

Review

NR4A Receptors in Immunity: Bridging Neuroendocrine and Inflammatory Pathways

Simone Lemes Ferreira ¹  and Natalia Santucci ^{1,2,*}¹ Instituto de Inmunología Clínica y Experimental de Rosario (IDICER-CONICET-UNR), Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Rosario S2000, Argentina; ferreiralemes@idicer-conicet.gob.ar² Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Rosario S2000, Argentina

* Correspondence: santucci@idicer-conicet.gob.ar

Abstract

Nuclear receptors (NRs) are ligand-activated transcription factors that mediate diverse cellular processes, including signalling, survival, proliferation, immune response and metabolism, through both genomic and non-genomic mechanisms in response to hormones and metabolic ligands. Given their central role in inter-organ, tissue, and cellular communication, NRs are critical for maintaining homeostasis and have become a major focus in biomedical research and drug discovery due to their association with numerous diseases. Among NRs, the NR4A subfamily (NR4A1/Nur77, NR4A2/Nurr1, and NR4A3/Nor1) responds to various stimuli—such as insulin, growth factors, inflammatory cytokines, and β -adrenergic signals—though their endogenous ligands remain unidentified. Their expression is tissue-dependent, particularly in energy-demanding tissues, where they modulate leukocyte function and promote an anti-inflammatory profile. Like other NRs, NR4As regulate acute and chronic inflammation by suppressing pro-inflammatory transcription factors (e.g., NF- κ B) or enhancing their inhibitors, thereby polarising macrophages toward an anti-inflammatory phenotype. This review summarises current knowledge on the role of NR4A receptors in immune responses. Given their well-documented involvement in autoimmune diseases, inflammatory conditions, and cancer, elucidating their contributions to neuro-immune-endocrine crosstalk may uncover their therapeutic potential for immunopathological disorders.

Keywords: nuclear receptors; NR4A subfamily; NR4A1/Nur77/NBF1B; NR4A2/Nurr1; NR4A3/Nor1; immune response



Academic Editors: Ferenc A. Antoni and Stephen H. Safe

Received: 9 July 2025

Revised: 15 September 2025

Accepted: 18 December 2025

Published: 25 December 2025

Copyright: © 2025 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Nuclear receptors (NRs) are ligand-activated transcription factors that mediate diverse cellular processes, including signalling, survival, proliferation, immune response and metabolism, through both genomic and non-genomic mechanisms in response to hormones and metabolic ligands [1]. Essential for inter-organ, tissue, and cellular communication, NRs maintain homeostasis and are key targets in biomedical research due to their dysregulation in numerous diseases [2].

The NRs superfamily is classified into six subfamilies based on evolutionary sequence conservation. Structurally, NRs comprise four functional domains:

1. The variable N-terminal A/B domain, which contains the activation function-1 (AF-1) region and mediates interactions with coactivators and corepressors.

2. The highly conserved central C domain, housing the DNA-binding domain (DBD) for gene regulation via homo-/heterodimers or monomers.
3. The flexible hinge D domain, connecting the DBD to the ligand-binding domain (LBD) and facilitating LBD rotation; it also contains a nuclear localisation signal (NLS).
4. The C-terminal E domain, which includes the LBD and AF-2 region; ligand binding here induces conformational changes for cofactor recruitment [3,4].

The importance of NRs lies in their orchestration of developmental and homeostatic processes that modulate gene networks across cell types, thereby maintaining organ-specific functions. In disease, their transcriptional activity is often amplified in compensatory responses, underscoring their dual roles in physiology and disease [1]. Stromal and immune cells use NRs—regulated by lipophilic ligands (e.g., steroids, retinoids, phospholipids)—to fine-tune immune function via DNA binding, co-regulator recruitment, and chromatin remodelling [5]. NR dysregulation is thus linked to cancer, autoimmunity, and chronic inflammation [6].

While some NRs—e.g., glucocorticoid receptor (GR), retinoic acid receptor (RAR), and vitamin D receptor (VDR)—are well-established therapeutic targets, others like the NR4A subfamily (NR4A1/Nur77, NR4A2/Nurr1, NR4A3/Nor1) [7–9] are emerging as important players. Associated with the nervous system, they are now known to modulate immune homeostasis and inflammation context-dependently, responding to cytokines, peptide hormones, growth factors and cellular stress and acting through both genomic transcriptional programs and non-genomic actions to reshape inflammatory signalling [10].

