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Dietary cholesterol metabolite regulation of tissue immune cell development and function

Michela Frascoli,

Andrea Reboldi[*], **Joonsoo Kang**[*]

University of Massachusetts Chan Medical School, Department of Pathology, Worcester, MA USA 01655

Abstract

Obesity is considered the primary environmental factor associated with morbidity and severity of wide-ranging inflammatory disorders. Molecular mechanism linking high fat or cholesterol diet to imbalances in immune responses, beyond the increased production of generic inflammatory factors, is just beginning to emerge. Diet cholesterol byproducts are now known to regulate function and migration of diverse immune cell subsets in tissues. The hydroxylated metabolites of cholesterol oxysterols as central regulators of immune cell positioning in lymphoid and mucocutaneous tissues is the focus of this review. Dedicated immunocyte cell surface receptors sense spatially distributed oxysterol tissue depots to tune cell metabolism and function, to achieve the “right place at the right time” axiom of efficient tissue immunity.

Dysregulation of lipid metabolism, in particular elevated cholesterol levels in obesity, is invariably associated with chronic diseases of overt inflammation, including atherosclerosis, diabetes, dementia, psoriasis and gut dysbiosis. Commensurate with the clinical importance, cholesterol biosynthesis and cholesterol homeostasis have been the focus of intense investigation that gave rise to several classes of drugs to treat and prevent cardiovascular diseases by controlling serum cholesterol levels (1). Immune system-specific requirements for cholesterol are well established, although most studies have focused on specific cell types and only the most prominent genes of cholesterol biosynthesis, resulting in disconnect from integrative physiology. Moreover, the biology of cholesterol-derived metabolites in shaping tissue immune responses has been largely uncharacterized, despite the recognition of the bidirectional crosstalk between cholesterol homeostasis and immune system as a major determinant in the pathogenesis of metabolic diseases (2, 3).

Cholesterol is insoluble in water, and its transport into and within the body requires association with various chaperons and carrier proteins that are subsequently sensed by dedicated receptors. However, enzymatic addition of hydroxyl group(s) can reduce cholesterol hydrophobicity. Oxysterols are generated by cholesterol oxidation, involving enzymes with specificity for carbons at selected positions of the sterol ring. These hydrophilic byproducts can be more easily transported in aqueous environment, making them ideal as intercellular cues. Oxysterols have multifaceted effects on immune cells

[*]To whom correspondence should be addressed (andrea.reboldi@umassmed.edu, joonsoo.kang@umassmed.edu).

(Table 1), depending on their ability to be sensed by intracellular or surface receptors (4). Expression of certain oxysterol-generating enzymes are tissue-specific (5), and single cell RNAseq studies have begun to identity hematopoietic and non-hematopoietic cells that participate in the establishment of oxysterol depots(6–9). However, a tissue map of oxysterol network (complex oxysterol receptor expression patterns and unresolved oxysterol transport dynamics) remains poorly charted, hindering efforts to determine impacts of oxysterol on immune responses during infections and in steady versus diseased states. Recent advances in the mode by which the oxysterols 25-hydroxycholesterol (25-HC), 27-HC and their dihydroxy metabolites 7α25-HC and 7α,27-HC impact immune responses in tissues and lymphocyte development are beginning to reveal higher resolution molecular circuits linking cholesterol and inflammatory immune responses, and is the focus of this review. Emphasis here will be on those oxysterols with verified function in tissues to coordinate immune responses and readers are referred to other insightful reviews on cholesterol metabolism and immune system for a larger context (4, 10–12).

Oxysterol sensing inside the cells.

The enzymes involved in the generation of oxysterols are intracellular proteins that reside in either the endoplasmic reticulum (ER) or the mitochondria(5) (Fig. 1); their distinct location inside the cells suggests that active systems able to transport cholesterol metabolites must exist, but little is known beside the possible involvement of Oxysterol binding proteins(13), and Aster proteins (14).

Sterol response element-binding proteins (SREBPs).

25-HC, the product of the enzyme cholesterol 25-HC hydroxylase (CH25H), was initially identified as a sterol able to suppress cholesterol biosynthesis by preventing activation and nuclear translocation of SREBP transcription factors (15). SREBPs regulate the expression of enzymes in the cholesterol biosynthetic pathway, including 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and the low-density lipoprotein (LDL) receptor (16), which is responsible for cholesterol uptake. With high cholesterol and oxysterol concentration, SREBPs are retained in the ER by the multi-transmembrane SREBP cleavage-activating protein (SCAP), which binds the ER-resident insulin-induced gene (INSIG). Cholesterol itself can control SREBP activation by binding a sterol-sensing domain in SCAP, while 25-HC suppresses SREBP by binding INSIG. Reduced sterol levels induce SCAP detachment from INSIG through a conformational change (17–19). SCAP then escorts SREBPs into the Golgi, where proteases cleave SREBPs and activate them as transcription factors. Three SREBP proteins, SREBP1a, SREBP1c, and SREBP2, encoded by the genes *Srebf1* and *Srebf2*, exist. Although structurally similar, they have different tissue expression patterns, display preferences for transcription of lipogenic or cholesterologenic gene programming, and are distinctly regulated by cholesterol and oxysterols. These features suggest that variations in individual SREBP function might underpin vastly different tissue immune responses impacted by cholesterol.

