


New EMBO Member's Review

Nuclear receptor signalling in dendritic cells connects lipids, the genome and immune function

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Dendritic cells (DCs) are sentinels of the immune system and represent a heterogeneous cell population. The existence of distinct DC subsets is due to their inherent plasticity and to the changing microenvironment modulating their immunological properties. Numerous signalling pathways have impacts on DCs. It appears that besides cytokines/chemokines, lipid mediators also have profound effects on the immunogenicity of DCs. Some of these lipid mediators exert an effect through nuclear hormone receptors. Interestingly, more recent findings suggest that DCs are able to convert precursors to active hormones, ligands for nuclear receptors. Some of these DC-derived lipids, in particular retinoic acid (RA), have a central function in shaping T-cell development and effector functions. In this review, we summarize and highlight the function of a set of nuclear receptors (PPAR γ , RA receptor, vitamin D receptor and glucocorticoid receptor) in DC biology. Defining the contribution of nuclear hormone receptor signalling in DCs can help one to understand the regulatory logic of lipid signalling and allow the exploitation of their potential for therapeutic intervention in various immunological diseases.

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Immunological functions of dendritic cells serve the regulation of the adaptive immune response

Antigen presentation is a key step in engaging the adaptive immune response. Traditionally, macrophages and B cells were thought to be the only cell types able to present antigens to T cells and thus elicit immune response. The pioneering work of Steinman and Cohn showed that a third kind of antigen-presenting cell types, dendritic cells (DCs), are indispensable for the initiation of the adaptive immune response (Steinman and Cohn, 1973; Banchereau and Steinman, 1998). The migratory, tissue-resident DCs work at the interface of peripheral tissues and lymphoid organs. These cells are sentinels of the immune system, and they sense and translate environmental cues by sampling and processing extracellular and intracellular antigens (Figure 1). DCs are able to pick up antigens using various uptake mechanisms (Norbury, 2006; Savina and Amigorena, 2007). A key defining feature of this cell type is that after antigen uptake and processing, DCs migrate to lymph nodes, where they present antigens and stimulate T cells (Figure 1, insert). DCs are armed with numerous receptors that detect 'danger' signals in the surrounding environment. These signals, associated with an ongoing infection, such as pathogen-associated molecular patterns or pro-inflammatory cytokines, cause DCs to undergo phenotypic changes (maturation, activation) that maximize their ability to elicit proliferation of T cells. Mature DCs have an extraordinary capacity to activate naive T cells owing to the high expression of various costimulatory molecules (Ni and O'Neill, 1997). However, besides eliciting immune response, DCs could also provoke immunological tolerance by inducing deletion or anergy; thus, DCs contribute to limiting autoimmunity (Cools *et al.*, 2007). There are several mechanisms for the maintenance of peripheral tolerance, one of which is when external stimuli reprogramme DCs towards a less activated tolerogenic cell type.

DCs form a heterogeneous cell population, which could be classified as plasmacytoid or conventional DCs (Shortman and Naik, 2007). DCs could also be subdivided into migratory DCs, which reside in peripheral tissues, or lymphoid organ-resident DCs, which constitute 50% of the lymph node DCs, and all the splenic and thymic DCs (Villadangos and Schnorrer, 2007). The molecular details of the regulation of DC differentiation are still poorly characterized, although it was described and suggested that several cytokines and transcription factors are necessary for DC development

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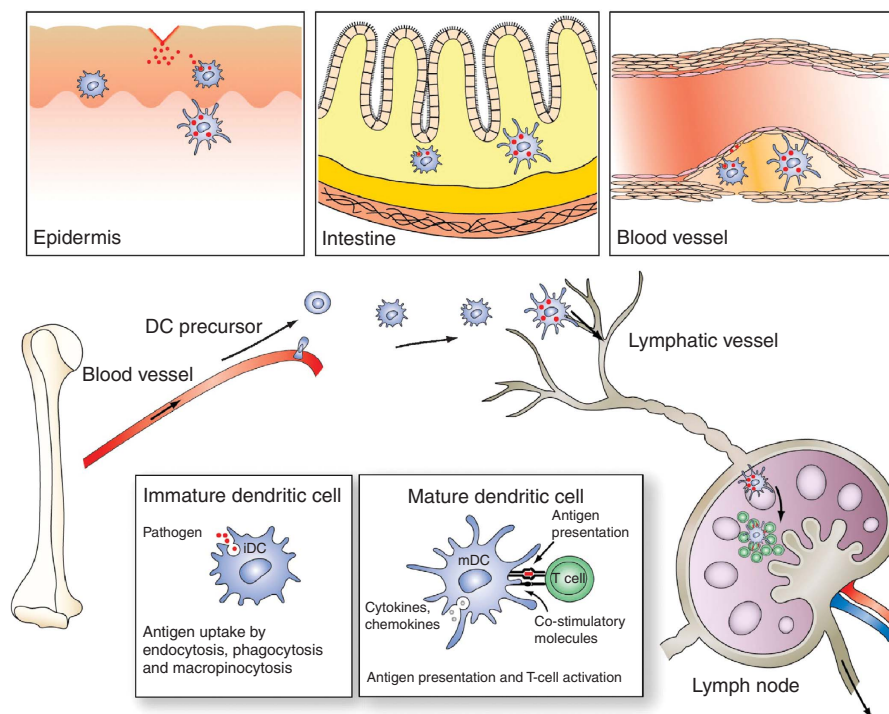


Figure 1 The immunological function of DCs. Differentiation and migration of tissue-resident DCs. DC precursors are bone marrow-derived cells that leave the blood vessel and reside in various tissues in the periphery (for example, epidermis, intestine or the vessel wall or the atherosclerotic plaque) as immature DCs. These cells are well armed for sampling antigens and can receive various cues from the surrounding tissues. Antigen uptake associated with ‘danger signals’ leads to DC maturation and migration of draining lymph nodes. In the lymph nodes, mature DCs present antigens to naive T cells and activate them.

