OPEN ACCESS Freely available online

ISSN: 2157-7560
Journal of
Vaccines & Vaccination

Opinion Article

Vaccine-Induced Transcriptional Alterations in Human Dendritic Cells

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ABSTRACT

The mechanisms through which microbial vaccines interact with human APCs are still unknown. The transcriptional programmes induced in human DCs by pathogens, innate receptor ligands, and vaccines are described here. We were able to construct a modular framework containing 204 transcript clusters after exposing DCs to influenza, Salmonella enterica, and Staphylococcus aureus. This framework is used to characterise the responses of 13 vaccines to human monocytes, monocyte-derived DCs, and blood DC subsets. Depending on the pathogen, adjuvant formulation, and APC targeted, different vaccines induce distinct transcriptional programmes. Fluzone, Pneumovax, and Gardasil, in turn, activate monocyte-derived DCs, monocytes, and CD1c+ blood DCs, highlighting the importance of APC specialization in vaccine response. Finally, blood signatures from people who have been vaccinated with Fluzone or who have been infected with influenza show a signature of adaptive immunity activation after vaccination and symptomatic infections, but not asymptomatic infections. These data, which are accessible *via* a web interface, may aid in the development of better vaccines.

Keywords: Vaccines; Immunology; Antigen; Mumps; Vaccination

DESCRIPTION

Vaccination, the most effective preventive measure against infectious diseases, is based on Antigen-Presenting Cells presenting microbial antigens to the adaptive immune system. This process generates protective immune responses mediated by T and B cells [1]. Many empirically developed vaccines have proven effective against potentially fatal infections such as poliomyelitis, measles, pertussis, smallpox, and mumps. Nonetheless, the lack of effective vaccines against modern pandemics such as human immunodeficiency virus, tuberculosis, and malaria highlights the importance of better understanding the immunological mechanisms involved in vaccination.

Vaccination is dependent on Dendritic Cells (DCs), as evidenced by the loss of immune sensitization to cell-associated antigen in DC-depleted mice [2]. Multiple DC subsets have been identified in both mice and humans in the blood, skin, lymphoid, and mucosal tissues. In human blood, these include CD1c+ DCs, which are equipped with a wide range of Pattern Recognition Receptors (PRRs) and are good inducers of both CD8+ and CD4+ T-cell responses; CD141+ DCs, which efficiently cross-present necrotic and non-self antigens to CD8+ T cells; plasmacytoid DCs, which secrete large amounts of type-I Interferon (IFN) on challenge with viruses and nucleic acids. Toll-like Receptors (TLRs), C-type lectin receptors, nucleotide-binding oligomerization domain-like receptors, and helicases are all expressed differently by different DC subsets. The role of these subsets in mounting specific immune responses to various vaccines is largely unknown [3-5]. DCs respond to pathogenic signals by transcribing different sets of genes that interact in a complex way, as evidenced by the antagonistic relationship between antiviral and antibacterial pathways. Systems biology techniques like genome-wide microarrays provide molecular snapshots of disrupted pathways. Previous research in blood leukocytes and tissues has shown that microarrays can be used to characterise the molecular mechanisms involved in infection, cancer, autoimmunity, and vaccination, resulting in diagnostic and therapeutic advances. DC transcriptional programmes have been studied *in vitro* and *in vivo* using microarrays and small interfering RNA in mammalian cells at steady state and in

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Received: 10-Aug-2022, Manuscript No. JVV-22-18545; **Editor assigned:** 15-Aug-2022, Pre QC No. JVV-22-18545 (PQ); **Reviewed:** 31-Aug-2022, QC No. JVV-22-18545; **Revised:** 06-Sep-2022, Manuscript No. JVV-22-18545 (R); **Published:** 14-Sep-2022, DOI: 10.35248/2157-7560.22.13.494.

Citation: Palcka K (2022) Vaccine-Induced Transcriptional Alterations in Human Dendritic Cells. J Vaccines Vaccin. 13:494.

response to various pathogen-associated molecular patterns. Dimension-reducing approaches, such as gene co-expression module frameworks, have made it easier to interpret these complex data sets. Simultaneously, systems vaccinology has emerged as a discipline that employs systems biology approaches to investigate vaccine mechanisms of action and identify immunological correlates of protection. Despite these efforts, there is still a significant gap in understanding of how vaccines interact with human DC subsets and how this results in the development of protective immunity.

We used a multi-step approach to understand human DC responses to vaccine challenge *in vitro* in this study. We created a novel transcriptional modular framework *in vitro* from pathogen-stimulated DCs and validated it in an independent data set of DCs stimulated with microbial components and inflammatory cytokines. We then used this framework to characterise the early response of human DCs and their precursors to 13 microbial vaccines, identifying shared and unique transcriptional networks in response to each pathogenic challenge.

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