recruitment of Tregs to sites of immune inflammation, the relationship between Bregs and the gut microbiome requires further investigation.

Regulatory B cells

Breg cells can dampen inflammation by regulating the differentiation of T cells into Tregs. Bregs can attenuate inflammation through the secretion of IL-10 (Br1) and TGF-α (Br3). IL-10 has been shown to have an immunosuppressive effect through the dampening of Th2 inflammatory processes by binding to T cell receptors and blocking co-stimulatory signalling. Meanwhile, TGF-α binds T cell receptors to encourage the maturation of Tregs, which have the capacity to inhibit the activation of effector T cells. The disruption of TGF-α receptor signalling has been shown to increase susceptibility to allergic asthma development in mice, while IL-10 has been implicated in humans. In addition, it is thought that the inhibitory immunoglobulin, IgG4, secreted by Bregs, protects against the inflammatory action of IgE by interfering with allergen-IgE interactions and binding to excess allergen, as shown in Figure 1.[11,12,13]

Using mouse models of arthritis, Rosser et al. suggest that the gut microbiota may increase IL-1α and IL-6 production to encourage the differentiation of IL-10-producing Bregs in the spleen and mesenteric lymph nodes.[14] While only produced in conventionally housed mice, IL-1α and IL-6 directly promote Breg cell differentiation and IL-10 production. It has been observed that mice that do not have the IL-6 receptor (IL-6R) or IL-1 receptor 1 (IL-1R1) on B cells show lower levels of IL-10-producing B cells. Moreover, mice lacking these receptors develop more severe forms of arthritis compared to controls. Interestingly, Rosser et al. showed that the disruption of the gut microbiome through antibiotic treatment or changes in the sterility of housing conditions reduces the number and activity of Breg cells.[14] While these findings have been replicated in models of autoimmunity, further research still needs to be conducted in the context of allergic diseases.[15]

METHODS BY WHICH ONE CAN ACHIEVE MORE TOLEROGENIC CONDITIONS IN EARLY LIFE TO PREVENT ALLERGIC DISEASE WILL BE VITAL IN ALLEVIATING ECONOMIC BURDENS ON HEALTH SYSTEMS WORLDWIDE.

DISCUSSION

Given the increase in the prevalence of asthma over the past several decades, it is predicted that by 2025 the number of individuals affected worldwide will increase to 400 million people.[16] While it is thought that allergic asthma is the consequence of inappropriate immune activation in response to innocuous allergens, further investigation may reveal these immune responses to be appropriated by pathogenic microbiome compositions. Consequently, methods by which one can achieve more tolerogenic conditions in early life to prevent allergic disease will be vital in alleviating economic burdens on health systems worldwide. Finally, manipulating the early life environment to optimize the regulatory pathways of B cells provides a promising and necessary avenue for primary prevention strategies. ■

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EDITED BY ANNA GOSHUA AND ARLINDA DENG

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