Review

Nuclear Receptors as Autophagy-Based Antimicrobial Therapeutics

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Abstract: Autophagy is an intracellular process that targets intracellular pathogens for lysosomal degradation. Autophagy is tightly controlled at transcriptional and post-translational levels. Nuclear receptors (NRs) are a family of transcriptional factors that regulate the expression of gene sets involved in, for example, metabolic and immune homeostasis. Several NRs show promise as host-directed anti-infectives through the modulation of autophagy activities by their natural ligands or small molecules (agonists/antagonists). Here, we review the roles and mechanisms of NRs (vitamin D receptors, estrogen receptors, estrogen-related receptors, and peroxisome proliferator-activated receptors) in linking immunity and autophagy during infection. We also discuss the potential of emerging NRs (REV-ERBs, retinoic acid receptors, retinoic acid-related orphan receptors, liver X receptors, farnesoid X receptors, and thyroid hormone receptors) as candidate antimicrobials. The identification of novel roles and mechanisms for NRs will enable the development of autophagy-adjunctive therapeutics for emerging and re-emerging infectious diseases.

Keywords: nuclear receptors; autophagy; infections; host defense

1. Introduction

Autophagy, an intracellular process, is a defense against intracellular pathogens involving lysosomal degradation [1–6]. The signaling factors and mechanisms through which invading microbes are selectively targeted by xenophagy or LC3-associated phagocytosis (LAP) have been reported [7]. A variety of pathogens—including Mycobacterium tuberculosis (Mtb), Salmonella enterica serovar Typhimurium, Listeria monocytogenes, Legionella pneumophila, Anaplasma phagocytophilum, Coxiella burnetii, Francisella tularensis, and Brucella spp.—can be targeted by autophagy [7]. These and other pathogens, including viruses and protozoa, have evolved means of evading or circumventing autophagy, enabling their replication within host cells [5,6,8–14].

The nuclear receptor (NR) superfamily proteins regulate genes involved in cell survival, signaling, metabolism, and reproduction [15–17]. NRs promote host defense against infections by regulating innate immunity, the transcription of antimicrobial genes, and signaling pathways [18,19]. NRs are implicated in the regulation of autophagy at transcriptional and post-translational levels [17,20–23]. Modulating NR activity by targeting the NR domains or by promoting ligand activation/suppression, modulation of the NR-DNA interaction, and/or the recruitment of coactivators may be effective against, for example, cancer, metabolic and immune diseases, inflammation, and neurodegeneration [17,24–27].

The interaction of host autophagy with pathogens has been reviewed by others [28–31]. Here, we discuss the roles of autophagy-related genes (ATGs) in the immune response to pathogens and how
various NR ligand-based approaches are being implemented for antimicrobial modalities based on autophagy activation.

2. Overview of Autophagy and Autophagy-Related Genes

A series of ATGs play critical roles in autophagy initiation, elongation, and maturation, and are also involved in other physiological responses, including membrane trafficking and signaling pathways [32–35]. ATG proteins in complexes with other cofactors/regulators modulate autophagy [36]. However, unlike in canonical autophagy, non-canonical autophagy does not necessarily require double-membraned autophagosome formation involving canonical initiation, nucleation, and an elongation step [37]. For example, a double-membraned autophagosome constituted from multiple isolated membranes is found in some cases of xenophagy, and even a single-membrane bound phagosome is formed in LAP [37]. Therefore, distinct subsets of ATGs are required for the activation of non-canonical autophagy LAP [38] or selective autophagy [34].

The roles of ATGs differ according to the type of autophagy. Rubicon plays opposite roles in (macro)autophagy and LAP; it is a negative regulator of autophagy, but promotes Beclin-1/VPS34 kinase activity in the phagosome [34,39]. Selective autophagy receptors have both a cargo recognition function and interact with the autophagosome [40,41]. The selective autophagy receptor p62/AQSTM1 plays several roles in numerous biological processes [42,43]. During nonselective autophagy, p62 degradation reflects activation of the autophagic flux, as the cargo receptor p62 is essential for selective autophagy [41]. Therefore, the overlapping cooperative and antagonistic roles of ATGs in autophagy need to be taken into account when developing host-directed therapeutics [34,44,45].

Model studies using vertebrates (mice) and invertebrates (Caenorhabditis elegans and Drosophila) and involving tissue-specific ATG deletion or overexpression have provided pathogenetic insight by identifying autophagy-dependent and -independent functions of ATGs [46,47]. Additionally, the dysregulation or mutation of ATGs is associated with diverse human diseases [34]. In response to stresses, ATG upregulation at the transcriptional level induces autophagy in a manner requiring numerous transcription factors and signaling cofactors [48–50]. In addition, the effect of ATGs and non-ATG proteins on autophagy is modulated by posttranslational modifications, including phosphorylation, glycosylation, ubiquitination, acetylation, and lipidation [48,51–55].

Antibacterial autophagy modulates bacterial replication and promotes innate immunity in host cells. Increasing evidence has shown that various intracellular bacteria, such as Mtb, Salmonella, Listeria, and Legionella, could be targeted by autophagy activation [7,56]. Autophagy not only directly causes microbial degradation, but also functions as a host defense system by participating in intracellular signaling, lysozyme secretion, the ubiquitin pathway, and antigen presentation [4]. However, these pathogens have also evolved strategies to evade or subvert host autophagy to survive within host cells, resulting in persistent infection and pathogenesis [57]. Similarly, autophagy is one of the key defense mechanisms in protecting against viral infections [58]. It regulates the immune response through the selective degradation of immune components associated with viral particles, followed by virus-derived antigen presentation to T lymphocytes to coordinate adaptive immunity. However, viruses manipulate and exploit autophagy for their immune evasion, replication, and release from host cells [59,60]. It is surprising that even if viruses target similar host defense pathways during the infection state, they differ in ways and functional outcomes, depending on each species of virus [59]. In order to increase the understanding on the role of autophagy dominating viral infections, not only common pathways, but also various species-specific studies, should be conducted in parallel. So far, the exact functions of ATG proteins and the detailed mechanisms that control autophagy during viral infection have not been elucidated [59].

In this review, we focus on the pathophysiological roles and mechanisms underlying the NR-mediated regulation of autophagy, including the activation of antimicrobial responses in various infection models.
3. Overview of Nuclear Receptors

The NR superfamily classes are divided into four classes based on structural and functional characteristics, i.e., steroid receptors (Class I), retinoid X receptor (RXR) heterodimers (Class II), homodimeric orphan receptors (Class III), and monomeric orphan receptors (Class IV) [15,61]. The NR superfamily is classified as the endocrine, adopted orphan, and orphan subfamilies, depending on the existence of ligands [61] (Figure 1). The differences in NR classes include their biological function, binding to a ligand or DNA, and tissue specificity. All members of the NR superfamily have a variable N-terminal domain (NTD), a DNA binding domain (DBD), a ligand-binding domain (LBD), and a variable C-terminal domain. NR DBD contains different DNA-binding recognition sequences and two zinc finger motifs for binding to chromatin [61,62]. NRs play a crucial role in the recruitment of co-activators within the nucleus, although there is marked variability among the binding of NTDs to co-activators [15].

**Figure 1.** A summarized figure for autophagy genes and different classes of nuclear receptors (NRs). Autophagy processes such as macroautophagy, LC3-associated phagocytosis (LAP), and xenophagy involve different autophagy-related genes (ATGs) or cargo receptors, such as p62, NDP52, and optineurin. The upper panel highlights the different sets of autophagy genes involved in vesicle nucleation, autophagosomal formation, and the maturation of autolysosomes. The NR superfamily classes are divided into three or four subclasses according to their structural and functional characteristics and their ligands. NRs are implicated in the regulation of autophagy at transcriptional and post-translational levels. Understanding the mechanisms by which NRs regulate the expression and post-translational modification of ATGs will facilitate the development of novel host-directed antimicrobial agents.

A total of 48 intracellular proteins have been identified as NRs [63]; among them, several members are critical in the regulation of host immune responses to infection. These NRs include the vitamin D receptor (VDR), also known as nuclear receptor subfamily 1, group I, member 1 (NR1I1) [64–66]; estrogen-related receptor-α (ERRα; ESRRA; NR3B1) [20,67]; ERRγ (ESRRG; NR3B3) [68]; liver X receptor-α (LXRα; LXRα; NR1H3) [69]; peroxisome proliferator-activated receptor-α (PPARα; PPARA;
NR1C1) [70–72]; PPARγ (PPARG; NR1C3) [73–75]; the glucocorticoid receptor (GR; GCR; NR3C1) [76]; estrogen receptor-α (ERα; ESR1; NR3A); ERβ (ESR2; NR3A2) [77,78]; the xenobiotic pregnane X receptor (PXR; NR1I2) [79–81]; rev-Erb-α (REV-ERBα; NR1D1) [82,83]; farnesoid X receptors (FXRs; NR1H4) [75,84]; nuclear receptor 4A (NR4A) family members; nuclear receptor related 1 protein (NURR1; NR4A2); and neuron-derived orphan receptor 1 (NOR1; NR4A3) [85]. The NRs are endogenously activated by small lipophilic ligands, such as steroid hormones, retinoids, and phospholipids; however, some of the NRs have been classified as ‘orphan’ members as their ligands have not yet been identified [86]. The ligands can cross the plasma membrane, directly interact with NRs inside the cells, and modulate gene transcription through different mechanisms [87].

In class I NRs or steroid receptors, ligand binding at the plasma membrane is followed by a signal transduction cascade including enzymatic phosphorylation, which results in the translocation of transcription factors into the nucleus [61,88]. ER, a member of the class I NR superfamily, is anchored in the cytoplasm by a chaperone protein such as heat shock protein 90 (HSP90). After ligand binding, the receptor is freed from the chaperone, causing homodimerization and nuclear translocation. In the nucleus, the ligand-receptor complex associates with the transcriptional coactivator and activates the target gene [89]. Selective estrogen receptor modulators (SERM) such as tamoxifen and bazedoxifen have been suggested to have antitubercular activity [90,91].

The class II receptor family includes the thyroid hormone receptor (TR), VDR, retinoic acid receptor (RAR), and PPAR [61]. They are typically present in the nucleus and generally form heterodimers with RXR [92]. The heterodimers are bound to their response element, even in the absence of a ligand, where gene activation is repressed through interaction with a nuclear co-repressor (NCoR) and silencing mediator for retinoic acid and thyroid hormone receptor (SMRT) corepressor complexes. Binding of the ligand causes displacement of the NCoR/SMRT co-repressor, allowing transcriptional activation to occur [89,93]. For VDR, 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3), which is the active form of vitamin D3 (hereafter referred to as vitamin D), acts as a ligand and activates functional VDR, which then recognizes and binds to vitamin D response elements (VDREs) located in the promoter region of target genes to control the transcription of those genes [94]. VDR signaling activation during infection leads to innate immune signals for the production of antimicrobial peptides (AMPs), such as human cathelicidin AMP (CAMP) and β-defensin 2, which are important in coordinating vitamin D-induced antimicrobial responses [95]. PPARs include three different isotypes: PPARα, PPARβ/δ (PPARD; NR1C2), and PPARy. Each isoform has a different distribution and ligands [96]. They are activated after the binding of endogenous ligands, such as fatty acids and their derivatives, or synthetic modulators, such as GW7647 and GW501516, to the ligand-binding domain. PPARs form heterodimers with RXR, which, after ligand binding, results in the transactivation or repression of target genes through PPAR responsive elements (PPREs) [96,97]. LXRs are the NRs which bind oxidized cholesterol derivatives such as oxysterols and intermediates of the cholesterol biosynthesis pathway [98]. The modulation of gene expression by LXR involves direct activation, repression, and transrepression [99], and exhibits anti-inflammatory properties, as well as antimicrobial effects [98].

Class III and IV receptors include the dimeric and monomeric orphan receptors, respectively. ERRα, one of the orphan nuclear receptors, is not regulated by the presence of natural ligands, but is regulated by post-transcriptional modifications, such as phosphorylation, sumoylation, or acetylation of the N-terminal domain [23,100], and is essential for antimicrobial host defense [23]. Other members of orphan NR include retinoic acid-related orphan receptors (ROR), whereas FXR and REV-ERB have been classified as adopted orphan receptors [92]. In addition, NRs are important in the regulation of autophagy [17,20,27,101], not only at the level of the transcription of ATGs, but also at the post-transcriptional level, by regulating protein–protein interactions, post-translational modification, and epigenetic mechanisms [21–23,76,102]. The contributions of NR modulation to defense against pathogens are beginning to be deciphered. Here, we focus on the roles of VDR, ER, ERR, and PPAR in autophagic host defense against infection and discuss other NRs as links between autophagy and innate
immunity during infection (Figure 2). A deeper understanding of NR signaling and its underlying mechanisms will facilitate the development of autophagy-based host-directed anti-infectives.