(Zenke and Hieronymus, 2006; Wu and Liu, 2007). Flt3 ligand is critical for the development of both conventional and plasmacytoid DC differentiation; in contrast, GM-CSF promotes only conventional DC development (Wu and Liu, 2007). In addition, in humans, treatment with IL-4 and GM-CSF cytokine is used for the *ex vivo* generation of monocyte-derived DCs (Sallusto and Lanzavecchia, 1994). Much less is known about the transcriptional regulation of DC development, and only a few putative ‘master’ transcription factors have been identified so far (Zenke and Hieronymus, 2006). A microarray study indicated that some nuclear proteins/transcription factors, including PPAR γ and LXR α nuclear hormone receptors, are induced during monocyte-derived DC development (Le Naour *et al*, 2001). Our global gene expression profiling also showed that 20 out of 48 nuclear receptors are present in human monocyte-derived DCs (L Nagy *et al*, unpublished results). These findings indicate that nuclear receptors are likely to have functions in the differentiation and function of this cell type.

Nuclear hormone receptors are ligand-activated transcription factors that modulate gene expression through binding to specific hormone response elements. It is well established that ligands/hormones (i.e. retinoids (metabolites of vitamin A), vitamin D, glucocorticoids (GCs)) of nuclear receptors, besides regulating development and metabolism, also have an impact on the immune system. It was assumed that the main immune targets of these ligands are lymphocytes. Now this picture is being altered by findings that activators of these receptors can also modulate DC differentiation and function. In the first part of this review, we will provide an introduction to the function of lipids in DC biology, and

then summarize the potential function of nuclear hormone receptors in DC differentiation and function. We will focus on RXR heterodimeric receptors (PPAR, RAR, LXR and vitamin D receptor (VDR)) and also discuss the potential function of GC receptors in DC function. In the second part, we will provide an overview on how endogenous ligand production for these receptors is taking place in DCs.

DCs are exposed to lipids

In the body, there are several tissue compartments in which DCs are likely to be exposed to large amounts of lipids. An obvious one is the gut-associated lymphoid tissue (GALT) where diet-derived lipids, fatty acids, retinoids and cholesterol are abundant (Figure 1). In the small intestine, the lamina propria is important to maintain peripheral tolerance towards commensal bacterial flora (Nagler-Anderson and Shi, 2001), and the dietary lipid mediators might contribute to this type of tolerance. It is well established that the atherosclerotic plaques contain macrophages and T cells; however, DCs were also detected in the plaques (Bobryshev and Lord, 1995; Angeli *et al*, 2004). In this microenvironment, cells are encountering oxidized low-density lipoproteins (oxLDL). In addition, several other active lipid mediators might be present, which could modulate the migratory and immunological properties of the cells (Figure 1).

Tissue-resident DCs sense and translate environmental cues by sampling and processing protein antigens; however, these cells can also present lipid/glycolipid antigens through CD1 cell surface molecules (Brigl and Brenner, 2004). CD1s molecules are critical for the presentation of various bacterial

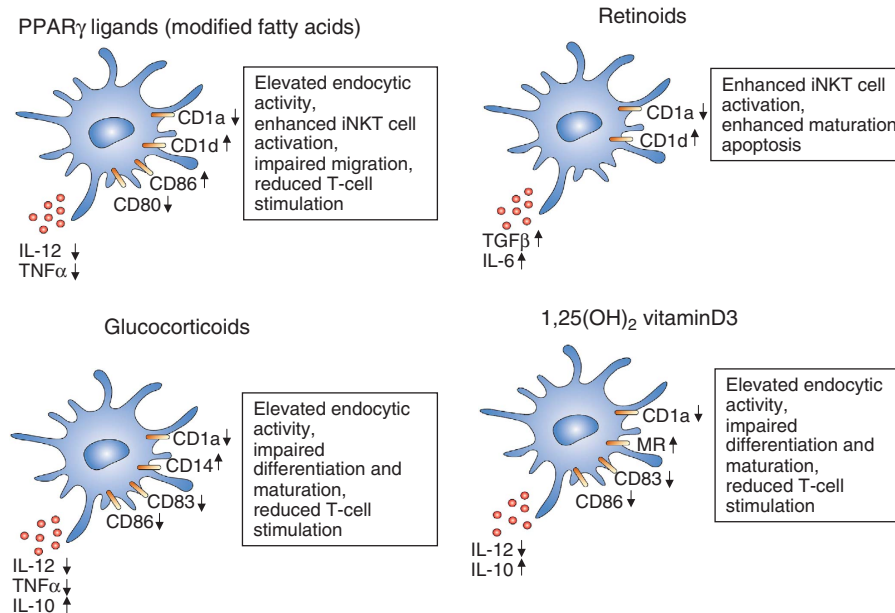


Figure 2 Effects of nuclear receptor agonists on the immunophenotype of DCs. Characteristic changes of cell surface markers and cytokine production on DCs on nuclear receptor activation. Here, we summarize the effects of PPAR γ activators, retinoids, glucocorticoids and the active form of vitamin D on monocyte-derived DCs.

