The Nobel Prize in Physiology or Medicine 2011 was awarded to Ralph M. Steinman, Jules A. Hoffman and Bruce A. Beutler for the discovery of essential elements of innate immunity, in particular dendritic cells (DCs) and toll-like receptors (TLRs). Antigens become immunogenic and capable of triggering an adaptive immune response involving antigen-specific, MHC-restricted effector T cells, only if they are captured and presented by "accessory" cells. In 1972, Ralph M. Steinman and Zanvil Cohn identified in lymphoid tissues, cells with treelike, arborescent morphology that they named "dendritic cells" (DC) (from the greek word “tree” for tree, δέντρον) with a superior ability to induce alloreactive T cell proliferation in vitro (1978) and to stimulate the rejection of kidney allotransplants in rodents (1982). Thirty years after their discovery, DC are now known to play a seminal role in bridging innate and adaptive immunity. In addition, DC are being used in numerous clinical studies all over the world to increase immunity to infectious or tumor-associated antigens. This effort involved the contribution of an international network of basic and clinical scientists spearheaded by Ralph M. Steinman to define appropriate culture conditions to generate ex vivo DC from circulating or bone marrow precursors, to define-functionally distinct DC subsets, to identify their maturation pathways including those relying on the stimulation of TLRs, and finally to develop DC based-vaccines to immunize patients infected with HIV or affected by cancer. Here, we will detail the history of DC and outline the therapeutic implications of Ralph M. Steinman’s seminal discovery.

**The Discovery of Dendritic Cells (DC)**

The very question of the sixtees as to how an « antigen» could elicit an immune response specifically directed against itself was initially adressed by Sela et al. and Sir MacFarlane Burnet.¹ The pivotal step forward was the discovery of immune response genes which mapped to the MHC II region,² the description of MHC class I-restricted presentation of viral antigens and then the engagement of T cell receptor with MHC/peptide complexes (P. Doherty, R. Zinkernagel, A. Townsend, E. Unanue, J. Strominger, P. Bjorgman, D. Wiley). Ironically, the antigen processing and presentation phenomenon was not known in 1972 when DC were first discovered.

When dissecting which cell type of the spleen was indispensable for mounting a humoral immune response against sheep red blood cells, Steinman made its first conceptual observation of a radioresistant accessory cell bearing a stellate shape and continually extending and retracting its dendrites towards other lymphocytes.

In three papers published in the Journal of Experimental Medicine in the early
1970’s, Steinman and Cohn described this new cell type that they named “dendritic cell” (DCs). Using refined purification techniques and the generation of monoclonal antibodies that specifically recognized antigens expressed by DC, such as DCIR-2 and CD11c, Maggi Pack and Ralph M. Steinman demonstrated that DCs were 100 times more potent than total splenocytes (containing 1% DC) in driving allogeneic T cell proliferation in a standard mixed leukocyte reaction (MLR) in vitro. In 1983, Michel Nussenzweig showed that DC depletion using anti-DCIR-2-antibody strongly reduces, albeit not totally, allogeneic T cell proliferation demonstrating the DC critical role in driving MLR in vitro. Seven years later, the residual MLR activity was attributed to a residual DCIR-negative DC subset expressing DEC205 on the surface, a molecule shown by the Shortman’s group to be expressed by a subset of spleen DC.

The primary proof of concept that DC are unique antigen presenting cells in vivo was demonstrated in experimental organ transplant studies showing that transfer of donor DC break tolerance to kidney grafts whereas DC depletion from pancreatic islets grafts prolonged graft survival in vivo.

Steinman and Nussenzweig next demonstrated that DCs (but not macrophages nor B cells) were uniquely able to elicit a hapten-specific CD8+ T cell response in an autologous setting. In collaboration with Kayo Inaba (Kyoto, Japan), he also demonstrated the key role of DC in priming autologous helper T CD4+ (TH1) responses required for antibody formation against a soluble protein. Other labs have then isolated DC in the afferent lymph in various species and tissues, leading to a seminal report of DC nomenclature published by several investigators.

