The role of dendritic cells in vertebrates: a review

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Abstract

Dendritic cells are essential for the induction of adaptive immune responses. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system through a complex mechanism. Therefore, knowledge of this cell type is required to understand also the evolution of immune system in vertebrates. In fact from the amphioxus is possible to follow the evolution of these cells until the man where dendritic cells are present in myeloid and plasmacytoid lines. Besides recent studies define dendritic cells as an independent lineage of hematopoietic cells originating from a common precursor and distinct transcription factors, during the natural history, control the development of these cells until man. Using a comparative approach based on phenotype and function, this review attempts to give a key to classify DC in all classes of vertebrates.

Key words: dendritic cells, immunitary system, vertebrates

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Introduction

The skin is a barrier against water loss and penetration of potentially noxious agents and actively contrasts several of those agents through specific cells and molecules. In fish, the scales form a protective layer and the diverse shapes of different fins provide scaffolds for different ways of locomotion and other functions. In amphibians, the need to live in both water and land has driven the formation of complicated glandular systems, turning the skin into chemical factories. When reptiles started to appear on land, the formation of effective barriers in the suprabasal epidermis was an essential novelty. Also, reptiles evolved scales which are used mainly for defence, but also for locomotion and communication. As animals moved toward endothermy, heat preserving skin appendages, hair and feathers, evolved from scales and contributed to the formation of the mammalian and avian classes [1]. The need to contrast infections has led the skin to become populated by cells of the immune system, among which peculiar dendritic, antigen presenting cells have evolved, which are Langerhans cells [LCs].

Immune functions as phagocytosis and production of cytokines like interleukin [IL]-1 and tumour necrosis factor [TNF] have already emerged 700 million years ago in starfishes and sponges. Functions representatives of innate immunity — including recruitment of phagocytic cells, oxidative burst, killing by bactericidal proteins [lysozymes, defensins and others] and opsonization by complement analogous proteins — were maintained during phylogenesis and are found in insects as well as mammals. The importance of the underlying molecular mechanisms is reflected in homology of conservative regions. One of the biggest evolutionary steps happened 500 million years ago when Placoderms developed a jaw. This step probably was associated with and led to the development of gut associated immune system. The system was the basis to create the genetic basis to establish variability and diversity of proteins, as immunoglobulins, through recombination and mutation [2].

Dendritic cells [DCs] and their importance in antigen presentation came into focus of interest in the last half century. They have myeloid and lymphoid origin, include subtypes with characteristic membrane markers [clusters of differentiation: CD] and cytokine profile and may appear mature or immature with distinctive functional ability.

Dendritic cells are capable of presenting antigens through major histocompatibility complex [MHC] I and II. They stimulate both primary and secondary immune response and seem to be unique in the ability to stimulate primary responses. Depending on conditions not yet clear, they can also induce active tolerance [3, 4], therefore DCs are primary regulators of acquired immune response; they also participate to natural immune response.

The phenotype and functions of DCs and their precursors in the skin and in other tissues are best characterized in humans and mice, however analogous cells have been identified and in some cases even generated in vitro in many different species adapting methods developed for humans and mice [5].

Cells with features of DCs have been identified in sharks [6, 7], bony fishes [7-12], amphibians [13-17], reptiles [18-20], birds [21-25], and mammals. Dendritic cells proper have not yet been demonstrated in agnatha vertebrates nor amphioxus, however in the latter paralog genes of MHC complex have been identified, as well as two populations of lymphocyte-like cells [26-28]. Factors that regulate and stimulate the differentiation and maturation of DCs – among which IL-1, IL-4, granulocyte-macrophage colony stimulating factor [GM-CSF], IL-6, TNF, pro-opiomelanocortin derived peptides – are similar [paralogs] among vertebrates, to the extent that human factors can stimulate fish cells to differentiate into DCs in culture [10, 26], and some date back to starfishes and sponges [29]; a proto-MHC has been identified in placozoans [2], suggesting that the evolution of immune system has started very early in the animal kingdom. Transcription factors that mediate those stimuli are maintained through vertebrates and are strictly correlated with those that

regulate immune responses in non-vertebrate chordates [amphioxus]; among them, homologs of zinc finger proteins ZBTB46 and DC-SCRIPT/ZNF366 [30] and NF-κB [26]. The common phenotype is characterized by the expression of ATPase and S100 antigen [13, 15, 18, 20]; although not all CD surface antigens may yet be explored, some have proved to be highly conserved, such as MHC-II, CD8a [11], CD83 [already found in sharks and crucial for antigen presentation [7, 31], CD86, langerin/CD207 [typical of LCs] [9, 12], and others, including Toll-like receptors and other pattern recognition receptors.