Current understanding of the NR4A receptors establishes that they are induced by hormonal and metabolic signals, thereby acting as molecular bridges that translate endocrine conditions into transcriptional programs within immune cells [11]. By directly regulating key inflammatory transcription factors, such as NF- κ B, and modulating metabolic genes, NR4As integrate neuroendocrine cues with innate immune pathways to fine-tune inflammatory responses and maintain tissue homeostasis. This review aims to summarise the current knowledge on these receptors, with a specific focus on their immunoregulatory functions and their emerging therapeutic potential.

2. General Characteristics of NR4A Subfamily

The NR4A subfamily comprises three transcription factors—NR4A1 (Nur77), NR4A2 (Nurr1), and NR4A3 (Nor1)—within the 48-member nuclear receptor superfamily. They share the characteristic NR modular structure, with a ligand-independent AF-1 region, a central DBD, and a C-terminal LBD containing the AF-2 region. While structurally similar, the N-terminal domain shows only 26–28% sequence homology among NR4A members, yet it is critical for transcriptional regulation, post-translational modifications, and functional diversification [10,12,13].

NR4A receptors bind DNA as monomers to NGFI-B response elements (NBRE; AAAG-GTCA) or as homodimers/heterodimers with RXRs to Nur response elements (NuRE; ER6: TGATATTN₆AAATGCCA) or DR5 elements [14,15]. Despite their structural similarities, each members exhibit cofactor and response element preferences, contributing to their functional diversity [16]. Initially linked to the nervous system function, NR4A receptors are now known to be widely expressed and regulate proliferation, apoptosis, and metabolism in a tissue-specific manner [13].

NR4As are immediate early genes, induced rapidly by diverse stimuli, including T-cell receptor activation, cellular stress, GPCR signalling, and cAMP pathways [17,18]. Classified as orphan receptors, no endogenous ligands have been definitively identified. Their LBDs feature a collapsed orthosteric pocket obstructed by hydrophobic residues, hindering conventional ligand binding [19]. According to current models, activity is

primarily regulated via post-translational modifications, protein–protein interactions, and cellular localisation [20,21]. However, emerging evidence suggests the LBD may adopt alternative conformations that bind unsaturated fatty acids, prostaglandins, and dopamine metabolites, though the physiological relevance remains unclear [22].

In immune cells, NR4A receptors modulate Nuclear Factor κ B (NF- κ B) activity, particularly in myeloid cells. NR4A receptors generally suppress this pathway at several levels, with their loss contributing to hyperinflammatory responses [10]. In lymphoid cells, they are rapidly upregulated by B- and T-cell receptor signalling [23–25], inflammatory cytokines, and stress [11,26–28]. During thymocyte development, they promote apoptosis of self-reactive T-cells [26,29]. In mature T-cells, they influence effector differentiation—including Th1, Th17, and regulatory T-cell (Treg) functions [30–33]—and NR4A1 prevents exhaustion in chronic CD8⁺ T-cell responses [34] while enhancing Treg suppression [26]. In B-cells, NR4A receptors regulate survival, proliferation, and antibody production, with dysregulation linked to autoimmunity and lymphoproliferative disorders [35].

The diverse, context-dependent functions of NR4A receptors highlight their potential as therapeutic targets for immune-related diseases. The following sections will explore these roles in greater detail, focusing on their contributions to myeloid and lymphoid cell function.

3. NR4A Receptors in Myeloid Cells

Myeloid cells—including monocytes, macrophages, dendritic cells (DCs), and granulocytes—play central roles in innate immunity and inflammation. These cells patrol tissues for pathogens and damage, responding through phagocytosis, cytokine/chemokine secretion, and antigen presentation to bridge innate and adaptive immunity. Myeloid cells exhibit remarkable plasticity, adopting either pro-inflammatory (e.g., M1 macrophages) or anti-inflammatory (e.g., M2 macrophages, tolerogenic DCs) phenotypes depending on microenvironmental cues. Dysregulation of myeloid function contributes to various diseases, from atherosclerosis to cancer, where aberrant cytokine production or immunosuppressive behaviour can either exacerbate pathology or hinder therapy. NR4A1–3 nuclear receptors are well-established as key regulators of myeloid cell differentiation, metabolic reprogramming, and effector functions. Their critical roles in macrophages and dendritic cells make them attractive therapeutic targets, while their functions in neutrophils and mast cells are still under investigation [18]. The main functions described for NR4A receptors in myeloid cells are summarised in Figure 1.

