City University of Hong Kong
Department of Biomedical Sciences
presents a seminar

"DENDRITIC CELLS: FROM INNATE IMMUNITY TO AUTOIMMUNE DISEASES"

by

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Abstract

Dendritic cells (DCs) are professional antigen presenting cells and are key immune cells of innate immunity. After antigen encounter, activated DCs migrate to lymphoid tissue and present processed antigen to T cells. Through MHC restricted antigen binding to T cell receptor, interactions between co-stimulatory molecules and cytokine production, DCs determine the outcome of T effector differentiation. DCs bridge innate and adaptive immunity and are crucial regulators of immune tolerance in the periphery. In the steady state, immature DCs with low co-stimulatory molecule expression induce and maintain peripheral tolerance. In autoimmunity, self-antigens are presented by DCs to autoreactive T cells which provide B cell help, leading to production of autoantibodies and formation of immune-complexes. Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease that affects predominantly young women and is more common among Asians than Caucasians. Circulating monocytes in SLE are characterized by hyperactive DC-like phenotype with enhanced antigen presentation capability. We described a c-type lectin receptor expressed on myeloid cells that was aberrantly expressed on monocytes in active SLE patients leading to production of cytokines involved in inflammation and promotion of pro-inflammatory immune response.

While corticosteroid and immunosuppressive agents are mainstay of treatment of SLE patients and are associated with significant adverse effects, cell-based therapy targeting DCs emerges as novel therapeutic option in the restoration of immune tolerance. Ex vivo manipulation of DCs to acquire tolerogenicity has been studied extensively in the past few years in the field of autoimmunity and transplant immunology, exploiting the properties of immature DCs in the induction of immune tolerance. Using pharmacological treatment of monocyte-derived DCs from SLE patients, we were able to generate tolerogenic DCs of semi-mature phenotype that possessed suppressive effect on T cell activation and proliferation, and induced IL-10 producing T cells with regulatory function on allogeneic T cells. These tolerogenic DCs also downregulated pro-inflammatory cytokine production by naïve and memory T cells. With a view to designing cell-based therapy with sustained tolerogenicity in vivo, we transduced bone marrow-derived DCs (BMDCs) from wild type mice (MRL/MpJ), which shared the same genetic background as the spontaneous lupus MRL/lpr mice, by lentiviral shRNA vector that modulated RelB expression. RelB is a transcription factor in the NF-κB family that plays a key role in the regulation of DC maturation. RelB shRNA BMDCs demonstrated stable semi-mature phenotype, and downregulated IFN-γ and IL-17 producing splenic T cells from MRL/MpJ and MRL/lpr mice in vitro. Splenic T cells primed by RelB shRNA BMDCs demonstrated antigen-specific suppressive effect on allogeneic T cells. Adoptive transfer experiments are needed to examine the in vivo effect of these DCs on amelioration of disease severity in murine lupus model.

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All are welcome