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The Nobel Prizes of 2011

Dendritic cells (DC) and their Toll-like receptors (TLR): Vital elements at the core of all individual immune responses. On the Nobel Prize in Physiology or Medicine 2011 awarded to Bruce A. Beutler, Jules A. Hoffmann, and Ralph M. Steinman*

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Resum. La protecció de la integritat dels individus que exerceix el sistema immunitari enfront dels patògens té mecanismes molt efectius però invariants que s'agrupen sota el terme *immunitat innata*. A diferència de la *immunitat adaptativa* (desenvolupada per immunoglobulines i limfòcits), la immunitat innata no millora amb contactes successius (no té la memòria immunològica que, per exemple, s'indueix amb les vacunes) sinó que es manté globalment inalterable al llarg de la vida de l'individu. A diferència del reconeixement específic dels receptors per a l'antigen —immunoglobulines i receptors de limfòcits T (TCR)— de la immunitat adaptativa, la immunitat innata actua enfront del perill dels patògens, mercès al reconeixement dels Patrons Moleculars Associats a Patògens (PAMPs), un reconeixement potser menys sofisticat però tant o més eficaç que el de la immunitat adaptativa. Els receptors d'aquests patrons moleculars de perill són diversos i en destaquen els TLR (de l'anglès: *Toll-like receptors* o receptors de tipus *Toll* —el nom recorda el concepte de «peatge al que és estrany»— descrits inicialment en cèl·lules de la mosca *Drosophila melanogaster*). La seva descripció es deu principalment als treballs dels doctors Bruce A. Beutler i Jules A. Hoffmann, que amb els seus estudis de l'activació de la immunitat innata mitjançada els TLR, han aconseguit el reconeixement de l'Acadèmia Sueca. Junt amb ells, el tercer guardonat amb el Nobel ha estat el doctor Ralph M. Steinman, pel descobriment de les cèl·lules dendrítiques (DC, de l'anglès, *dendritic cells*), un subtipus cellular de la immunitat innata que determina la resposta (o la tolerància) de la immunitat adaptativa. Malauradament, el doctor Steinman va morir víctima d'un càncer just abans que l'adjudicació del premi es fes pública (tot i que el jurat ja ho havia decidit i, per això, va poder i va voler mantenir la concessió). Aquests treballs han revolucionat la comprensió del sistema

Summary. The protection of the personal integrity, which is exercised by the immune system against pathogens, has very effective and invariant mechanisms; these invariant mechanisms are grouped under the concept of 'innate immunity.' Unlike 'adaptive immunity' (developed by lymphocytes and immunoglobulins), innate immunity is not improved with consecutive contacts (it has not got the immunological memory, as vaccines induce) and overall innate immunity remains unchanged throughout the life of each individual. Unlike the specific recognition of receptors for antigen (TCR and immunoglobulins) of adaptatitve immunity, the innate immune response acts in front of danger of pathogens thanks to the recognition of Pathogen Associated Molecular Patterns (PAMPs), a recognition perhaps less sophisticated but equally or even more effective than adaptative immunity. There are several receptors of these molecular patterns of danger, and among them the Toll-Like Receptors (TLRs)—whose name recalls the concept of "toll that which is strange"—originally described in cells of *Drosophila melanogaster*. The description of TLRs is mainly due the work of Drs. Bruce A. Beutler and Jules A. Hoffmann who were recognized by the Swedish Foundation for their activation studies of innate immunity by TLRs. Next to them, the third Nobel awarded was Dr. Ralph M. Steinman for his description of Dendritic Cells (DCs), a cell subtype of the innate immune response that determines the response (or the tolerance) of adaptative immunity. Unfortunately, Dr. Steinman died of cancer just before the concession of the prize was made public (the jury had already made its decision being this the reason for keeping the prize). These studies have revolutionized our understanding of the immune system, leading to the description of new diseases (new immunodeficiencies, or intraindividual variations that partly explain some diseases), the emergence of new therapies (there are approved treatments based on the presentation by DCs) and very promising new fields of research to improve strategies with vaccines and treatments for infections, cancer and several inflammatory diseases.

Keywords: innate immunity · dendritic cells · Toll · TLR · inflammation

* Based on the lecture given by the author at the Institute for Catalan Studies, Barcelona, on 14 December 2011, and at the Octubre Centre of Contemporary Culture, Valencia, on 16 January 2012 for the Nobel Prize Cycle.