3.1. Macrophages

Macrophages serve as crucial sentinels of the innate immune system, responding to infection or injury by producing effector molecules like nitric oxide (NO) and pro-inflammatory cytokines. The robust inflammatory response of classically activated (M1) macrophages is supported by profound metabolic reprogramming that fuels their antimicrobial functions [36]. NR4A receptors are potently induced by various inflammatory stimuli, including cytokines, TLR ligands, and oxidised lipids, suggesting their involvement in macrophage inflammatory responses. The NF- κ B signalling pathway appears to be a principal regulator of inducible NR4A expression in these cells [18].

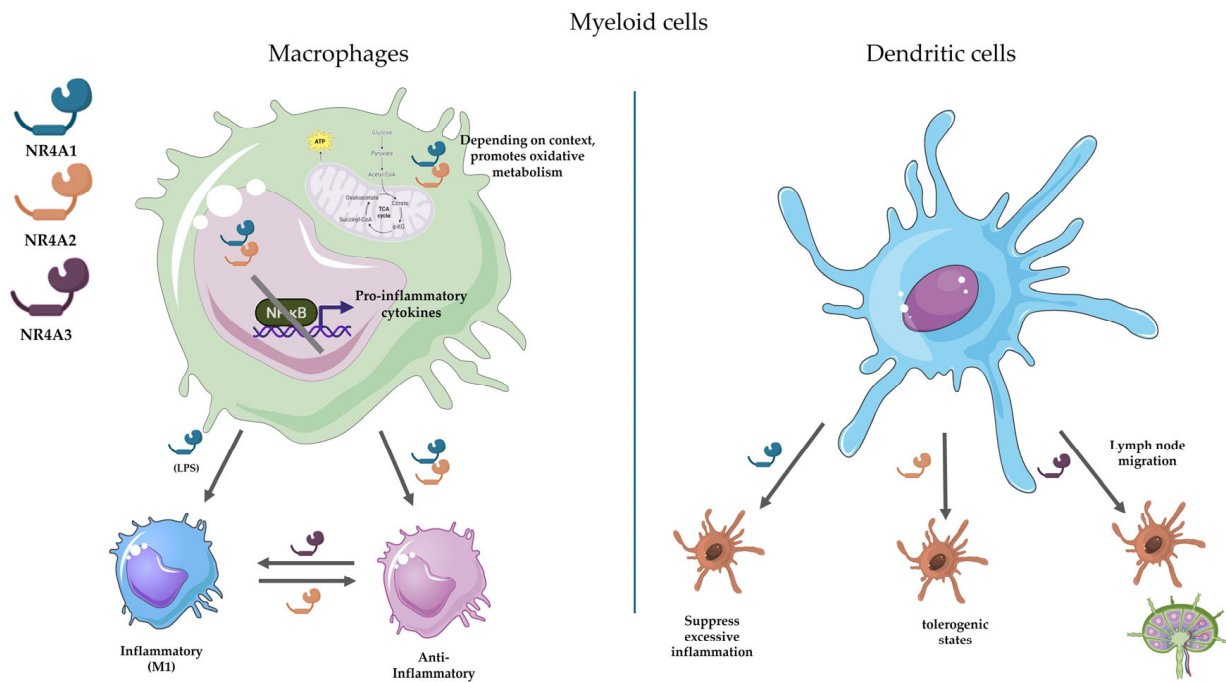


Figure 1. Regulatory roles of NR4A receptors in macrophages and DCs. Macrophages and DCs utilise NR4A receptors (NR4A1, NR4A2, NR4A3) to fine-tune immune responses. In macrophages, NR4A1 suppresses NF- κ B activity (except for TNF- α) and reprograms metabolism (e.g., via SDH and TCA cycle) to restrain inflammation, while promoting M2-like polarisation. Furthermore, NR4A2 inhibits TLR4-induced inflammation via SUMOylation-mediated NF- κ B/p53 displacement and enhances M2 polarisation, while NR4A3 promotes monocyte adhesion in atherosclerosis and modulates M1/M2 marker expression (e.g., suppresses IL-10 in M2 macrophages). In DCs, NR4A1 limits hyperinflammatory cytokine production (IL-6, TNF α) and T-cell stimulation, with NR4A2 driving a tolerogenic DC differentiation and Treg expansion. By its part, NR4A3 facilitates CCR7-dependent DC migration to lymph nodes and monocyte-to-DC differentiation. Figure created with BioRender.com and Servier Medical Art.