Amphioxus

Amphioxi [collectively indicated as amphioxus] are a group of species basal in the chordates. Their genome has a large degree of synteny with that of vertebrates and they are well-accepted as a model vertebrate ancestor. Coelomocytes, free phagocytes in the coelomic cavity, are present in amphioxus and macrophage-like cells have been found in amphioxus gut mucosa and participate in defence against bacterial infection [32]; amphioxus may be a key intermediate between natural and acquired immunity, since it shows an adaptive response based on domain recombination [26-28, 33] and expresses two macrophage migration inhibitory factors [MIF] [34-35], a cytokine involved in lymphocyte-macrophage interaction [36], and at least one acidic lysozyme, a type of defensive molecule present in vertebrates but absent from urochordata [37].

Fish

Jawed fishes are the earliest vertebrates capable of adaptive immunity, and the molecular machinery necessary for antigen processing and presentation is present and functional in these species [38], in much the same way as in mammals [39]. Cells expressing homologs of CD83 [7] and DCs in lymphoid organs have been identified in sharks [6]. Cells containing Birbeck-like granules and expressing langerin/CD207 have been found in several bony fish species [9, 12]; a DC-like phagocytic cell line has been described in Atlantic salmon [40]; and a population of leukocytes coexpressing MHC-II and CD8alpha is present in the trout skin. This population constitutes • 1.2% of the total leukocyte population in the skin, shows phenotypical and functional characteristics of semimature DCs and expresses CD141 and CD103 homologs [11]. Lugo-Villarino et al. [2010, 41] described the existence of dendritic antigen presenting cells in zebrafish based on morphology, staining characteristics, and functional assays involving the measurement of antigen specific recall responses, however the ability of these cells to stimulate primary immune responses has still to be challenged.

Amphibians

The existence of DCs in amphibian epidermis was demonstrated for the first time in 1990 [42]. These cells are similar to mammalian LCs and express MHC-II, ATPase, a non-specific esterase and vimentin [13, 15]: Birbeck granules have not yet been described in amphibians, despite the fact that they are present both in bony fish and reptiles. The study of DCs in amphibians seems to be much less advanced than in other species.

Reptiles

ATPase positive dendritic cells were detected in turtle skin and display structures similar to Birbeck granules [18, 43], they are positive for S100 [20]. Similar cells have been found in newts [14], Xenopus [15, 16], and Lacerta vivipara [44]. The density and staining intensity of LCs in reptile skin undergo seasonal variations with a maximum in spring and autumn and a minimum in summer and winter. This hints to a dependency of the immune system of lower vertebrates on environmental factors such as the annual cycle of daylight and temperature [45].

Birds

Carrillo-Farga et al. [1991] [42] first described the presence of ATPase positive DCs, morphologically similar to LCs, in the avian epidermis. These cells were MHC-II positive and contained Birbeck granules. Two decades later, Igyarto et al. [2006] [46]

showed that ATPase+ epidermal DCs also express CD45 and vimentin, similar to mammalian LCs and opposite to keratinocytes. These cells were further distinguished into groups based on the expression of MHC II and CD3: type I epidermal DCs are MHC II+ CD3- and represent the avian analogues of mammalian LCs; they are capable of antigen uptake and presentation. In the chicken, there are two isoforms of CD1, CD1-1 and CD1-2 [46].

Mammals

Functional phenotypes of DCs have been well studied in mammals. Particular attention has been reserved to humans and mouse, the most extensively studied model for immune response in mammals.

Humans

Two main classes of DCs have been identified in humans: myeloid DCs [mDCs] and plasmacytoid DCs [pDCs]. The former are known since longer time and may appear in tissues in two different states, immature and mature. Immature mDCs are found in not-inflamed peripheral tissues and can absorb and process antigens. Mature mDCs are found in lymphoid organs and also in peripheral tissues upon inflammation; they present antigens to lymphocyte and elicit and regulate acquired immune response. Myeloid DCs also concur to regulate natural immune responses and inflammation through secretion of molecules and interaction with many cell types [47-50].