glycolipid/peptidolipid antigens (Willcox *et al*, 2007), but the ways in which endogenous lipids are recognized and presented are still poorly characterized (Tsuji, 2006). An interesting aspect of lipid antigen presentation is that extracellular lipid particles facilitate the uptake of pathogen-derived CD1 ligands. For example, apoptotic bodies from mycobacterium-infected macrophages are efficient vehicles for lipid uptake of uninfected DCs (Schaible *et al*, 2003); in addition, a CD1d ligand precursor is delivered to DCs by apolipoproteins (van den Elzen *et al*, 2005). These results underscore the notion that the local lipid environment has the ability to modify the lipid presentation capacity of DCs. In addition, lipid-derived mediators also elicit intracellular signalling, which alters the maturation and immunogenicity of the antigen-presenting cells. Human monocyte-derived DC maturation is induced by oxLDL exposure and this effect is mediated by lysophosphatidyl choline through the activation of a G-protein-coupled receptor (Coutant *et al*, 2002). DCs also sense and integrate lipid signals through PG receptors; for example, DC migration and cytokine production could be modulated by PGE2 and LTB4. PGD is also an important modulator of DC function (Harizi and Gualde, 2005). As we have briefly highlighted, DCs sense the lipid environment by various cell membrane receptors, and now there is an increasing amount of evidence to suggest that DCs could also survey the lipid environment by lipid sensing nuclear hormone receptors. In the following section, we summarize the potential function of these lipid-activated nuclear receptors in DCs.

The function of lipid-activated nuclear hormone receptors PPARs and LXRs in DCs

Candidates for sensing the lipid environment in DCs are the PPAR receptors. PPARs are fatty acid sensors that regulate various facets of lipid metabolism. There are three isoforms of PPARs, α , γ and δ/β . These receptors have key physiological

functions; for example, PPAR α promotes fatty acid oxidation in the liver (Lefebvre *et al*, 2006), PPAR γ is indispensable for adipocyte differentiation and generally stimulates lipid storage (Willson *et al*, 2001), and PPAR δ is an important regulator of skeletal muscle lipid oxidation (Barish *et al*, 2006). Recent findings indicated that these receptors, especially PPAR γ , have important functions in DC biology (Figure 2). Initially, a comprehensive microarray study indicated that in humans, monocyte-derived DCs have an elevated expression of PPAR γ (Le Naour *et al*, 2001). This finding was consistent with a previous observation indicating that IL-4 is a positive regulator of PPAR γ in human and murine monocytes/macrophages (Huang *et al*, 1999). Later, it was confirmed by several laboratories that both the mRNA and also the protein of PPAR γ are induced in human monocyte-derived DCs (Gosset *et al*, 2001; Nencioni *et al*, 2002; Szatmari *et al*, 2004). In addition, we found that the *bona fide* PPAR γ target (FABP4/aP2) is highly upregulated upon PPAR γ ligand treatment in developing human DCs. Moreover, *ex vivo* cultured blood-derived conventional (CD1c+) DCs also express PPAR γ . Finally, in human lymphoid tissues (tonsils), several PPAR γ and S100 double-positive cells were detected, suggesting that at least a sub-population of lymphoid tissue DCs express this receptor (Szatmari *et al*, 2004). Murine splenic CD11c+ DCs also express PPAR γ (Faveeuw *et al*, 2000) and this nuclear receptor was detected in bone marrow-derived murine DCs (Hammad *et al*, 2004). The changes in PPAR γ expression during various stages of DC development are still poorly characterized; however, it was described that the CD1a-negative population of monocyte-derived DCs express more PPAR γ than the CD1a-positive counterparts (Gogolak *et al*, 2007).

The effects of PPAR γ activators on the immunological function and phenotype of *ex vivo* cultured DCs were investigated in detail. PPAR γ -activated immature DCs have an enhanced phagocytic activity; in addition, these cells possess