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immunitari i han motivat la descripció de noves malalties (noves immunodeficiències o variacions intraindividuals que expliquen, en part, algunes malalties), l'aparició de noves teràpies (ja hi ha tractaments aprovats basats en la presentació per DC) i nous camps de recerca més que prometedors per a la millora de les estratègies de les vacunes i dels tractaments de les infeccions, el càncer i les malalties inflamatòries.

Paraules clau: immunitat innata · cèl·lules dendrítiques · Toll · TLR · inflamació

Introduction

The Nobel Prize in Physiology or Medicine 2011 was divided, one half jointly to Bruce A. Beutler and Jules A. Hoffmann "for their discoveries concerning the activation of innate immunity" and the other half to Ralph M. Steinman "for his discovery of the dendritic cell and its role in adaptive immunity." (Fig. 1)

To achieve effective action targeted at a specific element, this element must be recognized. Furthermore, when the action to be performed is destructive to the element recognized, it is also essential that targeted elements are distinguished from ourselves, which implies the ability to distinguish between the two. This is the quasi-philosophical concept underlying the immune system's mechanism of action. This system is defined by its ability to recognize and discriminate self (individual host) from non-self (antigen), ... and to attack and destroy the latter. This is true for what for decades was considered the most important (and most characteristic) feature of the immune system: specific or adaptive immunity. In this kind of immunity, specific clonal recognition feeds the immunological memory. Indeed, the concept provided the basis for the development of vaccines, beginning with Edward Jenner's (1798) empirical work. Those efforts eventually gave immunology the undeniable honor of being the medical discipline that enabled the first disappearance of a disease, smallpox (disappearance certified by the World Health Organization in 1979) [11].

The adaptive immune elements that recognize self from non-self were extensively studied throughout the 20th century, during which the molecular (antibodies, T-cell receptors or TCR, major histocompatibility complex or MHC, etc.) and cellular (T and B lymphocytes, antigen-presenting cells, etc.) bases of this specific recognition were clearly established. In fact, during that time much of the attention in the field of immunology was focused on what is called adaptive or specific immunity (antibodies, TcR, MHC, lymphocytes, etc.), characterized by a specific, clonal, memory-based recognition that has been analyzed in depth as a model of cellular complexity. The elements of immunity that do not 'improve with time' (have no memory) and have little specificity, known as innate or natural immunity, were also studied by several immunologists, although this research often remained in a second level.

Fig. 1. From left to right Bruce A. Beutler, Jules A. Hoffmann © The Nobel Foundation. Photos: Ulla Montan; and Ralph M. Steinman © Rockefeller University.

Despite the detailed knowledge of immunity's reliance on specific, clonal recognition and thus on memory, there have always been two 'squeaky wheels,' (observations that did not fit into what was known) concerning 'simple' and specific antigen recognition:

- First, the need to use adjuvants in immunizations, which has been called the 'dirty and little secret of immunology' [8]: that is, to obtain an efficient immune response, the antigen alone is not enough. Rather, it has to be 'soiled' with substances that do not in themselves induce a specific response but which promote an effective immune response against the antigen when administered in combination.
- Second is what has been called the 'evolutionary lesson on immunity.' If we analyze the immune response (the host's defenses against microorganisms) in different species, it becomes clear that there is immune protection in species that have no lymphocytes and therefore do not have the molecular and cellular elements that enable a specific, clonal response from memory [12]. Thus, in evolutionarily less-developed species there is 'immunity without lymphocytes,' and even immunity without 'specific' receptors.

These two controversial facts gave rise to the immunological concept that not only does the immune system recognize and distinguish between self and non-self, but also between self and non-infectious/dangerous and non-self and infectious/dangerous in a twofold recognition capacity in which the function of adaptive immunity (self/non-self) complements that of innate immunity (dangerous/non-dangerous). Thus, during the course of evolution, the ability of innate immunity to recognize

what is infectious/dangerous became a critical factor that allowed the adaptive response against non-self to be effective (combining the first signal from the antigen receptor with a second signal from a costimulatory molecule). Furthermore, in the absence of this ability (because the antigen is non-dangerous), antigenic recognition leads to the anergy of adaptive immunology (Fig. 2), and thus a program not to respond. Therefore, the 'equations of the immune response' can be explained by innate immunity:

