New Aspects of the Involvement of B and T Cells in the Mechanisms of Immunotherapy

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Better understanding of the mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumors, organ transplantation, chronic infections and pregnancy is in an exciting development phase that may lead to a variety of targeted therapeutic approaches. Recent progress in the interaction between immune/inflammatory cell subsets via cytokines, particularly the extension of the knowledge on reciprocal regulation and counter balance between subsets of Th1, Th2, Th9, Th17, Th22, follicular helper T cells and different subsets of T regulatory cells, as well as corresponding and co-orchestrating B cell, NK cell, dendritic cell and innate lymphoid cell subsets bring new possibilities for immune intervention.

The pivotal role of Treg cells in inducing and maintaining immune tolerance has been demonstrated during the last 15 years, where their adoptive transfer was shown to prevent or cure several T-cell mediated disease models, including asthmatic lung inflammation, autoimmune diseases and allograft rejection. In addition, subsets of CD8+ T cells, γδ T cells, DC, IL-10-producing B cells, NK cells and resident tissue cells, which may promote the generation of Treg cells, may contribute to suppressive and regulatory events.

B cells contribute to immune responses essentially through antigen presentation to T cells, secretion of cytokines and production of antibodies after differentiation to plasma cells. When they receive the right survival signals plasma cells can reside for many years in dedicated niches in the bone marrow and continuously produce antibodies independent of exposure to antigen. Upon activation IgM+IgD+ naïve B cells may undergo class switch recombination (CSR) leading to the expression of IgA, IgG or IgE antibodies.

Human B cells express several toll like receptors (TLR) including TLR1, 6, 7,
8, 9 and 10. TLR7 (activated by single stranded RNA) and TLR9 (activated by hypomethylated CpG DNA) are the highest expressed TLRs on B cells. IL-10 is a key regulator of inflammatory responses and protects the host from tissue damage as a result of excessive inflammation. It suppresses antigen presentation through downregulation of class II major histocompatibility complex molecules and co-stimulatory molecules on antigen presenting cells. Furthermore it suppresses the production of pro-inflammatory chemokines and cytokines. On the other hand, IL-10 enhances the survival, proliferation, differentiation and isotype switching of human B cells. IL-10 augments IgG4 production, whereas it inhibits IL-4-induced IgE CSR. IL-10-mediated immunosuppressive functions of B cells have been described in murine models of autoimmunity, infection, and cancer. Patients treated for rheumatoid arthritis with the B cell depleting antibody rituximab who showed exacerbation of ulcerative colitis and development of psoriasis illustrate the relevance of immune regulatory functions of human B cells. Interestingly, an increase in IL-10-producing B cells also occurs during ultra rush high dose allergen-specific immunotherapy of venom allergic individuals by bee venom (BV-SIT). Regulatory B cells expressing IL-10 suppress immune responses and the lack or loss of regulatory B cells leads to exacerbated symptoms in experimental autoimmune encephalitis, chronic colitis, contact hypersensitivity, collagen-induced arthritis and non-obese diabetic mouse models. Another B cell-related immune regulatory response restricted to humans is induction of non-inflammatory IgG4 antibodies, which is characteristic for high dose antigen tolerance models. Several molecules including CD25 and PD-L1 were upregulated in IL-10-producing B cells. Br1 cells potently suppressed antigen-specific CD4+ T cell proliferation whereas other B cells did not. Furthermore we demonstrate that human Br1 cells show selectively increased production of IgG4. B cells specific for the major bee venom allergen phospholipase A2 that were isolated from beekeepers had increased expression of IL-10 and IgG4. Human Br1 cells may regulate humoral and cellular immunological tolerance through suppression of T cells responses and production of anti-inflammatory IgG4 antibodies.