3.1.1. NR4A1

NR4A1 plays complex roles in macrophage biology, upregulating genes involved in inflammation, apoptosis, and cell cycle regulation. In the context of immune response, while it generally suppresses NF- κ B activity and limits inflammatory cytokine production, its effects on the highly inflammatory cytokine Tumor Necrotic Factor α (TNF- α) appear distinct—neither expression nor secretion of this cytokine is altered in NR4A1-deficient macrophages. This exception may relate to succinate dehydrogenase (SDH) activity, which exerts independent anti-inflammatory effects [36]. NR4A1 deficiency leads to enhanced NF- κ B activation, evidenced by increased p65 phosphorylation, and promotes a pro-inflammatory macrophage phenotype [10].

Beyond inflammation regulation, NR4A1 influences macrophage metabolism. Growing evidence highlights the intricate link between immune response and cellular metabolism, demonstrating that metabolic reprogramming—including rewiring of the TCA cycle and activation of alternative shunt pathways—is essential for activated macrophages to produce inflammatory effector molecules efficiently [37]. Koenis et al. demonstrated that NR4A1 modulates mitochondrial metabolism to restrain excessive inflammatory responses [36]. It is worth mentioning that, as depicted in Figure 1, in a sepsis model, LPS stimulation of TLR4 triggers NR4A1 phosphorylation via p38 α , leading to NF- κ B p65 release and pro-inflammatory gene transcription [38].

NR4A1 also contributes to macrophage differentiation, with its expression increasing during the transition from classical M1 to non-classical M2 monocytes in murine models [18]. NR4A1-deficient macrophages from atherosclerotic mice show elevated pro-inflammatory markers (e.g., MHC class II) and reduced anti-inflammatory markers (e.g., Arginase-1), supporting its role in polarisation [39,40].

3.1.2. NR4A2

NR4A2 was first linked to NF- κ B regulation through studies in TLR4-stimulated microglia, where its depletion exacerbated pro-inflammatory responses. Upon TLR4 activation, NR4A2 undergoes SUMOylation and phosphorylation, enabling it to bind phosphorylated NF- κ B/p65 at target gene promoters. This interaction recruits the CoREST repressor complex, displacing NF- κ B/p65 and suppressing pro-inflammatory gene expression [10,41].

In macrophages, NR4A2 expression is induced through the PI3K-Akt-mTOR pathway, which attenuates innate inflammatory responses. NR4A2 promotes M2 polarisation and protects against endotoxin-induced sepsis, suggesting it functions as an inflammatory brake [42]. Interestingly, in autoimmune conditions like bullous pemphigoid, pro-inflammatory macrophages show elevated NR4A2 levels, possibly representing a compensatory mechanism to restrain inflammation [43].

3.1.3. NR4A3

NR4A3 demonstrates distinct functions in macrophage biology. Silencing NR4A3 in human IL-4-polarized macrophages downregulates alternative activation markers (Mannose Receptor, IL-1Ra, CD200R, F13A1, IL-10, PPAR γ) while increasing MMP9 expression and activity—typically associated with M1 phenotypes [44]. In atherosclerosis, NR4A3 promotes early disease events by enhancing monocyte adhesion to endothelium. Inflammatory signals like NF- κ B activate NR4A3, which induces expression of adhesion molecules (either directly on monocytes or indirectly via endothelial VCAM-1/ICAM-1 upregulation), facilitating immune cell recruitment to vascular walls [45].

3.2. Dendritic Cells

DCs are professional antigen-presenting cells that bridge innate and adaptive immunity by activating pathogen-specific T-cells, playing essential roles in both initiating adaptive immunity and maintaining immune tolerance [46]. As shown in Figure 1, their development from bone marrow progenitors involves upregulated expression of all three NR4A receptors during the transition from pre-DCs to mature DCs [18].

