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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-Δ12,14-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

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

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

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 αβ T-cell receptors with little diversity.

NUCLEAR FACTOR κB (NF-κB): A family of transcription factors that promotes the expression of a variety of inflammatory mediators. NF-κB is present in an unstimulated state in the cytoplasm, where it is bound by IκB, 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 D_3 by means of UV light.

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