ROLE OF BLOOD MYELOID AND PLASMACYTOID DENDRITIC CELLS IN CHRONIC RENAL FAILURE AND KIDNEY TRANSPLANTATION

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by

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Abstract

Immune protection against pathogens in humans relies on a coordinated response of both innate and adaptive immune systems. Dendritic cells (DCs) are a group of rare, heterogeneous population of professional antigen-presenting cells that can initiate primary immune responses, and hence have the ability to regulate both innate and adaptive immune responses. There are two clinically relevant DC subsets: myeloid DCs (MDCs) and plasmacytoid DCs (PDCs), which are crucial in antibacterial, antiviral, and antitumour immunity. Precursor DCs are generated from haematopoietic progenitor cells in the bone marrow, and enter tissues as immature DCs. They encounter foreign antigens (e.g., bacteria, tumour antigens) resulting in the secretion of various cytokines (e.g., interferon [IFN]) leading to activation of cells, including natural killer (NK) cells, macrophages, and eosinophils. Following antigen capture and processing, DCs undergo maturation and subsequently migrate to secondary lymphoid tissues where they present processed antigen-peptide complexes to major histocompatibility complexes (MHC), which allow for selection and expansion of antigen-specific CD4 T-helper cells to eliminate the invading pathogens. DCs have not been extensively studied in chronic renal failure (CRF) patients, including those maintained on dialysis and renal transplantation. We hypothesized that CRF patients maintained on renal replacement therapies, including dialysis and renal transplant patients, have a functional deficiency in circulating blood DCs predisposing these patients to a higher rate of clinical infections and malignancies. From our studies, we determined that circulating PDCs, but not MDC precursors, are reduced in numbers in the peripheral blood of dialysis and transplant patients. MDCs isolated from dialysis patients were functional abnormal, attributed to the presence of soluble uraemic...
toxins (including small and large molecular weight toxins) present in the serum of these patients. In contrast, MDC isolated from renal transplant patients were functionally normal and the numbers and function of these cells correlated with renal function (measured as glomerular filtration rate). We then demonstrated that more efficient dialysis to enhance clearance of uraemic toxins in haemodialysis patients resulted in the reversal of MDC (but not PDC) functional impairment. We next investigated whether the reduction in PDC in transplant patients predisposes to Epstein-Barr virus (EBV) associated disorders. To address this question, a humanised immunodeficient non-obese diabetic severe combined immunodeficient (NOD-SCID) mouse model was established. NOD-SCID mice reconstituted with human mononuclear cells depleted of PDC had significantly enhanced mortality from disseminated EBV infection, whereas mice reconstituted with mononuclear cells enriched with PDC had significantly delayed mortality from EBV-induced lymphoproliferative disease. We next investigated the mechanisms underlying anti-EBV immunity. In response to EBV, PDC were able to activate innate immunity (secretion of IFN-α and activating NK cells) and adoptive immunity (activating T cells) that is dependent on toll-like receptor signaling. We show for the first time that EBV signals through TLR-9-dependent mechanism. Our studies have demonstrated that DC deficiencies are prevalent in dialysis and transplant patients, which may be partially improved with more efficient dialysis or achieving normal renal function through transplantation. We have also shown that PDC deficiency is crucial in anti-viral immunity in transplant patients and strategies to augment PDC numbers and function in these patients are warranted.