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Review

The significance role of regulatory T cells in the persistence of infections by intracellular bacteria

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ABSTRACT

Regulatory T cells (Treg cells), are considered as effective immune cells playing a key role in immune response during cancers, autoimmune and infectious diseases. Regulatory T lymphocytes are divided into two main subgroups: natural Treg cells that generated during maturation in the thymus and have the suppressive activity that is critical for the establishment and maintenance of homeostasis in the body and induced Treg cells (iTreg) that are originated from naive T cells following the self-antigen recognition. In recent years, the roles of Treg in immune responses to microbial infections have received increased attention in researches. Several reports suggested the pivotal role of Treg cells in controlling responses to bacterial infections and demonstrated the impact of regulatory cells on one or more stages in the pathogenesis of bacterial infections. In this review, we describe the significance of regulatory T cells in the immunopathology of bacterial infections by focusing on specific bacterial infections including Mycobacteria, *Listeria monocytogenes*, and Bordetella pertussis. Moreover, suppressive mechanisms of regulatory T cells during bacterial infection including cell–cell contact, local secretion of inhibitory cytokines and local competition for growth factors will be discussed.

1. Introduction

The key role of the immune system is the protection of human bodies from invading pathogens with minimizing harm to the cells and tissues around the desired position. Among the various immune cells that are fighting against pathogens, regulatory T cells play an important role in controlling innate and adaptive immunity (Cohn, 2008; Mohammadnia-Afrouzi et al., 2017). Current knowledge regarding Treg cells is based on the analysis of experimental models that investigate Treg mediated immune responses in the fields of tolerance and autoimmune, tumor, and T cells hemostasis (Levine et al., 2017; Soltanzadeh-Yamchi et al., 2018; Tanaka and Sakaguchi, 2017; Khalili et al., 2018; Fehervari, 2014). However, the excessive immune response during infections might be associated with severe side effects which should be adequately controlled. In this context, many studies were performed to identify the mechanisms involved in the suppressive function of Treg cells on immune responses during bacterial infections. Therefore, in this review, we discuss the importance of regulatory T cells in the immunopathology of bacterial infections by focusing on specific bacterial infections including Mycobacterium tuberculosis, *Listeria monocytogenes*, and Bordetella pertussis.

2. Regulatory T cell

Treg cells were described for the first time in the early 1970s and were called suppressor cells (Mohammadnia-Afrouzi et al., 2017; Reichert et al., 2017). In spite of many efforts, this issue was abandoned in the late 1980s due to problems in the identification and isolation of inhibitors(Hill et al., 2007). In 1995, Sakaguchi et al. showed that the interleukin-2 receptor α-chain (CD25) could serve as a phenotypic marker for CD4 + Treg cells(Sagaguchi et al., 1995). These observations led to the resumption of Tregs research and this research field has evolved rapidly ever since. At present, various subsets of both $CD25^+$ and $CD25^-$ Treg cells populations have been described (Tiwari et al., 2018). The various Treg cells subtypes are now divided based on cell surface markers, cytokines production, and action mechanisms. In addition to the expression of CD25 in Treg cells, these cells also exhibit other activation markers. However, it should be noted that none of these markers exclusively identify Treg cells and they can also be expressed on activated T cells and various antigen-presenting cells (APCs).

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More recent studies have identified the transcription factor forkhead box P3 (FOXP3) as a more exclusive intracellular marker for the identification of Treg cells (Olsson et al., 2018). Also, FOXP3 is also a crucial transcription factor for the development and functionality of CD4 + CD25+ Treg cells (Minton, 2018). Despite the experimental documents for the existence of Treg cells, the phenotype and function of these cells still remain unclear. According to the experimental models used to analyze Treg cells, they can be divided into two major cell populations: naturally occurring Treg cells and induced Treg cells (Karkhah et al., 2018; Chavele and Ehrenstein, 2011).

2.1. Natural regulatory Tcells (nTregs)

The nTregs consist of $CD4^+$ T cells that mature in the thymus to regulatory T cells. They represent about 10% of the peripheral $CD4^+$ T cell population and are distinguished by the high expression of CD25 and, although low expression levels of CD45 RB (MR et al., 2016; Ebrahimpour et al., 2017; Zelenay et al., 2005; Benoist and Mathis, 2012). Additional surface molecules that have been associated with at least subpopulations of naturally occurring Treg cells are GITR (TNFRSF18), CD152 (CTLA-4), CD103 (αE-integrin) and CD134 (OX40) (Vernal and Garcia-Sanz, 2008).

However, none of these molecules is exclusive to Treg cells, and there is evidence for $CD4^+$ T cells and even for $CD8^+$ T cells that express regulatory functions. Therefore, this is a major challenge for identifying a specific and reliable functional marker for these cells (van Olffen et al., 2009). In contrast to this, the expression of Foxp3 performs to be an exclusive and crucial attribute of naturally occurring Treg cells (Munn, 2010). Naturally occurring Treg cells need TCR signals for activation. Naturally occurring Treg cells appear to be mainly restricted by self-antigens. Despite intensive research, the mechanisms underlying the suppressive functions of naturally occurring Treg cells are still incompletely comprehended (Schmidt et al., 2012).