![Figure 2. Schematic representation of the signaling pathways of nuclear receptors (NRs) in autophagy-mediated host defense. NRs, including the vitamin D receptor (VDR), estrogen receptor (ER), estrogen-related receptors (ERRs), and peroxisome proliferator-activated receptors (PPARs) have been shown to play critical functions in the regulation of autophagy-mediated host defensive immune responses during infection. These NRs regulate and participate in the autophagic signaling pathways not only at the transcriptional level, but also at the post-transcriptional level. VDR is one of the best characterized NRs related to autophagic function against various infections. It is well-known that VDR signaling increases autophagy activation via the induction of cathelicidin, which is a small cationic antimicrobial peptide. In addition, VDRs functionally link adaptive and innate immune responses by regulating downstream pathways of autophagy. ER activates autophagy by increasing reactive oxygen species (ROS) generation and Akt/mammalian target of rapamycin (mTOR) signaling. ERRs, which are one of the orphan family members of NR, also regulate a variety of cellular responses, including autophagy. The induction of PGC-1α upregulates the ERRα to promote mitophagy and an antimicrobial effect through sirtuin 1. PPARα activation leads to the expression of transcription factor EB (TFEB) and its nuclear translocation, resulting in the enhancement of lysosomal biogenesis. PPARβ/δ prevents harmful ER stress by increasing autophagy markers Beclin-1 and LC3 II.](image)

4. Vitamin D Receptor in Autophagy-Mediated Defense against Infection

VDR signaling ameliorates infection and inflammation [66,67,103,104]. Studies on the role of vitamin D in innate immunity have revealed that autophagy enhances phagosomal maturation and lysosomal function, and ameliorates inflammation and antimicrobial protein generation [67,105,106]. A physiological level of the active form of vitamin D (1α,25-dihydroxycholecalciferol) or functional activation of VDR signaling promotes autophagy activation in human monocytes or monocytic cells by inducing the synthesis of cathelicidin—a cationic antimicrobial peptide—which promotes phagosomal maturation in the presence of intracellular Mtb [107–109] or Mycobacterium marinum [110]. In addition, vitamin D treatment and TLR8-mediated VDR signaling activation enhanced autophagy
in human macrophages in a manner dependent on the ATG5 and Beclin-1, thereby inhibiting human immunodeficiency virus (HIV)-1 replication or the co-infection of HIV and Mtb [111–113]. Vitamin D-mediated autophagy and cathelicidin expression are negatively regulated by prostaglandin (PG)E2—an arachidonic acid-derived lipid mediator—via E prostanoid (EP)2 and EP4 receptors [114].

Vitamin D supplementation in mice significantly induced VDR, cathelin-related antimicrobial peptide (CRAMP), and LC3B expression, but decreased the collagenase matrix metalloproteinase-1 [115]. A structural equation modeling analysis suggested that vitamin D-mediated autophagy reduces necrosis [115]. Additionally, clinical trials of vitamin D as adjunctive therapy to standard anti-tuberculosis (TB) treatment showed a significant decline in intracellular Mtb growth and the levels of proinflammatory cytokines/chemokines [116,117], but no clear effect on long-term sputum-smear conversion [118]. These data suggest that the vitamin D-autophagy pathway is associated with clinical recovery from TB. Nevertheless, further studies are needed to determine the effects and risks of vitamin D adjunctive therapy, as discussed by others [95,119,120]. We limit the discussion in this review to clinical trials of vitamin D therapy in TB and other infectious diseases.

IFN-γ, which is an important cytokine in the adaptive Th1 immune response, alone [121] or in combination with the CD40 ligand [122], enhanced VDR-mediated antimicrobial defense in human monocytes/macrophages in vitamin D-sufficient serum. Vitamin D treatment was required for the expression of IL-12 [123], and the combination of IL-12 and IL-18 in human macrophages enhanced the cell-autonomous production of IFN-γ and the autophagy-cathelicidin pathway, which upregulated the antimicrobial response to Mtb [124]. Therefore, functional VDR signaling links the adaptive and innate immune responses by regulating autophagy, phagosome-lysosome fusion, and cytokine production in Mtb infection.

Vitamin D treatment reversed the influenza A virus-induced inhibition of autophagic flux by inducing the expression of syntaxin-17 and the V-type proton ATPase subunit (ATP6V0A2) [125]. In addition, probiotic lactic-acid bacteria isolated from kimchi activated VDR-autophagy responses and enhanced the expression of ATG16L1 and Beclin-1, resulting in an anti-inflammatory and anti-infective effect in the intestines [126]. Vitamin D treatment restored the lysosomal function impaired by Helicobacter pylori in gastric epithelial cells, by activating—protein disulfide isomerase family A member 3 (PDIA3) receptor and upregulating mucolipin-3 (MCOLN3)-mediated Ca²⁺ release [106]. In an animal study of Aspergillus fumigatus infection, vitamin D treatment led to autophagic homeostasis by reducing the number of autophagy-mediated lysosomes and regulatory T-cells, thus enhancing the antimicrobial response [127]. Moreover, vitamin D suppressed rotavirus infection by upregulating the autophagy gene Beclin-1 and promoting autophagic maturation and cathelicidin gene expression [128]. Although vitamin D-induced autophagy is critical for an effective immune response, further studies are needed to determine the ability of vitamin D to prevent and treat infectious diseases in humans. The studies on VDR-related autophagy during infection are summarized in Table 1.
Table 1. Vitamin D receptor (VDR) in autophagy-mediated host defense against infections.

| Ligand/Activator | Pathogen/Disease | Study Model | Autophagy | Effects | Mechanism of Action | Ref. |
|------------------|------------------|-------------|-----------|---------|---------------------|------|
| **Vit-D**        | **H. pylori**    | Human gastric epithelial cell lines, clinical specimens | ↑ | Bacterial eradication | Activation of PDIA3 receptor and nuclear translocation of PDIA3-STAT3 complex to induce autophagosomal degradation independent of VDR | [106] |
|                  | **Mtb**          | Human primary monocytes, MDMs, THP-1, and RAW264.7 cells | ↑ | Antimicrobial | Beclin-1 and Atg-5 activation mediated through hCAP18/LL-37-dependent MAPK and C/EBPβ activation | [107] |
|                  | PG2E, human macrophages | Intracellular Mtb survival | PG2E inhibits hCAP18/LL-37 expression and vitamin D-induced cathelicidin and autophagy by dampening expression of VDR | [114] |
|                  | **Mouse model**  | ↑ | Antimicrobial | Vit-D supplementation on 2nd-line anti-TB therapy leads to suppression of MMP1 | Induction of VDR, CRAMP, LC3B, and caspase-3 | [115] |
|                  | ↓ | Antimicrobial | Delayed formation of lysosomes against infection | Modulation of Dectin-1, ROS, and LC3 expression | [127] |
| **Vit-D-sufficient human serum** | **M. marinum** | Human monocytes (THP-1) | ↑ | Antimicrobial | Induction of endogenous CAMP and its colocalization with autophagolysosome | [110] |
|                  | **Mtb**          | CD40L, IFN-γ, human PBMC | ↑ | Antimicrobial | Induction of CYP27B1, VDR, cathelicidin, and DEFB4 | [112] |
|                  | **IFN-γ, human macrophages** | ↑ | Antimicrobial | Vitamin D-dependent autophagy and autophagolysosomal fusion by IFN-γ | VDR-dependent induction of cathelicidin and DEFB4 by IFN-γ | [123] |
|                  | **A. fumigatus** | Alveolar macrophages | ↓ | Antimicrobial | Delayed formation of lysosomes against infection | Modulation of Dectin-1, ROS, and LC3 expression | [127] |
| **PBA+Vit-D** | **Mtb lipoprotein LpqH** | Human primary monocytes | ↑ | Antimicrobial | Induction of endogenous CAMP and its colocalization with autophagolysosome | [110] |
|                  | PBMCs and MDMs from TB patients | ↑ | Antimicrobial | Increased LC3 expression, decreased hCAP18/LL-37 mRNA | [116] |
|                  | ↑ | Antimicrobial | Increased LC3 expression, decreased hCAP18/LL-37 mRNA | Increased LL-37 | [117] |
|                  | ↑ | Antimicrobial | Increased serum Vit-D levels after PBA+Vit-D supplementation | [118] |
| **LAB** | **S. enterica** | HCT116, MEFs cell lines, in vivo mice | ↑ | Anti-inflammatory | Enhanced expression of Beclin-1 and ATG16L1 | Increased expression of VDR and cathelicidin | [126] |
| **Vit-D**        | **HIV**          | Human MDMs | ↑ | Inhibition of virus replication | PI3K-, ATG-5-, and Beclin-1-dependent autophagy activation | [111] |
|                  | **HIV, Mtb**     | Human MDMs | ↑ | Inhibition of virus replication and mycobacterial growth | Induced expression of CAMP | [112] |
|                  | **Influenza A**  | A549 cell lines | ↑ | Antiviral | Restoration of virus-induced inhibition of autophagic flux through Syntaxin-17 and ATP8A2 | [125] |
|                  | **Rotavirus**    | Pigs, IPEC-J2 cells | ↑ | Inhibition of virus infection | Regulation of autophagic maturation and expression of porcine cathelicidin genes | [128] |
| **TLR ligands** | **HIV**          | Human macrophages | ↑ | Reduced virus replication | Induced expression of CAMP, VDR, and CYP27B1 | [113] |

Vit-D, 1,25-dihydroxy vitamin D3; PDIA3, protein disulfide-isomerase A3; STAT3, signal transducer and activator of transcription 3; Mtb, Mycobacterium tuberculosis; MDM, monocyte-derived macrophages; hCAP18, human cationic antimicrobial protein; MAPK, mitogen-activated protein kinase; C/EBPβ, CCAAT/enhancer-binding protein beta; CAMP, cathelicidin antimicrobial peptides; TLR, toll-like receptor; PG2E, prostaglandin E2; PB, phenylbutyrate; XBP1, X-box binding protein 1; TB, tuberculosis; IFN, interferon; DEFB4, beta-defensin 2; PBMC, peripheral blood mononuclear cells; CYP27B1, cytochrome p450 27B1 or 25-Hydroxyvitamin D3 1α-hydroxylase; LAB, lactic acid bacteria; MEF, mouse embryonic fibroblasts; HCT116, human colon cancer cell line; ATG16L1, autophagy related 16 like 1; ROS, reactive oxygen species; HIV, human immunodeficiency virus; PI3K, phosphoinositide 3-kinases; ATP6V0A2, V-ATPase 16 kDa isoform a2.
5. Estrogen Receptors

Estrogen—a female sex steroid hormone—and its receptors (ERα and ERβ) reportedly modulate autophagy, which is implicated in various human diseases and the determination of cell fate [21,129]. Indeed, ERs and the downstream genomic and non-genomic signaling cascades affect the outcomes of tumorigenesis and angiogenesis in breast cancer [21,130]. In addition, ERα activation by estrogen enhances autophagy and tumor cell survival in papillary thyroid cancer by promoting reactive oxygen species (ROS) generation and the activation of extracellular signal-regulated kinases [131].

Estrogen modulators influence antimicrobial responses by influencing autophagy. The selective ER modulator bazedoxifene suppresses the intracellular growth of Mtb by activating autophagy via ROS generation and Akt/mammalian target of rapamycin (mTOR) signaling [90]. Tamoxifen (TAM) is a potent inhibitor of Shiga toxin trafficking and toxicity in a manner independent on ERs [132]. TAM also restricted Toxoplasma replication by inducing xenophagy or autophagy [133]. Long-term treatment with 17β-estradiol (E2) exerted a beneficial effect on endotoxemia-associated circulatory and multiple organ dysfunction in ovarietomized rats, which was mediated, at least in part, by autophagy activation [134]. Clarification of the mechanisms through which ERs modulate autophagy and/or host defense, as well as the crosstalk between autophagy and immunity in the context of ER signaling, is needed for the development of novel therapeutic modalities for infection and inflammation.

6. Estrogen-Related Receptors

ERRs are orphan members of the NR family, and are involved in a variety of biological responses, including cellular metabolism and energy control [135–137]. ERRα is a critical regulator of autophagy at transcriptional and post-translational levels, particularly in cooperation with sirtuin 1. These effects promoted the antimicrobial response to Mtb [23]. The thyroid hormone upregulated the expression of ERRα by inducing PGC-1α (PPARGC1A), thus modulating mitochondrial biogenesis and mitophagy. Mechanistically, the thyroid hormone upregulated the autophagy-regulating kinase ULK1 through ERRα, which was required for the autophagic clearance of mitochondria, i.e., mitophagy [138]. In contrast, the inhibition of ERRα activity by the inverse agonist XCT790 induced autophagy and promoted the clearance of toxic protein aggregates, enhancing its neuroprotective effect [139]. There is a role for ERRα in host defense between intracellular bacteria and viruses [23,140–142]. Therefore, future studies should clarify the role of ERRs in modulating autophagy and evaluate its therapeutic potential as an antimicrobial. The studies on ERs and ERRα-related autophagy during infection are summarized in Table 2.

Table 2. Estrogen receptors (ERs)/estrogen-related receptors (ESRRs).

| NRs | Ligands/Activator | Pathogen/Study Model | Autophagy | Effects | Mechanism of Action | Ref. |
|-----|------------------|----------------------|-----------|---------|---------------------|-----|
| ER  | Estrogen (E2)    | Thyroid cancer patients samples, Nthy-ori 3-1, PTC cell, BCPAP-ERα, MCF-7 cells | ↑         | Tumor cell survival | Generation of ROS, activation of ERK1/2 | [131] |
|     | Bazedoxifene     | Mtb/THP-1 cells      | ↑         | Inhibition of intracellular growth of Mtb | Increased ROS and phosphorylation of Akt/mTOR signaling | [90] |
| AICAR | Mtb/BMDMs, RAW264.7, HEK293T cells | ↑     | Antimicrobial host defense | Transcriptional activation of autophagy-related genes, and post transcriptional activation of autophagy through SIRT1 activation | [23] |
| ERRα| Thyroid hormone  | THRβ1-HepG2 cells, in vivo mouse model | ↑         | Mitophagy induction | Increased ESRRα expression via PPARGC1A Induction of ULK1 mRNA and protein through ESRRα-dependent transcription | [138] |
|     | XCT 790          | SH-SY5Y, HeLa cells, in vivo mice | ↑         | Neuroprotective | Regulation of autophagy by ERRα through its localization with autophagosome | [139] |

PTC, papillary thyroid carcinoma; MCF-7, breast cancer cell line; ERK1/2, extracellular signal-regulated protein kinase; mTOR, mammalian target of rapamycin; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; BMDM, bone marrow-derived macrophages; SIRT1, sirtuin 1; PPARGC1A, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ULK1, unc-51 like autophagy activating kinase.
7. Peroxisome Proliferator-Activated Receptors

7.1. Peroxisome Proliferator-Activated Receptor-α

The nutrient-sensing NRs, PPARα and FXR, play reciprocal functions in the regulation of autophagy; PPARα enhances and FXR suppresses autophagy to enhance lipolysis [22] and ciliogenesis [143]. PPARα ameliorates inflammatory and injurious conditions by inducing autophagy in various cells and tissues [144,145]. In addition, autophagy activation leads to PPARα activation by degrading nuclear receptor co-repressor 1 (NCoR1), which interacts with and suppresses the transactivation of PPARα [146].