(a) First signal + second signal (induced by innate signaling) = immune response
(b) First signal (recognition of the receptor for the T- or B-cell receptor antigen) = anergy

The history of the Nobel Prizes awarded to immunologists and the importance of the 2011 Prize

If we trace the history of the Noble Prizes granted to immunologists it becomes clear that contributions from adaptive immunology—from von Behring, in 1901, with his anti-diphtheria serum, to Doherty and Zinkernagel, the 1996 winners for MHC restriction—have been more frequently recognized than contributions from the field of innate immunology (Table 1). In fact, apart from the recognition of Mechnikov in 1908 (which acknowledged the conceptual clash that existed between the defenders of humoral immunity and the defenders of phagocytosis as the main element of defense) and Bordet in 1919 (in which, complement was largely understood as a complementary element of antibodies), research into the innate response was largely ignored until the 2011 prizes awarded to Beutler, Hoffmann, and Steinman. The recognition of Steinman's work was based on his having defined a component of innate immunity (dendritic cells) as the main instigator of adaptive immunity. Nonetheless, the 2011 prizes were the first to highlight the real importance of innate immunity.

Rediscovering the importance of innate immunity

Even if it can be argued that immunology has always taken innate immunity into account, it was only in the late 1980s that its importance came to the forefront of scientific contributions in this field. While numerous researchers participated in this development (e.g., Steinman), the studies by Charles Alderson Janeway, Jr., carried out between 1988 and 1989 [13,14], truly revived innate immunity and its importance, both theoretically and experimentally, by redefining the concept of recognition of dangerous and non-dangerous as the primary basis of the immune response. According to this concept, pathogen-associated molecular patterns (PAMPs), which signal danger, were described, as were pattern recognition receptors (PRRs). In fact, it is highly likely that if Janeway had not died in 2003 (with just 60 years of age), he would have been included in the group of researchers awarded the Nobel Prize in 2011. Perhaps part

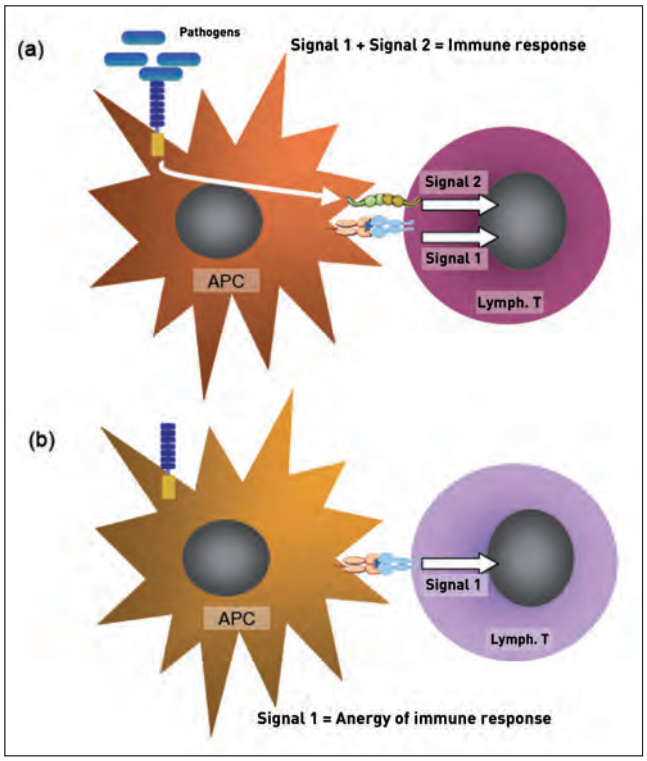

Fig. 2. 'Equations' of the immune response. (a) The immune response is effective when in addition to recognition (signal 1), there is an associated second costimulator signal (signal 2), acting as an accessory molecule and/or cytokine, which tends to be induced by recognition of pathogens/danger by the antigen-presenting cell. This effective simulation of T lymphocytes leads to their proliferation, maturation, and effector functions. (b) In the presence of antigen recognition only (signal 1), even though it is equally or even more specific, a situation of active tolerance called 'anergy' takes place such that T lymphocytes are programmed not to respond.

of the controversy over the 2011 Prize winners stems from the belief that Janeway's studies are the ones which really deserved recognition, as he was the leader of the important work in which his post-doc, Ruslan Medzhitov, demonstrated the role of Toll-like receptors and was the lead author on the publication. But since Janeway had passed away, probably many thought the 2011 Prize should not have been awarded to these studies. It is difficult to judge whether this is the real reason why the Nobel jury honored the contributions of Beutler's group, published in 1998 [19], instead of those of Medzhitov (and thus Janeway's group), published in 1997 [16]. In any event, beyond the issue of whether others may have deserved the 2011 Prize, there is no question that the discoveries made by all three winners were worthy of it. Below is a brief summary of the winners and their work.