a diminished migratory capacity (Angeli *et al*, 2003; Szatmari *et al*, 2004; Appel *et al*, 2005). PPAR γ -activated human DCs produce less IL-12 and TNF α ; moreover, these cells secrete lower amounts of MCP2, IP-10 and RANTES chemokines (Gosset *et al*, 2001; Nencioni *et al*, 2002) (Figure 2). Furthermore, PPAR γ -instructed DCs have an altered cell surface expression pattern of co-stimulatory molecules; they express less CD80 but increased CD86 (Gosset *et al*, 2001; Nencioni *et al*, 2002; Szatmari *et al*, 2004). These observations appeared to be consistent with a model in which PPAR γ -activated DCs skew the differentiation to a special DC subset that has a reduced Th1 activation capacity but an enhanced Th2 activation propensity (Faveeuw *et al*, 2000; Gosset *et al*, 2001). Others suggested that the activation of the PPAR γ pathway generally reduces/inhibits the immunogenicity of developing human DCs (Nencioni *et al*, 2002; Appel *et al*, 2005). Recently, in murine DCs, a similar effect was observed, suggesting that PPAR γ activation has a negative effect on the stimulatory capacity of DCs. More importantly, in the same report, PPAR γ -deficient DCs were used and the authors found that PPAR γ 's effects on the stimulatory capacity of the cells are receptor dependent (Klotz *et al*, 2007). However, the molecular mechanism of this negative regulation is not clear. By analogy, the anti-inflammatory properties of PPAR γ ligands are better characterized in murine macrophages. One suggested mechanism for this activity is the sumoylation of the receptor and recruitment of co-repressors on the promoter region of NF- κ B-binding sites of various inflammatory genes (Pascual *et al*, 2005). In DCs, it was suggested that the PPAR γ ligand treatment interfered with the activation of the NF- κ B and the MAP kinase pathways (Appel *et al*, 2005). Interestingly, besides these essentially inhibitory activities, PPAR γ appears to possess positive regulatory activities in immune cells as well. Our recent global gene expression profiling study revealed that on acute PPAR γ ligand treatment, more than 100 genes were immediately induced and most of these early activated genes fall into the lipid metabolism category (Szatmari *et al*, 2007). In contrast, immune response-related genes were induced only after 24 h or later, suggesting that PPAR γ activation directly regulates lipid metabolism of these cells but rather indirectly modifies the immune phenotype of DCs. As we have described in the previous section, DCs are able to present lipid antigens by CD1 antigen-presenting molecules. Our results indicated that the PPAR γ ligand coordinately regulates the CD1 gene family expression in human monocyte-derived DCs. PPAR γ -activated DCs express less CD1a (Nencioni *et al*, 2002; Szatmari *et al*, 2004), but have an elevated expression of CD1d. More importantly, the elevated expression of CD1d was coupled to the enhanced capacity to activate a CD1d-dependent cell type, the iNKT (invariant natural killer T) cells (Szatmari *et al*, 2004). The lack of iNKT cell activation has been implicated in the development of autoimmune conditions, suggesting that iNKT cells are intimately linked to sustaining immunological tolerance (Hammond and Kronenberg, 2003). We also defined the possible mechanism for this regulation: PPAR γ indirectly stimulated the expression of CD1d through the production of all-*trans* retinoic acid (ATRA), the natural ligand of RA receptors (RARs) (Szatmari *et al*, 2006a). Confirming this, it was reported recently that the human CD1d promoter contains a retinoid response element (Chen and Ross, 2007). We

also described that PPAR γ -activated DCs have an elevated expression of ABCG2, a xenobiotic transporter. These results suggested that the PPAR γ activation modifies the xenobiotic and drug resistance of human DCs (Szatmari *et al*, 2006b).

The functions of the other two PPAR receptors are poorly characterized in DCs. We and others described that DCs express very low levels of PPAR α . Consistent with this finding, PPAR α ligand treatment has only a marginal effect on monocyte-derived DC differentiation and function (Gosset *et al*, 2001; Szatmari *et al*, 2004). In contrast, it was shown that PPAR α is present in human epidermal DCs (Langerhans cells) and that the activation of the PPAR α pathway blocks the activation and migration of these skin DCs (Dubrac *et al*, 2007). Curiously, DCs also express PPAR δ (Szatmari *et al*, 2004), but the potential role of these receptors in DC function is not yet characterized. Another metabolite receptor, the liver X receptors (LXRs), the sensor of oxidized forms of cholesterol (Zelcer and Tontonoz, 2006), were reported to be upregulated during monocyte-derived DC development; moreover, LXR ligand-treated DCs have a reduced T-cell activation capacity (Geyeregger *et al*, 2007). These nuclear hormone receptors are metabolic sensors. The natural ligands of these receptors are poorly characterized (polyunsaturated fatty acids, oxidized fatty acids or cholesterol). Therefore, much remains to be discovered how the receptor's endogenous activation takes place. Nevertheless, high-affinity synthetic ligands for these receptors are available to probe their function in DCs *ex vivo* and potentially *in vivo*. In the next sections, we describe the potential function of two receptors having a high-affinity hormonal ligand in DC biology.

Vitamin D and GCs are modulators of DC differentiation and activation

Activators of GC and VDRs have profound immunosuppressive effects. It was assumed that lymphocytes are the main target of these compounds. However, several *in vitro* and some *in vivo* observations suggested that GCs and vitamin D also diminished the immunogenicity of DCs and that these effects might contribute to the impaired immune response and to the anti-inflammatory effects. There are a few recent reviews that provide an overview on the immunosuppressive effects of GCs and vitamin D on DCs (Abe and Thomson, 2003; Hackstein and Thomson, 2004; van Etten and Mathieu, 2005), and thus we only briefly discuss the effects of these ligands on DC biology.