PPARα modulates antimicrobial responses to Mtb, *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), or *Mycobacterium abscessus* by activating transcription factor EB (TFEB) [70–72]. In addition, PPARα deficiency resulted in an exaggerated inflammatory response to mycobacterial infection. Importantly, PPARα activation significantly reduced the lipid body number and size in macrophages infected with Mtb or *M. bovis* BCG, suggesting that PPARα contributes to lipid catabolism and reduces the foamy refuge during mycobacterial infection [72]. TFEB controlled the inflammatory response of host macrophages to Mtb or BCG infection [72]. However, TFEB was reportedly required for the induction of inflammatory cytokines and chemokines in macrophages infected with *Staphylococcus aureus* [147].

Numerous agents have been reported to activate PPARα and enhance TFEB, thereby promoting lysosomal biogenesis in models of chronic inflammatory and degenerative diseases [148–151]. Therefore, PPARα-activating drugs have potential for various infectious diseases. HIV infection inhibited autophagy in macrophages, promoting the intracellular survival of Mtb and non-tuberculous mycobacteria (NTM) [152]. The treatment of septic mice with the PPARβ/δ-agonist GW0742 improved long-term survival and protected against multiple organ injury and dysfunction by modulating inflammatory signaling and coagulation [156,157].

Amodiaquine, which is a selective anti-*Plasmodium falciparum* agent, suppresses autophagolysosomal degradation and PPARγ activity [158]. The PPARγ ligand HP24, which is a pyridinecarboxylic acid derivative, ameliorated the pathologic and inflammatory responses induced by *Trypanosoma cruzi* [159]. INT131, which is a novel non-thiazolidinedione and selective PPARγ modulator, has a beneficial anti-inflammatory effect on EcoHIV-infected glial cells and in a mouse model of EcoHIV infection [160]. However, whether PPARβ/δ or PPARγ activation exerts an antimicrobial effect by modulating autophagy is unclear. Further studies are needed to clarify the roles of PPARβ/δ and PPARγ in controlling the host response to infections in the context of autophagy activation. The studies on PPAR-related autophagy during infection are summarized in Table 3.
Table 3. Peroxisome proliferator-activated receptors (PPARs).

| NRs | Ligands/Activator | Pathogen | Pathogen/Study Model | Autophagy | Effects | Mechanism of Action | Ref. |
|-----|-------------------|----------|----------------------|-----------|---------|---------------------|------|
| PPARα | GW7647, Wy14643 | Mtb | BMDMs, in vivo mice | ↑ | Antimicrobial | Increased expression and nuclear translocation of TFEB | [72] |
| | Gemfibrozil | M. abscessus | BMDMs, in vivo mice | ↑ | Antimicrobial | Increased nuclear translocation of TFEB | [70] |
| PPARβ/δ | GW501516 | - | Human cardiac AC16 cells, in vivo mice | ↑ | Inhibition of palmitate induced ER stress | Upregulation of Beclin-1 and LC3H | [155] |
| PPARγ | HP24 | T. cruzi | Peritoneal macrophages, in vivo mice | - | Pro-angiogenic and anti-inflammatory | Induction of pro-angiogenic mediators (eNOS and VEGF-A) through PI3K/Akt/mTOR and PPARγ pathway Inhibition of NF-κB pathway in PPARγ-dependent manner | [159] |
| | INT131 | EcoHIV | Primary mouse glial cells, in vivo mice | - | Anti-inflammatory | Inhibition of proinflammatory cytokines | [160] |

TFEB, transcription factor EB; eNOS, endothelial NOS; VEGF-A, vascular endothelial growth factor A; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.
8. Other Nuclear Receptors Potentially Linking Autophagy and Host Defenses

8.1. REV-ERBα and REV-ERBβ

The adopted orphan NR—REV-ERBα—is involved in adipogenesis, muscle differentiation, glucose/lipid metabolism, and the circadian rhythm [161–163]. REV-ERBα links the circadian rhythm and autophagy, and directly regulates the rhythmic expression of ATGs in zebrafish [164]. The key transcriptional regulators TFEB and TFE3 are required for the expression of REV-ERBα [162], suggesting another link between autophagy and the circadian cycle.

During infection, REV-ERBα activation by GSK4112 exerted an anti-mycobacterial effect in macrophages by enhancing autophagy and lysosomal biogenesis and suppressing IL-10 synthesis [165]. However, the pharmacological activation of REV-ERBα and REV-ERBβ (NR1D2) using agonists inhibited autophagy and lipogenesis, thereby exerting an anticancer effect [163]. Moreover, the lysosomotropic REV-ERBβ ligand (ARN5187) inhibited autophagy and exerted a cytotoxic effect in breast cancer cells [166]. The over-expression of REV-ERBα in skeletal muscle induced mitochondrial activity and respiratory capacity, but repressed autophagy [167]. Therefore, REV-ERBα and REV-ERBβ may play diverse roles in autophagy regulation, depending on the cell type and pathological status. Because the circadian rhythm may be linked to the immune response to infection [168–170], further studies should clarify the roles of REV-ERBα and REV-ERBβ in autophagy, the circadian rhythm, and the immune response to bacterial and fungal pathogens.

8.2. Retinoic Acid Receptor-α (RARα; RARA; NR1B1), -β (RARβ; RARB; NR1B2), and -γ (RARγ; RARG; NR1B3)

All-trans retinoic acid and/or arsenic trioxide induced autophagy of the oncoprotein promyelocytic leukemia (PML)/RARα, suggesting RARα as a therapeutic target for acute PML [171,172]. In addition, RARα activated autophagy in human primary B cells [173] and various types of cancer cells [174,175]. The downregulation of RARα led to the upregulation of VDR expression in acute myeloid leukemia cells [176]. However, its role in autophagy during the antimicrobial response is unclear. RARα is reportedly a critical regulator of the maturation of monocyte-derived dendritic cells during HIV infection [177], although its relevance to autophagy has not been evaluated.

Similarly, little is known about the role of RARβ in the regulation of autophagy during infection. RARβ has a tumor suppressive function and is involved in cell differentiation and apoptosis. Interestingly, the human papillomavirus type 16 (HPV16) E7 oncoprotein upregulated the mRNA and protein levels of RARβ in cervical cancer cells and in the cervix of K14E7 transgenic mice [178]. During human adenovirus infection, the RARβ mRNA and protein levels were downregulated, but the overexpression of RARβ decreased human adenovirus production [179]. Therefore, RARβ may have therapeutic effects for adenovirus infection, although the autophagy-mediated suppression of infection is unclear in RARβ-induced antiviral and anticancer effects.

8.3. Retinoic Acid-Related Orphan-α (RORα; RORA; NR1F1), -β (RORβ; RORB; NR1F2), and -γ (RORγ; RORC; NR1F3)

RORs are important in the regulation of the circadian clock, metabolic homeostasis, and tumorigenesis [180,181]. Although RORs are emerging as therapeutic targets for tumors, their roles in the modulation of host defense during infection in the context of autophagy are unclear. Upon infection with highly pathogenic avian influenza viruses (HPAIV H5N1), RORα is synthesized and suppresses NF-κB signaling and the inflammatory response in monocytes, thereby contributing to the escape of H5N1 from the host inflammatory defenses [182]. RORα is a melatonin receptor and protects against ischemic heart injury and diabetic cardiomyopathy [183,184]. The effect of melatonin on autophagy regulation has been reported in various normal and cancer cells [185,186]. In addition, the protective effects of melatonin in various bacterial, viral, and parasitic infections have been characterized [187–191]. Melatonin treatment of Hodgkin lymphoma cells increased the expression of RORα, RORβ, and RORγ, and enhanced...
autophagy activation [192]. Therefore, it would be interesting to investigate the involvement of RORs in melatonin-mediated autophagy activation.

8.4. Farnesoid X Receptors-α (FXR-α)

As a nutrient-sensing and autophagy-regulating NR, FXR-α regulates hepatic autophagy to maintain the energy balance in the liver [22,193] and inhibits autophagy-mediated ciliogenesis [143]. The inhibitory effect of FXR-α is counteracted by PPAR-α, which activates autophagy [22,143,193]. Because PPAR-α is involved in the coordination of autophagy activation and antimicrobial defenses [72], it would be interesting to investigate the role of FXR-α.

In a model of cholestasis, the activation of autophagy maturation is inhibited in an FXR-dependent manner, partly as a result of the induction of Rubicon. However, ursodeoxycholic acid (UDCA), which is a non-FXR-agonistic bile acid, induced hepatic autophagy and reduced the expression of Rubicon, which is an inhibitor of autophagy [194]. In an autophagy-deficient liver, the expression of FXR and its downstream genes was inhibited, promoting cholestatic injury [195]. Therefore, the link between FXR and autophagy requires further investigation.

8.5. Liver X Receptor (LXR)-α (LXRα; NR1H3) and -β (LXRβ; NR1H2)

LXRα and LXRβ are negative regulators of cholesterol metabolism and inflammation [196,197]. Both LXRs are important in the antimicrobial response to viral and bacterial infections [75]. Three synthetic LXR agonists (T0901317, GW3965, and LXR-623) had a long-lasting inhibitory effect on hepatitis B virus replication and gene expression [198]. In addition, both LXRα and LXRβ were required for the suppression of gammaherpesvirus reactivation by downregulating fatty acid and cholesterol synthesis in macrophages [199], and for the inhibition of herpes simplex virus type 1 (HSV-1) by 25-hydroxycholesterol [200]. IL-36 and LXR signaling promoted anti-mycobacterial effects by inducing the expression of cholesterol-converting enzymes and regulating the expression of antimicrobial peptides [201]. In addition, LXR activation inhibited Salmonella infection by inducing the expression of the multifunctional enzyme CD38 [202]. LXRs are involved in the regulation of autophagy in various pathological conditions, including cancers [203,204]. Therefore, further studies on the involvement of LXRs in modulating autophagy during infection with intracellular microbes are required.

8.6. Thyroid Hormone Receptors-α (TRα; THRA; NR1A1) and -β (TRβ; THRB; NR1A2)

The thyroid hormone is a regulator of the metabolic rate, oxidative phosphorylation (OXPHOS), and ROS production [205,206], and a potent inducer of autophagy/mitophagy [207,208]. Thyroid hormone suppresses the hepatic carcinogenesis induced by the HBV X protein by promoting mitochondrial turnover via autophagy activation. In addition, thyroid hormone/TR-induced hepatic PINK1 expression is associated with hepatic cellular carcinoma (HCC) progression and a poor prognosis [209]. One might expect that thyroid hormone is involved in the modulation of host antimicrobial responses through autophagy. However, it remains to be determined whether both TRα and TRβ contribute to pathogenesis or protective immunity to broader ranges of infections through autophagy modulation. The studies on several NRs with potential roles in connecting autophagy and host defense are summarized in Table 4.
### Table 4. Several nuclear receptors (NRs) with potential functions in linking autophagy and host defense.

