Regulatory T Cells in Allergic Asthma

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T regulatory cells (Tregs) are a subset of T cell leukocytes that play a key role in modulating the immune system, maintaining tolerance to self-antigens and suppressing excessive immune responses that go on to harm the host. Much like T helper (Th) cells, Tregs belong to a broader class of CD4+ T cells that develop from pluripotent hematopoietic stems cells in the bone marrow and mature in the thymus. Within the context of allergic asthma, Tregs are central to the process of pulmonary regulation by continuously combatting both immunogenic and harmless antigens. By releasing cytokines such as IL-10 and TGF-ß, Tregs modulate the inflammatory Th2-type immune response which, when dysregulated can drive asthma development as well as the hallmark asthmatic signs- airway hyperresponsiveness, bronchoconstriction, and gland hyperplasia/ hypersecretion. This review will explore the function of Tregs as well as their modulatory role within allergic asthma.

ALLERGIC ASTHMA

According to Statistics Canada (2014), over 2.4 million Canadians aged 12 and older have been diagnosed with asthma.[1] Currently, it is thought that asthma is responsible for over 250,000 deaths annually and billions of dollars in healthcare expenditure, through both direct medical costs and indirect losses in labour productivity.[1,2] Asthma is a highly heterogeneous disease as its clinical presentation and immunological profile can vary substantially among those diagnosed.[3] There are many possible phenotypes of asthma such as allergic asthma, which is typically characterized by long term inflammation of the airways in response to inhaled substances, known as allergens.[3] Allergens such as pet dander, dust and mold, can cause difficulties in breathing and lead to a combination of hallmark symptoms such as bronchoconstriction, eosinophilia, airway remodeling, and airway hyper-responsiveness (AHR).[4] Diagnosis of allergic asthma requires demonstration of elevated serum immunoglobulin E (IgE) antibody levels as well as a positive skin-prick test, which identifies reactions to allergens.[5] Challenging subjects with inhaled allergen to which they have been sensitized, induces immediate release of bronchoconstriction mediators from airway mast cells and basophils.

REGULATORY T CELLS

T cells play an active role in cell-mediated immunity, an adaptive process of developing antigen (Ag)-specific T cells to eliminate viral, bacterial, or parasitic infections or malignant cells.[6] Before mature T cells gain a highly specialized function, they arise from pluripotent hematopoietic stem cells within the bone marrow and undergo lineage commitment based on stress signals.[6] Upon maturation, these cells, now known as naive T cells, circulate within the blood and do not become activated until foreign antigenic peptides come in contact with professional APCs such as dendritic cells (DCs), B cells and macrophages.[6] Upon activation, T cells will differentiate in an antigen-specific manner, and then proliferate and migrate to sites of inflammation. Many different subtypes of T cells exist, each with specialized roles in the body (Figure 1).[6] Regulatory T cells (Tregs) are a class of $CD4^+$ T cells (T-helper cells), which do not directly kill infected cells but activate cytotoxic cells to attack infected cells or stimulate B cells to secrete antibodies. Tregs play a key role in asthma but also aid in the maintenance of peripheral tolerance, modulation of immune responses and prevention of autoimmune diseases.[7] Although the role of Tregs is still not yet well understood, a review by Corthay et al. has outlined a framework of their major functions. These roles include the prevention of autoimmune and immunopathological diseases—by establishing and maintaining immunologic self-tolerance—as well as the induction of maternal tolerance to the fetus and regulation of other immune effectors and T cells.[7]

REGULATORY T CELLS IN ALLERGIC ASTHMA

Multiple interactions between leukocytes and stromal lung cells are central to the process of homeostatic pulmonary regulation which

continuously combat both immunogenic and harmless antigens.[8] Both structural and Tregs take part in a major pathway proposed to contribute to airway immunity.[8] Although, other immunological cells have shown regulatory potential, this paper will discuss Tregs and their ability to regulate and suppress immune activity in the lungs.[9]

A study by Goswami et al. demonstrated that airway epithelial cells can initiate an immune response upon exposure to peptide-breaking enzymes such as Retinal dehydrogenase 1 (RALDH-1), a retinoic acid producing enzyme that promotes development of immunosuppressive Tregs.[9] Since RALDH-1 is regulated by epithelial-derived matrix metalloproteinase-7 (MMP-7), a deficiency in MMP-7 leads to augmented levels of Tregs in the lung and thus, an attenuated response to the allergen challenge.[9] A cytokine synthesis inhibitory factor, interleukin 10 (IL-10), is an anti-inflammatory cytokine that is central in this process.[8] Tregs such as $CD25^{+}Foxp3^{+}$ Treg cells are not the only cells that secrete IL-10; $CD8^{+}$ T cells, and $CD4^{+}$ T helper cells (Th) cell population, namely Th1 cells, Th2 cells, and Th17 cells do so as well.[10] An abundance of studies have proposed a protective role of IL-10 in respiratory homeostasis.[10] Secretion of IL-10 by innate immune and antigen-specific T-cells, such as IL-10 secreting type 1 Treg (Tr1) cells have shown to limit inflammation and pathology in response to viral and bacterial pathogens by inhibiting Th1 response.[11]

