LUXEMBOURG INSTITUTE OF HEALTH
RESEARCH DEDICATED TO LIFE

LECTURE SERIES & WORKSHOPS

INFECTION & IMMUNITY

PhD NextImmune Retreat

08 MAY 2019
Wednesday

LECTURE
Location: Hotel Parc Alvisse, 120, route d'Echternach, Dommeldange
10.20 - 11.10 am

MEET THE SPEAKER/LUNCH
Location: Hotel Parc Alvisse, 120, route d'Echternach, Dommeldange
12.10 - 1.30 pm

7 8 9 10 11 12 1 2

SPEAKER

Prof Mübeccel AKDIS

Head of Immunodermatology,
Swiss Institute of Allergy and Asthma Research (SIAF), Davos
Titular Professor in Zurich University Medical Faculty

HOST:
Department of Infection and Immunity (LIH)

RESPONSIBLE LIH SCIENTIST:
Prof Dr Markus Ollert (markus.ollert@lih.lu)

For organizational purposes, all external participants should register for the lecture and/or lunch by email to florence.henry@lih.lu

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REGULATORY AND ANGIOGENIC NOVEL B CELL SUBSETS

ABSTRACT

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. 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. 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 class switch recombination. 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 showed exacerbation of ulcerative colitis and development of psoriasis illustrating 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. 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 were from the IgG4 isotype. Human Br1 cells may regulate humoral and cellular immunological tolerance through suppression of T cell responses and production of anti-inflammatory IgG4 antibodies.

Several B cells subsets have been described that express distinct polarized cytokine profiles. B cells were immortalized by transduction with Bcl6 and *Bcl-XL*, allowing *in vitro* expansion of B cells under IL-21 and CD40L stimulation. Clones were generated from immortalized B cell pools and transcriptomes were measured using RNAseq. Hierarchical clustering based on cytokine expression profiles was performed followed by differential expression analysis between clusters. A cluster of IgG4 clones that expressed pro-angiogenic cytokines including VEGF, CYR61, ADM, FGF2, PDGFA and MDK was identified. Supernatants from these clones efficiently promoted HUVEC tube formation demonstrating their pro-angiogenic potential. Further characterization led to identification of CD49b and CD73 as surface markers associated with pro-angiogenic B cells. The *in vivo* relevance of this novel B cell sunset was demonstrated by the observation that circulating CD49b+CD73+ B cells showed significantly increased frequency in melanoma patients and eosinophilic esophagitis patients, two diseases that are associated with angiogenesis. In conclusion, here we demonstrated a novel B cell subset with angiogenic property.