Nuclear liver X receptor (LXR).

LXRα and LXRβ are members of the nuclear hormone receptor family of transcription factors that control lipid homeostasis(20). LXRα is ubiquitously expressed, while LXRβ expression is higher in cells and tissues that are metabolically active (21). Oxysterols and other cholesterol metabolites were reported to activate LXRs (22), mainly from in vitro experiments (23) or in the liver (24). While deficiency of one or both LXRs impacts myeloid cells, lymphocytes, and stromal cells (25–27), no enzymatic deficiency in sterol intermediates from the cholesterol or cholesterol biosynthetic pathway have been shown to phenocopy the absence of LXRs. For example, while 25-HC has been implicated as a LXR agonist (28), macrophages that lack *Ch25h* show no alteration in LXR-dependent gene transcription (29). This suggests that LXR activation in distinct cells might be context dependent, with multiple different activators being generated in different local tissue niches.

Retinoic acid receptor related orphan receptor γ, T isoform (RORγt).

Oxysterols (22(R)-HC, 25-HC, 27-HC and 7β-27-HC), and cholesterol biosynthetic intermediates have been described as potential ligands for RORγt (30–33), an orphan nuclear receptor that is critical for lymphoid tissue organogenesis and the development and function of Type 3 cytokine (IL-17, IL-22) secreting lymphocytes (T3L, which can also produce GM-CSF and Amphiregulin. Human T3L is further characterized as IL-26 producers). However, mice and cells lacking specific cholesterol metabolites or unable to generate cholesterol biosynthetic intermediates failed to completely recapitulate RORγt deficiency (29, 34, 35), again raising the possibility that multiple agonists exist in vivo that regulate RORγt function.

Oxysterols and oxysterol byproducts as secondary messengers outside the cells.

Immune cell access to tissues has been largely described as a function of chemokine G-protein coupled receptors (GPCRs) that drives the cell migration in response to a spatial chemokine gradient(36), radiating from chemokine-producing cell(s), allowing directional migration of responding cells toward higher chemokine concentration locales. While this mode of action dovetails well with the need of immunocyte to move from blood into tissues and lymphoid organs(37–39), GPCRs that respond to signals other than proteins to mediate tissue dynamics within discrete sub-anatomical zones exist (40–44), suggesting that diverse enzymatic products are needed for efficient tissue zonation. While CXCR5 is critical for B cell access to B cell follicles, the 7α,25-HC and 7α,27-HC receptor GPR183 was initially identified as critical for a targeted migration of naïve B cells toward the outer follicle (45, 46), fine-tuning their positioning in the lymphoid organs.

The oxysterols 7α,25-HC and 7α,27-HC are synthetized from cholesterol by the action of CH25H and CYP27A1 that generate 25-HC and 27-HC, respectively, followed by the enzymatic activity of CYP7B1, which places a hydroxyl group at the 7α position. Genetic deletion of these enzymes revealed that both 7α,25-HC and 7α,27-HC drive migration of adaptive and innate immune cells in lymph node and spleen via GPR183 (47–55). The oxysterol-degrading enzyme HSD3B7, which generates bile acids (BA), has been shown

to be essential for establishing the oxysterol gradient in vivo that allows for directional Gαi-dependent migration (56). While GPR183 is widely expressed by immune cells (B and T cells, dendritic cells (DCs), eosinophils and innate lymphoid cells-3 (ILC3)) in human and rodent secondary lymphoid organs (8, 9, 57), anatomically discrete expression of oxysterol enzymes is predicted to direct distinct cells to specific tissue niches (58). Moreover, magnitude of GPR183 responses to 7α,25-HC and 7α,27-HC seems to be cell type specific, with B and T cell migration mostly dependent on CH25H, while DC migration requires both CH25H and CYP27A1 byproducts (59). We recently showed that increased dietary cholesterol enhanced 25-HC production in intestinal lymphoid organs (60). Coupled with the central role of 25-HC in the regulation of intracellular cholesterol metabolism (15) and its dependency on innate immune system cues (61–63), it is tempting to speculate that GPR183 represents a stereotypical surface receptor that integrates anatomical, metabolic, and immunological cues to shape immunocyte tissue migration.

