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Vaccines Based on Dendritic Cell Biology

Silvia B. Boscardin and Michel C. Nussenzweig
Laboratory of Molecular Immunology, The Rockefeller University, New York, New York, U.S.A.

Christine Trumpfheller and Ralph M. Steinman
Laboratory of Cellular Physiology and Immunology, The Rockefeller University, New York, New York, U.S.A.

INTRODUCTION

Vaccine development against many global infectious diseases as well as cancer will likely require strategies that lead to strong T cell immunity. Dendritic cells (DCs) are antigen-presenting cells that induce strong adaptive immunity and memory, particularly T cell–based responses, and are therefore an attractive target for studies of vaccine biology and the development of more effective vaccines.

In humans, DC-based vaccine strategies have to date used DCs that are loaded ex vivo with vaccine antigens and then reinfused, primarily in the setting of advanced cancer. This strategy will be reviewed briefly here but was the subject of a chapter in a prior edition of this textbook (1). Here we will emphasize a new approach that is the subject of preclinical studies in mice, which is to directly target vaccine proteins to DCs in vivo. The latter approach has the advantage over the former of being an off-the-shelf product rather than a patient-specific treatment.

The most successful vaccines to date are comprised of either attenuated or inactivated pathogens, for example, the Sabin and Salk polio vaccines, or recombinant or purified portions of a microbe, for example, the hepatitis B vaccine or the split influenza vaccine, respectively. Microbe-based vaccines may not be feasible or effective for several prevalent problems such as AIDS, malaria, tuberculosis and cancer. This chapter considers vaccines comprised of microbial proteins and designed on immunological principles based upon the biology of DCs.

To understand the rationale, we will first outline some intrinsic features of DCs that are important for the control of immunity: (*i*) their location and movements in vivo, which allows DCs to act as sentinels for antigen capture and clonal selection of T cells; (*ii*) the repertoire of antigen receptors expressed by DCs, which allow for greatly improved uptake of vaccine proteins; and (*iii*) maturation in response to an array of immunologically relevant stimuli, which allow DCs to control the quality of the immune response.

INNATE FUNCTIONS OF DENDRITIC CELLS THAT LEAD TO THE CONTROL OF ADAPTIVE IMMUNITY

Positioning and Homing of DCs

DCs are positioned along body surfaces, often intimately associated with the epithelium, and they are able to home to the T-cell areas of lymphoid organs. This distribution and movement is an important feature of the DC lineage. It allows DCs to sample environmental and self-proteins in the steady state, that is, in the absence of inflammation or infection, for the purpose of tolerance, while under conditions of perturbation, microbial and other antigens are presented for the purpose of immunity (2–4). DC migration into lymphoid tissues allows for productive interactions with T cells. This can now be visualized in living lymph nodes by intravital two-photon microscopy. Migrating mature DCs arrive in the T-cell area where they efficiently select T cells specific for the presented antigens (5–7). In the T-cell area, these DCs join a network that is already present in the steady state (8). Stable cell-cell contacts develop when antigen-bearing DCs encounter their cognate T cells, and these contacts persist at least 18 hours. Such contacts are apparent in the steady state, when DCs can be tolerogenic, and upon DC maturation, when immunity develops (9,10). In summary, the unique distribution of DCs positions them to capture antigens in peripheral tissues and then move to lymphoid organs. There, in the T-cell areas, DCs scan T cells circulating through lymphoid tissues and select antigen-specific clones from the repertoire, leading to the induction of either peripheral tolerance or immunity, as we will stress below.

DC Receptors and Their Expression by Different DC Subtypes

DCs express a large number of endocytic receptors capable of mediating adsorptive uptake. Many of these are C-type lectins, which can either be type II transmembrane proteins with a single, carboxyl terminal lectin domain, for example, Langerin/CD207, DC-specific intercellular adhesion molecule 3 grabbing non-integrin (DC-SIGN)/CD209, BDCA-2, DC-associated C-type lectin-1 (Dectin-1), DC inhibitory receptor-2 (DCIR-2), or type I proteins with multiple lectin domains, for example, mannose receptor (MR)/CD206, DEC-205/CD205. Additional endocytic receptors are FcγRs, which mediate presentation of immune complexes and antibody-coated tumor cells on both major histocompatibility complex (MHC) class I and II. DCs also capture dying cells, although the precise receptors that are employed are a subject of current research.

Interestingly, individual receptors can be expressed on distinct subsets of DCs. For example, Langerin/CD207 and DEC-205/CD205 are expressed on Langerhans cells (LCs) (11), while DC-SIGN/CD209 and MR/CD206 are highly expressed on dermal DCs (12) and monocyte-derived DCs (13). In mice, the CD8α-positive subset of DCs expresses