

The role of lipid-activated nuclear receptors in shaping macrophage and dendritic cell function: From physiology to pathology

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Nuclear receptors are ligand-activated transcription factors linking lipid signaling to the expression of the genome. There is increasing appreciation of the involvement of this receptor network in the metabolic programming of macrophages and dendritic cells (DCs), essential members of the innate immune system. In this review we focus on the role of retinoid X receptor, retinoic acid receptor, peroxisome proliferator-associated receptor γ , liver X receptor, and vitamin D receptor in shaping the immune and metabolic functions of macrophages and DCs. We also provide an overview of the contribution of macrophage- and DC-expressed nuclear receptors to various immunopathologic conditions, such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, asthma, and some others. We suggest that systematic analyses of the roles of these receptors and their activating lipid ligands in immunopathologies combined with complementary and focused translational and clinical research will be crucial for the development of new therapies using the many molecules available to target nuclear receptors. (*J Allergy Clin Immunol* 2013;132:264-86.)

Key words: *Macrophage, dendritic cell, lipid, nuclear receptor, retinoid X receptor, retinoic acid receptor, peroxisome proliferator-associated receptor, liver X receptor, vitamin D receptor, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, asthma*

Abbreviations used

ABC:	ATP-binding cassette
AP-1:	Activator protein 1
ATRA:	All-trans-retinoic acid
BAL:	Bronchoalveolar lavage
CIA:	Collagen-induced arthritis
9-cis-RA:	9-Cis-retinoic acid
DBD:	DNA-binding domain
DC:	Dendritic cell
15d-PGJ ₂ :	15-Deoxy- Δ 12,14-prostaglandin J ₂
FDA:	US Food and Drug Administration
GALT:	Gut-associated lymphoid tissue
HODE:	Hydroxyoctadecadienoic acid
IBD:	Inflammatory bowel disease
iNKT:	Invariant natural killer T
LBD:	Ligand-binding domain
LPA:	Lysophosphatidic acid
LXR:	Liver X receptor
MMP:	Matrix metalloproteinase
oxLDL:	Oxidized low-density lipoprotein
pDC:	Plasmacytoid dendritic cell
PPAR:	Peroxisome proliferator-associated receptor
RA:	Rheumatoid arthritis
RAR:	Retinoic acid receptor
RXR:	Retinoid X receptor
SLE:	Systemic lupus erythematosus
STAT:	Signal transducer and activator of transcription
TLR:	Toll-like receptor
Treg:	Regulatory T
TZD:	Thiazolidinedione
VDR:	Vitamin D receptor

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Terms in boldface and italics are defined in the glossary on page 265.

Immunology and metabolism are historically distinct disciplines bound together in the last 2 decades, when it became clear that obesity and different metabolic disorders affect immune homeostasis and, *vice versa*, **obesity**-induced insulin resistance and **atherosclerosis** are closely associated with chronic inflammation.¹ In obese patients lipid spillover and adipocyte-derived danger signals, including saturated fatty acids and heat shock proteins, induce chronic adipose tissue inflammation and consequential insulin resistance. Lipid accumulation is also observed in macrophages, leading to foam cell formation, a crucial early step during atherosclerosis. Accumulated cholesterol and other lipids are able to induce an inflammatory response through Toll-like receptor (TLR)-dependent and -independent mechanisms.² However, the connection of lipid metabolism and

immunity is not limited to dietary lipid overload–induced inflammation. Stromal cells and immune cells produce an array of lipid mediators, which shape the function of the immune system in physiologic and pathologic conditions through cell-surface and nuclear receptors. **Polyunsaturated fatty acid** derivatives, such as prostaglandins, leukotrienes, lipoxins, resolvins, and selectins, acting through G protein–coupled receptors, are important mediators either in the initiation or resolution of inflammation.^{3–5} Another group of lipids and their derivatives, including various fatty acids, oxysterols, **vitamin A**–derived retinoids and **vitamin D**, act via nuclear receptors also exerting a significant effect on various aspects of immune cell function.^{6,7} In this review we will briefly describe the physiologic role of lipid-activated nuclear receptors in the regulation of macrophage and dendritic cell (DC) functions. For a more comprehensive overview of the topic, we refer to our

recent review.⁸ Furthermore, we provide an overview of nuclear receptor–mediated macrophage and DC functions in different immunopathologic conditions, especially with regard to rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and asthma.

MACROPHAGES ARE MORE THAN PROFESSIONAL PHAGOCYTES

Ilya Mechnikov discovered macrophages and identified phagocytosis as the main macrophage function; together with Paul Ehrlich, he was awarded the Nobel Prize for his work in 1908.⁹ Since that time, it was shown that the phagocytic capacity of macrophages is an important process in the defense against infection and regeneration after tissue injury through the elimination of

GLOSSARY

ACTIVATOR PROTEIN 1 (AP-1): A family of transcription factors activated in T lymphocytes by T-cell receptor–mediated signals. An example of an AP-1 dimer is Fos and Jun.

ATHEROSCLEROSIS: A systemic disease of the large- and medium-sized arteries causing luminal narrowing as a result of the accumulation of lipid and fibrous material between the intimal and medial layers of the vessel. Coronary artery atherosclerosis leading to heart disease is the leading cause of death in men and women in the United States.

COACTIVATOR: Molecules that bind to DNA-bound transcription factors and increase gene activation. Coactivators can promote transcription initiation by interacting with components of the basal transcription machinery. Some coactivators possess intrinsic enzymatic activity (ie, histone acetyltransferase), allowing increased access to the DNA.

COREPRESSOR: Molecules that interact with DNA-bound transcription factors and inhibit gene transcription, either by competing for the binding sites with coactivators or by recruiting histone deacetylases.

FATTY ACID OXIDATION: The process in which fatty acids undergo β -oxidation in the mitochondria, resulting in the production of ATP.

IL-10: A cytokine produced primarily by mononuclear phagocytic cells, as well as CD25⁺CD4⁺ Treg cells and T_H1 and T_H2 lymphocytes. IL-10 has many biologic functions, including inhibiting antigen-presenting cells, decreasing MHC class II expression, decreasing CD80 (T-cell costimulator) expression, inhibiting T_H1 and T_H2 cytokine production, and inhibiting IgE production and eosinophil activation.

IFN- γ : A cytokine with a multitude of effects in addition to promoting CD4⁺ T-cell differentiation into T_H1 cells. Other actions of IFN- γ include activation of macrophages, upregulation of MHC class II expression, maturation of CD8⁺ T cells into cytotoxic T cells, and activation of endothelial cells and neutrophils, as well as promotion of antiviral defenses.

INDUCIBLE NITRIC OXIDE SYNTHASE (iNOS): An enzyme that catalyzes the adduction of nitrogen from L-arginine to molecular oxygen, forming nitric oxide and L-citrulline. iNOS is found in macrophages, fibroblasts, neutrophils, and smooth muscle. Many proinflammatory cytokines increase iNOS expression.

LISTERIA MONOCYTOGENES: An anaerobic, gram-positive rod capable of causing bacteremia and meningitis. The bacteria are frequently found in soil, decaying vegetation, and water. Most human cases are secondary to contaminated foods, such as cheeses and deli meats. The bacteria can be found in the stool of healthy adults. The elderly, neonates, and immunosuppressed patients appear more susceptible to invasive disease.

LOW-GRADE INFLAMMATION: Chronic mild neutrophilia has been documented with obesity. Typically, low-grade inflammation is associated with an increased C-reactive protein level. Adipose tissue secretes TNF, IL-6, and macrophage chemoattractant protein 1.

NATURAL KILLER T (NKT) CELL: A subset of lymphocytes that express surface molecules characteristic of both natural killer (CD16) and T cells (CD3). They express $\alpha\beta$ T-cell receptors with little diversity.

NUCLEAR FACTOR κ B (NF- κ B): A family of transcription factors that promotes the expression of a variety of inflammatory mediators. NF- κ B is present in an unstimulated state in the cytoplasm, where it is bound by κ B, an inhibitory protein.

OBESITY: Body weight greater than what is considered healthy for a given height. Obesity is defined by the National Institutes of Health as a body mass index (BMI) of 30 or greater. A BMI of 40 or greater is considered extreme obesity. A normal BMI is 18.5 to 24.9. Per the Centers for Disease Control and Prevention, 35.7% of US adults and approximately 17% (or 12.5 million) of children and adolescents are obese.

PLASMACYTOID DENDRITIC CELL (PDC): A type of DC with a distinct histologic morphology that can produce high levels of type I interferons. Plasmacytoid DCs are thought to play special roles in antiviral host defense and autoimmunity.

POLYUNSATURATED FATTY ACID: Fatty acids that have many chemical bonds in each molecule in which 2 or 3 pairs of electrons are shared by 2 atoms (double bond). From a dietary perspective, polyunsaturated fats can be divided into omega-6 and omega-3 (the first double bond in the hydrocarbon chain occurs between the third and fourth carbon atoms from the methyl end of the molecule) polyunsaturated fats.

SUMOYLATION: A protein modification involving the addition of a member of the small ubiquitin-related modifier family (SUMO).

TNF- α : A cytokine derived from mononuclear phagocytes, as well as natural killer cells, endothelial cells, mast cells, activated lymphocytes, and neutrophils. Its most potent inducer is LPS acting through Toll-like receptor 4. TNF- α activates neutrophils and has a cytotoxic effect on cancerous cells. It is a key mediator in sepsis and toxic shock.

VITAMIN A: A fat-soluble compound with 2 main forms: provitamin A carotenoids found in plants (eg, β -carotene) and preformed vitamin A found in animal sources (eg, retinoic acid). Vitamin A deficiency is the third most common nutritional deficiency in the world. In addition to immune dysfunction, vitamin A deficiency can lead to xerophthalmia, night blindness, retinopathy, and poor bone growth. Ancient Egyptians discovered that night blindness could be treated by consumption of liver.