A special type of immature mDCs is LCs, found in stratified squamous epithelia. They were initially identified as a specific population thanks to a peculiar, disc shaped organelle, the Birbeck granule [51], which is involved receptor-mediated endocytosis [52] More recently, langerin/CD207 has been identified as a marker of these cells: it is a membrane C-type lectin [53-54] that recognizes mannosylated ligands found on the surface of a wide range of pathogens including viruses, bacteria, fungi, and protozoa [55] and is used by the cell for absorption of soluble ligands and traffic through Birbeck granules to endosomes, a step in antigen processing for presentation to lymphocytes. Langerin may be found in cells and be contained in endosomes also in the absence of Birbeck granules [53-58]. Other markers include ATPase, S100b, CD1a, besides MHC-II. CD1a is an MHC-I-like, non-polymorphic molecule through which microbial lipids can be presented to T cells [59]. It is conceived that epidermal LCs are continuously replaced from a resident precursor pool [perhaps by self-renewal] under steady-state conditions [54]; following inflammation LCs are repopulated by blood precursors, most likely monocytes [60]. Langerhans cells can mediate contact sensitization against low doses of haptens [61].

Connective tissue mDCs are characterized by the expression of CD11c and dendritic cell-specific ICAM-3-grabbing non-integrin [DC-SIGN]/CD209 [62].

All mDCs come to express co-stimulatory molecules upon maturation, including ICAM-1/CD54, CD80, CD86 [63-68], and also CD83 that has proved necessary to lymphocyte stimulation [31].

Plasmacytoid DCs are characterized by morphology, secretion of high amounts of type I interpherons [IFN-alpha, beta, omega] and life cycle; they may be found in normal lymph nodes, in blood and in inflamed peripheral tissues. CD303, i.e. BDCA-2, is the only marker exclusive to pDCs [69]. Plasmacyoid DCs express a different set of toll-like receptors [TLR] than mDCs [70], in particular, they recognize viral components through TLR7 and TLR9. At variance with mDCs, pDCs arise from a bone marrow common DC precursor [71, 72], circulate in the blood as already differentiated and enter lymphoid organs through high endothelial venules [HEV; 73]. A small number of pDCs has been found in normal skin [62, 74, 75], but in general they are not abundant in quiescent peripheral tissues while they are present in lymph nodes as about 20% of MHC class II positive cells and are rapidly recruited to sites in inflammation [75].

Mouse

Mouse epidermis hosts LCs, which express MHC-II, CD11b, CD40, CD86 and CD205, besides CD8 at low level. Mouse LCs do not express CD1a antigen but express langerin/CD207 which allows for specific recognition [53]. Most of the anti-murine langerin antibodies are directed against intracellular portions of the molecule. An antibody against a cell surface exposed epitope of langerin has been generated recently, however the fast internalization of extracellular langerin may make sorting tricky [62, 76, 77].

Mouse connective tissues mDCs express - among others - SIGNR3, the homologue of human DC-SIGN [78] other than CD11b and Sirpalpha [79].

Plasmacytoid DCs [pDCs] have been identified in mouse spleen, bone marrow, thymus and lymph nodes [80, 81]. These cells display characteristics different from other DC subsets and share most of the morphological and functional characteristics of their human counterparts. They enter lymph nodes directly from blood thanks to CD62L. Freshly isolated mouse pDCs express B220 and Gr-1 together with MHC-II, CD8α, CD11c and CD205, and lack costimulatory molecules. Other mouse pDCs-restricted surface markers have been identified with additional monoclonal antibodies, 120G8, 440c, and mPDCA-1 [80]. It has been suggested that mouse pDCs, as well as thymic $CD8\alpha^+$ DCs, are of lymphoid lineage. Most pDC develop from a common DC progenitor in the bone marrow that expresses cytokine receptors Flt3 [CD135], M-CSFR [CD115], and low levels of c-Kit [CD117]. $Flt3^+$ c-Kit^{low} is a broad definition of lymphoid progenitors, including the canonical IL-$7R\alpha^+$ common lymphoid progenitor, that can give rise to pDCs upon adoptive transfer. Therefore, at least a fraction of pDCs may be of lymphoid lineage derivation. A fully committed pDCs progenitor remains to be identified but may reside within the $Flt3^+$ $CD11c^+$ Ly-$6C^+$ population in the murine bone marrow [82]. Treatment of mice with FLT3-ligand [Flt3L] results in strikingly increased numbers of pDCs in bone marrow and spleen, whereas Flt3L-deficient mice have fewer pDCs. Therefore, Flt3L is considered the main cytokine for the development of these cells from hematopoietic stem cells in mice. In steady-state conditions, bromodeoxyuridine labeling experiments indicate that pDCs in mice have an average turnover of about 2 weeks whereas mDCs have a quicker turnover, of 3 to 5 days in the tissue [80].

Concluding remarks

The cellular immune system started with phagocytic mesenchymal cells. From fish dendritic cells are present, linking innate and adaptive immune responses. The comprehension of dendritic cells function is essential for the development of new treatments as well as opening new research opportunities. This quick review of the natural history of these cells in vertebrates, from amphioxus to humans, is meant as a framework to stimulate questions and research in the field.

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