From the Langerhans Cell to Nature’s Adjuvant: A Critical Step

In 1985, Steinman’s post-doctoral fellows Gerold Schuler and Nicki Romani first described the “maturation switch” of epidermal DC (also called Langerhans cells, Fig. 2) obtained ex vivo from skin explants. They showed that Langerhans cells expressing MHC class II were endowed with antigen presenting capacities when cultured in vitro in the presence of GM-CSF (reviewed in Ref. 17). A myriad of studies focusing on the regulation of antigen presentation through the maturation process led to the discovery of “pattern recognition receptors” recognizing “danger signals” – a notion first coined by Peter Janeway and Polly Matzinger. Such pattern recognition receptors include the Toll-like receptors (TLR), NOD-like receptors, the inflammasome plateform (described by Jürg Tschopp) and lectin-like receptors, which all act in concert on DC to promote antigen processing and presentation, increased expression of costimulatory molecules (members of the B7, TNF, and Notch families), secretion of cytokines and chemokines (IL-12, IFN type 1, IL-15) regulating DC ability to promote T helper differentiation (TH1, TH2, TH17, Treg, Tr1) (reviewed in Ref. 18).

In 1990, Steinman’s group first reported that DC loaded with any candidate antigen (protein or microbial) can trigger an antigen-specific T cell immune response in vivo, thus unravelling the first vaccination strategy that did not require the addition of exogenous “adjuvants” such as aluminium hydroxide or complete Freund’s suggesting that DCs behave as “nature’s adjuvants”.

In Michael Lotze’s laboratory (Pittsburgh, USA), Zitvogel and Mayordomo demonstrated that DCs pulsed with p53 or acid eluted tumor peptides can be used to promote tumor-specific T cell immune responses in vivo. Multiple studies, later confirmed that various antigen formulations (recombinant viruses, synthetic RNA, naked DNA, microbes, dying cells etc.) could be used to load ex vivo propagated DCs, which upon adoptive transfer, were potently immunogenic.

In 1999 and 2002, Zitvogel’s group showed that maturing DC were not only pivotal to control/switch adaptive immune responses by T cells but also to activate innate lymphocytes such as NK et NKT cells. Other groups highlighted that DC can interact with non-lymphocytic cells with potent roles in inflammation (such as neutrophils or injured epithelia) emphasizing that DC played a central role in orchestrating innate and adaptive immunity.
DC research was greatly facilitated when culture systems to generate DC in vitro became available. Federica Sallusto & Antonio Lanzavecchia as well as Christophe Caux & Jacques Banchereau paved the way to the various descriptions of culture conditions starting from monocytes (in GM-CSF+IL-4 or IL-13) or CD34+ progenitors (in SCF+GM-CSF+TNFa) (reviewed in Ref. 18). Similar to mice, human DC were also very potent at driving T cell immunity leading to an explosion of DC-focused studies in the literature (Fig. 1) and spurring the formation of several scientific societies devoted to DC biology and therapy (such as the “Club francophone des cellules dendritiques”). The discovery by Eugene Maraskovsky that the cytokine Fms like tyrosine kinase ligand (Flt3L) can drive DC expansion in vivo25 and subsequent studies showed that spleen CD8+DEC205+ DC excel in the cross-presentation of cell-associated antigens and in the differentiation of TH1 IFNγ producers, whereas spleen DCIR2/CLEC4A4+ cells were more potent in the presentation of antigens in MHC class II molecules and the differentiation of CD4+ T cells (26). In contrast to lymphoid tissue DC, the heterogeneity of non lymphoid tissue DC has only been recently recognized. Similar to lymphoid tissue, non lymphoid tissue also include at least two DC subsets including CD103/ITGAE specialized in MHC class I cross-presentation (Fig 3), whereas CD103-DC are more potent at driving CD4+ T cell responses (reviewed in Ref. 27). Regardless of their localization, DC subsets act in a coordinated fashion to bridge innate and adaptive immune responses in health and disease.28 In addition to tissue resident DC, studies pioneered by Eric Pamer’s group established that monocyte-derived DC also called inflammatory DC also form transiently in inflamed tissues and contribute to tissue immunity.29 Recent studies have now identified the successive steps that control DC differentiation and identified DC restricted precursors in the bone marrow30 as well as the transcription factors (Batf3, E2-2, the canonical Notch-RBP-J pathway, mTOR, IRF8…) that control DC differentiation and lineage specification.31, 32, 33, 34