VITAMIN D: A fat-soluble vitamin chemically related to steroids that is essential for normal bone and tooth structure and found especially in fish liver oils. Vitamin D can be ingested in food or synthesized in the skin through the conversion of 7-dehydrocholesterol into previtamin D₃ by means of UV light.

bacteria, injured host components, and apoptotic cells.¹⁰ However, the role of macrophages in the maintenance of immune homeostasis is not limited to phagocytosis. These cells also participate in antigen presentation, cytokine production, regulation of T-cell activation, induction and resolution of inflammation, and tissue regeneration.¹⁰⁻¹²

Polarization states and functional properties of macrophages largely depend on environmental signals, such as cytokines, pathogen-derived molecules, and lipid mediators. These microenvironmental stimuli generate a continuum of functional states. Two extremes of this continuum are classical and alternative macrophage activation, creating M1 and M2 macrophages, respectively.¹³ It has long been recognized that the T_H1-type cytokines *IFN- γ* and *TNF- α* or bacterial LPS promote classical macrophage activation characterized by a proinflammatory phenotype.¹³ In contrast to classical macrophage activation, T_H2-type cytokines, including IL-4 and IL-13, are able to induce alternative activation of macrophages with a characteristic molecular signature, biosynthetic activity, and anti-inflammatory properties, favoring tissue remodeling and regeneration.¹⁴ However, a growing body of evidence suggests that macrophages are able to switch their polarization state during the changing circumstances.¹¹ Among others, tumor-associated macrophages are a paradigm of this phenotypic plasticity.¹⁵

DCs ARE SENTINELS OF THE IMMUNE SYSTEM

Since the discovery of DCs in 1973 by Steinman and Cohn,¹⁶ our understanding of the importance of these members of innate immunity has been rapidly expanded, leading to the acknowledgement of the late Steinman's work with the Nobel Prize in 2011. The discovery of DCs provided a critical, previously missing link between innate and adaptive immunity, regulating essential aspects of both systems.¹⁷ DCs mostly reside in interfaces between the body and the environment (eg, the skin and mucosal surfaces), continuously monitoring their surroundings by capturing and processing antigens.^{18,19} At the same time, DCs sense pathogen-derived signals, cytokines, danger signals, and also lipids in the microenvironment. Integration of these signals determines the nature of the immune response, often leading to a maturation process and switch from antigen-sampling to antigen-presenting activity, which requires the expression of costimulatory surface molecules and migration to the draining lymph nodes, where they present antigens and induce tissue-specific T-cell responses.²⁰ Determined by the immunologic context, DCs can also elicit immune responses against pathogens by producing cytokines, such as type I interferons, or microbicidal enzymes, such as nitric oxide synthase.^{21,22} In addition, so-called tolerogenic DCs can provoke immune tolerance by promoting regulatory T (Treg) cell generation or inducing T-cell deletion/anergy.^{23,24}

The 2 main DC subsets in the steady state include *plasmacytoid dendritic cells* (pDCs) and conventional DCs, which possess distinct functional characteristics. However, similar to macrophages, microenvironmental stimuli define a broad range of DC subsets differing in function, location, migratory properties, maturity, and activation status.²⁵

NUCLEAR RECEPTORS LINK METABOLIC CHANGES TO GENOME EXPRESSION

As highlighted above, the phenotypic and functional heterogeneity of macrophages and DCs primarily stems from the

diversity of tissue microenvironments in which they reside. Changes in the local tissue environment alter the extracellular lipid milieu, which, in turn, modifies intracellular lipid metabolism. These extracellular and intracellular lipid signals can be directly translated into gene expression changes by nuclear receptors (Fig 1).

Nuclear receptors are transcription factors activated by lipid-soluble and therefore membrane-permeable ligands, regulating the expression of target genes involved in diverse physiologic processes. The conversion of lipid signals to transcriptional regulation is achieved with a conserved structure consisting of modular domains involved in specific functions (Fig 2). The N-terminal region harbors a variable domain mediating ligand-independent activation function. The highly conserved DNA-binding domain (DBD) contains 2 zinc-finger motifs targeting the receptor to specific DNA sequences known as hormone response elements. The C-terminal region encompasses the ligand-binding domain (LBD), which possesses the capability to selectively recognize specific lipid ligands and also creates a dimerization surface. Beyond that, the LBD is responsible for the ligand-induced changes in the transcriptional regulatory function of the receptor through interactions with *coactivator* and *corepressor* complexes. These interactions are primarily regulated by the ligand-induced conformational changes of the ligand-dependent activation function domain located in the C-terminal region of the LBD. The variable hinge region linking the DBD and LBD permits the structural flexibility of the receptor.²⁶

The superfamily of nuclear receptors comprises not only the classic endocrine receptors mediating the tissue-specific effects of steroid hormones, thyroid hormones, and fat-soluble vitamin A and D but also a large number of orphan receptors, the ligands and physiologic function of which were initially unknown. As a result of subsequent studies, many orphan receptors became "adopted"; that is, their naturally occurring ligands and biological function were identified (eg, retinoid X receptor [RXR], peroxisome proliferator-associated receptor [PPAR], liver X receptor [LXR], and Farnesoid X receptor). On the other hand, several orphan receptors have not yet been shown to bind a ligand under physiologic conditions (eg, retinoic acid receptor-related orphan receptor, chicken ovalbumin upstream promoter transcription factor, and germ cell nuclear factor).²⁷

In this review we will focus on nuclear receptor heterodimers consisting of an "adopted orphan," RXR, and its partners, retinoic acid receptor (RAR), PPAR, LXR, and vitamin D receptor (VDR) (Table I). RXR heterodimers can be classified into permissive and nonpermissive groups. Heterodimers containing a permissive partner (eg, PPAR/RXR and LXR/RXR) can be activated by the ligands of either partner. In contrast, nonpermissive heterodimers (eg, RAR/RXR and VDR/RXR) cannot be activated by an RXR agonist but only by an agonist of the dominant partner receptor.²⁸

RXR heterodimers, unlike steroid hormone receptor homodimers, generally bind to target genes in the absence of ligand exerting transcriptional repression by the recruitment of corepressor complexes through interactions with nuclear receptor corepressor proteins, such as nuclear receptor corepressor or silencing mediator of retinoid and thyroid receptors (Fig 3, A).²⁹

Binding of agonist ligand induces a conformational change of the receptor molecule, leading to the dissociation of corepressors and recruitment of coactivator complex necessary for transcriptional activation (Fig 3, B).²⁹

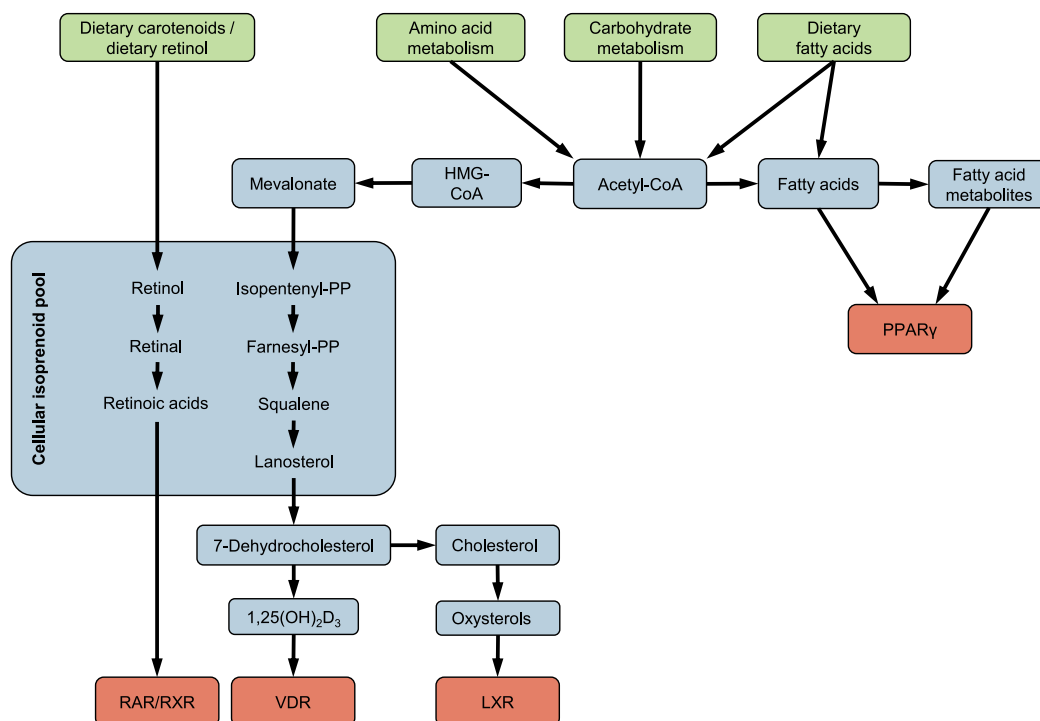


FIG 1. Pathways of lipid metabolism providing ligands for retinoid receptors, PPAR_γ, LXR, and VDR. The cellular isoprenoid pool is one of the main sources of nuclear receptor ligands. Some intermediates are omitted for clarity.

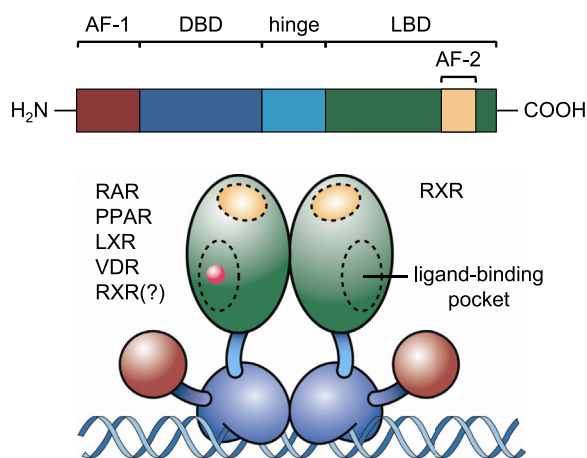


FIG 2. Domain structure of nuclear receptors. Colors on the domain structure above correspond to the identically colored domains on the schematic 3-dimensional structure below. AF-1, Ligand-independent activation function; AF-2, ligand-dependent activation function; DBD, DNA-binding domain, hinge region.

Certain RXR partners can also repress transcription in a ligand-dependent manner. This can be explained by 2 distinct mechanisms. First, some corepressors have been shown to bind to nuclear receptors in an agonist-dependent manner, resulting in the inhibition of target gene expression (Fig 3, C).^{30,31}

Second, negative regulation of transcription can also result from inhibiting the activity of other signal-induced transcription factors, such as *nuclear factor κB* (NF-κB) or *activator protein 1* (AP-1; Fig 3, D).³² This mechanism, which is known as

ligand-dependent transrepression, represents an intriguing cross-talk between signaling pathways initially thought to be distinct. Specifically, LXR and PPAR are capable of antagonizing inflammatory pathways by means of transrepression.³² The potential molecular mechanisms and cellular consequences of this phenomenon will be discussed below.

The importance of nuclear receptor-regulated pathways in maintaining a physiologic state is best illustrated by the fact that approximately 13% of US Food and Drug Administration (FDA)-approved drugs target one of the 48 known human nuclear receptors.³³ RXR heterodimers, as described in this review, are also targets of various compounds, with a broad spectrum of clinical use ranging from dermatology to oncology (Table I).