The immune cell migration in response to GPR183 ligands differs from migration in response to classic chemokine gradient in two ways. First, since oxysterol concentration in tissue is balanced by spatially defined pattern of enzymes that generate and degrade oxysterol intermediates, GPR183 equipped cells can reach discrete tissue depots of the ligand(s). This process might facilitate migration into survival or differentiation niches where cell-displayed or low-diffusible molecules are present. Second, modulation of GPR183 ligands in tissue might be extremely rapid as oxysterol concentration is mainly dependent on substrate abundance and enzymatic kinetics, without necessarily requiring de novo transcription and translation. While chemokine receptor and GPR183-dependent migrations are not mutally exclusive, and are likely to be integrated for immune cell localization, fine tuned regulation of $GPR183^{+}$ cell migration and GPR183 ligand production might be more prominent at muco-cutaneous barriers that are routinely exposed to fluctuation of metabolites, including lipids.

Oxysterols as BA precursors.

The generation of BA is the major mechanism of cholesterol catabolism as it transforms insoluble cholesterol to water-soluble byproducts that can be easily excreted from the body (64). Moreover, BA has emerged as a critical regulator of Th17 and FOXP3+ regulatory T cell (Treg) generation by interacting with RORγt (65–67). BA synthesis from cholesterol requires extensive enzymatic modifications that give rise to several oxysterols during intermediate reactions (68). Enzymes that catalyze 7α-hydroxylation of cholesterol (CYP7A1) or sterol precursors (CYP7B1) are required for the maintenance of the BA pool, and genetic deficiency in both mice and humans impacts BA and cholesterol metabolism (69–71). CYP27A1 and HSD3B7 are also involved in BA production (72, 73); the relative importance of each of these enzymes in the generation of BA that control Th17 and Treg differentiation in the gut is currently unknown.

Oxysterol function in tissues

Spleen

GPR183 ligands were initially identified in spleen (74, 75) as regulators of B cell positioning(45, 46, 76) and have been extensively reviewed elsewhere(4). Additional work has established that in addition to B cells, GPR183 also controls positioning and function of dendritic cells (77–79) and CD4 T cells (80, 81). GPR183 is intrinsically required in splenic dendritic cells for homeostasis and particulate antigen capture in the marginal zone bridging channel; and for effective antigen recognition and Tfh differentiation in CD4 T cells. Generation of GPR183 ligands that act on locally dispersed immune cells is dependent on discrete patterns of expression of enzymes in stromal cells (56, 79, 82) that allow GPR183 ligand gradient to be simultaneously generated in distinct anatomical locales. Whether splenic GPR183 ligand concentration, and associated GPR183-dependent immune processes, are regulated by additional cues such as infection, diet, or developmental stage-associated factors remains to be investigated.

Liver

Oxysterol and bile acid syntheses are prominent features of the liver. Genetic evidence exists for oxysterols (24-HC, 25-HC, 27-HC) as regulators of hepatic LXR activity (24). Despite the longstanding investigation of LXR modulation in bone marrow derived macrophages (BMDMs), data on Kupffer cells or monocyte- recruited macrophages are limited and variable in interpretations, with some suggesting a role for LXR as a negative regulator of macrophage homeostasis and innate responses (83), while others have concluded that LXRα agonism dampened hepatic inflammation and fibrosis by reducing the activation of hepatic stellate cell and Kupffer cell activation (84, 85).

Hepatic oxysterols control cholesterol biosynthetic gene expression. Mice with hepatocyte-specific deficiency of SREBP2 exhibit reduced LXR activity, suggesting that the cholesterol biosynthesis pathway generates an unknown LXR ligand(s) in the liver (86). Nonalcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease that can progress to nonalcoholic steatohepatitis (NASH), has been suggested to involve cholesterol overload (87). NASH is characterized by chronic inflammation and immune cell infiltration in the liver (88) and patients show increased in 7-hydroxylated oxysterols compared to healthy individuals. Mice lacking GPR183, CH25H, and CYP7B1 were indistinguishable from controls in a high-fat diet model of NASH (89), and an involvement of the GPR183-7α,25-HC axis in NASH patients has not been established.

Intestine

Oxysterol generation and uptake from diet, as well as oxysterol immunomodulatory activity have been prominently studied in the gut. We recently showed that 25-HC production in the Peyer’s patches (PPs) (90), secondary lymphoid organs that are only present in the small intestine in both human and mice, is modulated by dietary cholesterol and impacts the generation of antigen specific IgA during germinal center reaction(60). While GPR183 ligand is easily detectable in PPs and controls follicular B cell positioning (45, 76), the effect of 25-HC on IgA plasma cells requires SREBP2, but not GPR183 expression on B cells.