3.2.1. NR4A1

NR4A1 serves as a critical immunoregulator in DCs. Expressed across human and murine DC subsets, its expression rapidly increases upon TLR stimulation. NR4A1-deficient DCs display hyperinflammatory responses with enhanced NF- κ B-dependent cytokine production (IL-6, TNF α , IL-12) and increased T-cell stimulatory capacity [40,47]. Conversely, pharmacological activation of NR4A1 suppresses cytokine production and attenuates DC-driven allogeneic T-cell proliferation, positioning it as a key checkpoint against excessive immune activation [47].

3.2.2. NR4A2

While less abundantly expressed in DCs than in other family members [18], NR4A2 plays a specialised role in immune tolerance. Saini et al. demonstrated that NR4A2 drives a regulatory phenotype in bone marrow-derived DCs (BMDCs), suppressing autoimmune

neuroinflammation through Treg expansion. These findings suggest NR4A2 can reprogram immunogenic DCs toward tolerogenic states [48].

3.2.3. NR4A3

NR4A3 shows preferential expression in migratory DCs and is essential for their lymph node homing. NR4A3-deficient DCs exhibit reduced CCR7 expression—the key chemokine receptor for DC migration—both at steady-state and upon activation [46,49]. While NR4A3 does not directly bind the CCR7 promoter, it may regulate migration indirectly through transcription factors like FOXO1 or broader migratory programs [18,49].

Functional studies reveal that NR4A3 knockdown impairs DC-mediated T-cell proliferation, and NR4A3 KO mice show increased infection susceptibility due to DC migration defects [50]. Additionally, NR4A3 is required for *in vitro* monocyte-to-DC differentiation, with its absence causing up to 10-fold reductions in DC generation [18].

4. NR4A Receptors in Lymphoid Cells

Lymphoid cells—including T-cells, B-cells, and natural killer (NK) cells—form the backbone of adaptive and innate immunity. These cells coordinate antigen-specific responses (T- and B-cells) and provide rapid cytotoxic activity (NK cells). The NR4A nuclear receptors (NR4A1-3) critically regulate lymphoid cell function. As immediate-early, ligand-independent transcription factors, they tune antigen-receptor signalling, fate decisions, and metabolic/epigenetic programs in lymphocytes [26,51]. NR4A1 modulates T-cell activation and prevents autoimmunity, NR4A3 influences CD8⁺ T-cell exhaustion in chronic infections, and NR4A2 contributes to B-cell receptor signalling. Dysregulation of these pathways underlies various immune pathologies, highlighting their therapeutic potential: manipulating NR4As alters T-cell differentiation, exhaustion, and local humoral responses with emerging therapeutic promise and key open questions [29].

4.1. NR4A Receptors in T-Cell Biology

T-cells demonstrate remarkable functional diversity, with subsets specialised for distinct immune roles. CD4⁺ helper T-cells differentiate into lineages including Th1 (antiviral/antitumor), Th2 (anti-helminth/allergy), Th17 (mucosal defence/autoimmunity), and regulatory T-cells (Tregs; immune suppression). CD8⁺ cytotoxic T-cells directly eliminate infected or malignant cells. These subsets develop through thymic selection, where NR4A receptors play critical roles in both positive selection (promoting survival of useful clones) and negative selection (eliminating self-reactive cells) [29,52–54].

T-cells recognise foreign peptide–MHC complexes through their T-cell receptor (TCR), a highly diverse receptor generated via somatic gene rearrangement. Thymic selection plays a critical role in shaping the T-cell repertoire, ensuring self-tolerance while maintaining the ability to detect pathogen-derived antigens. During the CD4⁺CD8⁺ double-positive (DP) stage, thymocytes that fail to engage the TCR with peptide–MHC complexes undergo programmed cell death. In contrast, those with intermediate TCR affinity are positively selected to differentiate into either CD4⁺ or CD8⁺ single-positive T-cells. Thymocytes exhibiting excessive self-reactivity are eliminated through negative selection (primarily at the DP stage) or redirected into Treg lineages to promote immune tolerance. Following selection, mature thymocytes upregulate CCR7, enabling their migration to the medulla for further screening against tissue-restricted antigens [55].

4.1.1. CD4⁺ T-Cells

CD4⁺ T-cells orchestrate adaptive immunity by directing other immune cells. Activated by antigen-presenting cells, they differentiate into specialised subsets—including Th1, Th2, Th17, Tfh, and Tregs—each with distinct effector roles. While most effector cells

die after infection, some form long-lived memory populations [29]. Regarding the diverse repertoire of different populations of T-cells, the NR4A family is among the few factors directly implicated in T-cell tolerance, mediating thymic deletion and Treg differentiation to prevent autoimmunity (Figure 2) [56].