RETINOID RECEPTORS

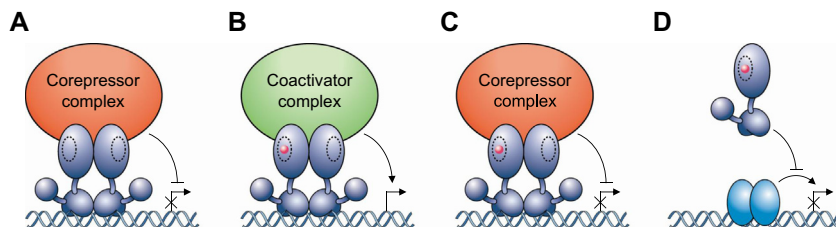
Vitamin A and its derivatives, retinoids, regulate a wide range of biological processes, including embryonic development, cell differentiation, homeostasis, and the metabolism.^{34,35} Active metabolites of vitamin A, all-trans-retinoic acid (ATRA), and its isomer, 9-cis-retinoic acid (9-cis-RA), bind 2 types of retinoid receptors, namely RAR and RXR, both possessing α, β, and γ iso-types encoded by separate genes.^{36,37} Retinoid receptors have different ligand specificities: ATRA is recognized by RARs, whereas 9-cis-RA is able to activate both RARs and RXRs.^{38,39}

RXR is a unique member of the nuclear receptor superfamily in terms of its dimerization properties because it forms heterodimers with one third of known human nuclear receptors, most of them requiring RXR as an obligatory partner for DNA binding and transcriptional regulation.²⁸ Thus the binding of RXR agonist to permissive RXR heterodimers leads to transcriptional changes

TABLE I. Lipids and FDA-approved drugs targeting RAR, RXR, LXR, PPAR γ , and VDR

Nuclear receptor	Physiological lipid ligand(s)	FDA-approved drugs targeting the receptor (based on Rask-Andersen et al Table S1 ³⁶⁵)	
		Drug name	Therapeutic class
RAR	ATRA	Adapalene	Dermatologic agent
		Alitretinoin	Antineoplastic agent
		Isotretinoin	Keratolytic agent
		Acitretin	Keratolytic agent
		Tazarotene	Keratolytic agent
		Tretinoin	Antineoplastic agent, keratolytic agent
RXR	9-cis-RA	Bexarotene	Antineoplastic agent
		Alitretinoin	Antineoplastic agent
		Tazarotene	Keratolytic agent
		Tretinoin	Antineoplastic agent, keratolytic agent
LXR	22(R)-hydroxycholesterol 24(S)-hydroxycholesterol 24(S),25-epoxycholesterol 27-hydroxycholesterol	No FDA-approved ligand available	
PPAR γ	Unsaturated fatty acids	Pioglitazone	Hypoglycemic agent
	15d-PGJ	Rosiglitazone	Hypoglycemic agent
	12-HETE, 15-HETE	Treprostinil	Antihypertensive agent; antithrombotic agent
	9-HODE, 13-HODE		
	oxLDL-derivatives		
	LPA		
	Serotonin metabolites		
VDR	1,25(OH) $_2$ D $_3$	Paricalcitol	Antiparathyroidal agent
		Calcipotriene	Dermatologic agent
		Calcitriol	Antiosteoporosis agent; antihypocalcemic agent
		Ergocalciferol	Antihypocalcemic agent

HETE, Hydroxyeicosatetraenoic acid.

**FIG 3.** Basic mechanisms of nuclear receptor action. **A**, Ligand-independent corepressor recruitment and gene repression. **B**, Ligand-dependent coactivator recruitment and gene activation. **C**, Ligand-dependent corepressor recruitment and gene repression. **D**, Ligand-dependent transrepression of gene activation mediated by other transcription factors.

affecting various nuclear receptor pathways simultaneously. However, the question of whether RXR has a heterodimer-independent function remains largely unanswered. The *in vivo* relevance of RXR homodimers and tetramers observed *in vitro* is not clear and is probably attributable to the absence of heterodimerization partners.⁴⁰⁻⁴² However, data from our group and others suggest that RXR homodimers might regulate gene expression independently of heterodimers.^{43,44} Nondetectable 9-cis-RA in several tissues supports that 9-cis-RA is not a universal RXR-activating agonist *in vivo*. Nonetheless, the existence of other endogenous RXR activators has not been shown thus far. None of the potential candidates, including phytanic acid⁴⁵ and docosa-hexaenoic acid,⁴⁶ have been proved to be *bona fide* activators of RXR *in vivo*.

Vitamin A deficiency (one of the major public health problems in the developing world) causes immune dysfunction and

increases susceptibility to infections,⁴⁷ suggesting a crucial role for retinoids in immune homeostasis.

Indeed, several lines of evidence suggest that activation of RAR and RXR affects the differentiation, function, and metabolism of myeloid cells (Figs 4 and 5).

RAR contributes to myeloid differentiation by upregulating several genes involved in the differentiation program, such as C/EBP ϵ ,⁴⁸ interferon regulatory factor 1,⁴⁹ CD18,⁵⁰ CD38,⁵¹ and RTP-801.⁵² Macrophage colony-stimulating factor and granulocyte-macrophage colony-stimulating factor were also reported to be induced by retinoic acid in bone marrow stromal cells.⁵³

Retinoids appear to have an anti-inflammatory effect on macrophages, as suggested by several *in vitro* results and reported suppressive effects on inflammatory disease models (see later). ATRA treatment suppressed TNF- α , IL-12, and nitric oxide production of activated macrophages and increased production of the

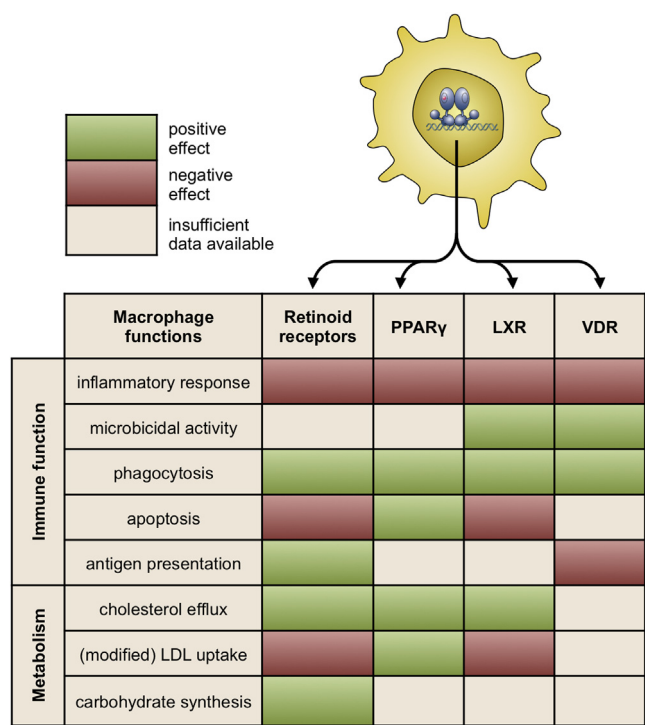


FIG 4. Metabolic and immune functions of macrophages influenced by retinoid receptors, PPAR γ , LXR, and VDR. A positive effect of nuclear receptor ligand on a macrophage function is indicated by *green*, a negative effect is indicated by *red*, and empty cells indicate that insufficient or no data are available regarding the effect of ligand on that particular function. *LDL*, Low-density lipoprotein.

immunoregulatory cytokine *IL-10*, presumably polarizing macrophages toward an anti-inflammatory phenotype.^{54,55} Moreover, retinoids might contribute to the attenuation of tissue damage elicited by macrophages through the induction of plasminogen activator inhibitor 2, a protein limiting extracellular proteolysis during inflammation.⁵⁶ The molecular mechanisms underlying the anti-inflammatory action of retinoids are still unclear; however, activation of RXR by 9-*cis*-RA decreased *IL-12* production through interaction with NF- κ B, suggesting cross-talk between retinoid receptors and inflammatory pathways.⁵⁷ RXR is also involved in the regulation of leukocyte chemotaxis because macrophages lacking RXR α exhibit reduced levels of CCL6 and CCL9, resulting in impaired recruitment of leukocytes to sites of inflammation and lower susceptibility to sepsis. This regulatory activity was shown to be independent of major RXR heterodimeric partners, suggesting that RXR homodimers might be responsible for it.⁵⁸

Retinoids also influence carbohydrate and lipid metabolism in macrophages by regulating certain biosynthetic pathways.^{59,60} Macrophage lipid metabolism is modulated by a regulatory network comprising the retinoid receptors, PPAR γ , and LXR. These receptors have a major role in regulating reverse cholesterol transport in macrophages and, as a result, prevent atherosclerosis. Ligand-activated PPAR γ , RAR, and also RXR induce CYP27, a mitochondrial P-450 enzyme capable of generating 27-hydroxycholesterol, an endogenous LXR activator.⁶⁰ Activation of LXR leads to cholesterol efflux from macrophages by upregulating ATP-binding cassette (ABC) transporters, such as ABCA1 and ABCG1.⁶¹⁻⁶³ The former is also directly induced by the RAR/RXR heterodimer in macrophages.⁶⁴ In addition, the RAR

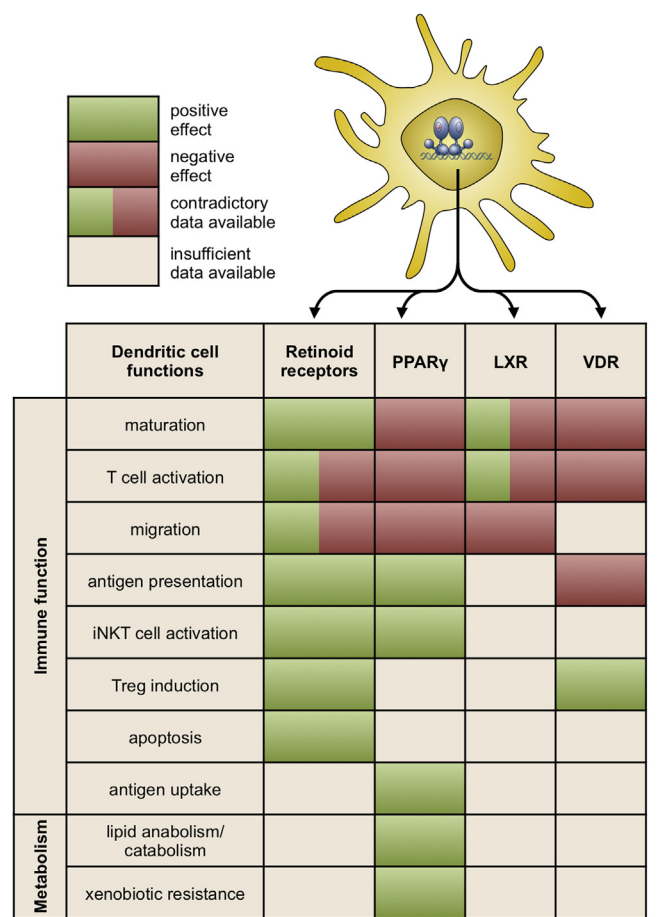


FIG 5. Metabolic and immune functions of DCs influenced by retinoid receptors, PPAR γ , LXR, and VDR. A positive effect of nuclear receptor ligand on DC function is indicated by *green*, negative effect is indicated by *red*, both *green* and *red* indicate that available data show contradiction, and empty cells indicate that insufficient or no data are available regarding the effect of ligand on that particular function.

activator AM580 is able to suppress scavenger receptor expression and macrophage foam cell formation, thus preventing atherogenesis in mice.⁶⁵ (For more details of PPAR γ - and LXR-regulated lipid homeostasis, see below.)