| NRs          | Ligands/Activator | Pathogen/Study Model | Autophagy | Effects | Mechanism of Action | Ref. |
|--------------|-------------------|----------------------|-----------|---------|---------------------|------|
| REV-ERBa     |                    |                      |           |         |                     |      |
|             | GSK4122            | Zebrafish            | Rhythmic with circadian clock | Regulation of autophagy rhythms | Direct regulation of NR1D1 and CEBPB by nutritional signals and circadian clock | [164] |
|             |                    |                      |           |         |                     |      |
|             | GSK4112            | Mtb/Human macrophages | ↑         | Antimicrobial | Modulation of LAMP1 and TFEB, repression of IL10 | [165] |
|             |                    |                      |           |         |                     |      |
|             | SR9009, SR9011     | Cancer cell lines, human glioblastoma stem cells, in vivo mice | ↓ | Anticancer | REV-ERB agonist inhibit autophagy (decreased LC3, increased p62, and increased LAMP1) and de novo lipogenesis to induce apoptotic responses | [163] |
| RARa         | ATRA               | HeLa, APL NB4 cells  | ↑         | Differentiation of APL cells | Inhibition of mTOR pathway to induce autophagy-dependent PML/RARA degradation | [171] |
| RORα         |                    |                      |           |         |                     |      |
|             |                    |                      |           |         |                     |      |
|             |                    |                      |           |         |                     |      |
| RORγ         | Melatonin          | Human HL cell line L428 | ↑         | Cell death | Induction of autophagic cell death by melatonin via increased level of RORC | [192] |
| FXR/PPARα    |                    | Mouse primary hepatocytes, mouse liver | FXR, ↓ PPAR, ↑ | - | FXR and PPAR compete for binding to common sites in autophagic gene promoters, with opposite transcriptional outputs | [22] |
|               |                    |                      |           |         |                     |      |
|               |                    | Mouse primary hepatocytes, mouse liver | FXR, ↓ PPAR, ↑ | - | FXR represses and PPAR facilitates cliogenesis | Regulation of expression of autophagic genes, FXR acts in opposite way with PPARA | [143] |
|               |                    |                      |           |         |                     |      |
|               |                    | Bile acids           | ↓         | Autophagy and Rubicon could be novel treatment target for cholestatic liver disease | Prevention of proper fusion of autophagolysosome with lysosomes by bile acids, through FXR-dependent induction of Rubicon | [194] |
|               |                    |                      |           |         |                     |      |
|               |                    | In vivo mice with hepatic deletion of Atg7 or Atg5 with or without Nrf2 codelletion | ↓         | Liver injury | NRF2 activation in autophagy deficiency leading to downregulation of FXR, causing cholestasis | [195] |
| LXR          |                    | HBV/primary human hepatocytes, HepaRG cells | - | Anti-HBV effects | Inhibition of cholesterol 7α-hydroxylase 1 (CYP7A1) mRNA levels | [198] |
|               |                    |                      |           |         |                     |      |
|               |                    | Melanoma and AML cell lines, AML patients samples, in vivo mice | ↑         | Anti-tumor | DDA acting as partial agonist on LXR to increase Nur77, Nor1, and LC3 expression | [204] |
|               |                    |                      |           |         |                     |      |
|               |                    | HepG2, Huh7 cells    | ↑         | Lipid metabolism | Uptregulation of C19orf80 expression, which is involved in lipid metabolism through breakdown of lipid droplets | [208] |
| TR           | T3                 | Mice model of hepatocarcinogenesis, HepG2 cells | ↑         | Inhibition of hepatic DNA damage, inflammation, and carcinogenesis | Induction of hepatic PINK1 expression, which ubiquitinates Hlf protein to trigger mitophagy | [209] |

CEBPβ, CCAAT/enhancer-binding protein beta; TFEB, transcription factor EB; TFEB, transcription factor E3; LAMP1, lysosomal-associated membrane protein 1; IL, interleukin; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; DRAM2, DNA-damage regulated autophagy modifier; PML, promyelocytic leukemia; ATRA, all-trans-retinoic acid; HPAIV, highly pathogenic avian influenza virus; APL, acute promyelocytic leukemia; MI/R, myocardial ischemia/reperfusion; HL, Hodgkin lymphoma; RPE, retinal pigment epithelium cells; NRF2, nuclear factor erythroid 2-related factor 2; HBV, hepatitis B virus; DDA, dendrogenin A; Nur77, nerve growth factor IB; Nor1, neuron-derived orphan receptor 1; T3, triiodothyronine; PINK1, PTEN-induced kinase 1.
9. Conclusions

Given the role of autophagy in controlling intracellular pathogens, there is an urgent need for autophagy-directed therapeutics and prophylactics. The targeting of autophagy in monocytes/macrophages stimulates the innate immune response, the dampening of inflammation and suppression of innate immunity, and the promotion of pathogen escape [210]. Therefore, a more comprehensive understanding of the molecular mechanisms of crosstalk between autophagy and the innate immunity system in acute vs. chronic infection by various pathogens in immunocompetent vs. immunocompromised hosts will facilitate the development of therapeutics and vaccines.

NR protects against a variety of infections and modulates autophagy during pathogen invasion. Early studies exploited VDR- or ERRα-targeted antimicrobial responses and were followed by several trials expanding the effects of other NRs. It is known that the ATGs involved in non-canonical autophagy are different from those involved in canonical autophagy, but only a few studies on NR-mediated non-canonical autophagy pathways have been reported to date [211]. We are only beginning to answer important questions on the NR regulation of autophagy and innate immune responses. It is important to understand the signaling networks connecting NRs, autophagy, and the inflammatory and immune responses according to the infection stage and pathogen. Such an enhanced understanding will facilitate the development of novel antimicrobials.

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References

1. Huang, J.; Brumell, J.H. Autophagy in immunity against intracellular bacteria. *Curr. Top. Microbiol. Immunol.* 2009, 335, 189–215. [CrossRef] [PubMed]
2. Siqueira, M.D.S.; Ribeiro, R.M.; Travassos, L.H. Autophagy and Its Interaction With Intracellular Bacterial Pathogens. *Front. Immunol.* 2018, 9, 935. [CrossRef] [PubMed]
3. Campoy, E.; Colombo, M.I. Autophagy in intracellular bacterial infection. *Biochim. Biophys. Acta* 2009, 1793, 1465–1477. [CrossRef]
4. Yuk, J.M.; Yoshimori, T.; Jo, E.K. Autophagy and bacterial infectious diseases. *Exp. Mol. Med.* 2012, 44, 99–108. [CrossRef] [PubMed]
5. Shahnazari, S.; Brumell, J.H. Mechanisms and consequences of bacterial targeting by the autophagy pathway. *Curr. Opin. Microbiol.* 2011, 14, 68–75. [CrossRef]
6. Huang, J.; Brumell, J.H. Bacteria-autophagy interplay: A battle for survival. *Nat. Rev. Microbiol.* 2014, 12, 101–114. [CrossRef]
7. Winchell, C.G.; Steele, S.; Kawula, T.; Voth, D.E. Dining in: Intracellular bacterial pathogen interplay with autophagy. *Curr. Opin. Microbiol.* 2016, 29, 9–14. [CrossRef]
8. Ogawa, M.; Nakagawa, I.; Yoshikawa, Y.; Hain, T.; Chakraborty, T.; Sasakawa, C. Streptococcus-, Shigella-, and Listeria-induced autophagy. *Methods Enzymol.* 2009, 452, 363–381. [CrossRef]
9. Ogawa, M.; Mimuro, H.; Yoshikawa, Y.; Ashida, H.; Sasakawa, C. Manipulation of autophagy by bacteria for their own benefit. *Microbiol. Immunol.* 2011, 55, 459–471. [CrossRef]
10. Lerena, M.C.; Vazquez, C.L.; Colombo, M.I. Bacterial pathogens and the autophagic response. *Cell Microbiol.* 2010, 12, 10–18. [CrossRef]
11. Ogawa, M.; Sasakawa, C. Bacterial evasion of the autophagic defense system. *Curr. Opin. Microbiol.* 2006, 9, 62–68. [CrossRef] [PubMed]
11. Radomski, N.; Rebbig, A.; Leonhardt, R.M.; Knittler, M.R. Xenophagic pathways and their bacterial subversion in cellular self-defense—phalphanutualpha rheopsiloniota—everything is in flux. *Int. J. Med. Microbiol.* 2018, 308, 185–196. [CrossRef] [PubMed]

12. Wu, Y.W.; Li, F. Bacterial interaction with host autophagy. *Virulence* 2019, 10, 352–362. [CrossRef]

13. Zhang, L.; Qin, Y.; Chen, M. Viral strategies for triggering and manipulating mitophagy. *Autophagy* 2018, 14, 1665–1673. [CrossRef] [PubMed]

14. Porter, B.A.; Ortiz, M.A.; Bratslavsky, G.; Kotula, L. Structure and Function of the Nuclear Receptor Superfamily and Current Targeted Therapies of Prostate Cancer. *Cancers (Basel)* 2019, 11, 1852. [CrossRef]

15. Meinsohn, M.C.; Smith, O.E.; Bertolin, K.; Murphy, B.D. The Orphan Nuclear Receptors Steroidogenic Factor-1 and Liver Receptor Homolog-1: Structure, Regulation, and Essential Roles in Mammalian Reproduction. *Physiol. Rev.* 2019, 99, 1249–1279. [CrossRef] [PubMed]

16. Wnuk, A.; Kajta, M. Steroid and Xenobiotic Receptor Signalling in Apoptosis and Autophagy of the Nervous System. *Int. J. Mol. Sci.* 2017, 18, 2394. [CrossRef]

17. Fiorucci, S.; Biagioli, M.; Sampola, A.; Distruiti, E. Bile Acids Activated Receptors Regulate Innate Immunity. *Front. Immunol.* 2018, 9, 1853. [CrossRef]

18. Bakke, D.; Sun, J. Ancient Nuclear Receptor VDR With New Functions: Microbiome and Inflammation. *Inflamm. Bowel Dis.* 2018, 24, 1149–1154. [CrossRef]

19. Kim, Y.S.; Siwal, P.; Kim, Y.S.; Yoshimori, T.; Jo, E.K. Autophagy-activating strategies to promote innate defense against mycobacteria. *Exp. Mol. Med.* 2019, 51, 1–10. [CrossRef]

20. Xiang, J.; Liu, X.; Ren, J.; Chen, K.; Wang, H.L.; Miao, Y.Y.; Qi, M.M. How does estrogen work on autophagy? *Autophagy* 2019, 15, 197–211. [CrossRef] [PubMed]

21. Lee, J.M.; Wagner, M.; Xiao, R.; Kim, K.H.; Feng, D.; Lazart, M.A.; Moore, D.D. Nutrient-sensing nuclear receptors coordinate autophagy. *Nature* 2014, 516, 112–115. [CrossRef] [PubMed]

22. Kim, S.Y.; Yang, C.S.; Lee, H.M.; Kim, J.K.; Kim, Y.S.; Kim, Y.R.; Kim, J.S.; Kim, T.S.; Yuk, J.M.; Dufour, C.R.; et al. ESRAA (estrogen-related receptor alpha) is a key coordinator of transcriptional and post-translational activation of autophagy to promote innate host defense. *Autophagy* 2018, 14, 152–168. [CrossRef] [PubMed]

23. Veras Ribeiro Filho, H.; Tambones, I.L.; Mariano Goncalves Dias, M.; Bernardi Videira, N.; Bruder, M.; Amorim Amato, A.; Migliorini Figueira, A.C. Modulation of nuclear receptor function: Targeting the protein-DNA interface. *Mol. Cell Endocrinol.* 2019, 484, 1–14. [CrossRef] [PubMed]

24. Neavin, D.R.; Liu, D.; Ray, B.; Weinshilboum, R.M. The Role of the Aryl Hydrocarbon Receptor (AHR) in Immune and Inflammatory Diseases. *Int. J. Mol. Sci.* 2018, 19, 3851. [CrossRef]

25. Scheschowitsch, K.; Leite, J.A.; Assreuy, J. New Insights in Glucocorticoid Receptor Signaling—More Than Just a Ligand-Binding Receptor. *Front. Endocrinol. (Lausanne)* 2017, 8, 16. [CrossRef]

26. Tripathi, M.; Yen, P.M.; Singh, B.K. Estrogen-Related Receptor Alpha: An Under-Appreciated Potential Target for the Treatment of Metabolic Diseases. *Int. J. Mol. Sci.* 2020, 21, 1645. [CrossRef]

27. Levine, B.; Kroemer, G. Autophagy in the pathogenesis of disease. *Cell* 2008, 132, 27–42. [CrossRef]

28. Deretic, V.; Levine, B. Autophagy, immunity, and microbial adaptations. *Cell Host Microbe* 2009, 5, 527–549. [CrossRef]

29. Deretic, V.; Saitoh, T.; Akira, S. Autophagy in infection, inflammation and immunity. *Nat. Rev. Immunol.* 2013, 13, 722–737. [CrossRef]

30. Keller, M.D.; Torres, V.J.; Cadwell, K. Autophagy and microbial pathogenesis. *Cell Death Differ.* 2020, 27, 872–886. [CrossRef] [PubMed]

31. Mizushima, N.; Yoshimori, T.; Ohsumi, Y. The role of Atg proteins in autophagosome formation. *Annu. Rev. Cell Dev. Biol.* 2011, 27, 107–132. [CrossRef] [PubMed]

32. Mizushima, N. The ATG conjugation systems in autophagy. *Curr. Opin. Cell Biol.* 2020, 63, 1–10. [CrossRef]

33. Levine, B.; Kroemer, G. Biological Functions of Autophagy Genes: A Disease Perspective. *Cell* 2019, 176, 11–42. [CrossRef]

34. Behrends, C.; Sowa, M.E.; Gygi, S.P.; Harper, J.W. Network organization of the human autophagy system. *Nature* 2010, 466, 68–76. [CrossRef] [PubMed]

35. Kang, R.; Zeh, H.J.; Lotze, M.T.; Tang, D. The Beclin 1 network regulates autophagy and apoptosis. *Cell Death Differ.* 2011, 18, 571–580. [CrossRef]