**Mouse and Human Genetics and Proof of Concept of DC Relevance in Pathophysiology**

The development of DC depletion models using transgenic mice expressing the diptheria toxin receptor under the CD11c (or langerin) promoter (pioneered by Jung and Littman, Refs. 35 and 36)
as well as mice deficient in DC-specific transcription factors or receptors (such as Batf3, IRF8, Ikaros, Flt3L, Siglec H, E2-2, Notch-RBP-J) have fuelled the literature with abundant lines of evidence on the role of DC in innate and adaptive immune responses. Alternative techniques consist of neutralizing/depleting antibodies (such as anti-PDCA1 Ab…)(reviewed in Ref. 18). The prominent role of cross-presentation by DC has been brought up in various model systems. The pathogenic contribution of DC in asthma, allergen rhinitis and lung viral infections has been reported by Bart Lambrecht and colleagues. Distinct DC subsets were involved in the entry and dissemination of certain pathogens or, in contrast, in mediating host resistance to infectious agents. Importantly, Robert Schreiber and Ken Murphy underscored the role of Batf3/CD103+ DCs in natural immunosurveillance against methylcholanthrene-induced sarcomas where the relevance of the IFNAR1 pathway (expressed in this DC subset) was already established.

Genetic data obtained in humans also underscore the contribution of DCs to the control of pathogens. Patients carrying mutations in the gene encoding interferon regulatory factor 8 (IRF8) exhibit defects in the differentiation of mononuclear phagocytes (with markedly reduced blood counts of monocytes and CD1c+ DC) and experience a primary immunodeficiency with enhanced susceptibility to mycobacterial infection including disseminated BCG disease.

**Dendritic Cells and Tolerance**

At the steady state, in the absence of inflammatory signals, DC engulf self and microenvironmental antigens and induce a state of tolerance to autoantigens through a mechanism that may involve the expression of PDL-1, FAS or TGFβ on DC (reviewed in Refs. 17 and 18). The proof of concept that DC could induce peripheral tolerance came from in vivo targeting of DC using the anti-DEC205 antibody fused to a candidate antigen (DEC205 being a receptor of endocytosis and processing of external antigens) or coinjection of anti-DEC205 Ab with dying tumor cells. In the absence of adjuvant, DC elicit an antigen-specific immune response culminating in the clonal deletion of specific TCR. In the presence of a maturing agent (such as anti-CD40 agonistic Ab or TLR3 ligands), potent antigen-specific TH1 immune responses were generated.

In addition, DC contribute to mounting regulatory Foxp3+ T cell (Tregs) responses in the thymus, in the periphery or to amplifying Tregs once elicited. Ghiringhelli et al. demonstrated the relevance of such observations in the setting of primary cancers where intratumoral DC expand Tregs through a mechanism involving membrane bound TGFβ.