Retinoids are involved in shaping DC function as well. However, the mainly *in vitro* studies dissecting retinoids' effects on DCs yielded contradictory results. This is probably attributable to the sensitive "context-dependent" responses of DCs (ie, a DC response elicited by a certain signal is dependent on other stimuli reaching the cell). As an illustration, retinoids induce DC apoptosis in the absence of inflammatory signals through RAR/RXR heterodimers. In contrast, in the presence of the inflammatory cytokine TNF- α , retinoids increase MHC class II and costimulatory molecule expression, induce the differentiation of immature DCs into mature DCs, enhance the antigen-specific T-cell response, and increase the DNA-binding activity of NF- κ B in DCs, again directly showing a cross-talk between retinoid signaling and inflammatory pathways.⁶⁶ As shown above, retinoid receptor activation induces an enzyme capable of generating an LXR agonist ligand.⁶⁰ Analogously, activated PPAR γ induces the expression of vitamin A-metabolizing enzymes, leading to an increase in the intracellular generation of the RAR agonist

retinoic acid and further supporting that distinct nuclear receptor pathways are able to interact at the level of ligand production.⁶⁷ Activation of RAR in DCs by intracellularly generated retinoic acid induces CD1d, an MHC class I-like molecule involved in lipid antigen presentation. Glycolipid antigens bound to CD1d are recognized by *natural killer T cells* carrying an invariant T-cell antigen receptor. Consequently, enhanced expression of CD1d on the surfaces of DCs results in enhanced invariant natural killer T (iNKT) cell activation.⁶⁷ In addition to driving immune responses to glycolipid antigens, this T-cell subset is also implicated in maintaining immunologic tolerance, whereas a deficiency in iNKT cells is associated with autoimmune diseases.⁶⁸ Thus exploring the role of nuclear receptors in dysregulated iNKT cell activation would be of great importance in uncovering the pathogenic processes underlying autoimmunity. Similar to PPAR γ agonists, TLR2 signaling induces the expression of the vitamin A-metabolizing enzyme retinaldehyde dehydrogenase type 2 in splenic DCs, leading to the synthesis of endogenous retinoic acid, which is capable of inducing forkhead box protein 3-positive Treg cells. Endogenous retinoic acid also induces suppressor of cytokine signaling 3 expression, which in turn suppresses the activation of the p38 mitogen-activated protein kinase, resulting in inhibition of proinflammatory cytokine production.⁶⁹ Consistent with these results, several articles report an anti-inflammatory effect of retinoids on DCs characterized by suppressed stimulatory capacity, increased IL-10 production, and decreased IL-12 production.⁷⁰⁻⁷²

It is not clear how retinoids affect the migratory properties of DCs. 9-Cis-RA was reported to decrease the migratory ability of DCs through downregulation of CCR7, whereas ATRA was found to increase matrix metalloproteinase (MMP) 9 activity, leading to enhanced mobilization.^{73,74} However, these effects were not proved to be RAR or RXR dependent, and thus knockout models are needed to clarify the exact mechanisms of retinoid action.

PPAR γ

Peroxisome proliferator-activated receptors (PPARs) bind various nonesterified and polyunsaturated fatty acids, prostanooids, or eicosanoids and turn these lipid signals into transcriptional changes affecting several aspects of lipid metabolism, including synthesis, transport, storage, mobilization, and oxidation.⁷⁵ The 3 members of the PPAR subfamily are PPAR α , PPAR γ , and PPAR β/δ . PPAR α is expressed most abundantly in the liver; PPAR γ is expressed in the adipose tissue, macrophages, and DCs; and PPAR β/δ is ubiquitously expressed.⁷⁵⁻⁷⁷ Here we focus on PPAR γ because it has been extensively reported as a modulator of macrophage and DC function. The relatively large ligand-binding pocket of PPAR γ makes it possible to bind a broad array of different lipid molecules, such as 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂),⁷⁸ lysophosphatidic acid (LPA),⁷⁹ serotonin metabolites,⁸⁰ or oxidized low-density lipoprotein (oxLDL)-derived hydroxyoctadecadienoic acids (HODEs) and hydroxyeicosatetraenoic acids.⁸¹ Synthetic ligands of PPAR γ , termed thiazolidinediones (TZDs), are used as insulin-sensitizing agents (Table I).⁷⁷

Although PPAR γ is not essential for monocyte/macrophage differentiation,⁸² it functions as an important modulator of macrophage lipid metabolism and a fine-tuner of immune functions (Fig 4).

It has long been known that PPAR γ activators inhibit proinflammatory cytokine production in monocytes and macrophages. This inhibitory effect not only affects the expression of cytokines, such as TNF- α , IL-1 β , IL-6, and IL-12,⁸³⁻⁸⁸ but also of enzymes mediating bacterial killing and tissue damage, such as *inducible nitric oxide synthase* (iNOS) and MMP-9, respectively.⁸⁹ PPAR γ also inhibits the expression of monocyte chemotactic protein 1 and its receptor CCR2 in macrophages,⁹⁰⁻⁹³ which might help to retain macrophages in sites of inflammation. Interestingly, according to the most widely accepted concept, the potential mechanism responsible for the anti-inflammatory effect of PPAR γ is independent of the DNA-binding ability and direct transcriptional activity of the receptor. Instead, PPAR γ interacts with transcription factors involved in proinflammatory signaling pathways, such as AP-1, NF- κ B, nuclear factor of activated T cells, and signal transducer and activator of transcription (STAT) 1, leading to failed induction of inflammatory response mediated by these transcription factors.³² The molecular details of this process, called transrepression, are not clear. It was proposed that ligand-dependent *SUMOylation* of the receptor prevents the degradation of corepressor complexes, resulting in repression of inflammatory genes, even in the presence of proinflammatory signals (eg, LPS).⁹⁴ However, this model has 2 caveats. First, PPAR γ expression is rapidly downregulated after LPS stimulus, which might lead to insufficient levels of SUMOylated receptor to efficient transrepression.⁹⁵ Second, the model does not explain how ligand binding of PPAR γ can induce the dissociation of the corepressor complexes required for target gene induction and also bind the corepressor complexes required for transrepression simultaneously.

PPAR γ agonists induce a surprisingly small number of genes while inhibiting the induction of a broad subset of inflammatory genes, suggesting that transrepression might be a primary mechanism responsible for the anti-inflammatory action of PPAR γ .⁸⁸

PPAR γ was also reported to be indispensable for alternative macrophage activation induced by the cytokine IL-4.⁹⁶ Although this effect has been proved to be mouse strain specific,⁹⁷ we also showed that IL-4 is upstream of the receptor and stimulates augmented PPAR γ activity through an interaction between PPAR γ and STAT6, a component of the IL-4-induced signal transduction pathway. On this basis, it is proposed that STAT6 acts as a licensing factor for PPAR γ to provide M2 macrophage-specific gene expression by enhancing its DNA binding.⁹⁸ The tight link between PPAR γ and IL-4 signaling is further supported by the fact that IL-4 induces the expression of PPAR γ and several enzymes capable of generating PPAR γ -activating ligands, such as 2/5-lipoxygenase (producing 13-HODE and 15-hydroxyeicosatetraenoic acid), autotaxin (producing LPA), and monoamine oxidase (producing serotonin metabolites).^{99,100}

Macrophage-expressed PPAR γ regulates not only immunologic but also metabolic processes at the cellular and systemic level. At the cellular level, PPAR γ and LXR form a regulatory circuit organizing cholesterol transport in macrophage-derived foam cells of atherosclerotic lesions. Oxidation of low-density lipoprotein in the artery wall is considered one of the essential early steps in the pathogenesis of atherosclerosis, followed by the generation of cholesterol-laden macrophages known as foam cells. The aggregation of foam cells forms the earliest macroscopic sign of atherosclerosis: the fatty streak.¹⁰¹ oxLDL induces PPAR γ expression in macrophages and also serves as a ligand source for the receptor through oxLDL-derived 9-HODE and 13-HODE, as mentioned above.⁸¹ Activation of PPAR γ increases

the expression of scavenger receptors (eg, CD36), which leads to further oxLDL uptake and subsequent PPAR γ activation, forming a positive feedback loop.⁸¹ Intriguingly, however, PPAR γ also activates a cholesterol efflux process, preventing the cell from cholesterol overload by inducing LXR function through 2 mechanisms. First, it induces the expression of LXR, and second, it induces CYP27, which is capable of generating 27-hydroxycholesterol, an endogenous LXR activator. Activation of LXR triggers ABCA1 and ABCG1 expression and subsequent cholesterol removal from the macrophage.^{60,102} Any disturbance in this regulatory circuit could lead to cholesterol overload of macrophages, contributing to atherogenesis.

PPAR γ expressed by macrophages infiltrating adipose tissue might influence metabolic processes at a systemic level in the setting of obesity and insulin resistance. The quantity of macrophages in adipose tissue shows a positive correlation with body mass index.¹⁰³ These macrophages typically have a classically activated phenotype, and thus presumably are among the factors promoting the persistent *low-grade inflammation* observed in obese subjects.¹⁰⁴ This chronic inflammatory state is believed to promote insulin resistance, terminating in type 2 diabetes.¹⁰⁴ Mice with PPAR γ -deficient macrophages were predisposed to diet-induced obesity and insulin resistance accompanied by increased expression of inflammatory mediators.^{96,105}

In addition, the effect of PPAR γ -activating TZDs used as antidiabetic agents was shown to be partly mediated by macrophages in mice.¹⁰⁵

Taken together, these observations suggest that PPAR γ -mediated transrepression of inflammatory pathways in macrophages might be a regulator of the physiologic metabolic state. However, it is important to note that these results cannot be generally applicable because others showed that loss of PPARs (or LXRs) in macrophages did not exert major effects on obesity or glucose tolerance in mice receiving a high-fat diet. In addition, rosiglitazone treatment effectively improved glucose tolerance in the absence of macrophage PPAR γ .¹⁰⁶

It appears that PPAR γ is also active in DCs of myeloid origin and is likely to be a regulator of many aspects of DC biology (Fig 5).¹⁰⁷⁻¹⁰⁹ Tissue-resident DCs are exposed to various lipids, raising the question of whether there are natural lipid mediators capable of PPAR γ activation. Indeed, several compounds have been shown to activate PPAR γ in DCs, such as 15d-PGJ₂,¹⁰⁸ LPA,¹¹⁰ and oxLDL.¹⁰⁹ However, most of our current knowledge on PPAR γ 's function in DCs is derived from synthetic agonist treatment *in vitro*. Data provided by these studies suggest that PPAR γ activation negatively affects functional maturation of DCs in response to environmental stimuli.¹¹¹ Activation of PPAR γ in human monocyte-derived DCs decreases secretion of IL-12, a pivotal cytokine in T_H1 polarization, and, moreover, reduces the expression of the chemokines CXCL10 and CCL5, which are involved in T_H1 lymphocyte recruitment.¹⁰⁷ PPAR γ agonists lead to a rearrangement of membrane-bound costimulatory molecules characterized by decreased expression of CD80, CD83, and CD40, whereas CD86 and the coinhibitory molecule B7H1 are upregulated.^{108,112} The net effect of these changes appears to be an inhibition of DC immunogenicity marked by diminished T-cell activation capacity.^{108,113} It seems that PPAR γ is involved in the regulatory network, stringently controlling the immunostimulatory capacity of DCs. Activation of PPAR γ has been shown to inhibit the nuclear localization of c-Rel and RelB, both of which are members of the NF- κ B family of transcription factors,

which are reported to be essential for normal DC function.^{108,114,115} In addition, activated PPAR γ interferes with the mitogen-activated protein kinase pathway through impaired phosphorylation of p38 and extracellular signal-regulated kinase 1, kinases located upstream in the signaling cascade mediating NF- κ B activation.¹¹⁵

PPAR γ ligand-activated DCs are not only less stimulatory but also migrate poorly in response to CCL19 and CCL21, chemokines essentially involved in the homing of DCs to the lymph nodes.^{115,116} This observation might be explained in part by the downregulation of their mutual receptor, CCR7.^{108,117}

However, one cannot exclude that some of the inhibitory effects of PPAR γ agonists are not receptor dependent because genetic evidence, or at least evidence for the requirement for the receptor, is still missing.

