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Mechanisms Driving Innate Regulation Of Immunological Tolerance To Apoptotic Cells Preventing Autoimmunity
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Innate immune responses to apoptosis are crucial for self-tolerance. Although upstream signals promoting recognition and processing of apoptotic cells have been extensively studied, downstream molecular mechanisms driving innate regulation of apoptotic cell responses are less understood. Here we report an unsuspected discovery that the ligand dependent transcription factor aryl hydrocarbon receptor (AhR) initiates tolerogenic signaling to apoptotic cells and prevents systemic autoimmunity. AhR is known to control xenobiotic stress responses and recently has been linked to modulation of T cell and DC function. In this study, we found that apoptotic cells induced AhR signals in tissue-resident MΦs and activation was dependent on DNA from apoptotic cells. AhR was required for apoptotic cell driven immune suppression as deletion of AhR abrogated IL-10, promoting the inflammatory cytokines IL-6 and IL-12, while supplementing IL-10 restored the regulatory phenotype of MΦs. Moreover, inhibition of the AhR pathway fundamentally altered immune responses to apoptotic cells resulting in proinflammatory cytokine production, increased effector T cell responses and abrogation of long-term allograft tolerance to apoptotic cell associated antigens. Further, mice lacking AhR developed spontaneous autoimmunity characterized by excessive macrophage and lymphocyte activation associated with renal pathology. Deficiency of AhR led to

breakdown in tolerance with rapid increases in anti-dsDNA and anti-histone antibody responses after chronic challenge with apoptotic cells. Similarly, when SLE-prone mice were treated with AhR antagonist they exhibited significantly elevated humoral auto-reactivity, augmented inflammatory cytokine production in MΦs, intensified autoreactive B and T cells, renal pathology, and mortality; while AhR agonist treatment resulted in significant reduction of autoimmune disease parameters compared to control mice. Collectively, the data demonstrate apoptotic cell activation of AhR is a key mechanism suppressing anti-apoptotic cell inflammatory responses preventing autoimmunity.

INDEX WORDS: Tolerance, Autoimmunity, Apoptosis, Inflammation, Spleen, Macrophage, Xenobiotic stress, Aryl hydrocarbon Receptor, DNA