36. Codogno, P.; Mehrpour, M.; Proikas-Cezanne, T. Canonical and non-canonical autophagy: Variations on a common theme of self-eating? *Nat. Rev. Mol. Cell Biol.* 2011, 13, 7–12. [CrossRef]
38. Heckmann, B.L.; Boada-Romero, E.; Cunha, L.D.; Magne, J.; Green, D.R. LC3-Associated Phagocytosis and Inflammation. *J. Mol. Biol.* 2017, 429, 3561–3576. [CrossRef]
39. Sun, Q.; Zhang, J.; Fan, W.; Wong, K.N.; Ding, X.; Chen, S.; Zhong, Q. The RUN domain of rubicon is important for hVps34 binding, lipid kinase inhibition, and autophagy suppression. *J. Biol. Chem.* 2011, 286, 185–191. [CrossRef]
40. Dikic, I.; Elazar, Z. Mechanism and medical implications of mammalian autophagy. *Nat. Rev. Mol. Cell Biol.* 2018, 19, 349–364. [CrossRef]
41. Sanchez-Martin, P.; Komatsu, M. Physiological Stress Response by Selective Autophagy. *J. Mol. Biol.* 2020, 432, 53–62. [CrossRef] [PubMed]
42. Sanchez-Martin, P.; Komatsu, M. p62/SQSTM1—steering the cell through health and disease. *J. Cell Sci.* 2018, 131. [CrossRef] [PubMed]
43. Jeong, S.J.; Zhang, X.; Rodriguez-Velez, A.; Evans, T.D.; Razani, B. p62/SQSTM1 and Selective Autophagy in Cardiometabolic Diseases. *Antioxid. Redox Signal.* 2019, 31, 458–471. [CrossRef]
44. Martinez, J.; Cunha, L.D.; Park, S.; Yang, M.; Lu, Q.; Orchard, R.; Li, Q.Z.; Yan, M.; Janke, L.; Guy, C.; et al. Noncanonical autophagy inhibits the autoinflammatory, lupus-like response to dying cells. *Nature* 2016, 533, 115–119. [CrossRef] [PubMed]
45. Wesselborg, S.; Stork, B. Autophagy signal transduction by ATG proteins: From hierarchies to networks. *Cell Mol. Life Sci.* 2015, 72, 4721–4757. [CrossRef]
46. Maruzs, T.; Simon-Vecsei, Z.; Csizmadia, T.; Juhasz, G. On the Fly: Recent Progress on Autophagy and Aging in Drosophila. *Front. Cell Dev. Biol.* 2019, 7, 140. [CrossRef]
47. Kuo, C.J.; Hansen, M.; Troemel, E. Autophagy and innate immunity: Insights from invertebrate model organisms. *Autophagy* 2018, 14, 233–242. [CrossRef]
48. Jin, M.; Klionsky, D.J. Regulation of autophagy: Modulation of the size and number of autophagosomes. *FEBS Lett.* 2014, 588, 2457–2463. [CrossRef]
49. Feng, Y.; Yao, Z.; Klionsky, D.J. How to control self-digestion: Transcriptional, post-transcriptional, and post-translational regulation of autophagy. *Trends Cell Biol.* 2015, 25, 354–363. [CrossRef]
50. Feng, Y.; He, D.; Yao, Z.; Klionsky, D.J. The machinery of macroautophagy. *Cell Res.* 2014, 24, 24–41. [CrossRef]
51. McEwan, D.G.; Dikic, I. The Three Musketeers of Autophagy: Phosphorylation, ubiquitylation and acetylation. *Trends Cell Biol.* 2011, 21, 195–201. [CrossRef] [PubMed]
52. Banreti, A.; Sass, M.; Graba, Y. The emerging role of acetylation in the regulation of autophagy. *Autophagy* 2013, 9, 819–829. [CrossRef] [PubMed]
53. Hamai, A.; Codogno, P. New targets for acetylation in autophagy. *Sci. Signal.* 2012, 5, pe29. [CrossRef]
54. Xie, Y.; Kang, R.; Sun, X.; Zhong, M.; Huang, J.; Klionsky, D.J.; Tang, D. Posttranslational modification of autophagy-related proteins in macroautophagy. *Autophagy* 2015, 11, 28–45. [CrossRef] [PubMed]
55. Di Malta, C.; Cinque, L.; Settembre, C. Transcriptional Regulation of Autophagy: Mechanisms and Diseases. *Front. Cell Dev. Biol.* 2019, 7, 114. [CrossRef] [PubMed]
56. Jo, E.K.; Yuk, J.M.; Shin, D.M.; Sasakawa, C. Roles of autophagy in elimination of intracellular bacterial pathogens. *Front. Immunol.* 2013, 4, 97. [CrossRef]
57. Campoy, E.; Colombo, M.I. Autophagy subversion by bacteria. *Curr. Top. Microbiol. Immunol.* 2009, 335, 227–250. [CrossRef]
58. Paul, P.; Munz, C. Autophagy and Mammalian Viruses: Roles in Immune Response, Viral Replication, and Beyond. *Adv. Virus Res.* 2016, 95, 149–195. [CrossRef]
59. Choi, Y.; Bowman, J.W.; Jung, J.U. Autophagy during viral infection—A double-edged sword. *Nat. Rev. Microbiol.* 2018, 16, 341–354. [CrossRef]
60. Kudchodkar, S.B.; Levine, B. Viruses and autophagy. *Rev. Med. Virol.* 2009, 19, 359–378. [CrossRef]
61. Mangelsdorf, D.J.; Thummel, C.; Beato, M.; Herrlich, P.; Schutz, G.; Umesono, K.; Blumberg, B.; Kastner, P.; Mark, M.; Chambon, P.; et al. The nuclear receptor superfamily: The second decade. *Cell* 1995, 83, 835–839. [CrossRef]
62. Umesono, K.; Evans, R.M. Determinants of target gene specificity for steroid/thyroid hormone receptors. *Cell* 1989, 57, 1139–1146. [CrossRef]
63. Huang, P.; Chandra, V.; Rastinejad, F. Structural overview of the nuclear receptor superfamily: Insights into physiology and therapeutics. *Annu. Rev. Physiol.* 2010, 72, 247–272. [CrossRef] [PubMed]
64. Jimenez-Sousa, M.A.; Martinez, I.; Medrano, L.M.; Fernandez-Rodriguez, A.; Resino, S. Vitamin D in Human Immunodeficiency Virus Infection: Influence on Immunity and Disease. *Front. Immunol.* **2018**, *9*, 458. [CrossRef] [PubMed]

65. Zdrenghea, M.T.; Makrinioti, H.; Bagacean, C.; Bush, A.; Johnston, S.L.; Stanciu, L.A. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev. Med. Virol.* **2017**, *27*. [CrossRef]

66. Wu, S.; Sun, J. Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection. *Discov. Med.* **2011**, *11*, 325–335.

67. Paik, S.; Kim, J.K.; Chung, C.; Jo, E.K. Autophagy: A new strategy for host-directed therapy of tuberculosis. *Virology* **2019**, *10*, 448–459. [CrossRef]

68. Kim, D.K.; Jeong, J.H.; Lee, J.M.; Kim, K.S.; Park, S.H.; Kim, Y.D.; Koh, M.; Shin, M.; Jung, Y.S.; Kim, H.S.; et al. Inverse agonist of estrogen-related receptor gamma controls Salmonella typhimurium infection by modulating host iron homeostasis. *Nat. Med.* **2014**, *20*, 419–424. [CrossRef]

69. Korf, H.; Vander Beken, S.; Steffensen, K.R.; Stijlemans, B.; Gustafsson, J.A.; Grooten, J.; Huygen, K. Liver X receptors contribute to the protective immune response against Mycobacterium tuberculosis in mice. *J. Clin. Investig.* **2009**, *119*, 1626–1637. [CrossRef]

70. Kim, Y.S.; Kim, J.K.; Hanh, B.T.B.; Kim, S.Y.; Kim, H.J.; Jeon, S.M.; Park, C.R.; Oh, G.T.; Park, J.W.; et al. The Peroxisome Proliferator-Activated Receptor alpha-Agonist Gemfibrozil Promotes Defense Against Mycobacterium abscessus Infections. *Cells* **2020**, *9*, 648. [CrossRef]

71. Kim, T.S.; Jin, Y.B.; Kim, Y.S.; Kim, S.; Kim, J.K.; Lee, H.M.; Suh, H.W.; Choe, J.H.; Kim, Y.J.; Koo, B.S.; et al. SIRT3 promotes antimycobacterial defenses by coordinating mitochondrial and autophagic functions. *Autophagy* **2019**, *15*, 1356–1375. [CrossRef]

72. Kim, Y.S.; Lee, H.M.; Kim, J.K.; Yang, C.S.; Kim, T.S.; Jung, M.; Jin, H.S.; Kim, S.; Jang, J.; Oh, G.T.; et al. PPAR-alpha Activation Mediates Innate Host Defense through Induction of TFEB and Lipid Catabolism. *J. Immunol.* **2017**, *198*, 3283–3295. [CrossRef] [PubMed]

73. Omeragic, A.; Kara-Yacoubian, N.; Kelschenbach, J.; Sahin, C.; Cummins, C.L.; Volsky, D.J.; Bendayani, R. Peroxisome Proliferator-Activated Receptor-gamma agonists exhibit anti-inflammatory and antiviral effects in an EcoHIV mouse model. *Sci. Rep.* **2019**, *9*, 9428. [CrossRef] [PubMed]

74. Leopold Wager, C.M.; Arnett, E.; Schlesinger, L.S. Mycobacterium tuberculosis and macrophage nuclear receptors: What we do and don’t know. *Tuberculosis (Edinb)* **2019**, *116S*, S98–S106. [CrossRef] [PubMed]

75. Leopold Wager, C.M.; Arnett, E.; Schlesinger, L.S. Macrophage nuclear receptors: Emerging key players in infectious diseases. *PLoS Pathog.* **2019**, *15*, e1007585. [CrossRef]

76. Petta, I.; Dejager, L.; Ballegeer, M.; Lievens, S.; Tavernier, J.; De Bosscher, K.; Libert, C. The Interactome of the Glucocorticoid Receptor and Its Influence on the Actions of Glucocorticoids in Combatting Infectious and Infectious Diseases. *Microbiol. Mol. Biol. Rev.* **2016**, *80*, 495–522. [CrossRef]

77. Montoya, M.C.; Krysan, D.J. Repurposing Estrogen Receptor Antagonists for the Treatment of Infectious Disease. *mBio* **2018**, *9*. [CrossRef]

78. Medina-Estrada, I.; Alva-Murillo, N.; Lopez-Meza, J.E.; Ochoa-Zarzosa, A. Immunomodulatory Effects of 17beta-Estradiol on Epithelial Cells during Bacterial Infections. *J. Immunol. Res.* **2018**, 2018, 6098961. [CrossRef]

79. Erickson, S.L.; Alston, L.; Nieves, K.; Chang, T.K.H.; Mani, S.; Flannigan, K.L.; Hirota, S.A. The xenobiotic sensing pregnane X receptor regulates tissue damage and inflammation triggered by C difficile toxins. *FASEB J.* **2020**, *34*, 2198–2212. [CrossRef]

80. Qiu, Z.; Cervantes, J.L.; Cicek, B.B.; Mukherjee, S.; Venkatesh, M.; Maher, L.A.; Salazar, J.C.; Mani, S.; Khanna, K.M. Pregnan X Receptor Regulates Pathogen-Induced Inflammation and Host Defense against an Intracellular Bacterial Infection through Toll-like Receptor 4. *Sci. Rep.* **2016**, *6*, 31936. [CrossRef]

81. Bhagyaraj, E.; Nanduri, R.; Saini, A.; Dkhar, H.K.; Ahuja, N.; Chandra, V.; Mahajan, S.; Kalra, R.; Tiwari, D.; Sharma, C.; et al. Human Xenobiotic Nuclear Receptor PXR Augments Mycobacterium tuberculosis Survival. *J. Immunol.* **2016**, *197*, 244–255. [CrossRef] [PubMed]

