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Role of innate B cells in antibody-mediated rejection

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Innate B cells secrete natural Abs without germinal center reaction and function quite differently from follicular (FO) B cells. Innate B cells include B-1a, B-1b, and marginal zone (MZ) B cells, which develop differently from each other and secrete different kinds of Abs that are autoreactive or cross-reactive to autoantigens in many instances. Innate B cells also have Ab-independent roles and function as excellent antigen-presenting cells supporting alloreactive CD4+ T cells and regulatory B cells that secrete IL-10. Therefore, innate B cells can play pro-inflammatory or anti-inflammatory roles in different contexts. To maintain allograft for an extended period, it will be essential to understand how the regulatory balance of innate B cells is held between two distinct states. B-1a cells become highly inflammatory cells secreting GM-CSF upon LPS stimulation and secrete beneficial natural Abs and IL-10 to maintain homeostasis. B-1b cells are CD5- B-1 cells that secrete anti-CHO (carbohydrate) Abs upon various kinds of infection. B-1b cells are producers of anti-ABO, xenoreactive, or anti-cancer CHO Abs. Since most B-1b anti-CHO Abs are cross-reactive to autoantigens, some tolerance mechanism, such as PD-1-PD-L1 interaction, prevents aberrant activation of B-1b cells in the healthy condition. However, the inflammatory process in the graft may promote the local production of anti-CHO Abs. The inflammation within the graft eventually leads to the production of CXCL13, which leads to the recruitment of FO B cells into the graft and the formation of tertiary lymphoid tissues within the graft. MZ B cells are innate B cells in the spleen which respond to blood-borne pathogens. MZ B cells can participate in the systemic Ab responses against soluble antigens from the graft. MZ B cells comprise less autoreactive CD80- and more autoreactive CD80+ cells with differential radioresistance and functional capacities. In summary, innate B cells perform homeostatic functions such as producing natural Abs and immunosuppressive cytokines. However, if not adequately regulated, they may become pro-inflammatory B cells that secrete autoreactive Abs and inflammatory cytokines, leading to graft rejection.