The immunosuppressive effects of GCs have been well documented and several studies have suggested that, among other cell types, DCs are also affected. GCs decrease the co-stimulatory molecule expression in murine DCs, and therefore these cells have a poor T-cell stimulatory capacity *in vitro* and *in vivo* (Moser *et al*, 1995). In humans, GC-treated monocyte-derived DCs have a reduced T-cell activation capacity; moreover, GCs interfere with the differentiation of DCs from monocytes (Piemonti *et al*, 1999; Rea *et al*, 2000) (Figure 2). The anti-inflammatory effects of GCs are well characterized, but the molecular mechanisms are still poorly defined (Hackstein and Thomson, 2004). It has been shown that GCs regulate the immune function of T cells and DCs parallelly by the coordinated activation of the GITR ligand in T cells and the induction of GITR receptors in plasmacytoid DCs. This signalling in DCs leads to a non-canonical

NF- κ B-dependent induction of indolamine 2,3-dioxygenase (IDO), a key enzyme that catalyses the initial and rate-limiting step in the degradation of tryptophan and a negative modulator of lymphocyte proliferation (Grohmann *et al*, 2007). In addition, GCs exert an IDO-dependent protection in a model of allergic airway inflammation. These observations clearly establish DCs as valid targets of GC action.

The active form of vitamin D also has immunosuppressive effects, and numerous studies have shown that the regulation of DC immunofunctions is an important part of this profound suppressive activity. $1\alpha,25$ dihydroxy vitamin D₃ highly suppresses the activation/maturation of DCs; moreover, these cells have diminished T-cell activation capacity (Penna and Adorini, 2000; Piemonti *et al*, 2000) (Figure 2). An *in vivo* murine model has also confirmed that the administration of VDR agonist negatively modulates the stimulatory capacity of DCs. Consistent with this finding, VDR-deficient mice have hypertrophy of subcutaneous lymph nodes and an elevated number of mature DCs (Griffin *et al*, 2001). The ways in which VDR carries out its functions, whether it interferes with positive signalling or induces suppressor molecules directly or simply inhibits DC differentiation and/or maturation is not clear. It was suggested that VDR transcriptionally represses the expression of one of the components of NF- κ B (RelB), thus blocking the activation of DCs (Dong *et al*, 2003) (Figure 2). The extent of this mechanism is not known.

In summary, the data obtained to date suggest that the activation of GC or VDR has profound inhibitory or immunosuppressive/tolerogenic effects in DCs' immunophenotype and that these pathways are potentially amenable to therapeutic exploitation. In the next section, we discuss the function of retinoids, which show a much more complex behaviour having both repressive and activator functions in DCs.

Regulation of DCs by retinoids

It is well known that retinoids (derivatives of vitamin A and ligands of RAR and RXR receptors) exert a modulatory effect on the immune system. Vitamin A deficiency causes immune dysfunction and increases the susceptibility of an individual to infectious diseases, thus contributing to elevated child morbidity and mortality (Underwood and Arthur, 1996). Retinoids modulate the differentiation and functions of both lymphocytes and DCs. There are conflicting results on whether retinoids enhance or repress the immunogenicity of DCs. It was reported that mouse splenic DCs are less stimulatory (Bedford and Knight, 1989) on RA treatment; however, retinoid-treated Langerhans cells have an enhanced T-cell activation capacity (Meunier *et al*, 1994). Moreover, RA promotes the differentiation and maturation of monocytes to DC-like cells (Mohty *et al*, 2003) and these compounds enhance the DNA-binding activity of NK- κ B, thus promoting the maturation of DCs (Geissmann *et al*, 2003) (Figure 2). It should be noted that retinoids also provoke apoptosis in developing DCs through RAR α -RXR heterodimers (Geissmann *et al*, 2003). It was also described that RA pretreated DCs, if injected into tumours in mice, showed an increased accumulation in draining lymph nodes. It was concluded that the enhanced DC migration was due to the elevated matrix metalloproteinase production and

the concurrently diminished expression of inhibitors of metalloproteinase (Darmanin *et al*, 2007). Moreover, RA-treated monocyte-derived DCs produce an elevated level of TGF β and IL-6 and these RA-instructed DCs acquire several attributes characteristic of mucosal DCs (Saurer *et al*, 2007). Our laboratory also investigated the effects of activation of the RARs using synthetic retinoids on human monocyte-derived DC differentiation and found that these cells have an enhanced iNKT cell activation capacity as a consequence of the induction of CD1d (Szatmari *et al*, 2006a); moreover, our gene expression profiling indicates that a large number of genes are regulated by retinoids leading to the activation of multiple pathways. All-*trans* RA is an agonist of RAR; however, an isomeric form, 9-*cis*-RA, can activate both RAR and RXR (Mangelsdorf and Evans, 1995); therefore, 9-*cis*-RA has pleiotropic effects and can modulate the activity of several nuclear receptors in principle. Interestingly, 9-*cis*-RA exerts a suppressive effect on human monocyte-derived DC differentiation, probably through the activation of the PPAR γ -RXR heterodimer (Zapata-Gonzalez *et al*, 2007). We also tested the effects of a synthetic and specific activator of RXR (LG268) on DC differentiation and obtained complex phenotypic changes, suggesting that probably multiple nuclear receptor heterodimers are affected (I Szatmari and L Nagy, unpublished results). Exposure to retinoids has a complex phenotype in DCs, and as we will demonstrate in the next section, RA has a profound effect on lymphocyte homing and activation as well.