82. Curtis, A.M.; Bellet, M.M.; Sassone-Corsi, P.; O’Neill, L.A. Circadian clock proteins and immunity. *Immunity* **2014**, *40*, 178–186. [CrossRef] [PubMed]
83. Gibbs, J.E.; Blaikley, J.; Beasley, S.; Matthews, L.; Simpson, K.D.; Boyce, S.H.; Farrow, S.N.; Else, K.J.; Singh, D.; Ray, D.W.; et al. The nuclear receptor REV-ERBalpha mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc. Natl. Acad. Sci. USA* 2012, 109, 582–587. [CrossRef] [PubMed]
84. Levy, G.; Habib, N.; Guzzardi, M.A.; Kitsberg, D.; Bomze, D.; Ezra, E.; Uygur, B.E.; Uygur, K.; Trippler, M.; Schlaak, J.F.; et al. Nuclear receptors control pro-viral and antiviral metabolic responses to hepatitis C virus infection. *Nat. Chem. Biol.* 2016, 12, 1037–1045. [CrossRef] [PubMed]
85. Prince, L.R.; Prosseda, S.D.; Higgins, K.; Carlring, J.; Prestwich, E.C.; Ogryzko, N.V.; Rahman, A.; Basran, A.; Falciani, F.; Taylor, P.; et al. NR4A orphan nuclear receptor family members, NR4A2 and NR4A3, regulate neutrophil number and survival. *Blood* 2017, 130, 1014–1025. [CrossRef]
86. Mazaira, G.I.; Zgajnar, N.R.; Lotufo, C.M.; Daneri-Becerra, C.; Sivils, J.C.; Soto, O.B.; Cox, M.B.; Caligniana, M.D. The Nuclear Receptor Field: A Historical Overview and Future Challenges. *Nucl. Receptor Res.* 2018, 5. [CrossRef]
87. Heldin, C.H.; Lu, B.; Evans, R.; Gutkind, J.S. Signals and Receptors. *Cold Spring Harb. Perspect. Biol.* 2016, 8, a005900. [CrossRef]
88. Avior, Y.; Bomze, D.; Ramon, O.; Nahmias, Y. Flavonoids as dietary regulators of nuclear receptor activity. *Food Funct.* 2013, 4, 831–844. [CrossRef]
89. Sever, R.; Glass, C.K. Signaling by nuclear receptors. *Cold Spring Harb. Perspect. Biol.* 2013, 5, a016709. [CrossRef]
90. Ouyang, Q.; Zhang, K.; Lin, D.; Feng, C.G.; Cai, Y.; Chen, X. Bazedoxifene Suppresses Intracellular Mycobacterium tuberculosis Growth by Enhancing Autophagy. *mSphere* 2020, 5. [CrossRef]
91. Jang, W.S.; Kim, S.; Podder, B.; Jyoti, M.A.; Nam, K.W.; Lee, B.E.; Song, H.Y. Anti-Mycobacterial Activity of Tamoxifen Against Drug-Resistant and Intra-Macrophage Mycobacterium tuberculosis. *J. Microbiol. Biotechnol.* 2015, 25, 946–950. [CrossRef] [PubMed]
92. Weikum, E.R.; Liu, X.; Ortlund, E.A. The nuclear receptor superfamily: A structural perspective. *Protein Sci.* 2018, 27, 1876–1892. [CrossRef]
93. Collingwood, T.N.; Urnov, F.D.; Wolff, A.P. Nuclear receptors: Coactivators, corepressors and chromatin remodeling in the control of transcription. *J. Mol. Endocrinol.* 1999, 23, 255–275. [CrossRef] [PubMed]
94. Haussler, M.R.; Whitfield, G.K.; Haussler, C.A.; Hsieh, J.C.; Thompson, P.D.; Selznick, S.H.; Dominguez, C.E.; Jurutka, P.W. The nuclear vitamin D receptor: Biological and molecular regulatory properties revealed. *J. Bone Miner. Res.* 1998, 13, 325–349. [CrossRef] [PubMed]
95. Chung, C.; Silwal, P.; Kim, I.; Modlin, R.L.; Jo, E.K. Vitamin D-Cathelicidin Axis: At the Crossroads between Protective Immunity and Pathological Inflammation during Infection. *Immune Netw.* 2020, 20, e12. [CrossRef]
96. Christofides, A.; Konstantinidou, E.; Jani, C.; Boussiotis, V.A. The role of Peroxisome Proliferator-Activated Receptors (PPAR) in immune responses. *Metabolism* 2020. [CrossRef]
97. Wagner, K.D.; Wagner, N. Peroxisome proliferator-activated receptor beta/delta (PPARbeta/delta) acts as regulator of metabolism linked to multiple cellular functions. *Pharmacol. Ther.* 2010, 125, 423–435. [CrossRef]
98. Glaria, E.; Letelier, N.A.; Valledor, A.F. Integrating the roles of liver X receptors in inflammation and infection: Mechanisms and outcomes. *Curr. Opin. Pharmacol.* 2020, 53, 55–65. [CrossRef]
99. Glass, C.K.; Rosenfeld, M.G. The coregulator exchange in transcriptional functions of nuclear receptors. *Genes Dev.* 2000, 14, 121–141.
100. Tremblay, A.M.; Wilson, B.J.; Yang, X.J.; Giguere, V. Phosphorylation-dependent sumoylation regulates estrogen-related receptor-alpha and -gamma transcriptional activity through a synergy control motif. *Mol. Endocrinol.* 2008, 22, 570–584. [CrossRef]
101. Massafra, V.; van Mil, S.W.C. Farnesoid X receptor: A “homeostat” for hepatic nutrient metabolism. *Biochim. Biophys. Acta Mol. Basis Dis.* 2018, 1864, 45–59. [CrossRef] [PubMed]
102. Singh, B.K.; Sinha, R.A.; Ohba, K.; Yen, P.M. Role of thyroid hormone in hepatic gene regulation, chromatin remodeling, and autophagy. *Mol. Cell Endocrinol.* 2017, 458, 160–168. [CrossRef] [PubMed]
103. Basu, J.; Shin, D.M.; Jo, E.K. Mycobacterial signaling through toll-like receptors. *Front. Cell Infect. Microbiol.* 2012, 2, 145. [CrossRef] [PubMed]
104. Weiss, S.T.; Litonjua, A.A. Vitamin D in Host Defense: Implications for Future Research. *Am. J. Respir. Cell Mol. Biol.* 2017, 56, 692–693. [CrossRef] [PubMed]
105. Del Pinto, R.; Ferri, C.; Cominelli, F. Vitamin D Axis in Inflammatory Bowel Diseases: Role, Current Uses and Future Perspectives. *Int. J. Mol. Sci.* 2017, 18, 2360. [CrossRef]

106. Hu, W.; Zhang, L.; Li, M.X.; Shen, J.; Liu, X.D.; Xiao, Z.G.; Wu, D.L.; Ho, I.H.T.; Wu, J.C.Y.; Cheung, C.K.Y.; et al. Vitamin D3 activates the autolysosomal degradation function against Helicobacter pylori through the PDI3 receptor in gastric epithelial cells. *Autophagy* 2019, 15, 707–725. [CrossRef]

107. Yuk, J.M.; Shin, D.M.; Lee, H.M.; Yang, C.S.; Jin, H.S.; Kim, K.K.; Lee, Z.W.; Lee, S.H.; Kim, J.M.; Jo, E.K. Vitamin D3 induces autophagy in human monocytes/macrophages via cathepsin d. *Cell Host Microbe* 2009, 6, 231–243. [CrossRef]

108. Jo, E.K. Innate immunity to mycobacteria: Vitamin D and autophagy. *Cell Microbiol.* 2010, 12, 1026–1035. [CrossRef]

109. Shin, D.M.; Yuk, J.M.; Lee, H.M.; Son, J.W.; Harding, C.V.; Kim, J.M.; Modlin, R.L.; Jo, E.K. Mycobacterial lipoprotein activates autophagy via TLR2/1/CD14 and a functional D receptor signalling. *Cell Microbiol.* 2010, 12, 1648–1665. [CrossRef]

110. Sato, E.; Imafuku, S.; Ishii, K.; Itoh, R.; Chou, B.; Soejima, T.; Nakayama, J.; Hiromatsu, K. Vitamin D-dependent cathelicidin inhibits Mycobacterium marinum infection in human monocyctic cells. *J. Dermatol. Sci.* 2013, 70, 166–172. [CrossRef]

111. Campbell, G.R.; Spector, S.A. Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response and interferon-gamma induce an antimicrobial response against Mycobacterium tuberculosis in human macrophages. *J. Biol. Chem.* 2011, 286, 18890–18902. [CrossRef] [PubMed]

112. Campbell, G.R.; Spector, S.A. Vitamin D inhibits human immunodeficiency virus type 1 and Mycobacterium tuberculosis infection in macrophages through the induction of autophagy. *PLoS Pathog.* 2012, 8, e1002689. [CrossRef] [PubMed]

113. Campbell, G.R.; Spector, S.A. Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response that inhibits human immunodeficiency virus type 1. *PLoS Pathog.* 2012, 8, e1003017. [CrossRef] [PubMed]

114. Wan, M.; Tang, X.; Rekha, R.S.; Muvva, S.; Brighenti, S.; Agerberth, B.; Haeggstrom, J.Z. Prostaglandin E2 suppresses hCAP18/LL-37 expression in human macrophages via EP2/EP4: Implications for treatment of Mycobacterium tuberculosis infection. *FASEB J.* 2018, 32, 2827–2840. [CrossRef] [PubMed]

115. Wahyunitisari, M.R.; Mertaniasih, N.M.; Amin, M.; Artama, W.T.; Koendhori, E.B. Vitamin D, cell death pathways, and tuberculosis. *Int. J. Mycobacteriol* 2017, 6, 349–355. [CrossRef] [PubMed]

116. Rekha, R.S.; Mily, A.; Sultana, T.; Haq, A.; Ahmed, S.; Mostafa Kamal, S.M.; van Schadewijk, A.; Hiemstra, P.S.; Gudmundsson, G.H.; Agerberth, B.; et al. Immune responses in the treatment of drug-sensitive pulmonary tuberculosis with phenylbutyrate and vitamin D3 as host directed therapy. *BMC Infect. Dis.* 2017, 18, 302. [CrossRef] [PubMed]

117. Mily, A.; Rekha, R.S.; Kamal, S.M.; Arifuzzaman, A.S.; Rahim, Z.; Khan, L.; Haq, M.A.; Zaman, K.; Bergman, P.; Brighenti, S.; et al. Significant Effects of Oral Phenylbutyrate and Vitamin D3 Adjunctive Therapy in Pulmonary Tuberculosis: A Randomized Controlled Trial. *PLoS ONE* 2015, 10, e0138340. [CrossRef] [PubMed]

118. Bekele, A.; Gebreselasie, N.; Ashenafi, S.; Kassa, E.; Aseffa, G.; Amogne, W.; Getachew, M.; Aseffa, A.; Worku, A.; Raqib, R.; et al. Daily adjunctive therapy with vitamin D3 and phenylbutyrate supports clinical recovery from pulmonary tuberculosis: A randomized controlled trial in Ethiopia. *J. Intern. Med.* 2018, 284, 292–306. [CrossRef] [PubMed]

119. Wallis, R.S.; Zumla, A. Vitamin D as Adjunctive Host-Directed Therapy in Tuberculosis: A Systematic Review. *Open Forum Infect. Dis.* 2016, 3, ofw151. [CrossRef]

120. Kearns, M.D.; Alvarez, J.A.; Seidel, N.; Tangpricha, V. Impact of vitamin D on infectious disease. *Am. J. Med. Sci.* 2015, 349, 245–262. [CrossRef]

121. Fabri, M.; Stenger, S.; Shin, D.M.; Yuk, J.M.; Liu, P.T.; Realegeno, S.; Lee, H.M.; Krutzik, S.R.; Schenk, M.; Sieling, P.A.; et al. Vitamin D is required for IFN-gamma-mediated antimicrobial activity of human macrophages. *Sci. Transl. Med.* 2011, 3, 104ra102. [CrossRef] [PubMed]

122. Klug-Micu, G.M.; Stenger, S.; Sommer, A.; Liu, P.T.; Krutzik, S.R.; Modlin, R.L.; Fabri, M. CD40 ligand and interferon-gamma induce an antimicrobial response against Mycobacterium tuberculosis in human monocytes. *Immunology* 2013, 139, 121–128. [CrossRef] [PubMed]

123. Gough, M.E.; Graviss, E.A.; May, E.E. The dynamic immunomodulatory effects of vitamin D3 during Mycobacterium infection. *Innate Immun.* 2017, 23, 506–523. [CrossRef] [PubMed]
124. Yang, R.; Yang, E.; Shen, L.; Modlin, R.L.; Shen, H.; Chen, Z.W. IL-12+IL-18 Cosignaling in Human Macrophages and Lung Epithelial Cells Activates Cathelicidin and Autophagy, Inhibiting Intracellular Mycobacterial Growth. *J. Immunol.* 2018, 200, 2405–2417. [CrossRef]

125. Godbole, N.M.; Sinha, R.A.; Tiwari, S.; Pawar, S.D.; Dhole, T.N. Analysis of influenza virus-induced perturbation in autophagic flux and its modulation during Vitamin D3 mediated anti-apoptotic signaling. *Virus Res.* 2020, 282, 197936. [CrossRef]

126. Lu, R.; Shang, M.; Zhang, Y.G.; Jiao, Y.; Xia, Y.; Garrett, S.; Bakke, D.; Bauerl, C.; Martinez, G.P.; Kim, C.H.; et al. Lactic Acid Bacteria Isolated From Korean Kimchi Activate the Vitamin D Receptor-autophagy Signaling Pathways. *Inflamm. Bowel. Dis.* 2020, 26, 1199–1211. [CrossRef]

127. Dai, J.; Liang, Y.; Li, H.; Zhou, W.; Wang, B.; Gong, A.; Zhang, R. Vitamin D enhances resistance to aspergillus fumigatus in mice via inhibition of excessive autophagy. *Am. J. Transl. Res.* 2018, 10, 381–391.