Jules A. Hoffmann: How Toll receptors define part of innate immunity in insects

Jules Alphonse Hoffmann was born in Echternach (Luxembourg) on 2 August 1941, the son of an entomologist (Joss Hoffmann, 1911–2000). In 1961, he attended the University of Strasbourg, where he studied biology and chemistry, earning his doctorate in sciences in 1969 under the supervision of

Table 1. List of Nobel Prize winners in Physiology and Medicine related to immunology (those related to innate immunity are shown in bold)

Year of prize	Winner	Concept recognized
1901	Emile von Behring (1854–1917)	Anti-diphtheria serum
1908	**Ilya Ilyich Metchnikoff (1845–1916)**	**Immunity (phagocytes)**
1908	Paul Ehrlich (1854–1915)	Immunity (concepts/humoral, …)
1913	Charles R. Richet (1850–1935)	Anaphylaxis
1919	**Jules Bordet (1870–1961)**	**Complement in immunity**
1930	Karl Landsteiner (1868–1943)	Blood groups
1951	Max Theiler (1899–1972)	Yellow fever vaccine
1957	Daniel Bovet (1907–1992)	Allergy treatment with anti-H1 drugs
1960	Peter Brian Medawar (1915–1987)	Acquired tolerance in transplants
1960	Frank Macfarlane Burnet (1899–1985)	Tolerance/clonal selection theory
1972	Gerald M. Edelman (1929–)	Immunoglobulin structure
1972	Rodney R. Porter (1917–1985)	Immunoglobulins and affinity chromatography
1977	Rosalyn Yalow (1921–2011)	Immunoassays: RIA
1980	George D. Snell (1903–1996)	MHCs of mice
1980	Jean Dausset (1916–2009)	MHC of humans
1980	Baruj Benacerraf (1920–2011)	MHC, immune response and allorecognition
1984	Niels K. Jerne (1911–1994)	Control and regulation of immunity
1984	George J.F. Köhler (1946–1995)	Monoclonal antibodies
1984	César Milstein (1927–2002)	Monoclonal antibodies
1987	Susumu Tonegawa (1939–)	Diversity of immunoglobulins
1990	Joseph E. Murray (1919–)	Kidney transplant
1990	E. Donnall Thomas (1920–)	Bone marrow transplant
1996	Rolf M Zinkernagel (1944–)	MHC-restriction to antigen recognition by TCR
1996	Peter C. Doherty (1940–)	MHC-restriction to antigen recognition by TCR
2008	Harald zur Hausen (1936–)	Description of the HPV and cervix cancer vaccine
2008	Françoise Barré-Sinoussi (1947–)	Description of HIV
2008	Luc Montagnier (1932–)	Description of HIV
2011	**Jules A. Hoffmann (1941–)**	**Toll in *Drosophila* as innate immunity**
2011	**Bruce A. Beutler (1957–)**	**TLRs in mice in innate immunity**
2011	**Ralph M. Steinman 1953–2011)**	**Dendritic cells**

Pierre Jolie. With this background, Hoffmann embarked upon a post-doctoral stay in Marburg and in 1978 rejoined the University of Strasbourg, where he would spend his entire research career, as a professor of zoology and general biology.

