Editorial Comment

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Dendritic cells, dendritic cell-based vaccines and Ralph Steinman

Immune reactions are central to many human diseases including those of infectious origin, many cancers, as well as autoimmune and hyperinflammatory conditions. Without induced immunosuppression, the immune system prevents transplantation of many organs. For many of these medical conditions, antigens (targets of the adaptive immune system) are known. Others are still being identified. One challenge in human medicine is to establish new antigen-specific therapies that can either enhance immune responses, as is critical for overcoming infection and cancer, or dampen those responses to suppress autoimmunity and hyperinflammatory conditions and allow transplantation. The current state of knowledge about dendritic cell (DC) biology bestows the opportunity to think concretely about new prevention and treatment strategies for using DC, either directly or indirectly, to combat human disease.

Dendritic cells

Dendritic cells (DC) are an important lineage of hematopoietic cells that control the immune system. Originally discovered by Ralph Steinman in the early 1970s [1; see below], and initially attracting only a few groups, DC research has literally exploded in the last 15 years or so. DC are found in most tissues and are comprised of several subpopulations. DC are key initiators of adaptive immune responses because of their unique abilities to sense, take up and process antigens to prime antigen-specific T cells and to guide their differentiation into specific subsets [2]. DC also fulfil a key function in their ability to silence T cells. Hence, DC control both the induction of immune responses, 'immunogenicity', and tolerance [2]. DC thus bridge innate immune responses to adaptive immunity [3].

Dendritic cell-based protein vaccination

The specialized properties of DC can be considered in vaccine design because antigens must reach DC (or specific DC subsets) to elicit an immune response. In the current issue of the *Journal of Internal Medicine* [4], Trumpfheller, Steinman and collaborators summarize their efforts to develop a safe T cell-based protein vaccine that exploits the pivotal role of DC in initiating adaptive immunity. In their excellent review, they focus on their studies related to HIV but, as is noteworthy, their system is also applicable to many other infectious diseases and human cancer.

Their strategy is to link protein antigen, here HIV gag-p24, with a monoclonal antibody (mAb) that efficiently and specifically targets the DEC-205 receptor on DC. DEC-205 was the first receptor discovered on DC that could mediate antigen up-take, processing and presentation [5]. When administered together with synthetic double-stranded RNA, as adjuvant, HIV gag-p24 is highly immunogenic in mice, rhesus macaques and, as described in the present review, in ongoing research in healthy human volunteers. Strikingly, the human subjects form both T- and B-cell responses (i.e. antibodies) to the DC-targeted protein. Thus, as nicely discussed in the present review, DC-targeted vaccines are a potential new platform, either alone or with highly attenuated viral vectors, to induce integrated immune responses against microbial or cancer antigens [4].

Ralph M. Steinman – 1943–2011

Ralph Steinman died on 30 September 2011, before the final completion of the review in the current issue of *Journal of Internal Medicine* [4].The review, possibly the last piece of work carried out by Steinman before his death, was completed by Christine Trumpfheller and collaborators soon after his death. In a greater perspective, the present review is not only a summary of recent exciting results from Steinman's laboratory. It is the result of a life-long scientific achievement by Steinman and his many collaborators from the very discovery of DC, and their function, to the development of current clinical applications [6]; some of the most promising ones discussed in the present review [4]. Steinman's earlier scientific achievements, leading up to the present studies, are briefly summarized below.

At the Rockefeller University, as a young post-doc with Z. Cohn in the early 1970s, Steinman set out to address a central problem in immunology, the

inability to induce antigen-specific responses by directly stimulating lymphocytes with antigen. At that time, it had been demonstrated that antibody responses to model antigens could not develop unless one added radio-resistant *accessory* cells to mixtures of B and T cells. Guided by these findings, and the insight that immune reactions occurred in secondary lymphoid organs, Steinman decided to study accessory cells in the spleen and lymph nodes of mice. There he observed cells irregular in shape that continually extended and retracted their processes in several directions. These cells differed from macrophages and lymphoid cells, and Steinman referred to them as 'dendritic cells' [1]. Steinman pioneered the methodology to enrich these cells. He and his collaborators made a series of discoveries over the next years leading to the insight that DC were of central importance in the generation of T-cell responses [7].

