

## INTERVIEW about

Dendritic Cell Maturation,  
function and B cells

with

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### What means: dendritic cells at the crossroads of innate and adaptive immunity?

**Jagadeesh Bayry:** Dendritic cells (DC) are professional antigen-presenting cells (APC) that are specialized in the uptake of antigens and their transport from peripheral tissues to the lymphoid organs. DC have evolved to monitor the environment, detect pathogens and trigger antigen specific T cell immune response, providing a link between the innate and adaptive immune systems. DC can take up a diverse range of antigens and present them to T cells as peptides bound to both surface major histocompatibility complex (MHC) class I and II products (1). To acquire naive T-cell stimulatory ability, DC must undergo maturation, which involves the up-regulation of MHC and of co-stimulatory molecules during the process of migration from periphery to T-cell areas of secondary lymphoid tissues. The

secretion of DC-derived immunoregulatory cytokines plays a crucial role in the cascade of events that occur during the priming of naive T cells. Because of their capacity to stimulate naive T cells, DC control the quality of the T cell immune response, driving naive T cells into distinct effectors. This antigen-specific, adaptive immune responses are critical for fight against pathogens. Conversely, DC are also critical to the induction and maintenance of self-tolerance in the steady state. DC can generate regulatory T cells that suppress activated T cells, a function of key importance in autoimmunity and transplant recipients. Thus, the heterogeneity of DC and their activation states afford investigators more opportunities to define and manipulate the immune response using these specialized leukocytes.

### Role of B cells in the maturation and function of dendritic cells?

**Jagadeesh Bayry:** Accumulating lines of evidence now indicate that B lymphocytes exert a profound regulatory effect on the maturation and function of DC (2). An overview of the recent results discussed herein reveals several different mechanisms through which B cells scrutinize the function of DC.

Several reports suggest that B lymphocytes have a critical role in the onset of Th2 response through regulating the level of DC-derived IL-12 (a key cytokine involved in the priming of Th1 immune

response), probably by promoting the production of IL-10. In addition, B lymphocytes produce several chemokines and cytokines such as B cell-derived membrane lymphotoxin, macrophage inflammatory protein (MIP)-1 $\alpha$ , MIP-1 $\beta$ , IL-16 and others that regulate the migration of DC to the lymphoid organs and mediating the cellular cross-talk among T-, B-cells, and DC.

B-lymphocytes can also regulate DC maturation and function via antibodies. DC can be activated or inhibited

through FcR by Abs or immune complexes (IC) formed by Abs depending on the kind of Fc receptor engaged. Thus, the Fc $\gamma$ R system represents a balance of activating and inhibitory receptors that determines the outcome of immune complex-mediated signaling on DC.

FcR-mediated uptake of IC promotes efficient MHC class I as well as class II-restricted Ag presentation by various DC subsets and dramatically lowers the dose of Ag required for T

cell activation. Fc $\gamma$ R are also critical for tumor-directed antibody-dependent cellular cytotoxicity by DC.

In addition to FcR-mediated regulation, B-lymphocytes can also modulate DC maturation via non-FcR mechanisms via circulating natural autoantibodies. Natural antibodies refer to the antibodies that are present in the serum of healthy individuals in the absence of deliberate immunization with the target antigen. Autoantibodies are the immunoglobulins that react with at least one self-antigen, whether they originate from healthy individuals or patients with autoimmune disease. Natural autoantibodies that bind to CD40 and B7-DC and that evoke important biological changes in the DC have been recently identified (2).

### What can be the therapeutic approach?

**Sridhar V Kaveri:** B cells produce and respond to chemokines and inflammatory cytokines that promote the organization of extra-follicular germinal center-like structures by activating DC, macrophages and T cells as in rheumatoid arthritis and lupus. Disturbances of B-cell homeostasis are characteristic features of these diseases (3).

FcR-mediated uptake and presentation of Ag by DC is implicated in several pathological conditions. Cross-linking of Fc $\gamma$ R by lupus-IgG induces the maturation of DC via NF- $\kappa$ B signaling. Similarly, Cross-linking of Fc $\gamma$ R on human plasmacytoid DC by IC containing lupus-IgG and nucleic acid (DNA and RNA) released by either necrotic or late apoptotic cells was shown to stimulate the production of IFN- $\alpha$  (4,5). The presence of such stimulatory IC could explain the ongoing production of IFN- $\alpha$  in lupus and might be of importance in the pathogenesis and therapeutic intervention of lupus.

Similarly, Fc $\epsilon$ R-mediated uptake of IgE-associated allergens

plays a pivotal role in the pathogenesis of allergic diseases that may critically lower the threshold of atopic individuals to mount allergen-specific T cell responses (6).

The emerging knowledge on the importance of B cells in the immunopathogenesis of several autoimmune diseases has provided a strong rationale to target B cells by therapeutic MAbs such as CD20 MAb (3).

On the other hand, efficient cross-presentation of Ag by DC pulsed with IC and efficient MHC class I and class II-restricted Ag presentation underlines a basis for an alternative approach in the immunotherapy of cancer and infectious diseases (7-9).

### REFERENCES

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