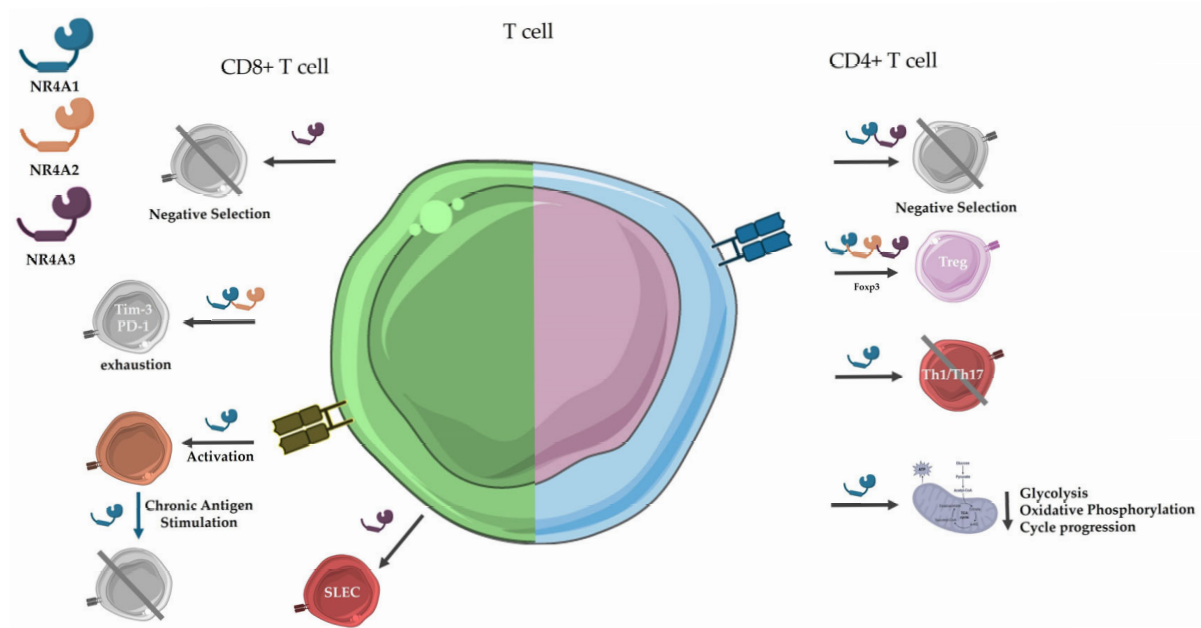


Figure 2. Roles of NR4A receptors in CD4+ and CD8+ T-cell biology. The figure summarises the involvement of NR4A family members in key T-cell processes. **CD4+ T-cells (right):** NR4A1 serves as a master regulator that suppresses effector T-cells (inhibits Th1/Th17 differentiation and IL-2/IFN- γ production via AP-1 competition), while promoting Treg development. In addition, constrains metabolic reprogramming (limits glycolysis/OXPHOS to prevent hyperactivation) and mediates thymic negative. Regarding NR4A2, it exhibits context-dependent roles, supporting Treg stability through Foxp3 enhancer regulation or paradoxically enabling Th17 maturation. With respect to NR4A3, it has redundant apoptotic functions with NR4A1 in thymic selection, with a strong correlation with high-affinity TCR signalling. Furthermore, it contributes to Treg lineage commitment (persistent expression in peripheral Tregs). **CD8+ T-cells (left):** NR4A1 exhibits dual roles: (1) Promotes initial T-cell activation (correlating with TCR signal strength) while establishing checkpoint control via IRF4 suppression; (2) Drives exhaustion (via PD-1/TIM-3 upregulation) and anergy under chronic stimulation. NR4A2 cooperates with NR4A1 in exhaustion and sustains CD28+ tissue-resident memory T (TRM) cells. NR4A3 regulates thymic negative selection (via strong TCR signals) and effector-memory balance by restricting bZIP transcription factor access to chromatin. Figure created with BioRender.com and Servier Medical Art.