2.2. Induced regulatory T cells (iTregs)

The second subtype of Treg cells - induced Treg cells - represents $CD4^+$ T cells that have acquired their suppressor activity during in vitro or in vivo activation. The iTreg cells are derived from $CD4^+CD25^-$ T cells and show variable expression of CD25 and other surface markers described for naturally occurring Treg cells (Chatenoud, 2011; Schmitt and Williams, 2013). Induced Treg cells require TCR stimulation for induction of suppressive functions and demonstrate limited proliferation in vitro. Depending on the experimental sample, regulation by iTregs is mediated through TGF- β and IL-10 (Cao et al., 2010). Induced Treg cells indicate specificity for self or foreign antigens. According to the current concept, these cells are derived from regular $CD4^+$ T cells in the peripheral immune system (Workman et al., 2009; Lin et al., 2013; Gonçalves et al., 2010). Critical determining factors for the development of i Treg cells include the type and differentiation status of the APC and the cytokine milieu during activation. Antigen presentation by immature DC presence of IL-10 and/or TGF-β during T cell activation apparently promotes differentiation of $CD4^+$ T cells into iTreg cells (Belkaid and Oldenhove, 2008; Karkhah et al., 2018).

3. Mechanism of Treg suppression

All types of Treg cells, both natural and induced, need TCR to perform a suppressive function, but their activity seems to be non-specific (Corthay, 2009). However, the mechanism of action of these cells has not yet been clearly explained. Therefore, the difference between in vitro and in vivo conditions is controversial. The latest detection of inhibitory mechanisms can eliminate in vitro and in vivo divisions. As recently reviewed, suppressive mechanisms have several modes of regulation that can be divided to three groups (Fig. 1); cell–cell contact, local secretion of inhibitory cytokines and local competition for growth factors (Liberal et al., 2015; Vignali, 2012; Josefowicz et al., 2012).

3.1. Cell–cell contact

Several in vitro studies have demonstrated that CD4+ CD25+ Tregs suppress production of IFN-γ by inhibiting effector T-cell via direct cell-to-cell contact through the surface markers including GITR and CTLA-4 (Shalev et al., 2011). The ligation of CD80/CD86 on the effector cells after interaction with CTLA-4 on the surface of regulator cells can transmit suppressive signals and it results in inhibition of the effector T cell function(Walker, 2013). As stated, Treg cells express CTLA-4, but its essential role for Treg cells activity is not clear. Various mechanisms of Treg CTLA-4 dependent regulation have been identified, including the delivery of signals B7 on active target T cells and/or B7 binding on dendritic cells activating indoleamine 2,3-dioxygenase (IDO) (Sojka et al., 2008; Kahler and Mellor, 2009). Reduced tryptophan concentration in culture medium has been reported to be associated with decreased activation of T cells and T cell deletion (Mbongue et al., 2015; Mohammadnia-Afrouzi et al., 2017).

CTLA-4 competes with CD28 for binding to B7. The affinity of CTLA4 for binding to B7 was estimated to be about 10 folds higher than the affinity of CD28 for this ligand. T cells proliferation is inhibited by binding of CTLA-4 to B7, in other words, CTLA-4 plays an important role in T-cell peripheral tolerance (Jain et al., 2010). These results indicate that CTLA-4 plays a functionally significant role in Treg cells suppressive activity. On the other hand, CTLA-4 knockout mice appear to have cells expressing the Treg-specific transcription factor FOXP3 which are capable of suppression. These observations reveal that CTLA-4 is not the only accessory molecule required for Treg cells function (Yamaguchi et al., 2013).

An interesting inhibitory pathway to enter the Treg cells field is the modulation of cyclic adenosine monophosphate (cAMP) levels in the target cells. Elevation of cAMP levels has long been associated with inhibition of cellular proliferation and differentiation and in lymphocytes causes' selective inhibition of cytokine gene expression, including IL-2, in part through protein kinase A (PKA)-blockade of nuclear factor-KB (NF-KB) activity or the activation of the transcriptional repressor inducible cAMP early repressor (ICER) (64). Recent evidence indicates that Treg cells can increase cAMP levels in the target cells through at least two mechanisms: directly by delivery of cAMP and indirectly by the local generation of adenosine (Rueda et al., 2016). In some studies, it was suggested that Treg cells, which express high levels of cAMP, transfer cAMP into the activated target cells via gap junctions (Bopp et al., 2009). Binding of adenosine to the adenosine A2A receptor can increase intracellular cAMP and in these current studies Treg cells generated adenosine suppressed proliferation and cytokine production by effector T cells (Ernst et al., 2010). However, it has not yet been concluded how the cAMP contributes to varying of Treg cell's inhibitory effects (Sojka et al., 2008).

3.2. Secretion of inhibitory cytokines

Studies show that the mechanism of secreted cytokines from T cells is inhibited by Treg cells. Other in vitro studies show that Tr1 cells and Th3 cells contribute to this suppressive activity of Treg cells by the production of immunosuppressive cytokines (IL-10, TGF-β) (Arce-Sillas et al., 2016). Therefore, TGF-β and IL-10 play an important role in the function of Treg cells. The participation of these cytokines might be affected by many physiological factors, including the nature of the target organ and the amount of inflammation. In fact, some autoimmune diseases are caused by the lack of IL-10 (e.g., colitis), while other autoimmune diseases are IL-10 independent (e.g., gastritis) and/or afflicted with TGF-β deficiency (e.g., diabetes) (Oh et al., 2017; Lee et al., 2007; Liu et al., 2003). Also, Treg cells prevent DC maturation and activation by secretion of cytokines, both in mice and human