**Clinical Trials with Dendritic Cells**

The pathophysiological relevance of DCs has been demonstrated in clinical settings. Thus, when applied to superficial cancers, some TLR7/8 agonists (such as Imiquimod/ALDARA®) stimulate the local generation of TRAIL and perforin-dependent killer pDCs, which may contribute to tumor regression in basal cell carcinoma or HPV-induced vulvar or cervix carcinomas. Indirect lines of evidence point to a pathogenic role for pDCs in psoriasis, inflammatory bowel disease and systemic erythematosus lupus, presumed through the secretion of TNFα, IL-23 and type 1 IFN type 1, respectively (reviewed in Ref. 8). Cornelis Melief’s group pioneered the field of overlapping long peptides that prime DC-dependent T cell responses in preclinical models and confer clinical benefit in vaginal in situ HPV-induced neoplasia. Matthew Albert and Nina Bhardwaj (from Steinman’s team) discovered that human monocyte-derived DC cross-present viral antigens from influenza infected fibroblasts to naïve influenza specific CD8+ T lymphocytes, suggesting that certain cell death modalities could mediate immunogenicity through host DC intervention (and not just tolerance, as always reported). Thus, myeloid DCs contribute to the therapeutic success of conventional chemotherapy of cancer (with anthracyclines or oxaliplatine). DC can engulf and process tumor associated antigens through mechanisms that involve the exposure of calreticulin on dying cells (which signals for DC-mediated engulfment of dead...
cells) and the presence of extracellular HMGBl (which binds to TLR4 on DC), respectively, leading to cross-priming of CD8+ Tc1 lymphocytes that are indispensable for tumor regression.49 In addition, the NLRP3 inflammasome of DC must be activated by purinergic P2RX7 receptors that sense the presence of extracellular ATP produced by dying cancer cells. This work has been applied to breast cancer patients in whom, loss-of-function alleles that reduce the affinity of HMGBl for TLR4 or that of P2RX7 for ATP are associated with shorter time to progression after adjuvant chemotherapy with anthracyclines.49

All the preclinical studies showing safety and efficacy of ex vivo propagated DC loaded with various antigen formulations convinced North American and European regulatory authorities to accept and launch clinical trials aiming at vaccinating cancer patients with DC. Dhodapkar, Bhardwaj and Steinman demonstrated that human autologous DC exposed to maturing agents and viral antigens (MP of Influenza virus) and/or helper proteins (KLH, TT) immunized healthy volunteers (at the levels of Tc1 and TH1 effector and memory responses).50,51 Clinical success was restrained by the migratory defects exhibited by ex vivo propagated DC to reach the lymph nodes and the lack of availability of ad hoc maturing adjuvants.52 However, two randomized Phase III trials (utilizing Provence, DENDREON, finally approved by the Food and Drug Administration) conducted in hormone resistant metastatic prostate cancer brought up the proof-of-principle that DCs exposed to a fusion protein coupling GM-CSF and a prostate specific antigen and peripheral leukocytes significantly prolong overall survival.53

Recent endeavours turned to the development of antibodies specific for subsets of human DC, harnessing the capacity of the targeted membrane receptors to mediate endocysis and processing of the antibody fused to a candidate antigen and a TLR agonist. Nussenzweig and Steinman pioneered the field launching the anti-MR and anti-DEC205 Ab coupled to a candidate viral or tumor antigen, showing a broader peptide repertoire and superior efficacy of antigen presentation compared with soluble antigens (as exemplified for HIV, malaria, Leishmania, and cancer).54 The biotech company CellDex is currently conducting Phase I trials in the USA using a humanized version of the anti-MR and anti-DEC205 antibody. Alternative antibodies targeting additional receptors (such as CLEC9A, LOX-1/OLR1, DCIR/CLEC4A, DC-SIGN/CD209, CD40) are being currently developed.55

Conclusion

Despite initial skepticism about the uniqueness of the DC, Steinman kept saying and proving that the existence of DC justified the link between the stress/injury occurring in peripheral tissues and clonal expansion/selection observed in lymphoid organs, thus opening therapeutic prospects for prophylactic and therapeutic vaccination (against cancer and microbes), as well as for inducing tolerance (for the treatment of allergy, transplantation and autoimmunity). Ironically, Ralph M. Steinman died from the “emperor of all maladies” (the title of a book on the history of cancer, authored by Siddhartha Mukherjee, that he offered to some of us), 48 hours before he was crowned with the 2011 Nobel Prize for Physiology and Medicine for his discovery of DC . Ralph M. Steinman had been struggling against pancreatic cancer for more than four years using his own DC generated by our dear colleague Karolina Palucka as tumor vaccines. Although Ralph failed to succeed in this final demonstration, we believe that DC-based vaccines significantly prolonged his life and that further studies on DC vaccines in cancer are critically needed to help transform life of others. For all of us, Ralph will always be.

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