Hoffmann's work has always revolved around the immunity of insects, especially *Drosophila melanogaster*, the most well-known animal model in genetics studies. Using this model and based on previous work describing the presence of powerful antimicrobial substances in insects (diptericin, drosocin, defensin, drosomycin, etc.), Hoffman's group was able to prove that one of the main inducers of the production of these microbicides is a membrane receptor, known as Toll. The name 'Toll' was conferred by Christiane Nüsslein-Volhard (a Nobel Prize winner in 1995), who studied the embryonic development and dorsoventral polarization of *Drosophila* [3,4]. She saw a strange phenotype in mutant fly larvae and exclaimed, "Das war ja toll!" (which in German means, "That was strange!"). By studying these larvae, she was able to define the existence of the Toll

membrane receptor, which induces nuclear activation through the Cactus–Dorsal pathway when it recognizes the *Spätzle* molecule. The mechanism of action of Dorsal is similar to that of the NF-κB transcription factor, a key element in activating the immune response and inflammation. Perhaps the term 'Toll,' with its German origin, has gained ground in English because it is associated with the concept of tolls, the fees paid to drive on certain roads, in an analogy of the basis of the function of these receptors.

The contribution of Hoffman's team came with their demonstration that stimulation capable of triggering the production of anti-fungal drosomycin is dependent upon the function of this Toll receptor [15], and thus is a prime element in innate immunity as a defense against fungi. Hoffmann's studies based on this finding were reported in his numerous original articles and reviews. These scientific contributions included the discovery that Toll is also activated by bacterial stimuli (via the protein that recognizes peptidoglycans, PGRP-SA) [17] and the description of DmMyD88 (*Drosophila's* counterpart to mammalian MyD88, the main adaptive molecule among the majority of Toll receptors and intracellular signaling) [28]. Conceptually, we could say that the studies performed by Hoffmann's team revealed the importance of the Toll/NF-κB innate recognition system, which has been conserved throughout evolution, from the appearance of the first sponges to the development of today's mammals (including humans).

Bruce A. Beutler: How mammalian TLRs (Toll-like receptors) recognize microbial substances and are primarily responsible for much of the innate response against the microorganism

Bruce Alan Beutler was born in Chicago, Illinois, USA, on 29 December 1957, the son of the renowned German-born hematologist and biomedical scientist Ernest Beutler. He lived in California from 1959 until 1977, when he moved back to Chicago to earn his doctorate in medicine. His interest in the biological underpinnings of illness led him to the laboratory of Abraham Braude (an expert in the biology of lipopolysaccharides, LPS) and defined his professional future. His initial basic studies involved the identification of the molecule responsible for cachexia (an extreme state of malnutrition, muscle atrophy, weakness, and other symptoms associated with major infections and cancer), which was named cachectin but turned out to be TNFα [5], which had already been discovered a decade earlier [10]. Yet, the lack of novelty of his discovery did not discourage Beutler, who went on to focus his attention on the mechanism of LPS action and to determine its true cellular ligand (even though CD14 is known to bind LPS, it is clear that it is not responsible for the latter's effect since it does not lead to intracellular signal transduction). Beutler's team adopted a genetic approach, mapping the gene responsible for LPS resistance in the C3H/HeJ mouse strain. The painstaking work of genomic mapping, carried out over several years, resulted in the identification of TLR4 as the receptor responsible for the flawed signaling in these mice and their resistance to LPS [19]. Toll-like receptors (TLR's) had already been identified, particularly by Janeway's group in a report published the year before [16], in which TLR itself was defined as a crucial element in activating adaptive immunity innately. However, the scientific contribution of Beutler's group is undeniably important: it states that TLR4 recognizes LPS and intracellularly induces cellular activation, which lies at the root of the recognition of dangerous patterns in innate immunity.

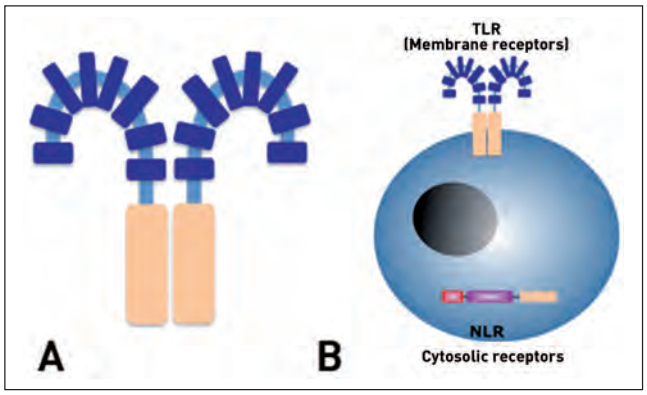

Fig. 3. TLRs and NLRs. (A) A TLR molecule. (B) Distribution of TLRs and NLRs in a cell (adapted from the schema developed by Dr Juan Ignacio Aróstegui, Hospital Clínic).