A single nucleotide polymorphism (SNP) in GPR183 has been linked to increased risk for ulcerative colitis and Crohn's disease (91, 92). In patients with GPR183 SNP, IBD susceptibility correlates with increased GPR183 expression on Th17 cells (92). Conversely, mice lacking GPR183 showed reduced overall inflammation (85, 86) in some, but not all, colitis models (93, 94). In the colon, GPR183 controls tissue positioning of ILC3, a process linked to *Ch25h* expression in stromal cells (94). Animals lacking GPR183 fail to form colonic lymphoid clusters and show blunted response to enteric bacterial infection (95). The discrepancy between intestinal immune cells controlled by GPR183 in mice and humans can be explained by the restricted specificity of murine Th17 cells to the gut commensal Segmented filamentous bacteria (96, 97), and the dominant role of murine ILC3 in maintaining the intestinal barrier function and tissue homeostasis(98, 99). In contrast, positioning and function of lymphoid tissue inducer cells (LTi), embryonically derived ILC3 that are required for normal PP and mesenteric lymph node (mLN) development, are not dependent on GPR183 despite their ability to respond to 7α,25-HC in vitro (94). Whether this difference arises from embryo-specific oxysterol function, production and/or sensing, or whether the embryonic hematopoietic system is uniquely insensitive to cholesterol metabolites is unknown.

The known GPR183-ILC3 axis in the gut impacts colon (94) and mLN (95), but it is unclear how cholesterol or oxysterols are disseminated throughout the gut from the site of cholesterol absorption, which is restricted to the proximal portion of the small intestine (100, 101). Cholesterol uptake from the diet is mediated by Niemann-Pick C1-Like 1 protein (NPC1L1) that is exclusively expressed on intestinal epithelial cells (IECs) (100, 101)These cells incorporate cholesterol and other lipids in chylomicrons, lipoprotein vesicles that assure delivery into lymphatics and eventually into the circulation (102, 103). Thus, one attractive hypothesis is that dietary cholesterol absorption regulates local oxysterol concentration in the gut by providing circulating cholesterol for subsequent enzymatic conversion, possibly by local stromal cells (95, 104). Additionally, diet-derived, IEC-packaged cholesterol might calibrate immune responses directly in the lamina propria of the duodenum that are propagated throughout the gut. Experimental approaches which combine conditional genetic deletion, dietary modulation, and pharmacological intervention will be required to tease apart the spatial generation and effector function of oxysterols in tissues.

Lung

Cholesterol is an integral component of the pulmonary surfactant (105) and modulation of cholesterol bioavailability impacts the function of pulmonary air-liquid interface (106). More than 80% of the lung cholesterol is derived from the plasma, making it particularly sensitive to dietary lipid intake, while the remaining cholesterol is synthetized by lung-resident cells (107). The lung is one of the organs with the highest amounts of *Ch25h* transcripts at steady state. At three days after birth in mice, fetal-origin alveolar macrophages (AM) abundantly express *Ch25h* (108). 25-HC can mediate either amplification or resolution of lung inflammation (109–112). It also has a direct effect on viral entry into airway epithelial cells in both mouse and human upon infection with influenza viruses (113) and might amplify the response to other RNA viruses (111, 114),

possibly by alteration of cholesterol-enriched cytomembrane. Similar to 25-HC, 27-HC is also expressed at high levels in the lung (115), is modulated during lung diseases (116, 117), and mediates antiviral effects by sequestration of viral particles in late endosome (118).

For lymphocytes, evidence for the role of cholesterol in shaping early life pulmonary innate and innate-like lymphocyte responses is just beginning to emerge. Lung innate-like T3L (iT3L, Tγδ17, MAIT17 and NKT17) express GPR183. They are able to colonize the newborn lungs (119, 120) and rapidly respond to pulmonary pathogens (121, 122). Tγδ17 cells originate from the thymus (123, 124) and comprise two distinct subsets: fetal Vγ4 and neonatal Vγ2 (TCRγ nomenclature of Garman and Raulet (125)) expressing cells that populate all mucocutaneus barrier tissues. Neonatal lung Tγδ17 cells are required for optimal response to flu virus during early life (126) and their maintenance in the lung depends on GPR183 (unpublished). Recently, it has been shown that embryonic macrophages allow for the expansion of invariant NKT cells that populate the barrier tissues, including the lung and skin (127). Cross-regulation of AM and early life dominant lung resident innate-like lymphocytes involving cholesterol byproducts may account for the noted age-associated differences in pulmonary immune responses. Focused studies on oxysterol network in the lung are warranted to test this possibility.