Several pathways have been identified that are positively regulated on PPAR γ activation. PPAR γ agonists enhanced mannose receptor-mediated endocytosis of ovalbumin antigen in mouse DCs.¹¹² PPAR γ also induced the scavenger receptor CD36, which is implicated in apoptotic cell uptake.^{107,108} Moreover, ABCG2 was directly induced by PPAR γ , which led to enhanced extrusion of the cytotoxic drug mitoxantrone, providing cytoprotection to human DCs.¹¹⁸

Global gene expression profile analyses revealed that activation of PPAR γ coordinately regulates the expression of CD1 proteins. These MHC class I-like molecules are required for lipid antigen presentation to T cells. Group 1 CD1 molecules (CD1a, CD1b, CD1c, and CD1e) present lipid antigens to conventional T lymphocytes, whereas group 2 CD1 molecules (CD1d) are involved in iNKT cell generation.¹¹⁹ PPAR γ -activated human DCs showed reduced expression of group 1 and enhanced expression of group 2 CD1 molecules, leading to the induction of iNKT cell expansion.¹⁰⁹ The enhanced expression of CD1d turned out to be an indirect effect through the activation of RAR, as mentioned above.⁶⁷ However, PPAR γ directly regulates cathepsin D, a protease capable of generating lipid transfer molecules, which facilitate lipid loading to CD1d molecules.¹²⁰

Interestingly, most of the "early" genes, which are induced after 6 hours of DC differentiation in the presence of PPAR γ agonist, are associated with various aspects of lipid metabolism, such as *fatty acid oxidation* or phospholipid and triacylglycerol synthesis. PPAR γ -activated DCs accumulated fewer lipid droplets, further suggesting that these cells have a modified lipid homeostasis.¹²¹ However, the link between lipid metabolism and immune function of DCs is still somewhat elusive.

LXR

LXR α and LXR β function as sensors of endogenous cholesterol metabolites and regulate different aspects of cholesterol and bile acid homeostasis.¹²² LXRs are activated by endogenous oxidized and hydroxylated cholesterol derivatives, including 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and synthetic agonists, such as T0901317 and GW3965 (Table I).¹²³⁻¹²⁷ Although LXR α and LXR β show significant sequence similarities in their DBDs and LBDs, their tissue expression patterns are different. Although LXR α expression is mostly restricted to metabolically active tissues, LXR β is ubiquitously expressed.¹²⁸

LXRs play diverse roles in macrophage biology (Fig 4). They are involved not only in the regulation of macrophage cholesterol homeostasis but also in the regulation of the macrophage

TABLE II. Selected human clinical studies targeting RXR heterodimers through oral administration of nuclear receptor ligands in patients with RA, IBD, SLE, and asthma

RA				IBD			
Authors	No.	Drug(s) used	Results	Authors	No.	Drug(s) used	Results
Vitamin A/retinoids				Wright et al, 1985 ²⁵³	86	Vitamin A vs placebo	→ Disease activity
PPARγ agonists				Lewis et al, 2008 ²⁷⁴	105	Rosiglitazone vs placebo	↑ Clinical response and remission → Endoscopic remission
Shahin et al, 2011 ²⁰¹	49	Usual treatment + pioglitazone vs usual treatment + placebo	↓ Disease activity	Liang 2008 ²⁷⁵	42	Rosiglitazone + 5-ASA vs 5-ASA	↓ Disease activity
Vitamin D				Miheller et al, 2009 ²⁸⁸	37	1,25(OH) ₂ vitamin D ₃ vs 25(OH) vitamin D ₃	↓ Disease activity (only 1,25[OH] ₂ D ₃)
Salesi and Farajzadegan, 2011 ²²⁶	117	Methotrexate + vitamin D vs methotrexate + placebo	→ Disease activity	Jørgensen et al, 2010 ²⁸⁹	108	Vitamin D vs placebo	↓ Relapse rate
Gopinath and Danda, 2011 ²²⁷	121	DMARD + calcium + vitamin D vs DMARD + calcium	↑ Pain relief	Racovan et al, 2012 ²²⁰	32,435	Calcium + vitamin D vs placebo	→ RA incidence

No FDA-approved LXR agonists are available for clinical use, and therefore clinical studies testing their effectiveness are not available.

↑, Increase; ↓, decrease; →, no change in parameter; 5-ASA, 5-aminosalicylate; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; FEF₂₅₋₇₅, forced expiratory flow, midexpiratory phase; HDL, high-density lipoprotein; No., number of participants.

inflammatory response, phagocytosis, and apoptosis. LXR activation prevents macrophage cholesterol overload by simultaneously inhibiting cholesterol uptake and increasing cholesterol efflux mediated by ABC transporters (eg, ABCA1 and ABCG1), as mentioned above.¹²⁹ Regarding the immunoregulatory role of LXR, mutual interactions were observed between LXR activation and pathogen-induced inflammation in macrophages. Endogenous and synthetic LXR ligands inhibit the expression of inflammation-related genes, such as iNOS, COX-2, and IL-6, after LPS stimulation.¹³⁰ This effect can be explained by the observation that a similar transrepression mechanism exists for LXR as for PPAR γ . It was reported that ligand binding results in the SUMOylation of the receptor, which inhibits LPS-induced corepressor clearance from the promoter of inflammatory genes.¹³¹ However, the same questions exist regarding this model as in the case of PPAR γ , as described above. Another piece of evidence supporting the link between LXR signaling and immune response is that TLR4, mediating LPS recognition, was identified as a direct LXR target gene, and LXR activation leads to the induction of TLR4 expression in human macrophages.¹³² Interestingly, however, short-term pretreatment with LXR agonists reduced LPS-induced inflammatory response, whereas long-term activation of LXRs resulted in an increased LPS response.¹³² Nevertheless, the interaction between LXRs and inflammation is not unilateral: pathogen-induced inflammation is also able to influence LXR activation. Microbial compounds activating TLR3 and TLR4 signaling pathways inhibit LXR target gene expression through interferon regulatory factor 3.¹³³ An *in vivo* role of macrophage-expressed LXRs in immune regulation was studied

in total LXR α and LXR β single- and double-knockout and bone marrow transplantation mouse models. Transplantation of LXR α/β double-knockout bone marrow into wild-type mice resulted in increased susceptibility to *Listeria monocytogenes* infection with enhanced macrophage apoptosis and defective bacterial clearance,¹³⁴ suggesting the involvement of LXRs in the regulation of phagocytic activity in macrophages. Indeed, it has been shown that LXR signaling activated by the uptake of apoptotic cells enhances the expression of Mer tyrosine kinase, a critical factor for phagocytosis.¹³⁵ Interestingly, LXRs expressed by macrophages and DCs also participate in the maintenance of neutrophil homeostasis *in vivo*. LXR signaling activated by apoptotic cell engulfment is required for efficient clearance of senescent neutrophils in mice. Furthermore, LXR activation in macrophages represses the production of the IL-23/IL-17/G-CSF granulopoietic cytokine cascade, an inducer of neutrophil production in the bone marrow.¹³⁶ An additional mechanism of LXR-dependent enhancement of phagocytosis is the increased expression of RAR α by LXR activation in human monocytes and macrophages. Increased RAR α expression results in increased transglutaminase 2 levels in the presence of RAR agonists, leading to enhanced phagocytic capacity.¹³⁷

Ultimately, some studies indicate that activation of the LXR/RXR heterodimer through either LXR or RXR prevents pathogen-induced macrophage apoptosis, a microbial strategy for eluding innate immune responses. The LXR/RXR heterodimer promotes macrophage survival by enhancing the expression of antiapoptotic regulators (eg, AIM/CT2, Bcl-XL, Birc1a, and SP α) and inhibiting the expression of proapoptotic regulators

TABLE II. (Continued)

SLE				Asthma			
Authors	No.	Drug(s) used	Results	Authors	No.	Drug(s) used	Results
				Checkley et al, 2011 ³³²	3,075	Vitamin A vs placebo	→ Spirometric parameters → Asthma incidence
Juarez-Rojas et al, 2012 ³¹⁴	30	Pioglitazone vs placebo	↑ HDL cholesterol ↓ Insulin resistance ↓ CRP	Richards et al, 2010 ³⁴³	34	Rosiglitazone vs placebo	↓ Late asthmatic reaction
				Spears et al, 2009 ³⁴⁴	46	Beclomethasone vs rosiglitazone	↑ FEV ₁ ↑ FEF ₂₅₋₇₅
Abou-Raya et al, 2012 ³¹⁹	267	Vitamin D vs placebo	↓ Disease activity				

(eg, caspases 1, 4, 11, 7, and 12 and Fas ligand) and thereby has a profound effect on antimicrobial responses.^{134,138}

LXRs are expressed both in peripheral blood–derived myeloid DCs¹³⁹ and in DCs of human reactive lymph nodes¹⁴⁰; however, the role of LXRs in DC immunogenicity is rather controversial (Fig 5). It has been described that LXR activation leads to the inhibition of LPS-induced human monocyte-derived DC maturation and IL-12 secretion. On LXR activation, inhibition of T-cell stimulatory capacity was also observed, partly as a result of the decreased LPS-induced expression of fascin, an actin-bundling protein critical for immunologic synapse formation and effective T-cell activation.¹³⁹ In contrast, we have shown that natural and synthetic LXR agonists promoted DC maturation and IL-12, TNF- α , IL-6, and IL-8 production and enhanced the capacity of DCs to induce CD4⁺ T-cell proliferation.¹⁴⁰ It appears that the migratory capacity of DCs is negatively regulated by LXR signaling because LXR agonists inhibited CCR7 expression and DC migration both *in vitro* and *in vivo*.^{116,141,142}

VDR

VDR binds the biologically active form of vitamin D: 1,25(OH)₂D₃. Ligand-activated VDR/RXR heterodimers participate in the control of several physiologic processes through the regulation of gene expression. Vitamin D is necessary for calcium absorption in the gut, as well as normal mineralization, growth, and remodeling of bone.¹⁴³ VDR is also expressed in numerous human and mouse immune cells, such as T cells, B cells, iNKT cells, macrophages, and DCs, modulating several aspects of the

immune response.¹⁴⁴ Interestingly, macrophages and DCs are also able to produce 1,25(OH)₂D₃ from its precursor, 25(OH)D₃, in response to various activating stimuli, suggesting that macrophage- and DC-derived 1,25(OH)₂D₃ can modulate the phenotype and function of immune cells in an autocrine or paracrine fashion.¹⁴⁵⁻¹⁵¹

It has long been known that 1,25(OH)₂D₃ and its analogs can induce macrophage differentiation from bone marrow precursors.¹⁵²⁻¹⁵⁴ However, VDR has proved dispensable for normal hematopoiesis (ie, monocyte/macrophage differentiation can occur in the absence of the receptor).¹⁵⁵ VDR activation in mature monocytes/macrophages has been demonstrated to result in diverse responses, including both positive and negative effects on immunogenicity, presumably depending on the immunologic context (Fig 4).