Beutler mainly carried out his studies first at Rockefeller University in New York, then at the University of Texas at Dallas (where he made the discovery that earned him the Nobel Prize). Since 2000 he has worked at the Scripps Research Institute in La Jolla, California.

The overall contribution of TLRs in our understanding of the recognition function in innate immunity is fundamental because it provides the molecular groundwork for the existence of PRRs as well as PAMPs and their signaling routes, all of which are integral to inflammatory and immune responses [6] (Fig. 3A). In fact, the 13 TLRs described comprise one of the main groups of PRRs, but there are also others. Thus, while TLRs are membrane-associated receptors that detect extracellular PAMPs (TLR1, TLR2, TLR4, TLR5, TLR6, TLR10) or PAMPs in vesicles (TLR3, TLR7, TLR8, TLR9), other receptors sense the cytoplasm of the cell. These NLRs (NOD-like receptors) include the NOD1 and NOD2 molecules (Fig. 3B). Together, the PRRs recognize the main elements that trigger inflammation, which is the physiopathogenic root of most (if not all) diseases.

Ralph M. Steinman: How innate immune cells (dendritic cells) trigger the adaptive response

Ralph Marvin Steinman was born in Montreal, Canada, on 14 January 1943. He studied biology and chemistry at McGill University and later earned a doctorate in medicine at Harvard Medical School in Boston (1968). In 1970, he joined Rockefeller University in New York, where he met other prominent scientists who influenced his career, including Dr Zanvil Cohn, with whom he described the existence of a previously undefined cell type, dendritic cells (DCs) [23–26]. Their name comes from the branching appearance of their extensions ('dendron' means

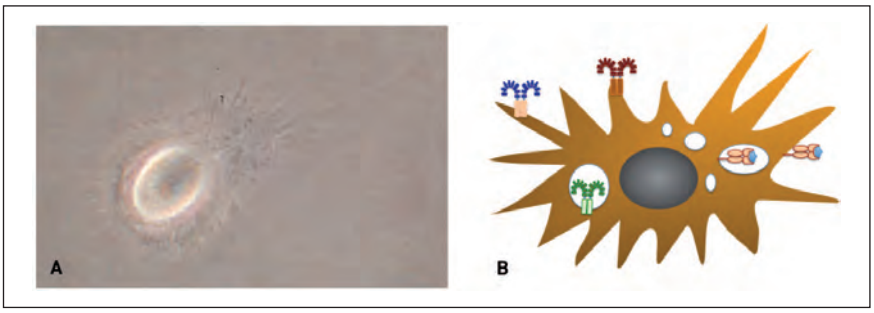

Fig. 4. A phase-contrast microscopic image (provided by Dr Miquel Caballero and Dr Ramon Vilella of the Hospital Clínic) and the general schema of a DC with surface expression of TLRs and intravesicular TLR. The presence of the MHC primarily on the cell surface or intracellularly is one of the elements that distinguishes mature from immature DCs, respectively.

'tree' in Greek). DCs capture and present antigen and, while quantitatively rather unimportant, they are much more efficient at antigen presentation to T lymphocytes (the first step in the adaptive immune response) than other antigen-presenting cells (APCs), such as macrophages and monocytes (Fig. 4A). DCs are actually APCs that can induce an initial response in vitro, demonstrating their effectiveness in activating T lymphocytes, especially those that have not been in contact with the antigen (so-called naive T lymphocytes). Since DCs are related to innate immunity (they have no specific receptors for the antigen) but induce adaptive immunity, they ultimately serve as a kind of 'bridge' between the two branches of the immune response.

Studies on DCs by Steinman and his group were conducted over the course of 30 years. Beginning with a simple yet elegant description of these cells, their properties, and their actions and, in recent work, with studies specifically demonstrating the importance of DCs [27], the persistence and conviction of Steinman and his group are worth highlighting; they are a paradigm of what an investigator immersed in his subject can achieve. In fact, for years many people did not attach any real importance to DCs, and while accepting the scientific validity of Steinman's contributions, other researchers showed little interest in pursuing their implications, with only a handful of outsiders acknowledging the real importance of DCs. Thus, it was Steinman's steadfastness that finally ensconced these cells in the place they deserve, as the backbone of the immune response.