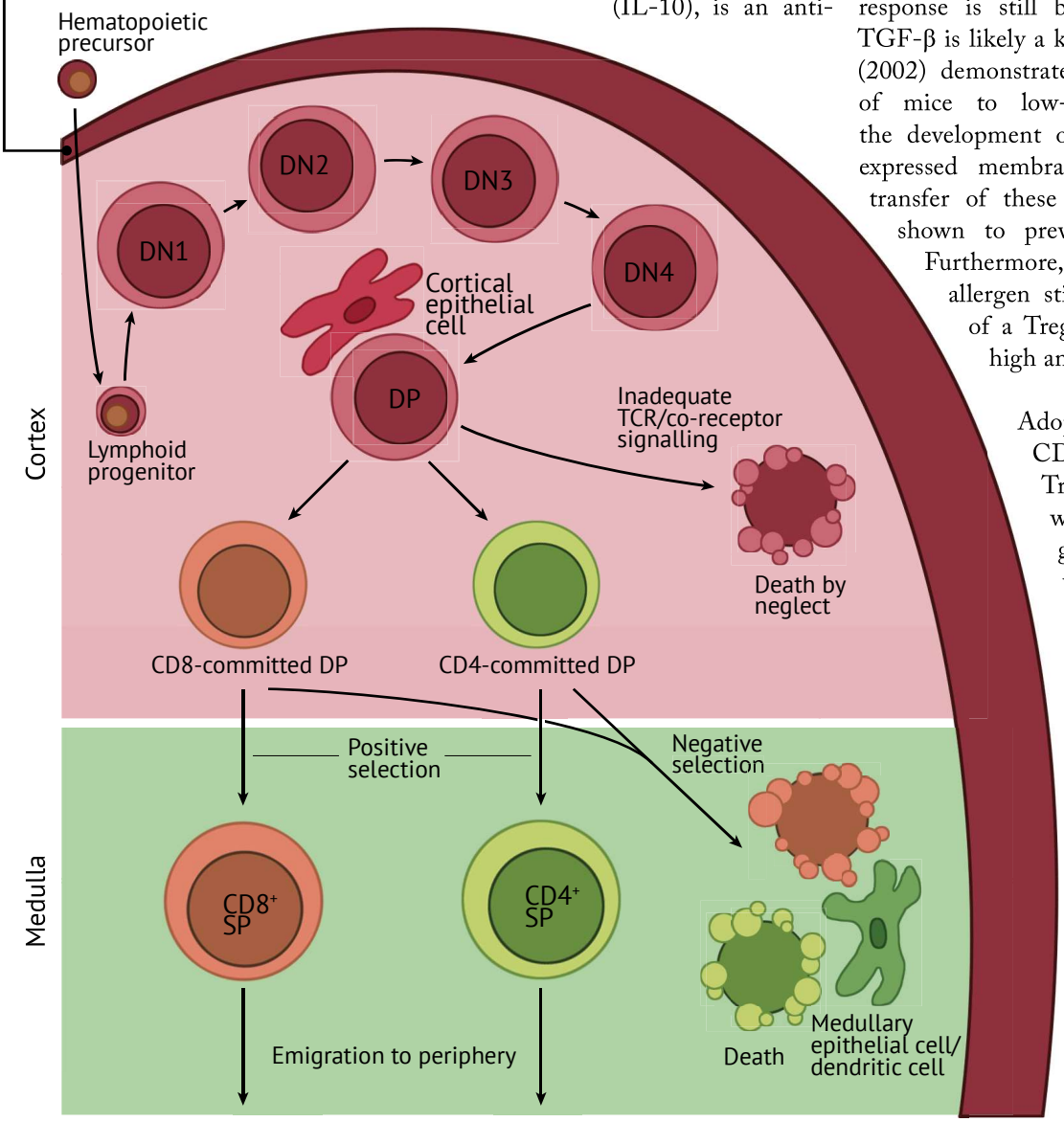

FIGURE 1:
Differentiation of T-cells within the thymus. Committed lymphoid progenitors arise in the bone marrow migrate to the thymus. Early committed T cells lack expression of T-cell receptor (TCR), CD4 and CD8, and are termed double-negative. Through a series of developments, these cells gain specific T-Cell receptors and markers. The process of positive and negative selection to allow for cells that are not harmful to self-cells and can successfully read MHC.[13]

