the setting of cancer, the accumulation and acquisition of suppressive function by Tregs is enhanced by the activity of both myeloid cells and γ/δ T cells in the local environment. It is also clear that future studies are needed to address the paradox of tumor-infiltrating γδ T cells in order to unearth the regulation of their cytotoxic as well as their suppressive function. While strides have been made with regards to the understanding of the mechanisms regulating the activation of these cells, it remains unclear if such stimuli confer a cytotoxic or suppressive phenotype within the context of the tumor microenvironment. Achieving clarity with regards to the phenotypic regulation of these cells, as well as the immunosuppressive mechanisms they employ, has the potential to facilitate improved immunotherapeutic applications for patients with cancer.

In closing, additional efforts to delineate the cellular intrinsic and extrinsic mechanisms driving the immunosuppressive network will further facilitate our understanding of this fundamental facet of immunity, and is likely to generate novel therapeutic approaches in settings of disease.

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