Several lines of evidence support the positive effects of vitamin D on monocyte/macrophage function. First, administration of 1,25(OH)₂D₃ leads to increased phagocytic activity¹⁵⁶ and also increases IL-1, prostaglandin E₂, and H₂O₂ production of peripheral blood–derived human monocytes.¹⁵⁷⁻¹⁵⁹ Second, 1,25(OH)₂D₃ can potentiate antimicrobial activity of macrophages through VDR-dependent induction of antimicrobial peptides, cathelicidin, and defensin B2/4.¹⁶⁰⁻¹⁶² This mechanism accounts for the previously observed effect of 1,25(OH)₂D₃ to effectively inhibit the proliferation of *Mycobacterium tuberculosis* in human monocytes and macrophages.^{163,164} The crucial role of vitamin D in the immune response against *M tuberculosis* is further supported by the efficiency of sunlight exposure in the treatment of tuberculosis,¹⁶⁵ as well as the association between

vitamin D deficiency and increased susceptibility to the disease.¹⁶⁶

Interestingly, VDR activation in monocytes/macrophages has been shown to induce a strong immunosuppressive effect as well. 1,25(OH)₂D₃ stimulation of human monocytes inhibited the expression of all 3 subtypes of MHC class II antigens (HLA-DR, HLA-DP, and HLA-DQ) involved in antigen presentation.^{156,167} VDR can also decrease the expression of IL-2, IL-6, IL-12, IFN- γ , and TNF- α , partly by interfering with the nuclear factor of activated T cells/AP-1- and NF- κ B-mediated proinflammatory pathways.¹⁶⁸⁻¹⁷⁰ Furthermore, 1,25(OH)₂D₃ was able to inhibit INF- γ -induced responses in murine macrophages, leading to the suppression of oxidative burst, microbicidal activity, and the downregulation of mediators involved in host defense (eg, CCL5, CXCL10, CXCL9, Fc γ RI, Fc γ RIII, and TLR2).¹⁷¹ However, the hormone had no effect on resting macrophages, suggesting that vitamin D might act as part of a mechanism limiting macrophage activation. The hypothesis of such a negative feedback loop is further supported by studies showing that LPS or TLR2 ligands induced both CYP27B1 enzyme, which is capable of producing 1,25(OH)₂D₃, and VDR.^{172,173} Activation of VDR by 1,25(OH)₂D₃, in turn, suppressed TLR2 and TLR4 expression, leading to an impaired inflammatory cell response to pathogen-associated molecular patterns.¹⁷⁴ This process, together with the aforementioned downregulation of proinflammatory mediators by activated VDR, could eventually result in taming of the immune response elicited by macrophages.

It is well established that 1,25(OH)₂D₃ inhibits the differentiation, maturation, and immunostimulatory capacity of human and mouse DCs (Fig 5).¹⁷⁵ The biological relevance of this effect is the generation of a tolerogenic DC phenotype characterized by low surface expression of MHC class II and costimulatory molecules (eg, CD40, CD80, and CD86) and high expression of inhibitory molecules (eg, immunoglobulin-like transcript 3) accompanied by decreased secretion of IL-12 and increased production of CCL22 and IL-10.¹⁷⁶⁻¹⁸³ This tolerogenic DC phenotype is associated with Treg cell induction, T-cell anergy, and effector T-cell death, thus playing a crucial role in maintaining immune tolerance against self-antigens.²⁴

MACROPHAGE- AND DC-EXPRESSED NUCLEAR RECEPTORS IN IMMUNOPATHOLOGY RA

RA is a chronic symmetric polyarthritis affecting primarily the small joints of the hands and feet. RA is characterized by inflammation and hyperplasia of the synovial membrane, which leads to the formation of pannus (an invasive tissue composed of mesenchymal and bone marrow-derived cells), which erodes the articular cartilage and the adjacent bone, leading to instability and deformity of the joint. In the later stages of the disease, severe systemic complications arise, including cardiovascular, pulmonary, neurological, and skeletal disorders, potentially reducing the lifespan of patients.¹⁸⁴

Activated macrophages in the synovial membrane produce proinflammatory cytokines (eg, IL-1, IL-6, and TNF- α), chemokines (eg, IL-8 and monocyte chemoattractant protein 1), and growth factors (eg, GM-CSF), thus promoting monocyte and lymphocyte recruitment and activation.¹⁸⁵ Macrophages also contribute to neovascularization of the hyperplastic synovial membrane and degradation of the extracellular matrix by producing proangiogenic

factors (eg, IL-8 and vascular endothelial growth factor) and MMPs (eg, MMP-1 and MMP-9), respectively.¹⁸⁶ The inflammatory milieu of the joint might also facilitate the differentiation of macrophages into osteoclasts, which are mainly responsible for subchondral bone erosion.¹⁸⁷ The degree of synovial macrophage infiltration correlates with radiologic progression of joint destruction,¹⁸⁸ which indicates the central role of macrophages in the pathogenesis of RA.

DCs are also abundant in rheumatoid synovium, playing a central role in breaking self-tolerance through presentation of autoantigens, production of proinflammatory factors, and induction of T_H1- and T_H17-type T-cell differentiation from naive T cells.^{189,190} Generation of tolerogenic DCs capable of Treg cell induction and autoreactive T-cell deletion could be a potential new therapeutic tool for treating RA.¹⁹¹

Nuclear receptor ligands have been shown to modulate macrophage and DC phenotypes in RA in a number of experimental models and clinical studies.

In a mouse collagen-induced arthritis (CIA) model, which is the gold standard *in vivo* model for RA studies,¹⁹² treatment with the RAR agonist ATRA attenuated the clinical and histologic signs of arthritis, including reduced macrophage infiltration of the synovium¹⁹³ and inhibition of the differentiation of bone marrow-derived monocytes/macrophages into osteoclasts.¹⁹⁴

Several studies reported the suppression of arthritis on administration of PPAR γ ligands, either endogenous 15d-PGJ₂, or synthetic TZDs, in the setting of CIA and adjuvant-induced arthritis murine models of RA.¹⁹⁵⁻¹⁹⁹ This effect is at least partly attributable to the anti-inflammatory action of PPAR γ ligands, which result in decreased plasma levels of IL-1 β , IL-6, and TNF- α proinflammatory cytokines and inhibition of iNOS expression in the joints.¹⁹⁶⁻¹⁹⁸ Similar to ATRA, PPAR γ ligands decreased synovial mononuclear cell infiltrate, as well as osteoclast differentiation of monocytes/macrophages.^{195,199} Interestingly, the effective doses of PPAR γ agonists resulted in a weight gain of animals, probably because of the induction of adipocyte differentiation.¹⁹⁸

Synovial macrophages and peripheral blood-derived monocytes of patients with RA showed enhanced expression of PPAR γ with increased MMP-9 activity.^{195,200} In a recent clinical trial supplementation of the usual treatment of patients with the TZD pioglitazone resulted in a marked reduction in disease activity scores and serum levels of the inflammatory marker C-reactive protein compared with the usual treatment alone. In accordance with results from the animal model, 25% of the patients showed weight gain during the trial.²⁰¹ *In vitro* results showed that PPAR γ agonists can inhibit TNF- α - and osteoprotegerin ligand-mediated osteoclast differentiation.^{202,203} However, the PPAR γ agonist rosiglitazone promoted activator of nuclear factor- κ B ligand-induced osteoclast differentiation in a PPAR γ -dependent manner.²⁰⁴ The latter study is supported by the observation that TZD treatment causes a higher rate of bone fractures in patients.²⁰⁵

There are conflicting results regarding the effect of the LXR agonist on RA progression.

According to Asquith's group, activation of LXR leads to the exacerbation of articular inflammation,^{206,207} whereas Park et al²⁰⁸ showed a reduction in disease severity in the same CIA model.

The positive effect of vitamin D and its analogs on articular inflammation has been proved in different animal models of RA.²⁰⁹⁻²¹² Either vitamin D or VDR deficiency resulted in an

increased recruitment of macrophages and DCs to the arthritic synovium.^{211,212} Moreover, VDR-deficient monocytes were proinflammatory and hyperresponsive to TNF- α stimulation, also showing enhanced osteoclast differentiation potential.²¹¹ Synovial DCs from vitamin D-deficient animals showed an altered phenotype characterized by increased lymphocyte-stimulatory properties and increased expression of inflammation-associated genes.²¹²

On the basis of the promising results from animal models, there is a growing body of human studies that suggest that vitamin D modulates the clinical course of RA through its immunomodulatory effects.

In patients with RA, VDR is highly expressed in synovial macrophages,²¹³ which are also capable of synthesizing the VDR agonist 1,25(OH) $_2$ D $_3$.²¹⁴⁻²¹⁶ Several large cohort studies were performed in recent years addressing the possible link between vitamin D intake and the risk for RA, yielding contradictory results. A prospective cohort study of 29,368 women aged 55 to 69 years showed an inverse association between daily vitamin D intake and risk for RA.^{217,218} However, a subsequent study with a larger cohort consisting of 186,389 women did not show any protective effect of vitamin D intake on RA.²¹⁹ The recent calcium and vitamin D supplementation trial of the Women's Health Initiative seems to confirm the latter study's results, showing no significant effect of calcium and vitamin D supplementation on RA incidence.²²⁰ In contrast, several clinical studies report that low serum levels of vitamin D in patients with RA are associated with increased disease activity.²²¹⁻²²⁵ Oral administration of vitamin D in patients with active RA showed an improvement in disease activity; however, these results were nonsignificant, which suggests the need for studying larger patient groups or using larger vitamin D doses.^{226,227} Approximately 80% of vitamin D synthesis is sunlight dependent, resulting in serum levels being lowest in winter and spring. Intriguingly, the low levels of vitamin D that occur in winter and spring are associated with increased risk of RA onset.^{228,229} In addition, North European countries have higher RA incidence rates than South European countries.²³⁰

A new immunotherapeutic approach aims to use the immunoregulatory role of vitamin D by generating tolerogenic DCs through dexamethasone, vitamin D, and TLR4 agonist treatment of the patients' monocyte-derived DCs. This approach proved to be effective in a CIA model,²³¹ and a phase I study in patients with RA is currently being conducted.²³²

IBD

Crohn disease and ulcerative colitis, together often referred to as IBD, are conditions with overlapping clinical and pathologic features, both of which are characterized by chronic relapsing inflammation of the gastrointestinal tract, resulting in abdominal pain, frequent diarrhea, gastrointestinal bleeding, and malnutrition. IBD is thought to result from a dysregulated mucosal immune response to normal luminal bacteria in genetically susceptible subjects.²³³

Macrophage and DC subsets of the gut-associated lymphoid tissue (GALT) exhibit peculiar phenotypes, often possessing both macrophage and DC surface markers, as well as macrophage- and DC-like morphologic and functional characteristics.²³⁴ Aberrant activation of these mononuclear phagocytes is proposed to be one of the crucial early steps during the pathogenesis of IBD.²³⁵⁻²³⁹

The lipid microenvironment of the lamina propria, where macrophages and DCs reside, shapes the immune response both in physiologic and pathologic conditions.