Brain

Oxysterol metabolism in the brain has been long considered to be controlled primarily by de novo cholesterol synthesis (128). CYP46A1 regulates cholesterol levels in the brain by converting it into 24-HC (129). Polymorphisms in CYP46A1 are associated with increased risk of Alzheimer's Disease (AD), but whether 24-HC can influence immune cells during the disease initiation or progression is largely unknown. GPR183 ligand is present in the brain (48), but little is known about its regulation. CYP27A1 required for 27-HC production is not expressed in the brain under homeostatic conditions. However, 27-HC can cross the blood-brain barrier and enter the brain (130), where it undergoes enzymatic conversion before export into the circulation (131). Mutations in *CYP27A1* leads to Cerebrotendinous Xanthomatosis (132), with gut specific symptoms due to defective BA generation, and brain degeneration due to accumulation of cholesterol and cholestanol (133). CYP7B1 that converts 25-HC into 7α,25-HC is expressed in the brain (134), and *CYP7B1* deficiency is responsible for Spastic Paraplegia Type 5 (135), a neurodegenerative disorder driven by the accumulation of neurotoxic level of oxysterols. Mice deficient in *Cyp7b1* also show increased 25-HC amounts in the brain (136). *Ch25h* expression is not observed in healthy microglial cells, a primary candidate for 25-HC production in utero and during neonatal window (137). However, amounts of *Ch25h* transcripts increase with age, possibly due to the emergence of IFN-responsive microglia (137) and it is rapidly upregulated during inflammatory insults, including in AD and Experimental Autoimmune Encephalomyelitis, a mouse model of multiple sclerosis (138). For the latter, Th17 cells are pathogenic (29) and GPR183 can enhance trafficking of encephalitic CD4 T cells (139, 140). In mice, fetal-derived, commensal-independent, GPR183+ Tγδ17 cells (141) infiltrate the meninges after birth, with life-long persistence (142, 143). They have been implicated in anxiety-like behavior, in line with the critical impact of maternal IL-17 in fetal cortical brain developmental abnormalities leading to autism-like symptoms(144,

145). Involvement of oxysterols in immunocyte-mediated brain inflammation is plausible given the well-established link between neurons and tissue T3L, especially Tγδ17 cells in mucocutaneous tissues (146), and is an active area of investigation.

Skin

Dermal Vγ2+ Tγδ17 cells are essential for assuring skin barrier homeostasis by fortifying epithelial cells after birth in response to commensal bacteria, although their development, unlike that of fetal Tγδ17 cells, is not wholly dependent on microbiota (147). We have recently discovered that neonatal Tγδ17 cell positioning and maintenance in the murine dermis require GPR183. Moreover, in the Imiquimod (TLR7 agonist) induced, neonatal Tγδ17 cell-dependent psoriasis model, genetic and diet modulated GPR183 ligand availability dominantly specifies psoriatic responses. Interfollicular epidermal (IFE) cells, basal keratinocytes located at the dermal-epidermal border, express high levels of CH25H, and neonatal Tγδ17 cells are localized at the border. The expression pattern of cholesterol processing enzymes is likely conserved in the skin of mice and humans (148), although in the latter fibroblasts may play a more prominent role in oxysterol generation.

Other skin resident lymphoid cells of early life have intimate relationship with keratinocytes. Majority of Treg express GPR183 and they colonize the neonatal skin to mediate tolerance to commensal bacteria. In addition, Treg localize in the hair follicle bulge to regulate epithelial stem cell differentiation (149) Type 2 cytokine (IL-4, 5, 13) producing innate lymphoid cells-2 (ILC2), which are seeded in the skin during fetal development as precursors, function within the upper hair follicle. They control sebaceous gland (SG) function by regulating commensal bacteria (150). Sebocytes, specialized epithelial cells that secrete a complex mixture of lipids (sebum) including cholesterol, express the oxysterol sensors LXR and SREBP. The relationship between SG, SG-associated ILC, cholesterol metabolites and immune cell function is unknown.

GPR183 expressing immunocytes are confined to the dermis at steady state, but the domain of oxysterol impact is likely widespread, especially during skin damage. GPR183 ligand is made from 25-HC, which also dampens SREBP2 activity (60, 151). In the skin, genetic ablation of SREBP2 in macrophages leads to enhanced wound healing, by promoting epithelialization, angiogenesis, and myofibroblast-induced wound contraction(152). Moreover, 25-HC has been shown to mediate protection against bacterial pore-forming toxins in the skin, via IFN-dependent cholesterol metabolism reprograming in myeloid cells (153, 154). Thus, it is possible that alteration of 25-HC and other cholesterol metabolite bioavailability in the skin, possibly via dietary cholesterol, modulates the balance between inflammatory and reparative responses.