DC as a factory of ligands for nuclear receptors

In this review, we have systematically analysed the potential function of the activation of various nuclear receptors in DC development and function. It should be emphasized that most studies used high-affinity synthetic ligands for the activation of the nuclear hormone receptors and for probing their biological functions. Two important issues need to be considered. One is whether the natural activators of these receptors have similar effects on DCs. The other is whether DCs are actively participating in the production of nuclear hormone receptor ligands or simply get those through endocrine or paracrine mechanisms. It should be noted that in the serum, a large number of compounds are present as biologically inactive precursors. However, on activation (oxidation/hydroxylation), the inactive compounds can be converted to the active forms. For example, vitamin D₃ must be hydroxylated to $1,25$ dihydroxy vitamin D₃, which is a high-affinity ligand of VDR (Okuda *et al*, 1995), and vitamin A (retinol) first gets oxidized to retinaldehyde; thereafter, this compound is converted to RA, which is an agonist of RARs (Duester, 2000). Similarly, cortisone is converted to cortizole, a ligand of GR (Seckl and Walker, 2001) (Figure 3). Additionally, hydroxylation of cholesterol at the position of 27 leads to 27-hydroxy-cholesterol, a potent activator of the LXR receptors (Fu *et al*, 2001), and finally polyunsaturated fatty acids are oxidized by lipoxygenases and these oxidized compounds are relatively potent ligands of the PPAR γ receptor (Nagy *et al*, 1998; Huang *et al*, 1999). The organic and cellular localization of these steps and the enzymes that catalyse these reactions are well characterized for some cell types. Most of these chemical transformations occur in the liver and

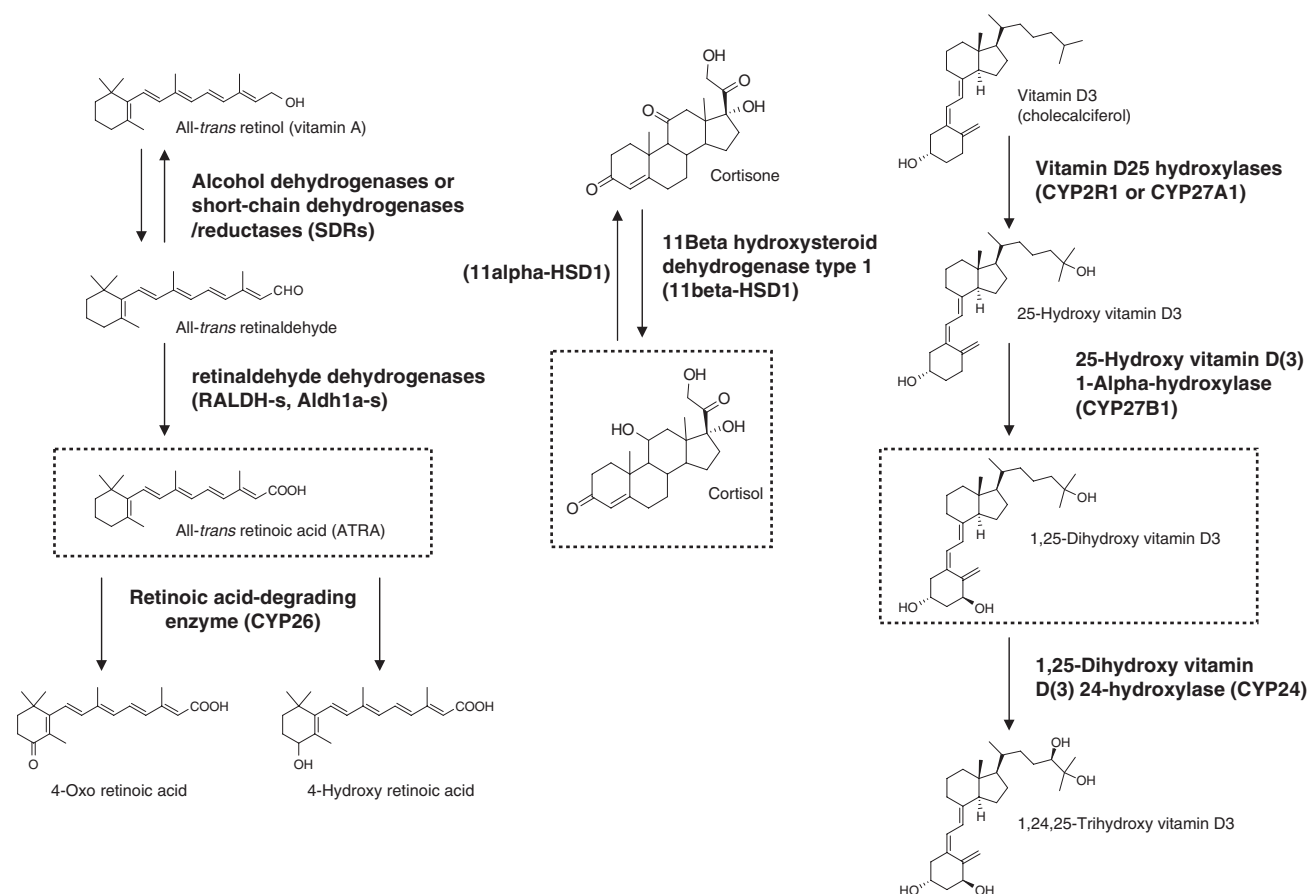


Figure 3 The chemical structures and conversion steps of three nuclear hormone receptor ligand precursors (vitamin A, cortisone and vitamin D) to the active compounds. Most of these chemical reactions can occur in DCs.

the kidney but, significantly, some of these steps can also be found in DCs.