128. Tian, G.; Liang, X.; Chen, D.; Mao, X.; Yu, J.; Zheng, P.; He, J.; Huang, Z.; Yu, B. Vitamin D3 supplementation alleviates rotaviruses infection in pigs and IPEC-J2 cells via regulating the autophagy signaling pathway. *J. Steroid Biochem. Mol. Biol* 2016, 163, 157–163. [CrossRef]

129. Wei, Y.; Huang, J. Role of estrogen and its receptors mediated-autophagy in cell fate and human diseases. *J. Steroid Biochem. Mol. Biol.* 2019, 191, 105380. [CrossRef]

130. Lipovka, Y.; Konhilas, J.P. The complex nature of oestrogen signalling in breast cancer: Enemy or ally? *Biosci. Rep.* 2016, 36. [CrossRef]

131. Fan, D.; Liu, S.Y.; van Hasselt, C.A.; Vlantis, A.C.; Ng, E.K.; Zhang, H.; Dong, Y.; Ng, S.K.; Chu, R.; Chan, A.B.; et al. Estrogen receptor alpha induces prosurvival autophagy in papillary thyroid cancer via stimulating reactive oxygen species and extracellular signal regulated kinases. *J. Clin. Endocrinol. Metab.* 2015, 100, E561–E571. [CrossRef] [PubMed]

132. Selyunin, A.S.; Hutchens, S.; McHardy, S.F.; Mukhopadhyay, S. Tamoxifen blocks retrograde trafficking of Shiga toxin 1 and 2 and protects against lethal toxicosis. *Life Sci. Alliance* 2019, 2. [CrossRef] [PubMed]

133. Dittmar, A.J.; Drozda, A.A.; Blader, I.J. Drug Repurposing Screening Identifies Novel Compounds That Downregulate Type I Interferon Induction by Inhibiting TBK1-IRF3 Interaction. *J. Immunol.* 2017, 201, E5706–E5715. [CrossRef] [PubMed]

134. Chung, M.T.; Lee, Y.M.; Shen, H.H.; Cheng, P.Y.; Huang, Y.C.; Lin, Y.J.; Huang, Y.Y.; Lam, K.K. Activation of Autophagy by a Small Molecule Inverse Agonist of Estrogen-related Receptors. *J. Immunol.* 2019, 202, 1637–1649. [CrossRef] [PubMed]

135. Giguere, V. Transcriptional control of energy homeostasis by the estrogen-related receptors. *Biosci. Rep.* 2008, 28, 677–696. [CrossRef] [PubMed]

136. Huss, J.M.; Garbazc, W.G.; Xie, W. Constitutive activities of estrogen-related receptors: Transcriptional regulation of metabolism by the ERR pathways in health and disease. *Biochim. Biophys. Acta* 2015, 1852, 1912–1927. [CrossRef]

137. Audet-Walsh, E.; Giguere, V. The multiple universes of estrogen-related receptor alpha and gamma in metabolic control and related diseases. *Acta Pharmacol. Sin.* 2015, 36, 51–61. [CrossRef]

138. Singh, B.K.; Sinha, R.A.; Tripathi, M.; Mendoza, A.; Ohba, K.; Sy, J.A.C.; Xie, S.Y.; Zhou, J.; Ho, J.P.; Chang, C.Y.; et al. Thyroid hormone receptor and ERRalpha coordinately regulate mitochondrial fission, mitophagy, metabolic control and related diseases. *Acta Pharmacol. Sin.* 2018, 39, 157–163. [CrossRef]

139. Suresh, S.N.; Chavalmane, A.K.; Pillai, M.; Ammanathan, V.; Vidyaladhara, D.J.; Yarreipangh, H.; Rai, S.; Paul, A.; Clement, J.P.; Alladi, P.A.; et al. Modulation of Autophagy by a Small Molecule Inverse Agonist of ERRalpha Is Neuroprotective. *Front. Mol. Neurosci.* 2018, 11, 109. [CrossRef]

140. Sonoda, J.; Laganiere, J.; Meh, I.R.; Barish, G.D.; Chong, L.W.; Li, X.; Scheffler, I.E.; Mock, D.C.; Bataille, A.R.; Robert, F.; et al. Nuclear receptor ERR alpha and coactivator PGC-1 beta are effectors of IFN-gamma-induced host defense. *Genes Dev.* 2007, 21, 1909–1920. [CrossRef]

141. Hwang, J.; Purdy, J.G.; Wu, K.; Rabinowitz, J.D.; Shenk, T. Estrogen-related receptor alpha is required for efficient human cytomegalovirus replication. *Proc. Natl. Acad. Sci. USA* 2014, 111, E5706–E5715. [CrossRef] [PubMed]

142. He, X.; Ma, S.; Tian, Y.; Wei, C.; Zhu, Y.; Li, F.; Zhang, P.; Wang, P.; Zhang, Y.; Zhong, H. ERRalpha negatively regulates type I interferon induction by inhibiting TBK1-IRF3 interaction. *PLoS Pathog.* 2017, 13, e1006347. [CrossRef]
143. Liu, Z.Q.; Lee, J.N.; Son, M.; Lim, J.Y.; Dutta, R.K.; Maharjan, Y.; Kwak, S.; Oh, G.T.; Byun, K.; Choe, S.K.; et al. Ciliogenesis is reciprocally regulated by PPARα and NR1H4/FXR through controlling autophagy in vitro and in vivo. *Autophagy* 2018, 14, 1011–1027. [CrossRef] [PubMed]

144. Jiao, M.; Ren, F.; Zhou, L.; Zhang, X.; Zhang, L.; Wen, T.; Wei, L.; Wang, X.; Shi, H.; Bai, L.; et al. Peroxisome proliferator-activated receptor alpha activation attenuates the inflammatory response to protect the liver from acute failure by promoting the autophagy pathway. *Cell Death Dis.* 2014, 5, e1397. [CrossRef] [PubMed]

145. Zhou, Y.; Chen, X.; Qu, N.; Zhang, B.; Xia, C. Chondroprotection of PPARalpha activation by WY14643 via autophagy involving Akt and ERK in LPS-treated mouse chondrocytes and osteoarthritis model. *J. Cell Mol. Med.* 2019, 23, 2782–2793. [CrossRef]

146. Saito, T.; Kuma, A.; Sugiura, Y.; Ichimura, Y.; Obata, M.; Kitamura, H.; Okuda, S.; Lee, H.C.; Ikeda, K.; Kanegae, Y.; et al. Autophagy regulates lipid metabolism through selective turnover of NCoR1. *Nat. Commun.* 2019, 10, 1567. [CrossRef]

147. Visvikis, O.; Ihuegbu, N.; Labed, S.A.; Luhachack, L.G.; Alves, A.F.; Wollenberg, A.C.; Stuart, L.M.; Stormo, G.D.; Irazoqui, J.E. Innate host defense requires TFEB-mediated transcription of cytoprotective and antimicrobial genes. *Immunity* 2014, 40, 896–909. [CrossRef]

148. Chandra, S.; Roy, A.; Patel, D.R.; Pahan, K. PPARalpha Between Aspirin and Plaque Clearance. *J. Alzheimers Dis.* 2019, 71, 389–397. [CrossRef]

149. Chandra, S.; Roy, A.; Jana, M.; Pahan, K. Cinnamic acid activates PPARalpha to stimulate Lysosomal biogenesis and lower Amyloid plaque pathology in an Alzheimer’s disease mouse model. *Neurobiol. Dis.* 2019, 124, 379–395. [CrossRef]

150. Chandra, S.; Jana, M.; Pahan, K. Aspirin Induces Lysosomal Biogenesis and Attenuates Amyloid Plaque Pathology in a Mouse Model of Alzheimer’s Disease via PPARalpha. *J. Neurosci.* 2018, 38, 6682–6699. [CrossRef]

151. Ghosh, A.; Jana, M.; Modi, K.; Gonzalez, F.J.; Sims, K.B.; Berry-Kravis, E.; Pahan, K. Activation of peroxisome proliferator-activated receptor alpha induces lysosomal biogenesis in brain cells: Implications for lysosomal storage disorders. *J. Biol. Chem.* 2015, 290, 10309–10324. [CrossRef] [PubMed]

152. Sharma, V.; Makhdoomi, M.; Singh, L.; Kumar, P.; Khan, N.; Singh, S.; Verma, H.N.; Luthra, K.; Sarkar, S.; Kumar, D. Trehalose limits opportunistic mycobacterial survival during HIV co-infection by reversing HIV-mediated autophagy block. *Autophagy* 2020. [CrossRef] [PubMed]

153. Rusmini, P.; Cortese, K.; Crippa, V.; Cristofani, R.; Cicardi, M.E.; Ferrari, V.; Vezzoli, G.; Tedesco, B.; Meroni, M.; Messi, E.; et al. Trehalose induces autophagy via lysosomal-mediated TFEB activation in models of motoneuron degeneration. *Autophagy* 2019, 15, 631–651. [CrossRef] [PubMed]

154. Khan, S.H.; Jasuja, R.; Kumar, R. Trehalose induces functionally active conformation in the intrinsically disordered N-terminal domain of glucocorticoid receptor. *J. Biol. Mol. Struct. Dyn.* 2017, 35, 2248–2256. [CrossRef]

155. Palomer, X.; Capdevila-Busquets, E.; Bottero, G.; Salvado, L.; Barroso, E.; Davidson, M.M.; Michalik, L.; Wahl, W.; Vazquez-Carrera, M. PPARbeta/delta attenuates palmitate-induced endoplasmic reticulum stress and induces autophagic markers in human cardiac cells. *Int. J. Cardiol.* 2014, 174, 110–118. [CrossRef]

156. Busch, D.; Kapoor, A.; Rademann, P.; Hildebrand, F.; Bahrami, S.; Thiemermann, C.; Osuchowski, M.F. Delayed activation of PPAR-beta/delta improves long-term survival in mouse sepsis: Effects on organ inflammation and coagulation. *Innate Immun.* 2018, 24, 262–273. [CrossRef]

157. Kapoor, A.; Shintani, Y.; Collino, M.; Osuchowski, M.F.; Busch, D.; Patel, N.S.; Sepodes, B.; Castiglia, S.; Fantozzi, R.; Bishop-Bailey, D.; et al. Protective role of peroxisome proliferator-activated receptor-beta/delta in septic shock. *Am. J. Respir. Crit. Care Med.* 2010, 182, 1506–1515. [CrossRef]

158. Kim, T.H.; Kim, H.K.; Hwang, E.S. Novel anti-adipogenic activity of anti-malarial amodiaquine through suppression of PPARgamma activity. *Arch. Pharm. Res.* 2017, 40, 1336–1343. [CrossRef]

159. Penas, F.N.; Carta, D.; Cevey, A.C.; Rada, M.J.; Pierzalisi, A.V.; Ferlin, M.G.; Sales, M.E.; Mirkin, G.A.; Goren, N.B. Pyridinecarboxylic Acid Derivative Stimulates Pro-Angiogenic Mediators by P13K/AKT/mTOR and Inhibits Reactive Nitrogen and Oxygen Species and NF-kappaB Activation Through a PPARgamma-Dependent Pathway in T. cruzi-Infected Macrophages. *Front. Immunol.* 2019, 10, 2955. [CrossRef]

160. Omeragic, A.; Saikali, M.F.; Currier, S.; Volsky, D.J.; Cummins, C.L.; Bendayan, R. Selective peroxisome proliferator-activated receptor-gamma modulator, INT131 exhibits anti-inflammatory effects in an EcoHIV mouse model. *FASEB J.* 2020, 34, 1996–2010. [CrossRef]
161. Raghuram, S.; Stayrrook, K.R.; Huang, P.; Rogers, P.M.; Nosie, A.K.; McClure, D.B.; Burris, L.L.; Khorasanizadeh, S.; Burris, T.P.; Rastinejad, F. Identification of heme as the ligand for the orphan nuclear receptors REV-ERBalpha and REV-ERBbeta. Nat. Struct. Mol. Biol. 2007, 14, 1207–1213. [CrossRef]

162. Pastore, N.; Vainshtein, A.; Herz, N.J.; Huynh, T.; Brunetti, L.; Klisch, T.J.; Mutarelli, M.; Annunziata, P.; Kinouchi, K.; Brunetti-Pierri, N.; et al. Nutrient-sensitive transcription factors TFEB and TFE3 couple autophagy and metabolism to the peripheral clock. EMBO J. 2019, 38. [CrossRef] [PubMed]

163. Sulli, G.; Rommel, A.; Wang, X.; Kolar, M.J.; Puca, F.; Saghatelian, A.; Plikus, M.V.; Verma, I.M.; Panda, S. Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. Nature 2018, 553, 351–355. [CrossRef] [PubMed]

164. Huang, G.; Zhang, F.; Ye, Q.; Wang, H. The circadian clock regulates autophagy directly through the nuclear hormone receptor Nr1D1/Rev-erbalpha and indirectly via Cebpb/C/ebpbeta in zebrafish. Autophagy 2016, 12, 1292–1309. [CrossRef] [PubMed]

165. Chandra, V.; Bhagyaraj, E.; Nanduri, R.; Ahuja, N.; Gupta, P. NR1D1 ameliorates Mycobacterium tuberculosis clearance through regulation of autophagy. Autophagy 2015, 11, 1987–1997. [CrossRef] [PubMed]

166. De Mei, C.; Ercolani, L.; Parodi, C.; Veronesi, M.; Lo Vecchio, C.; Bottegoni, G.; Torrente, E.; Scarpelli, R.; Marotta, R.; Ruffilli, R.; et al. Dual inhibition of REV-ERBbeta and autophagy as a novel pharmacological approach to induce cytotoxicity in cancer cells. Oncogene 2015, 34, 2597–2608. [CrossRef]

167. Woldt, E.; Sebiti, Y.; Solt, L.A.; Duhem, C.; Lancel, S.; Eckkhoute, J.; Hesselink, M.K.; Paquet, C.; Delhaye, S.; Shin, Y.; et al. Rev-erb-alpha modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. Nat. Med. 2013, 19, 1039–1046. [CrossRef]

168. Costantini, C.; Renga, G.; Sellitto, F.; Borghi, M.; Stincardini, C.; Pariano, M.; Zelante, T.; Chiarotti, F.; Bartoli, A.; Mosci, P.; et al. Microbes in the Era of Circadian Medicine. Front. Cell Infect. Microbiol. 2020, 10, 30. [CrossRef]

169. Tognini, P.; Thaiss, C.A.; Elinav, E.; Sassone-Corsi, P. Circadian Coordination of Antimicrobial Responses. Cell Host Microbe 2017, 22, 185–192. [CrossRef]

170. Man, K.; Loudon, A.; Chawla, A. Immunity around the clock. Science 2016, 354, 999–1003. [CrossRef]

171. Isakson, P.; Bjoras, M.; Egbada, O.S.; Simonsen, A. Autophagy contributes to therapy-induced degradation of the PML-RARA oncoprotein. Blood 2010, 116, 2324–2331. [CrossRef] [PubMed]

172. Zeng, C.W.; Chen, Z.H.; Zhang, X.J.; Han, B.W.; Lin, K.Y.; Li, X.J.; Wei, P.P.; Zhang, H.; Li, Y.; Chen, Y.Q. MIR125B1 represses the degradation of the PML-RARA oncoprotein by an autophagy-lysosomal pathway in acute promyelocytic leukemia. Autophagy 2014, 10, 1726–1737. [CrossRef] [PubMed]