The development in the 1980s of monoclonal antibodies to DCs changed the approach to their study. Steinman and others contributed to defining two stages of sequential differentiation in DCs: immature DCs, programmed to act as antigen capturers, and mature DCs, in which, following antigen capture, the immature cells differentiate to become APCs, providing the costimulation needed for T lymphocytes to develop an efficient response to the antigen presented [18,25]. It should be noted that physiologically mature DCs are practically the only APCs that can induce effective activation of naive T lymphocytes (Fig. 4B). Generally speaking, other APCs do not tend to induce the proliferation of these cells and may even prompt them to enter anergy.

Current and future biomedical relevance of TLRs and DCs

While these two core contributions, i.e., TLRs and DCs, significantly enhanced our understanding of the innate response, they became even more relevant when their application and functions could be explained in the context of the overall immune response (including the adaptive response). In fact, the presence of TLRs on DCs is one of the determining factors in the maturation of these cells: the recognition of PAMPs by TLRs of immature DCs induces DC maturation and thus, TLRs increases the ability of these cells, now as 'professional' APCs, to present the antigens captured during their immaturity.

For this reason, TLRs are one of the elements that explain both the 'dirty and little secret' of immunology (that antigens must be 'soiled' with PAMPs in order for them to develop an efficient immune response) [8], and the 'lesson learned from evolution' (the immune system is efficient in many species that have no lymphocytes, and the innate response alone is often enough to eliminate pathogens) [12].

Meanwhile, DCs are the 'bridge' needed for the innate response to allow an effecient response and together with it, a kind of protection with immune memory and specificity.

Accordingly, the use of stimulants by TLRs has opened up new opportunities for vaccines, by introducing adjuvants, i.e., PAMP molecules that induce the immune response, to potentiate immunizations; for example, in the new malaria vaccine currently being developed [1]: thus, an antigen already studied but discarded as ineffective has gained renewed interest by being matched with a different adjuvant. Moreover, some TLR polymorphisms have become logical explanations for the differences in the behaviors among different individuals to the same microorganism—such as polymorphisms in TLR5 and legionellosis [9]—and for how harmful mutations trigger immunodeficiencies that challenge our concept of what constitutes an immunodeficiency (such as mutations in TLR3 and herpes simplex encephalitis [30]). Similarly, it is now recognized that mutations in elements common to TLR interactions (e.g., MyD88 or IRAK4) also define novel types of immunodeficiencies, such as the deficiency of MyD88 [29], or processes associated with cancer [20]. Overall, TLR's can be seen as a key to our understanding of aging, atherosclerosis, autoimmunity, and other related phenomena. Through these receptors, we may be able to modify the behavior of many diseases in which inflammation plays a key role.

But it is in the field of DCs in which direct applications are already being developed; for example, extension of the survival of a patient with pancreatic cancer for many years by administering a tumor vaccine with DCs. This may have been the case with Steinman himself, who was diagnosed with cancer in 2005 but who died sometime later, in 2011, just be-

fore the awarding of the Nobel Prize was made public (the jury had already decided, this decision being the reason for the preservation of the prize). In addition, the American Food and Drug Administration, which regulates the introduction of medicines into the US market, has accepted *sipuleucel-T* (APC 8015, Provenge®, Dendreon Corp., Seattle WA) as a treatment for prostate cancer, even though, rather than being a drug, it is a process that entails extracting DCs and re-infusing them in the same patient [22]. There is also now a great deal of data showing that the applications of DCs are not limited to inducing anti-infectious (such as therapeutic vaccines for HIV infection [7]) and anti-tumor responses, but include the option to modulate and change certain undesirable responses, such as by inducing tolerogenic DCs against immunity or inflammation.

Therefore, with our knowledge of TLRs and DCs and thus our improved understanding of the role of the immune response in inflammation as well as pathological processes, new opportunities have arisen to develop effective therapies for a wide range of disorders and diseases. It is not too bold, then, to predict that in the forthcoming years these conceptual contributions will form the basis (as they already have in some cases) of a wide range of medical activities that will help to improve the health of humanity.

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To learn more:

http://www.nobelprize.org/nobel_prizes/medicine/laureates/2011/

* References 15, 19 and 23-26 are the main publications that suppot the award.

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