Thymus

Arguably the strongest evidence to date of the importance of oxysterol sensing by T cells is the observation that there exists a thymic epithelial niche of GPR183 ligand production and that neonatal Tγδ17 cells must sense oxysterols for proper maturation and homing to the skin and lung (Frascoli et al, 2022 submitted). Cholesterol processing enzymes, in particular *Ch25h*, but excluding the BA-generating *Hsd3b7*, are prominently expressed in

medullary thymic epithelial cells (mTEC), which are also the source of key chemokines such as CCL21, required for normal αβ T cell selection. *Ch25h+* mTECs are distinct from Aire+ mTECs that mediate negative selection of tissue antigen specific αβ T cells and for perinatal Treg cell generation. The oxysterol thymic niche discovered in mice is remarkably conserved in the human thymus (8), and given that the sole function of the thymus is to generate fit and useful T cells, such an evolutionary conservation supports the functional primacy of oxysterol sensing in some thymic-derived GPR183+ cells. In mice, neonatal thymic Tγδ17 cell maturation for export is independent of commensals, and perhaps T cell receptor signaling (123, 155). That cholesterol metabolites may be the central arbiter of postnatal Tγδ17 thymic selection presages that GPR183+ T3L effector function is calibrated by cholesterol and oxysterol bioavailability in tissues. Human Vδ2+ T cells that are the focus of cancer immunotherapy clinical trials recognize isopentenyl pyrophosphate produced by the mevalonate pathway that generates de novo cholesterol. Future studies will need to tackle the overriding question of how and why sensing of bioavailable cholesterol and cholesterol metabolites by immunocytes is intimately intertwined into the regulatory circuits that control their function.

Conclusions

In a dozen year since the first report of immunocyte regulation by oxysterols it has become apparent that lymphocyte migration and function in tissues is finely tuned by lipid processing stromal and myeloid cells. Conversion of cholesterol into immune modulatory lipids is a multistep cell relay system that is likely to involve diverse sensory cells that monitor tissue fitness and environmental perturbations. As a major component of the relay GPR183 has garnered interest as the prototypic oxysterol-dependent cell surface modulator of T3L in mucocutaneous tissues. Detailed parsing of diet-derived cholesterol regulation of T3L should lead to definitive molecular insights into the correlative link between diet and human lymphocyte-driven tissue inflammatory diseases. Progress in this area will require basic mapping of human oxysterol regulatory circuits in mucocutaneus tissues. Much is unknown in the transport of oxysterols in and out of the cells and the full understanding of how diet and inflammatory cues modulate oxysterol bioactivity will require not only the complete charting of the pathway generating immunodulatory lipids in tissues but also the cellular processes that construct and sustain these lipid depots, in health and disease.

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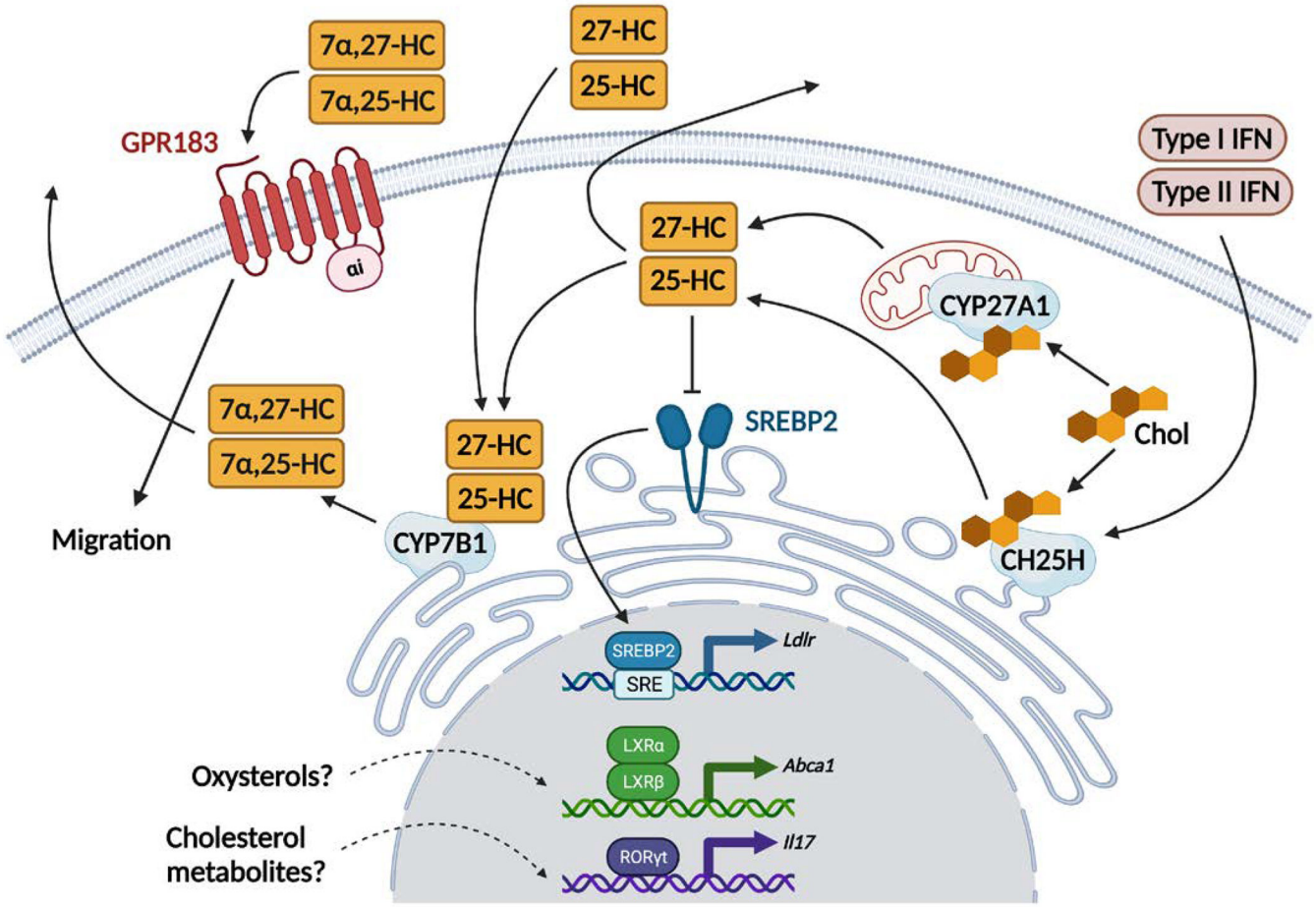