173. Eriksen, A.B.; Torgersen, M.L.; Holm, K.L.; Abrahamsen, G.; Spurkland, A.; Moskaug, J.O.; Simonsen, A.; Blomhoff, H.K. Retinoic acid-induced IgG production in TLR-activated human primary B cells involves ULK1-mediated autophagy. Autophagy 2015, 11, 460–471. [CrossRef] [PubMed]

174. Chen, Z.H.; Wang, W.T.; Huang, W.; Fang, K.; Sun, Y.M.; Liu, S.R.; Luo, X.Q.; Chen, Y.Q. The IncRNA HOTAIRM1 regulates the degradation of PML-RARA oncoprotein and myeloid cell differentiation by enhancing the autophagy pathway. Cell Death Differ. 2017, 24, 212–224. [CrossRef]

175. Brigger, D.; Schlafi, A.M.; Garattini, E.; Tschan, M.P. Activation of RARalpha induces autophagy in SKBR3 breast cancer cells and depletion of key autophagy genes enhances ATRA toxicity. Cell Death Dis. 2015, 6, e1861. [CrossRef]

176. Marchwicka, A.; Cebrat, M.; Laszkiewicz, A.; Slizewskis, L.; Brown, G.; Marcinkowska, E. Regulation of vitamin D receptor expression by retinoic acid receptor alpha in acute myeloid leukemia cells. J. Steroid Biochem. Mol. Biol. 2016, 159, 121–130. [CrossRef] [PubMed]

177. Johnson, J.S.; De Veaux, N.; Rives, A.W.; Lahaye, X.; Lucas, S.Y.; Perot, B.P.; Luka, M.; Garcia-Paredes, V.; Amon, L.M.; Watters, A.; et al. A Comprehensive Map of the Monocyte-Derived Dendritic Cell Transcriptional Network Engaged upon Innate Sensing of HIV. Cell Rep. 2020, 30, 914–931 e919. [CrossRef] [PubMed]

178. Gutierrez, J.; Garcia-Villa, E.; Ocadiz-Delgado, R.; Cortes-Malagon, E.M.; Vazquez, J.; Roman-Rosales, A.; Alvarez-Rios, E.; Celik, H.; Romano, M.C.; Uren, A.; et al. Human papillomavirus type 16 E7 oncoprotein upregulates the retinoic acid receptor-beta expression in cervical cancer cell lines and K14E7 transgenic mice. Mol. Cell Biochem. 2015, 408, 261–272. [CrossRef] [PubMed]

179. Wang, X.; Zhang, Q.; Zhou, Z.; Liu, M.; Chen, Y.; Li, J.; Xu, L.; Guo, J.; Li, Q.; Yang, J.; et al. Retinoic acid receptor beta, a potential therapeutic target in the inhibition of adenovirus replication. Antiviral Res. 2018, 152, 84–93. [CrossRef]
180. Fan, J.; Lv, Z.; Yang, G.; Liao, T.T.; Xu, J.; Wu, F.; Huang, Q.; Guo, M.; Hu, G.; Zhou, M.; et al. Retinoic Acid Receptor-Related Orphan Receptors: Critical Roles in Tumorigenesis. *Front. Immunol.* **2018**, *9*, 1187. [CrossRef] [PubMed]

181. Jetten, A.M. Retinoid-related orphan receptors (RORs): Critical roles in development, immunity, circadian rhythm, and cellular metabolism. *Nucl. Recept. Signal.* **2009**, *7*, e003. [CrossRef] [PubMed]

182. Friesenhagen, J.; Viemann, D.; Borgeling, Y.; Schmolke, M.; Spiekermann, C.; Kirschnek, S.; Ludwig, S.; Roth, J. Highly pathogenic influenza viruses inhibit inflammatory response in monocytes via activation of rar-related orphan receptor RORalpha. *J. Innate Immun.* **2013**, *5*, 505–518. [CrossRef] [PubMed]

183. He, B.; Zhao, Y.; Xu, L.; Gao, L.; Su, Y.; Lin, N.; Pu, J. The nuclear melatonin receptor RORalpha is a novel endogenous defender against myocardial ischemia/reperfusion injury. *J. Pineal Res.* **2016**, *60*, 313–326. [CrossRef] [PubMed]

184. Zhao, Y.; Xu, L.; Ding, S.; Lin, N.; Ji, Q.; Gao, L.; Su, Y.; He, B.; Pu, J. The nuclear melatonin receptor RORalpha is a novel endogenous defender against myocardial ischemia/reperfusion injury. *J. Pineal Res.* **2016**, *60*, 313–326. [CrossRef] [PubMed]

185. Mirza-Aghazadeh-Attari, M.; Mohammadzadeh, A.; Adib, A.; Darband, S.G.; Sadighparvar, S.; Mihanfar, A.; Majidinia, M.; Yousefi, B. Melatonin-mediated regulation of autophagy: Making sense of double-edged sword in cancer. *J. Cell Physiol.* **2019**, *234*, 17011–17022. [CrossRef]

186. Boga, J.A.; Caballero, B.; Potes, Y.; Perez-Martinez, Z.; Reiter, R.J.; Vega-Naredo, I.; Coto-Montes, A. Therapeutic potential of melatonin related to its role as an autophagy regulator: A review. *J. Pineal Res.* **2019**, *66*, e12534. [CrossRef]

187. Brazao, V.; Santello, F.H.; Colato, R.P.; do Prado, J.C., Jr. *T. cruzi* infection among aged rats: Melatonin as a promising therapeutic molecule. *Exp. Gerontol.* **2020**, *133*, 110922. [CrossRef]

188. Daryani, A.; Montazeri, M.; Pagheh, A.S.; Sharif, M.; Sarvi, S.; Hosseinzadeh, A.; Reiter, R.J.; Hadighi, R.; Joghataei, M.T.; Ghaznavi, H.; et al. The potential use of melatonin to treat protozoan parasitic infections: A review. *Biomed. Pharmacother.* **2018**, *97*, 948–957. [CrossRef]

189. Hu, W.; Deng, C.; Ma, Z.; Wang, D.; Fan, C.; Li, T.; Di, S.; Gong, B.; Reiter, R.J.; Yang, Y. Utilizing melatonin to combat bacterial infections and septic injury. *Br. J. Pharmacol.* **2017**, *174*, 754–768. [CrossRef]

190. Vielma, J.R.; Bonilla, E.; Chacin-Bonilla, L.; Mora, M.; Medina-Leendertz, S.; Bravo, Y. Effects of melatonin on oxidative stress, and resistance to bacterial, parasitic, and viral infections: A review. *Acta Trop.* **2014**, *137*, 31–38. [CrossRef]

191. Anderson, G.; Reiter, R.J. Melatonin: Roles in influenza, Covid-19, and other viral infections. *Rev. Med. Virol.* **2020**, *30*, e2109. [CrossRef] [PubMed]

192. Yan, G.; Lei, H.; He, M.; Gong, R.; Wang, Y.; He, X.; Li, G.; Pang, P.; Li, X.; Yu, S.; et al. Melatonin triggers autophagic cell death by regulating RORC in Hodgkin lymphoma. *Biomed. Pharmacother.* **2020**, *123*, 109811. [CrossRef] [PubMed]

193. Preidis, G.A.; Kim, K.H.; Moore, D.D. Nutrient-sensing nuclear receptors PPARalpha and FXR control liver energy balance. *J. Clin. Investig.* **2017**, *127*, 1193–1201. [CrossRef] [PubMed]

194. Panzitt, K.; Jungwirth, E.; Krones, E.; Lee, J.M.; Pollheimer, M.; Thallinger, G.G.; Kolb-Lenz, D.; Xiao, R.; Thorell, A.; Trauner, M.; et al. FXR-dependent Rubicon induction impairs autophagy in models of human cholestasis. *J. Hepatol.* **2020**, *72*, 1122–1131. [CrossRef] [PubMed]

195. Khambu, B.; Li, T.; Yan, S.; Yu, C.; Chen, X.; Goheen, M.; Li, Y.; Lin, J.; Cummings, O.W.; Lee, Y.A.; et al. Hepatic Autophagy Deficiency Compromises Farnesoid X Receptor Functionality and Causes Cholestatic Injury. *Hepatology* **2019**, *69*, 2196–2213. [CrossRef]

196. Endo-Umeda, K.; Makishima, M. Liver X Receptors Regulate Cholesterol Metabolism and Immunity in Hepatic Nonparenchymal Cells. *Int. J. Mol. Sci.* **2019**, *20*, 5045. [CrossRef]

197. Liu, Y.; Qiu, D.K.; Ma, X. Liver X receptors bridge hepatic lipid metabolism and inflammation. *J. Dig. Dis.* **2012**, *13*, 69–74. [CrossRef]

198. Zeng, J.; Wu, D.; Hu, H.; Young, J.A.T.; Yan, Z.; Gao, L. Activation of the liver X receptor pathway inhibits HBV replication in primary human hepatocytes. *Hepatology* **2020**. [CrossRef]

199. Lange, P.T.; Jondle, C.N.; Darrah, E.J.; Johnson, K.E.; Tarakanova, V.L. LXR Alpha Resticts Gammaherpesvirus Reactivation from Latently Infected Peritoneal Cells. *J. Virol.* **2019**, *93*. [CrossRef]
200. Liu, Y.; Wei, Z.; Zhang, Y.; Ma, X.; Chen, Y.; Yu, M.; Ma, C.; Li, X.; Cao, Y.; Liu, J.; et al. Activation of liver X receptor plays a central role in antiviral actions of 25-hydroxycholesterol. *J. Lipid Res.* 2018, 59, 2287–2296. [CrossRef]

201. Ahsan, F.; Maertzdorf, J.; Gublich-Bornhof, U.; Kaufmann, S.H.E.; Moura-Alves, P. IL-36/LXR axis modulates cholesterol metabolism and immune defense to *Mycobacterium tuberculosis*. *Sci. Rep.* 2018, 8, 1520. [CrossRef] [PubMed]

202. Matalonga, J.; Glaria, E.; Bresque, M.; Escande, C.; Carbo, J.M.; Kiefer, K.; Vicente, R.; Leon, T.E.; Beceiro, S.; Pascual-Garcia, M.; et al. The Nuclear Receptor LXR Limits Bacterial Infection of Host Macrophages through a Mechanism that Impacts Cellular NAD Metabolism. *Cell Rep.* 2017, 18, 1241–1255. [CrossRef] [PubMed]

203. Silvente-Poirot, S.; Segala, G.; Poiriot, M.C.; Poiriot, M. Ligand-dependent transcriptional induction of lethal autophagy: A new perspective for cancer treatment. *Autophagy* 2018, 14, 555–557. [CrossRef]

204. Segala, G.; David, M.; de Medina, P.; Poiriot, M.C.; Serhan, N.; Vergez, F.; Mougel, A.; Saland, E.; Carayon, K.; Leignadier, J.; et al. Dendrogenin A drives LXR to trigger lethal autophagy in cancers. *Nat. Commun.* 2017, 8, 1903. [CrossRef] [PubMed]

205. Sinha, R.A.; Bay, B.H.; Zhou, J.; Wu, Y.; Farah, B.L.; Ohba, K.; Lesmana, R.; Gooding, J.; Yen, P.M. Thyroid hormone induction of mitochondrial activity is coupled to mitophagy via ROS-AMPK-ULK1 signaling. *Autophagy* 2015, 11, 1341–1357. [CrossRef]

206. Cioffi, F.; Senese, R.; Lanni, A.; Goglia, F. Thyroid hormones and mitochondria: With a brief look at derivatives and analogues. *Mol. Cell Endocrinol.* 2013, 379, 51–61. [CrossRef]

207. Sinha, R.A.; You, S.H.; Zhou, J.; Siddique, M.M.; Bay, B.H.; Zhu, X.; Privalsky, M.L.; Cheng, S.Y.; Stevens, R.D.; Summers, S.A.; et al. Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. *J. Clin. Investig.* 2012, 122, 2428–2438. [CrossRef]

208. Tseng, Y.H.; Ke, P.Y.; Liao, C.J.; Wu, S.M.; Chi, H.C.; Tsai, C.Y.; Chen, C.Y.; Lin, Y.H.; Lin, K.H. Chromosome 19 open reading frame 80 is upregulated by thyroid hormone and modulates autophagy and lipid metabolism. *Autophagy* 2014, 10, 20–31. [CrossRef]

209. Chi, H.C.; Chen, S.L.; Lin, S.L.; Tsai, C.Y.; Chuang, W.Y.; Lin, Y.H.; Huang, Y.H.; Tsai, M.M.; Yeh, C.T.; Lin, K.H. Thyroid hormone protects hepatocytes from HBx-induced carcinogenesis by enhancing mitochondrial turnover. *Oncogene* 2017, 36, 5274–5284. [CrossRef]

210. Tao, S.; Drexler, I. Targeting Autophagy in Innate Immune Cells: Angel or Demon during Infection and Vaccination? *Front. Immunol.* 2020, 11, 460. [CrossRef]

211. Felzen, V.; Hiebel, C.; Koziolek-Drechsler, I.; Reissig, S.; Wolfrum, U.; Kogel, D.; Brandts, C.; Behl, C.; Morawe, T. Estrogen receptor alpha regulates non-canonical autophagy that provides stress resistance to neuroblastoma and breast cancer cells and involves BAG3 function. *Cell Death Dis.* 2015, 6, e1812. [CrossRef] [PubMed]

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