NR4A1

NR4A1 serves as a master regulator of CD4+ T-cells. While expressed at low levels in naïve cells, it rapidly induces upon antigen engagement [29]. suppresses effector T-cell responses by inhibiting Th1/Th17 differentiation and cytokine production (IFN- γ , IL-17) while promoting Treg development and function [33]. Mechanistically, NR4A1 competes with AP-1 transcription factors at shared DNA binding sites, directly repressing IL-2 transcript [51]. It also modulates T-cell metabolism, with NR4A1 deficiency leading to enhanced glycolysis and oxidative phosphorylation that fuels unchecked proliferation [57,58].

T-cells dynamically reprogram their metabolism to fuel immune responses. Quiescent naïve cells rely on oxidative phosphorylation (OXPHOS). Upon activation, effector cells shift to aerobic glycolysis for rapid proliferation and effector molecule synthesis. Memory cells regain metabolic flexibility, using efficient OXPHOS for a rapid recall. This hierarchy

ensures that energy is appropriately allocated across differentiation states [59]. NR4A1 has emerged as a critical regulator interfacing T-cell metabolism with functional outcomes [57].

As depicted in Figure 2, it was demonstrated that NR4A1 constrains T-cell activation by limiting both cell cycle progression and metabolic reprogramming. Genetic ablation of NR4A1 results in hyperactive CD4⁺ T-cells exhibiting elevated oxidative respiration, glycolytic flux, and glycolytic capacity—metabolic changes that likely fuel the unchecked proliferation observed in NR4A1-deficient T-cells [58]. Mechanistically, NR4A1 appears to function as a metabolic checkpoint, preventing excessive activation by modulating both mitochondrial and glycolytic pathways; however, the precise molecular targets remain under investigation [57].

At the transcriptional level, NR4A1 exerts broad immunosuppressive effects by competing with pro-inflammatory signalling networks. Chromatin immunoprecipitation sequencing (ChIP-seq) analyses reveal that NR4A1 co-localises with both canonical NBRE motifs and AP-1 consensus sequences, suggesting functional antagonism with bZIP transcription factors [51]. This competition was experimentally validated through multiple approaches: NR4A1 overexpression reduces c-Jun occupancy at shared genomic targets, while electrophoretic mobility shift assays (EMSAs) and luciferase reporter systems demonstrate direct repression of AP-1-driven transcription [29]. Notably, this molecular interplay inhibits IL-2 production—a critical growth factor for T-cell expansion—providing a mechanism for NR4A1-mediated suppression of effector responses. The ability of NR4A1 to simultaneously modulate metabolic programs and compete with activation-associated transcription factors positions it as a multifaceted regulator of T-cell homeostasis.

The NR4A family, particularly NR4A1, plays indispensable roles in thymocyte development and selection. During thymic education, NR4A1 expression dynamically responds to TCR signal strength, with the highest induction in thymocytes undergoing negative selection [27,59]. This expression pattern correlates with its dual mechanisms of clonal deletion: (1) transcriptional upregulation of pro-apoptotic BIM (Bcl2l11) through canonical nuclear receptor activity, and (2) direct mitochondrial targeting, where it binds BCL-2, exposing its BH3 domain to trigger caspase-independent apoptosis [27,60]. While these pathways ensure elimination of strongly self-reactive clones, the contextual signals determining whether NR4A1 promotes deletion or Treg differentiation remain incompletely understood. A study conducted by Moran et al. [59] highlights NR4A1's quantitative response to TCR signal intensity, with graded expression levels potentially serving as a rheostat for selection outcomes.

NR4A1 plays a central role in Tregs. These cells represent a specialised CD4⁺ lineage critical for maintaining immune tolerance. Their suppressive arsenal includes cell-contact-dependent mechanisms (CTLA-4, CD25), anti-inflammatory cytokines (IL-10, TGF- β), and active suppression of pro-inflammatory signals (IFN- γ , IL-2) [61]. Tregs further modulate immune responses by restraining dendritic cell-mediated T-cell priming and inhibiting follicular helper T (Tfh) cell differentiation, with specialised follicular regulatory T (Tfr) cells directly regulating germinal centre reactions [61].

In the same line of evidence, NR4A1 is proposed as a master regulator of Treg biology through multiple non-redundant functions. It directly activates Foxp3 transcription—the lineage-defining transcription factor—and maintains Treg stability by sustaining expression of effector molecules (Ikzf4, CD25) while repressing inflammatory cytokines (IL-4, IL-21) [24,26,61,62]. In NR4A1-deficient models, Tregs lose Foxp3 expression and aberrantly differentiate into Th2 and Tfh-like cells, culminating in fatal autoimmunity [27,62]. The preferential enrichment of NR4A1 in peripheral Tregs versus conventional T-cells [27] underscores its specialised role in preserving immune tolerance beyond thymic development.