Figure. 1. Oxysterol production and sensing.

Cholesterol (Chol) derived from the diet or produced intracellularly can be metabolized to generate immune modulating oxysterols. First, the endoplasmic reticulum (ER) resident enzyme cholesterol 25-hydroxylase (CH25H) adds a hydroxyl group at position 25 of cholesterol to synthetize 25-hydroxycholesterol (25-HC). Then in the ER the cytochrome P450 7B1 (CYP7B1) mediates the hydroxylation at the 7α position of 25-HC to generate 7α,25-dihydroxycholesterol (7α,25-HC). GPR183, a G-protein coupled receptor known to mediate migration of several immune cells in tissues, is the receptor for 7α,25-HC. CYP7B1 also produces a second, less potent GPR183 ligand, the oxysterol 7α,27-dihydroxycholesterol (7α,27-HC) converting 27-HC generated from cholesterol by the mitochondrial enzyme sterol 26-hydroxylase (CYP27A1). Type I and Type II Interferons (IFNs) induced by viruses and bacteria drive the expression of CH25H. 25-HC restrains the activation of the sterol response element binding protein 2 (SREBP2, expressed in both lymphocytes and myeloid cells) directly in the ER and prevents SREBP2 translocation to the Golgi (not depicted), leading to eventual deficits in the transcription of genes involved in cholesterol metabolism. Generation and sensing of oxysterols can be uncoupled such that oxysterols produced in trans can engage surface receptors or internalized and transported to ER and nucleus. In vitro experiments have suggested that oxysterols can bind to the nuclear

receptors LXR (α and β) and RORγt (expressed in T cells and ILCs only). However, in vivo data supporting such interactions are sparse.