While IL-10 has a clear role in inflammation resolution, TGF-β is known to both initiate acute airway remodeling when induced by Th2 cytokines and initiate resolution of inflammation through tissue repair and remodeling.[12] Whether chronic asthma develops as a result of poor inflammatory resolution or due to aberrant tissue repair response is still being researched, however TGF-β is likely a key mediator.[12] Akbari et al (2002) demonstrated that repeated exposure of mice to low-dose allergen promoted the development of a Treg population that expressed membrane-bound TGF-β.[13] The transfer of these cells to naive mice was shown to prevent allergic sensitization. Furthermore, a higher dose of inhaled allergen stimulated the development of a Treg population that secreted high amounts of IL-10.[13]

Adoptive transfer of $CD4^{+}$ $CD25^{+}$ Treg cells, a class of Tregs with $CD25^{+}$ markers, was shown to suppress allergic inflammation and AHR via a mechanism dependent upon IL-10.[8] Importantly, when $CD4^{+}$ $CD25^{+}$ Tregs were given to a diseased individual, existing inflammation was downregulated and further airway remodeling was prevented.[14] On the other hand, depletion of $CD4^{+}CD25^{+}$ Tregs before sensitization to allergen was shown to magnify the severity of inflammation and AHR in the lungs.[14] Depletion of $CD4^{+}25^{+}$ Tregs

resulted in increased numbers of airway APCs especially dendritic cells, as demonstrated with higher expression of activation markers, major histocompatibility complex class II, CD80, and CD86 and enhanced potential to promote effector T cell proliferation.[8] Collectively, this information suggests that Tregs are implicated in regulation of allergic asthmatic immune symptoms, potentially through secretion of IL-10 and TGF-β and by restraining function of APCs such as dendritic cells.[8]

CURRENT TREATMENTS

Although the exact function, number of subtypes, and specific mechanisms pertaining to Tregs are currently being investigated, there are several treatments that can ameliorate allergic asthma symptoms by increasing or restoring Treg function.[8] Allergen immunotherapy involves administering increasing doses of an allergen to which a client is sensitized in careful clinical conditions in order to increase tolerance to this allergen.[8] Immunological studies have shown that immunotherapy can inhibit allergen-specific Th2 cell responses and promote an increased frequency of Treg IL-10-secretion immediately following therapy.[9] Other treatments include Vitamin D and corticosteroid administration which have been historically used for controlling symptoms.[8] Several studies have demonstrated that glucocorticoid treatment (both inhaled and systemic) correlates with increased IL-10 and Foxp3 gene and and/or protein expression in patients.[15] Glucocorticoids, along with the active form of vitamin D, 1α,25-dihydroxyvitmain D3, have shown to recruit IL-10-secreting tregs in both mouse models and humans.[16] This information collectively implies that broad-acting drugs such as corticosteroids or vitamin D can maintain, restore, or enhance Treg cell function in asthma through a mediatory capacity.[8]

FUTURE DIRECTIONS

Overall, there is a growing body of evidence suggesting a key role of Tregs in the intricate immunological homeostatic environment of the lung.[8] However, a stronger understanding of Treg pathways within lung homeostasis is needed. Evidence of other regulatory cell populations such as IL-10 secreting natural killer (NK) cells, IL-17-producing γδ and NK cells have shown to suppress antigen-specific effector function and may be implicated in pulmonary infections.[8,9] Furthermore, studies analyzing antigen-specific Tregs would be beneficial as currently, the exact subtypes and differentiation pathways of Tregs are not elucidated; therefore, studying the interaction between T cell lineage and environment may provide more insight.[7,8] Ultimately, further investigation into the developmental and maturation process of Treg cells, as well as their effector functions, will be required. This may provide a better understand the pathobiology of allergic asthma and novel therapeutic management strategies. ■

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Mr. John-Paul Oliveria is a PhD candidate in Medical Science at McMaster University, performing research in the cardio-respiratory lab under the supervision of Dr. Gauvreau. His research interests mainly include looking at the role of various B cell subtypes in allergic asthma. As an outstanding graduate student, Oliveria has been awarded both the Graduate Program Outstanding Achievement Award and a Graduate Student Teaching Assistant Excellence Award in May 2016.

EDITED BY AVRILYNN DING AND ARLINDA DENG

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