Since the early discovery of DC, Steinman's group made many more discoveries providing deeper insights into DC functions. They described in detail the particular features of DC, for example, their ability to sample antigens in the periphery and then to migrate to lymph nodes where they stimulate immune cells. Seminal discoveries also included the ability of DC to induce tolerance [8]. Several investigators learned from Steinman's laboratory how to generate large numbers of DC from progenitor cells. More recent activities in Steinman's laboratory, as well as from others, have involved attempts to use DC in settings of immunotherapy for induction of immunity, either directly or indirectly [9].

The 2011 Nobel Prize in Physiology or Medicine

For his original discoveries of 'the dendritic cell and its role in adaptive immunity', Ralph Steinman was awarded the 2011 Nobel Prize in Physiology or Medicine (http://www.nobelprize.org). The Nobel Committee of the Karolinska Institutet emphasized that the award acknowledges the discovery and characterization of a new type of cell, the DC, and its ability to activate T cells. The committee concluded that the findings by Steinman, as well as the other 2011 Nobel Prize Laureates, Jules Hoffmann and Bruce Beutler, had made it possible to develop '…new methods for preventing and treating disease, for instance with improved vaccines against infections and in attempts to stimulate the immune system to attack tumors' (http://www.nobelprize.org). It is truly regrettable that Ralph Steinman never got to know the decision of the Nobel Assembly, which was unaware of Steinman's death at the time of their decision on 3 October 2011.

Concluding remarks

Ralph Steinman's death at 68 years of age was a great loss for all of us working within the field of DC biology, immunology and its applications. Steinman was not only a great basic scientist. He was passionate about making the leap from the bench to the bedside [6]. He often talked, and wrote, about the underappreciated need to create sizable scientific enterprises that will bring new methods, concepts and coordination to the studies of diseases in patients [9, 10]. In this context, he identified the DC as one key target cell in the design of new treatments for human disease including infectious diseases and cancer [9]. We shall remember Ralph Steinman not only for his seminal discoveries of the DC and its function, but also for his translational ambitions in medical sciences. The studies presented in the current issue of the *Journal of Internal Medicine* are one excellent example of this.

Conflict of interest

The author has no commercial conflict of interest.

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References

1 Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J Exp Med* 1973; **137:** 1142–62.
2 Bancherau J, Steinman RM. Dendritic cells and the control of immunity. *Nature* 1998; **392:** 245–52.
3 Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R. Toll-like receptors control activation of adaptive immune responses. *Nat Immunol* 2001; **2:** 947–50.
4 Trumpfheller C, Longhi MP, Caskey M *et al.* Dendritic cell-targeted protein vaccines: a novel approach to induce T cell immunity. *J Int Med* 2012; **271:** 183–92.
5 Jiang W, Swiggard WJ, Heufler C, Peng M, Mirza A, Steinman RM. The receptor DEC-205 expressed by dendritic cells and

thymic epithelial cells is involved in antigen processing. *Nature* 1995; **375:** 151–5.
6 Nussenzweig MC, Mellman I. Ralph Steinman (1943–2011) immunologist and cheerleader for dendritic-cell biology. *Nature* 2011; **478:** 460.
7 Steinman RM, Witmer MD. Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice. *Proc Natl Acad Sci USA* 1978; **75:** 5132–6.
8 Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003; **21:** 685–711.
9 Steinman RM, Banchereau J. Taking dendritic cells into medicine. *Nature* 2007; **449:** 419–26.
10 Steinman RM. Dendritic cells: understanding immunogenicity. *Eur J Immunol* 2007; **37:** S53–60.

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