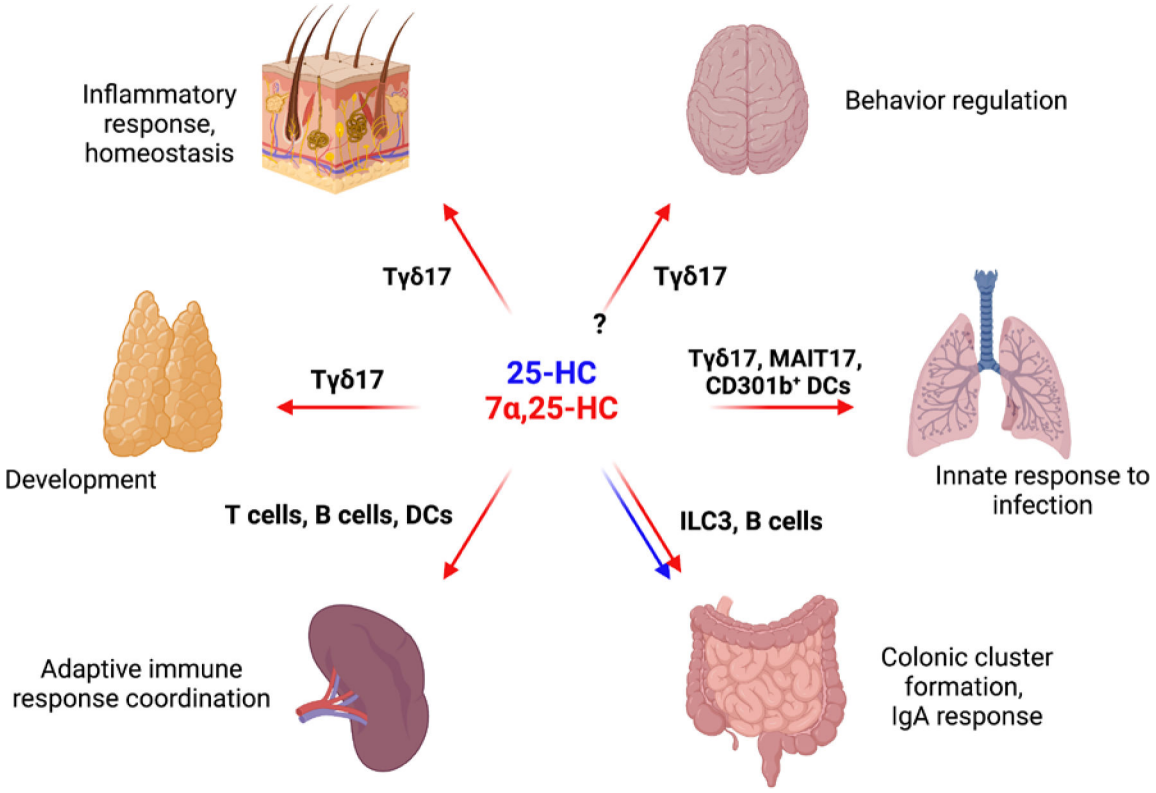

Figure. 2. Tissue functions of oxysterols.

Overview of oxysterol acitivities in different tissues. Red and blue arrows represent defined function of 7α,25-HC and 25-HC in tissues, respectively. In the skin, IL-17 production by neonatal GPR183$^+$ Tγδ17 cells is dependent on 7α,25-HC. Basal keratinocytes express CH25H that synthetize 25-HC, and characterization of the immune or non-immune cells expressing CYP7B1 responsible for the terminal production of GPR183 ligand in the skin is in progress. Tγδ17 cell maturation in the thymus is controlled by *Ch25h*-expressing medullary thymic epithelial cells (mTEC). Additional thymocyte subsets regulated by oxysterol depots have only been cursorily surveyed. In the spleen, CD4 T cells, follicular B cells and dendritic cells rely on GPR183 to position in discrete sub-anatomical locations (outer T cell zone, outer B follicle, and bridging channel, respectively) to assure efficient antigen capture, antigen presentation, and T and B cell activation. *Ch25h* is expressed by splenic stromal cells, in particular by marginal reticular cells, interfollicular reticular cells and high endothelial cells, while *Cyp7b1* expression appears more broadly distributed. In the gut, Peyer's patch follicular dendritic cells produce 25-HC to restrain SREBP2 in germinal center B cells and permit the differentiation of IgA-secreting plasma cells. In the colonic lamina propria, fibroblastic stromal cells provide a local source of 7α,25-HC to guide ILC3 migration and colonic lymphoid cluster formation. Lung alveolar macrophages are noted for their capacity to produce high amounts of CH25H, and their role in regulating GPR183$^+$ IL-17/22 producing innate-like T cells and CD301b$^+$ DCs (and other myeloid cells) is just beginning to be explored. Brain Tγδ17 cells that regulate anxiety-like behaviors express

GPR183, but whether oxysterols are involved, and if so, the source(s) of the GPR183 ligand, remain to be determined.

Table 1.

Cells producing oxysterols and cells responding to oxysterols

Source	Oxysterol	Target cells	Effect	Mechanism	in vitro	in vivo
Stromal cells (SC)	7α,25-HC	B/T cells, DCs, ILC3, eosinophils	Migration	GPR813 ligand	Yes	Yes
SC	7α,27-HC	DC	Migration	GPR813 ligand	Yes	Yes
SC	7α,27-HC	CD4 T cells	IL-17 production	RORγt ligand	Yes	Young animals only
Unknown	7β,27-HC	CD4 T cells	IL-17 production	RORγt ligand	Yes	Young animals only
Macrophages (Mph)	25-HC	Mph	Inflammasome inhibition	AIM2	Yes	Yes
Mph	25-HC	Mph	Inflammatory cytokine release	Not LXR	Yes	Yes
Mph	25-HC	Mph	Antiviral	Membrane cholesterol/ Viral components	Yes	Yes
Follicular DC	25-HC	B cells	Altered PC differentiation	SREBP2	Yes	Yes
Mph	27-HC	Mph	Inflammatory cytokine release	Estrogen receptor α	Yes	No
Tumor	22-HC	Myeloid	Migration	CXCR2	Yes	Exogenous 22-HC