The vitamin A metabolite retinoic acid plays a central role in regulating the balance between immunity and tolerance in the intestinal immune system. Retinoic acid, which is produced by intestinal epithelial cells, drives the differentiation of tolerogenic DCs,²⁴⁰ which are capable of Treg cell induction through a TGF- β - and retinoic acid-dependent mechanism.²⁴¹⁻²⁴³ Moreover, ATRA was reported to program DCs to a mucosal phenotype with TGF- β and IL-6 secretion and the capacity to augment mucosal homing and IgA response of lymphocytes.²⁴⁴ Lamina propria macrophages might also generate a milieu ideal for Treg cell differentiation by secreting IL-10 and retinoic acid.²⁴⁵ At the same time, ATRA inhibits the IL-6-driven induction of T $_H$ 17 cells, which promote inflammation and autoimmunity; thus by shifting the Treg/T $_H$ 17 balance, it potentiates dampening of the inflammation.²⁴⁶ On this basis, one could predict that retinoic acid might suppress inflammatory responses through Treg induction and T $_H$ 17 suppression *in vivo*, whereas vitamin A (and concomitant retinoic acid) deficiency might result in the exacerbation of inflammation. This was found to be the case in animal models of IBD.^{72,247,248} Nevertheless, there is little evidence of a correlation between vitamin A deficiency and disease activity in patients with IBD,²⁴⁹ even though 15% of 20% of the patients are vitamin A deficient.²⁵⁰⁻²⁵² However, early clinical studies did not show any beneficial effects of vitamin A supplementation in patients with Crohn disease.^{253,254}

PPAR α and PPAR γ ligands have been shown to reduce the severity of colitis in different experimental animal models of IBD.²⁵⁵⁻²⁶² Coadministration of selective PPAR γ and RXR α agonists suppressed trinitrobenzene sulfonic acid-induced colitis in a synergistic manner, confirming the *in vivo* relevance of the permissive activation of PPAR/RXR heterodimers.²⁶³ Interestingly, 5-aminosalicylate, which is a widely used drug in the treatment of IBD, was reported to act through a PPAR γ -dependent mechanism.²⁶⁴ The role of PPAR α , which is expressed by mononuclear phagocytes, has to be elucidated in cell-specific knockout animals, whereas the crucial role of macrophage-expressed PPAR γ in attenuation of colonic inflammation has been clearly described by using macrophage-specific deletion of PPAR γ in mice. Macrophage-specific PPAR γ deficiency led to a significantly worsened disease activity in a dextran sodium sulfate-induced colitis model.^{93,265} Significantly fewer Treg cells were observed in mesenteric lymph nodes of mice deficient in the macrophage PPAR γ , whereas infiltration of macrophages expressing high levels of the costimulatory molecule CD40 increased, suggesting the contribution of macrophage PPAR γ in regulating the functional and homing properties of GALT cells.²⁶⁵ Human genetic evidence for the involvement of PPAR γ in patients with IBD was provided by us, reporting that the Pro12Ala polymorphism showed a significant association with the development of Crohn disease in a Hungarian cohort.²⁶⁶

The ligand-binding cavity of PPARs makes it possible to bind an array of fatty acids and convert their signals to transcriptional regulation, and thus dietary fatty acids might influence colonic inflammation through binding to PPARs. Several fatty acids have been shown to ameliorate colitis through the activation of PPAR γ in animal models, such as conjugated linoleic acid,²⁶⁷⁻²⁶⁹ α -eleostearic acid,²⁷⁰ puniceic acid,²⁷¹ and abscisic acid.²⁷² Dietary supplementation of these compounds can serve as an adjuvant

treatment for patients with IBD; however, human studies are needed to validate the positive effects observed in murine models. Despite the encouraging results in patients with IBD using rosiglitazone alone or in combination with 5-aminosalicylate,²⁷³⁻²⁷⁶ alternative TZDs need to be tested because of the known adverse effects associated with long-term use of rosiglitazone,^{277,278} which resulted in the FDA restricting the use of rosiglitazone in 2010 and the European Medicines Agency completely banning it.

The crucial importance of VDR in maintaining physiologic GALT function is underscored by the fact that VDR knockout mice were extremely sensitive to experimentally induced colitis,²⁷⁹⁻²⁸² partly because of impaired T-cell homing to the gut, resulting in a dysregulated antimicrobial activity against commensal bacteria.²⁸³ Similar to RA, IBD incidence shows a north-to-south gradient,^{284,285} suggesting that sunlight-dependent vitamin D levels might affect the susceptibility for dysregulated intestinal inflammation. Indeed, higher intake of vitamin D appear to reduce the risk for IBD,²¹⁷ whereas vitamin D deficiency is associated with higher disease activity.^{286,287} In addition, vitamin D supplementation was reported to be beneficial in patients with Crohn disease.^{288,289} Moreover, on the basis of animal studies, administration of vitamin D with dexamethasone, instead of dexamethasone alone, could be a beneficial combination therapy, which probably skew DCs toward a tolerogenic phenotype.^{290,291}

SLE

SLE is a chronic, complex autoimmune disease of unknown cause affecting most of the vital organ systems, including the skin, joints, heart, lungs, kidneys, and the nervous system. SLE is considered a disorder of the adaptive immunity characterized by the loss of tolerance to self-antigens, generation of autoreactive T and B cells, and production of autoantibodies, causing formation and deposition of immune complexes with subsequent tissue inflammation and damage throughout the body. However, the importance of innate immunity in the initiation and maintenance of the disease has been recognized in the past decade. Macrophage abnormalities, such as aberrant surface marker expression (eg, FcγR and costimulatory and adhesion molecules), dysregulated cytokine production, and defective phagocytosis of cellular debris have been shown to be associated with SLE.²⁹² Intriguingly, serum from patients with SLE induced the differentiation of monocytes into DCs with a potent capacity to present self-antigens.²⁹³ The role of DCs in the pathogenesis of SLE is further supported by the observation that DCs from patients with SLE showed enhanced expression of costimulatory molecules and T-cell activation capacity.²⁹⁴⁻²⁹⁶ In addition, nephritic kidneys and cutaneous lesions of patients with SLE show a high degree of pDC infiltration.^{297,298} pDCs are capable of producing high amounts of IFN-α, which is considered one of the central pathogenic cytokines in SLE.²⁹⁹ Moreover, prolonged persistence of apoptotic cells because of impaired phagocytosis by tissue-resident macrophages leads to secondary necrosis, which, in turn, fuels DC activation and SLE progression.^{300,301}

Although the nuclear receptor ligand estrogen is proposed to be one of the key factors determining the predilection of SLE for female patients,³⁰² the link between nuclear receptor signaling and SLE pathogenesis is largely unexplored.

Regarding the effect of vitamin A derivatives, ATRA treatment was shown to be beneficial in murine models of SLE, resulting in

prolonged survival, inhibition of glomerular injury, and proteinuria.³⁰³⁻³⁰⁵ However, the RAR or RXR dependency of this effect was not demonstrated.

The effectiveness of PPARγ agonists on experimental SLE models has also been examined in recent years. Both rosiglitazone and pioglitazone ameliorated the autoimmune phenotype by decreasing antinuclear antibody titer and lupus-nephritis.³⁰⁶⁻³⁰⁸ The mechanism responsible for the positive effect of rosiglitazone was demonstrated to be induction of adiponectin secretion, supporting the anti-inflammatory role of this adipocyte-derived cytokine.³⁰⁶ Interestingly, increased adiponectin levels were found in patients with SLE,^{309,310} raising the question of whether adiponectin is a cause or a consequence (ie, whether it promotes disease progression through a possible proinflammatory action or participates in dampening tissue inflammation).

A critical role of the macrophage-expressed PPARγ/RXRα heterodimer in SLE initiation was proposed in a recent study by showing that mice with PPARγ- or RXRα-deficient macrophages have glomerulonephritis and antinuclear antibodies, resembling the characteristics of human SLE.³¹¹ PPARγ knockout and RXRα knockout macrophages of these mice showed impaired clearance of apoptotic cells caused by the failed induction of the PPARγ- and RXRα-regulated gene network involved in apoptotic cell uptake, including CD36, Mer tyrosine kinase, transglutaminase 2, and certain opsonins. PPARγ and RXRα deficiency in macrophages also led to diminished induction of the anti-inflammatory phenotype and subsequent self-tolerance in response to apoptotic cells.³¹¹ The mechanism underlying this phenomenon is most likely the lack of PPARγ-mediated transrepression of inflammatory pathways induced by apoptotic cells, as described earlier.³¹²

It was also shown that CD40/CD40 ligand signaling, which is involved in autoimmunity, increases PPARγ expression in patients with active SLE and that PPARγ, in turn, negatively modulates CD40/CD40 ligand signaling as part of a negative feedback mechanism.³¹³

Altogether, these results suggest that PPARγ agonists could serve as potential steroid-sparing drugs in the prevention of organ damage in patients with SLE. Although TZDs are already in clinical use, only 1 clinical trial has been performed with patients with SLE, yielding promising results.³¹⁴

As mentioned earlier, LXR signaling is also essential for effective apoptotic cell clearance by macrophages. Indeed, defective apoptotic cell engulfment in LXRα/β knockout mice led to the development of autoantibodies and deposition of immune complexes, resulting in glomerulonephritis.¹³⁵ In addition, systemic administration of LXR agonist ameliorated lupus-like autoimmune disease in experimental animals,¹³⁵ suggesting that LXR agonists might have utility in the therapy of SLE. Importantly, however, there are no FDA-approved LXR-activating drugs on the market at the present time.

Patients with SLE tend to avoid sun exposure, which is a trigger of lupus flares. Partly as a result of sun avoidance, vitamin D deficiency appears to be more prevalent among patients with SLE than among the healthy population.³¹⁵ According to studies on relatively large cohorts (290 and 378 patients, respectively), vitamin D deficiency and SLE disease activity show a significant correlation.^{316,317} Consistent with these results, recent clinical trials reported beneficial effects of vitamin D supplementation in patients with SLE.^{318,319} As an evidence of vitamin D's action, the aforementioned immunostimulatory effect of serum from

patients with SLE on normal monocytes appears to be partly reversed by vitamin D.^{320,321}

These results further support the role of vitamin D in regulating immune homeostasis and draw attention to the critical importance of adequate vitamin D supplementation in patients with autoimmune disorders.