The most studied nuclear receptor ligand in the context of DCs is RA, the active form of vitamin A. In a breakthrough study, Iwata *et al* (2004) discovered that murine intestinal DCs produce and release RA, and this DC-derived RA instructs the gut-homing tropism of T cells by the induction of the expression of $\alpha 4\beta 7$ integrin and CCR9 receptors. This study established that a DC-derived nuclear receptor ligand is able to reprogramme the local T cells and imprint T-cell tropism. Interestingly, several recent publications suggest that RA, in combination with other immunological mediators, modulates the differentiation of various lymphocyte populations in the GALT. In the intestine, RA blocks the IL-6- and TGF β -driven induction of the pro-inflammatory IL-17-producing T (Th17) cells, but promotes the differentiation of the tolerogenic regulatory T (Treg) cells (Mucida *et al*, 2007). These findings were confirmed by others: intestinal DC-produced RA enhances the TGF β -dependent conversion of peripheral T cells to Foxp3-positive Treg cells, suggesting that RA works as a mediator of gut/oral tolerance *in vivo* (Benson *et al*, 2007; Coombes *et al*, 2007; Sun *et al*, 2007). Gut-associated DCs also promote B cell gut tropism by the upregulation of the aforementioned receptors; additionally, they enhance the IL-6-dependent IgA secretion of B cells (Mora *et al*, 2006). Collectively, these findings underscore that DC-derived RA has a prominent function in the regulation of gut-associated immune processes. It should be

mentioned that RA itself could induce the expression of $\alpha 4\beta 7$ and CCR9 on T cells and thus imprint gut tropism, but for the study of the other effects of RA on lymphocytes, in most cases DC-T cell co-cultures were used. Therefore, formally, it is possible that RA also affects the immunophenotype of the DCs and that these 'reprogrammed' DCs promote Treg development or B-cell IgA production. Another interesting point is to address which factors regulate RA production and which enzymes are responsible for the unique capacity of the intestinal DCs to produce RA. There is a remarkable selectivity of this phenotype. *In vivo*, only intestinal DCs of the Peyer patches and mesenteric lymph node DCs produced RA. In contrast, non-gut lymphoid tissue DCs are unable to generate RA (Iwata *et al*, 2004). Intestinal DCs express several enzymes that might participate in RA synthesis, the most important ones being the retinaldehyde dehydrogenases (RALDHs), which catalyse the retinaldehyde oxidation to RA (Figure 2). DCs of Peyer's patches mostly express RALDH1 (Aldh1a1); in contrast, mesenteric lymph node DCs mostly express RALDH2 (Aldh1a2) (Iwata *et al*, 2004). A specialized sub-population of mesenteric lymph node DCs, CD103+ cells, promote the generation of Treg cells and these DCs show an elevated expression of RALDH2 (Coombes *et al*, 2007). Interestingly, we observed that PPAR γ -instructed human monocyte-derived DCs also produce RA; moreover, RALDH2 and RDH10 (retinol dehydrogenase 10) enzymes were upregulated in these cells (Szatmari *et al*, 2006a). It is well established that RALDH2 is indispensable for embryonic

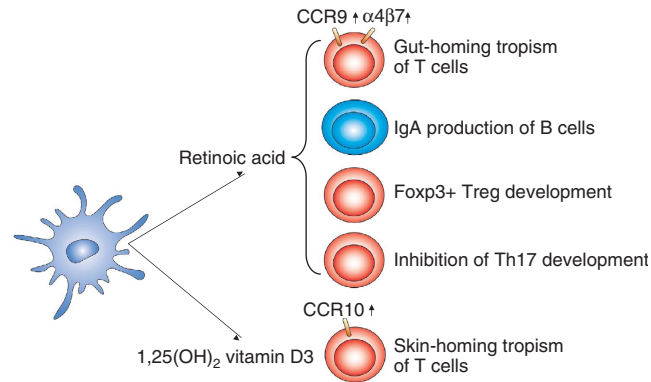


Figure 4 DC-produced nuclear receptor ligands modulate T-cell development and homing. Intestinal DCs produce the active form of vitamin A (retinoic acid). In contrast, skin DCs could secrete the active form of vitamin D (1,25 dihydroxy vitamin D₃). Retinoic acid (RA) imprints gut-homing tropism of lymphocytes by inducing α4β7 integrin and CCR9 receptor; in addition, RA contributes to B-cell IgA production; moreover, this compound promotes FoxP3⁺ Treg cell differentiation but blocks Th17 T-cell development. 1,25 Dihydroxy vitamin D₃ primes skin-homing tropism of T cells by inducing CCR10.

RA production (Niederreither *et al*, 1999). Significantly, a recent report suggested that RDH10 might catalyse the first oxidation step of retinol, a critical step for embryonic RA generation (Sandell *et al*, 2007). Further investigations are needed to define what kind of mechanisms regulate RA production in DCs and which enzyme/s is/are rate limiting for RA synthesis. Once these issues are clarified, one would be able to define the *in vivo* contribution of DC-derived RA signalling in the various immunological processes described earlier and also beyond those.

