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Engineering immunity: Modulating dendritic cell subsets and lymph node response to direct immune-polarization and vaccine efficacy

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ABSTRACT

While successful vaccines have been developed against many pathogens, there are still many diseases and pathogenic infections that are highly evasive to current vaccination strategies. Thus, more sophisticated approaches to control the type and quality of vaccine-induced immune response must be developed. Dendritic cells (DCs) are the sentinels of the body and play a critical role in immune response generation and direction by bridging innate and adaptive immunity. It is now well recognized that DCs can be separated into many subgroups, each of which has a unique function. Better understanding of how various DC subsets, in lymphoid organs and in the periphery, can be targeted through controlled delivery; and how these subsets modulate and control the resulting immune response could greatly enhance our ability to develop new, effective vaccines against complex diseases. In this review, we provide an overview of DC subset biology and discuss current immunotherapeutic strategies that utilize DC targeting to modulate and control immune responses.

1. Introduction

Vaccination has been the most effective public health strategy to control, and in some cases achieve global eradication of infectious diseases. However, the full potential of vaccines is far from realized. Patients affected by devastating diseases, whether infectious (e.g. HIV, dengue virus and other emerging pathogens), endogenous (e.g. cancer or diabetes) or behavioral (e.g. drug addiction), are candidates for new vaccines and immunotherapies; but developing effective vaccines against these diseases have proven extremely challenging. Therefore, new approaches to (a) mount robust and sustained immune responses and (b) finely control the immune polarization to specific phenotypes that are therapeutic or protective for the specific condition, are critically needed. Investigation of more potent antigen and adjuvant combinations, incorporation of "smart" delivery vehicles, optimization of administration route and technique, and targeting specific cell types in the innate and adaptive immune system, are a few of the strategies being explored to achieve this.

It is known that lymphoid organs, especially lymph nodes, are hubs for immune cell interaction and play an indispensable role in providing an environment suitable for generation and maturation of the adaptive immune response. The classical adaptive response is initiated by antigen presenting cells (APCs) that encountered foreign and/or pathogenic material in peripheral tissues and migrated through lymphatic circulation to present antigen to T cells in the draining lymph nodes. Professional APCs encompass mainly dendritic cells (DCs) and macrophages in the periphery and it is now thought that DCs are the primary APCs responsible for signaling and directing T cell activity. Furthermore, it is now recognized that based on primary location, DCs can be sub-categorized into many functionally distinct groups, extending the influence that DCs have on immunity. There is a significant body of literature dedicated to vaccine design with peripheral DC activation, migration and antigen presentation in mind.

In addition to DC subsets in the periphery, there are also lymphoid-resident DC subsets that have significant impact on T cell maturation [1–3]. This discovery has sparked new research focused on targeting vaccine components directly to lymph nodes through the lymphatic vasculature or through systemic delivery. While others have investigated direct delivery to the lymph node using intranodal injection, we believe that this approach may be unnecessarily invasive, and will not be discussed in this review. When designing vehicles and approaches to target direct lymph node delivery, it is essential to keep in mind interstitial and lymphatic physiology and how this plays a role in regulating transport to the lymph nodes. These parameters are nicely highlighted in recent reviews by Thomas et al. and Swartz et al. [4,5], and readers are referred to those for further detail. In this review, we will focus on

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our current knowledge of DC subset biology and provide an investigative comparison between vaccine strategies targeting peripheral (i.e. skin) or lymphoid-resident DCs, including their major benefits and disadvantages as well as how these findings should shape vaccine design. Since most vaccines currently available and in development are administered via the subcutaneous or intramuscular routes, we will focus on delivery through these routes. In addition, commonalities and differences between murine and human DC subsets and related immune responses are also indicated, when known.

2. DC subsets: an overview

Based on our most recent knowledge of DC biology, there are several anatomically and functionally distinct DC subsets in peripheral tissues. In this section, we will discuss some of the key subsets and their functional differences. Table 1 provides a summary of these DC subsets, along with surface markers used to distinguish and isolate them, the related maturation markers and primary cytokine types that the cells secrete upon activation and maturation.

Additionally, Fig. 1 delineates the skin, lymphatics, and lymph node biointerface; designating the relevant anatomy, various DC subsets present, and highlighting that peripheral DCs must migrate to the local immune hubs (i.e. draining lymph nodes) in order to initiate a robust adaptive, systemic immune response.

2.1. Secondary lymphoid organ resident dendritic cells

Secondary lymphoid organ resident dendritic cells were the first to be classified in the mouse system by Steinman and Cohn over 40 years ago [28]. Since their initial discovery and characterization, our understanding of their complexity has greatly increased, leading to multiple sub-classifications with very different functions. To date, these DCs are placed into two subsets based on their expression of CD8α and CD11b and their corresponding functions or in a third subset, which is the plasmacytoid DC.

Table 1
DC subset biology.[a, b, c]

DC subset	Primary location	Species	Phenotype	Function[a]	Source
CD8α +	Lymphoid tissue	Mouse (M)	$CD205^{+}$ $CD11b^{lo/-}$ MHC I Clec9A TLR 3 $CD205^{lo}$	Cross presentation CD8 + T cell priming Maintain self-tolerance	[1,2,6,7]
CD8α −	Lymphoid tissue	M	$CD11b^{+}$ $CD4^{+/-}$ MHC II TLR 7	CD4 + T cell activation	[2,7,8]
Plasmacytoid (pDC)	Blood/lymphoid tissue/inflammatory tissue	M/Human (H)	$CD11c^{lo}$ TLR 7 TLR 9 Langerin $^{+}$	Type I interferon secretion Promote wound repair	[9–12]
Langherans	Epidermis	M/H	$CD205^{+b}$ $CD11b^{+}$ $EpCAM^{+}$ MHC I (M)[c] MHC II (M) HLA-DR (H) $Langerin^{+}$	CD4 + T cell priming Th2/Th17 induction Treg induction Cross presentation **	[13–16]
CD103 +	Dermis	M	$CD11b^{lo/-}$ $CD11c^{+}$ MHC I MHC II Clec9A TLR 3 $Langerin^{-}$	CD8 + T cell priming Cross presentation Th1/Th17 induction	[15,17–19]
CD11b +	Dermis	M	$CD11b^{+}$ $CD11c^{+}$ MHC II $Langerin^{-}$	Treg induction Th induction	[17,20,21]
CD1a +	Dermis	H	$CD205^{+}$ $CD11c^{+}$ $HLA\text{-}DR^{+}$ $Langerin^{-}$	CD8 + T cell priming CD4 + T cell proliferation	[22,23]
CD14 +	Dermis	H	$CD11c^{+}$ $DCSIGN^{+}$ $CD206^{+}$ $HLA\text{-}DR^{+}$ $BCDA3^{+}$	CD4 + T cell activation Th2 induction	[24,24,25]
CD141 +	Blood/lymphoid tissue/dermis	H	$CD11c^{+}$ $CD1a^{-}$ $CD11b^{lo}$ $HLA\text{-}DR^{+}$	Cross presentation	[11,26,27]
Mo-derived	Blood/inflammatory tissue	M/H	$Ly6C^{+}$ $CD11b^{+}$ $CD11c^{+}$ MHC II	Infiltrate inflammatory tissue	[11,14]

[a] DC subsets not limited to these functions; those listed are discussed in this review.
[b] Expression of CD205 may be inflammation dependent in humans.
[c] Controversial whether mLCs cross present.

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