Asthma

Asthma is a disorder characterized by episodic reversible airflow obstruction associated with airway hyperresponsiveness. The main pathologic features underlying these symptoms are chronic airway inflammation and concomitant remodeling of the bronchial wall. The key players in the pathogenesis of asthma are evidently T_H2 lymphocytes promoting IgE production and recruitment of mast cells and eosinophil granulocytes, thus driving the inflammatory response to aeroallergens.

Nevertheless, there is an increasing appreciation of the role of pulmonary macrophages and DCs in contributing to the development and progression of asthma caused by a perturbation in their physiologic sentinel role. Macrophages modulate airway smooth muscle contractility and also appear to have an important role in preventing airway allergic responses. Emerging evidence indicates that pulmonary macrophages of asthmatic patients show dysfunctional activation, leading to the absence of their inhibitory function limiting T_H2 responses.³²² DCs are recruited and activated by most of the clinically relevant allergens either directly or indirectly through modifying the function of the airway epithelium. Activation of DCs is followed by migration to the local lymph nodes, where they, similar to basophils and mast cells, are capable of inducing T_H2 polarization and promote allergic responses.^{323,324}

Little is known about the effect of nuclear receptors in pulmonary macrophages and DCs, especially in the context of asthma pathogenesis. The reason for this is that essential data from disease models in nuclear receptor total and cell-specific knockout animals are still not available. Thus even though ligand treatment in murine models of asthma produced promising results, the contribution of macrophage- and DC-expressed nuclear receptors to the pathogenesis is hard to evaluate.

Data regarding the effect of retinoid receptor ligands in asthmatic patients are scarce and inconsistent. Liposomally encapsulated ATRA delivered to the airways before allergen challenge attenuated the asthma phenotype in mice.³²⁵ Interestingly, however, liposomal ATRA administered intraperitoneally at the time of sensitization to ovalbumin allergen exacerbated the allergic response, leading to enhanced allergen-specific IgE response and increased bronchoalveolar lavage (BAL) eosinophilia.³²⁶ A potential role of retinoid receptors in skewing the immune response toward the T_H2 type is further supported by the observation that inhibition of RXR prevented experimental allergic inflammation of the airways in mice.³²⁷ Consistent with these results, a high-level vitamin A diet in mice increased the allergic IgE response and airways hyperresponsiveness.³²⁸ Thus it can be hypothesized that high intake of vitamin A increases the risk for asthma. A prospective birth cohort study of 4089 newborn infants appears to support this hypothesis because children supplemented with vitamins A and D in a water-soluble form with a presumably higher bioavailability had an almost 2-fold increased risk of asthma by the age of 4 years compared with children supplemented with these vitamins in an oil-based form.³²⁹

Nonetheless, 2 case-control studies revealed that children with asthma have significantly lower vitamin A levels, and thus it seems that oil-based supplementation in the first years of life is still needed.^{330,331} Interestingly, however, a study conducted in an area with chronic vitamin A deficiency showed that vitamin A supplementation early in life did not affect the prevalence of asthma or measures of airways obstruction in participants aged 9 to 23 years,³³² and thus further studies would need to elucidate the role of vitamin A supplementation in affecting asthma risk or severity.

The beneficial effects of PPAR γ agonists, administered either orally or inhalationally, in murine models of asthma are more definite, as shown by several studies reporting decreased antigen-induced airway hyperresponsiveness, lung inflammation, eosinophilia, cytokine production (eg, IL-4, IL-5, and IL-13), mucus production, and serum levels of antigen-specific IgE.³³³⁻³⁴¹ Furthermore, when compared with dexamethasone in terms of effectiveness, pioglitazone demonstrated similar abilities to suppress cockroach allergen-induced allergic response in mice.³⁴² Human studies aimed at verifying these results reported modest effects of TZDs. Rosiglitazone attenuated late asthmatic reactions but not early asthmatic reactions to inhaled allergen challenge³⁴³ and significantly improved lung function (FEV₁ and forced expiratory flow, midexpiratory phase), but not asthma symptoms, compared with beclomethasone in the difficult-to-treat group of asthmatic smokers.³⁴⁴ Given the essential role of pulmonary macrophages and DCs in maintaining immune homeostasis in the lung, one could predict that ligand-activated PPAR γ in these cell types might contribute to the positive effects of agonist treatment demonstrated in mice and human subjects. PPAR γ protein expression, as detected only in BAL fluid macrophages and not in eosinophils or neutrophils, reduced after allergen challenge in asthmatic patients, suggesting the existence of dysregulated PPAR γ signaling in alveolar macrophages of asthmatic patients.³⁴⁵ The suppressive effect of DC-expressed PPAR γ activation was clearly demonstrated in an asthma model based on intratracheal transfer of ovalbumin-pulsed DCs. Transfer of rosiglitazone-pretreated and ovalbumin-pulsed DCs reduced the proliferation of allergen-specific T cells in the draining mediastinal lymph nodes and reduced BAL eosinophilia after allergen challenge compared with that seen in control mice sensitized only with ovalbumin-pulsed DCs. Interestingly, rosiglitazone treatment of DCs also increased the production of IL-10 by T cells in the draining lymph nodes, which contributed to the suppression of airway inflammation. The PPAR γ dependency of this effect was confirmed by using a PPAR γ antagonist, which restored the suppressive effect of rosiglitazone on DCs.¹¹⁷ Consistent with these results, sirtuin-1, an NAD⁺-dependent protein deacetylase, was shown to repress PPAR γ activity in DCs, thereby promoting DC maturation toward a pro- T_H2 phenotype capable of inducing allergen-specific T cells and therefore initiating airway allergic inflammation.³⁴⁶ Thus activation of PPAR γ expressed by DCs appears to have an inhibitory effect on T_H2 responses, which might be responsible in part for the beneficial effects of PPAR γ ligands in asthmatic patients.

There is no observational evidence on whether activation of VDR in macrophages or DCs affects the development of asthma. Although VDR knockout mice do not have experimental allergic asthma,³⁴⁷ this appears to be mainly attributable to the defective differentiation of iNKT cells.³⁴⁸ Several lines of evidence suggest the central role of the vitamin D endocrine system in the generation of T_H2 -driven allergic airway inflammation in human

subjects as well. Certain VDR polymorphisms are associated with asthma,^{349,350} and vitamin D deficiency was identified as a risk factor for childhood or severe adult asthma in several studies.³⁵¹⁻³⁵⁵ Consistent with these results, a meta-analysis of 4 large-cohort studies reported that higher maternal vitamin D intake was associated with reduced odds of childhood wheeze.³⁵⁶ Interestingly, however, one of the studies mentioned earlier showed that vitamin D administered in water-soluble form increased the risk for childhood asthma, further suggesting the need for determining an optimal dose and form of vitamin D supplementation.³²⁹ The ongoing Vitamin D and Omega-3 Trial, with 20,000 participants, aims to investigate whether vitamin D and omega-3 fatty acids influence the risk for asthma among patients with cancer, diabetes, cardiovascular diseases, autoimmune disorders, and other conditions.³⁵⁷ This trial is expected to identify patient groups in which proper vitamin D supplementation is needed and to explore the potential adverse effects of long-term supplementation, which would limit its utility in patients with certain disorders. However, the optimal intake of vitamin D still remains elusive, and hence further studies are needed to firmly establish recommendations.

EMERGING IMPORTANCE OF MACROPHAGE- AND DC-EXPRESSED NUCLEAR RECEPTORS IN PATIENTS WITH OTHER DISEASES

RA, IBD, SLE, and asthma represent growing public health problems and thus are subjects of intensive research. Nevertheless, as highlighted above, our understanding of the contribution of myeloid cells and nuclear receptors in pathogenesis is still limited. Also, significant progress has been made in recent years in elucidating the role of nuclear receptor signaling in patients with other disorders, as characterized by the contribution of macrophages and DCs.

In animal models of Alzheimer disease, multiple sclerosis, and ischemic stroke, PPAR γ agonists have been shown to suppress the inflammatory response of microglial cells (the specialized macrophages of the central nervous system), reducing neuronal inflammation and brain damage.³⁵⁸ Furthermore, induction of ABCA1 and apolipoprotein E in microglial cells by PPAR γ , LXR, or retinoid receptors increased the clearance of plaque-forming amyloid β . As a result, the cognitive function of experimental animals improved, indicating that nuclear receptors might be promising therapeutic targets for the treatment of Alzheimer disease.^{359,360}

The induction of ABCA1 by nuclear receptors appears to be beneficial in HIV infection as well. PPAR γ - and LXR-mediated upregulation of ABCA1 led to cholesterol efflux, resulting in the depletion of cholesterol from the plasma membrane, which, in turn, decreased the ability of DCs to capture HIV-1 virus.¹¹⁶ Moreover, treatment of macrophages with PPAR γ and LXR agonists has been shown to repress the transcription of HIV-1.³⁶¹

Although dysregulated nuclear receptor functions have been shown in cancer cells,³⁶² the role of nuclear receptors in cancer cell-associated stromal and immune cells is still elusive. The importance of the tumoral lipid microenvironment is indicated by the observation that tumor cells produce LXR-activating lipids, which inhibit CCR7 expression of DCs and therefore their migration to draining lymph nodes. This mechanism dampens the anti-tumor immune response elicited by DCs.¹⁴² Activation of PPAR γ in tumor-bearing animals increased lung cancer progression and

metastasis in a macrophage-dependent manner, suggesting a potential role of PPAR γ expressed by tumor-associated macrophages in promoting tumor progression.³⁶³ Considering the profound effects of nuclear receptors on immune homeostasis, the emerging field of tumor immunity will, in all likelihood, reveal important functions of nuclear receptor signaling in immune cells, either limiting or paradoxically promoting tumor progression.³⁶⁴

CONCLUDING REMARKS

We have attempted to illustrate above that the connections between the metabolism and the immune system are much more widespread than previously suspected. Although there are many lipid-activated pathways, a particularly important one is the nuclear receptor-mediated pathway, which provides a direct link between lipid and metabolic changes to gene expression. A systematic evaluation of the contribution of components of this signaling network is possible through use of tissue-specific knockout and appropriate animal models. This is a huge task and will take a considerable amount of time but will bring about a much better understanding of the role and contribution of the individual receptors to physiologic and pathophysiologic processes. Translation of the results to human disease will come after completing this research, but it will not be easy because of the obvious species-specific differences. Therefore clinical research would need to come at least halfway by carrying out studies on patients with immunopathologic conditions, including genome-wide association studies, expression profiling, and biomarker discoveries in patients treated with activators or inhibitors of nuclear receptors (see Table II for a summary of major human studies completed thus far). Additional metabolomic approaches would need to analyze the pathologic changes in the extracellular and intracellular lipid milieu presumably affecting nuclear receptor signaling in immune cells of diseased subjects. Only the combination of animal model-based basic research and complementary high-quality and focused clinical studies leads to better understanding, diagnosis, and ultimately treatment of human immunologic diseases.

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