DCs are also able to activate other vitamins: the inactive form of vitamin D, 25-hydroxy vitamin D₃, is converted to 1α,25 dihydroxy vitamin D₃ during the *ex vivo* differentiation of human DCs. This conversion is catalysed by 25(OH)D₃-1 α hydroxylase, which is present in developing DCs; in addition, this enzyme is upregulated on maturation of DCs (Fritsche *et al*, 2003; Hewison *et al*, 2003). Consistent with these findings, the production of the VDR ligand is claimed to negatively regulate the early differentiation of monocyte-derived DCs. Of note, dermal DCs are able to directly convert vitamin D₃ to 1,25 dihydroxy vitamin D₃ in the skin, and this active form of vitamin D instructed the local T cells to express CCR10, thus enabling them to migrate to the epidermis (Sigmundsdottir *et al*, 2007). Remarkably, these results suggested that similar to RA, which elicits gut-homing specificity of T cells, the active form of vitamin D imprints skin-homing specificity of T cells (Figure 4).

Human monocyte-derived DCs are also able to convert the inactive cortisone to the high-affinity GR ligand, cortisone as a result of the upregulation of 11β hydroxysteroid reductase. In addition, DC differentiation is inhibited by the administration of physiological concentration of cortisone, suggesting that this pathway enhances the GC-dependent negative modulation of DC development (Freeman *et al*, 2005). Finally, as far as the PPAR_γ ligand is concerned, we observed that during monocyte-derived DC development the *bona fide* PPAR_γ targeting the *FABP4/aP2* gene is upregulated, especially when we culture the cells in human serum instead of FBS (Szatmari *et al*, 2004). We extended this finding and observed that most of these genes whose expression was upregulated on synthetic PPAR_γ ligand treatment also showed an elevated expression if DCs were cultured in human serum-containing

medium (Szatmari *et al*, 2007). These results suggested that in the presence of human serum, the PPAR_γ ligands are generated/accumulated in DCs. Further experiments are warranted to identify the PPAR_γ activators. Indeed, a recent paper suggested that lysophosphatidic acid and cardiolipin are abundant components of the human serum and that these lipid species might contribute to the activation of PPAR_γ (Leslie *et al*, 2008).

These results underscore the notion that, remarkably, DCs are actively participating in the production of several ligands of nuclear receptors. The production of ligands appears to be tightly controlled, however. Moreover, some of these ligands are likely to be released and are able to locally modulate the function of other immune cell types.

Concluding remarks: DCs as potential therapeutic targets

The functional characterization of DC is an intensively investigated area in immunology. DCs are indispensable for the initiation of primary immune response, but now it is well established that these cells are able to orchestrate the entire immune response, including the regulation of peripheral immune tolerance. Therefore, it is of importance to identify and characterize the regulatory processes underpinning these changes. It is becoming increasingly evident that members of the nuclear hormone receptor superfamily are involved in the regulation of DC biology. This group of transcription factors also represents a gateway to manipulating DCs for therapeutic use. In clinical practice, tumour antigen-loaded DCs are intensively investigated tools to elicit antitumour immune response. *Ex vivo* differentiated DCs may be loaded with tumour antigens and injected back to patients, or they can be used for *ex vivo* expansion of antitumour lymphocytes. Improving anticancer immunotherapies appear to largely depend on how DC immunogenicity, survival and migration are regulated, and thus it is very important to find ways to modulate antigen presenting, migratory capacity and viability of DCs (Nencioni *et al*, 2008). There are several ways to manipulate DCs *ex vivo*; administration of cytokine cocktails or other signal molecules can modify the DC function and activation state. As we have

demonstrated in this review, natural or synthetic ligands of nuclear hormone receptors can also modulate DC functions. In the future, it will be important to explore and exploit the benefit of ligand treatment to modulate DC immunogenicity *in vivo*. An inverse relationship should also be considered. The metabolic state of the patient might affect his/her immune responses. DCs express several lipid sensor nuclear hormone receptors (i.e. PPAR γ LXR α). Thus, in patients with an altered lipid profile, these receptors might be overactivated and this can adversely modify the immune phenotype of their DCs. As an example, we have described that serum lipoproteins skewed DC development towards a CD1a⁻ DC phenotype, which has a distinct cytokine and chemokine production profile (Gogolak *et al*, 2007).

Until now, most of the studies on nuclear receptors used *ex vivo* DC models and only a few reports investigated tissue-specific nuclear receptor knockout models (Griffin and Kumar, 2003; Klotz *et al*, 2007). In the future, it will be of great importance to generate DC-specific nuclear receptor deletion models. These models will almost certainly prove to be helpful to define the receptor specificity of the effects of receptor agonists. In addition, these systems will help to define the *in vivo* function of these receptors in DCs. The *in vivo* approaches might also clarify some of the controversies that still exist in the field. However, as we have emphasized concerning human immunotherapy, *ex vivo* DC models are also used. Thus, it is important to characterize the *in vitro*

effects of ligands of nuclear hormone receptors, not in small part, because there are major differences between mice and humans regarding DC functions, and murine models might not always be predictive of human responses. DCs are a very heterogeneous cell population (Villadangos and Schnorrer, 2007), and until now most data were derived from human monocyte-derived DCs. In the future, it would also be important to define the function of nuclear receptors/ligands on the various subtypes of DCs and DC precursors. And, finally, activators of nuclear receptors are widely used in clinical practice, for example, ligands of the PPAR γ (rosiglitazone and pioglitazone) are applied to treat type II diabetes (Willson *et al*, 2001); in addition, GCs are frequently used as immunosuppressive agents. Defining the exact functions of these activators in various immune cell types could help in exploiting their potential for therapeutic intervention against various immunological diseases.

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