NR4A1's functional impact varies across T-cell subsets and activation contexts. In Tfh cells, its effects appear context-dependent, modulating but not being essential for their development [61]. Notably, NR4A1 induction provides a sensitive biomarker of recent TCR engagement, outperforming traditional markers like CD69 in specificity for antigen receptor signalling [63]. This property, combined with its roles in metabolic regulation, apoptosis induction, and transcriptional modulation, makes NR4A1 an attractive target for immunotherapeutic interventions. Ongoing research continues to elucidate how NR4A1 integrates these diverse functions to maintain immune homeostasis while permitting appropriate responses to pathogens.

NR4A2

While NR4A1 and NR4A3 serve as primary regulators of Treg biology, NR4A2 exhibits unique and context-dependent functions in immune homeostasis. Unlike its family members, NR4A2 protein remains undetectable in stimulated thymocytes despite mRNA expression, suggesting divergent regulatory mechanisms during thymic selection [64]. In mature CD4⁺ T-cells, NR4A2 demonstrates partial functional redundancy with other NR4As, as evidenced by only modest reductions in Foxp3 and CD25 expression in NR4A2 single-knockout models [61]. However, its specific capacity to suppress IL-4 promoter activity in reporter assays [27] and maintain Treg identity through conserved Foxp3 enhancer elements (CNS1/2) [65–67] indicates specialised roles in peripheral immune regulation.

NR4A2 presents a paradoxical association with autoimmune inflammation. In multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), T-cells show marked upregulation of NR4A2 transcripts, and the receptor overexpression enhances production of pathogenic cytokines IFN- γ and IL-17 [27]. However, mechanistic studies reveal that NR4A2 is required for terminal Th17 differentiation through an IL-21-dependent autocrine loop. NR4A2-deficient Th17 precursors maintain ROR γ t expression but fail to upregulate IL-23R or produce IL-17/IL-21, defects rescued by exogenous IL-21 [30]. This establishes NR4A2 as a critical checkpoint in Th17 maturation, explaining its dual association with both disease pathogenesis and developmental control of this inflammatory lineage [68].

Recent work by Zhang et al. [69] identified NR4A2 as the crucial molecular link between coactivator signalling and Treg differentiation. Their studies demonstrated that (1) SRC2 (Steroid Receptor Coactivator 2) physically interacts with NFAT1 to drive NR4A2 transcription, (2) SRC2 deficiency impairs NR4A2 expression and FoxP3 induction, causing autoimmune pathology, and (3) NR4A2 restoration rescues Treg development in SRC2-knockout cells. Mechanistically, SRC2 recruits NFAT1 to the NR4A2 promoter, creating a feed-forward loop that amplifies FoxP3 expression. This SRC2-NFAT1-NR4A2 axis represents a novel therapeutic target for modulating immune tolerance, with NR4A2 serving as the essential transcriptional bridge between upstream signalling and Treg lineage commitment [69].

NR4A3

This receptor plays dual yet distinct roles in thymocyte development and Treg differentiation. During thymic selection, NR4A3 functions redundantly with NR4A1 to enforce central tolerance, particularly in mediating negative selection of self-reactive thymocytes [60]. Both nuclear receptors trigger apoptosis through a shared mitochondrial pathway—following nuclear export, they bind and convert anti-apoptotic BCL-2 into a pro-apoptotic form by exposing its BH3 domain [29]. This non-transcriptional mechanism complements their transcriptional regulation of apoptotic genes, providing a fail-safe for eliminating autoreactive clones.

NR4A3's role shifts markedly during Treg development, where its persistent expression serves as a molecular signature of ongoing differentiation [70,71]. Unlike NR4A1, which responds to transient TCR signals, NR4A3 specifically integrates strong, sustained TCR stimulation through direct induction by NFAT transcription factors: NFAT, AP1, and NF- κ B [71]. Notably, NFAT directly induces NR4A3 [72] linking sustained TCR signals to Treg lineage commitment. This higher activation threshold positions NR4A3 as a specialised sensor of prolonged antigen recognition—the type of signal that drives Treg lineage commitment rather than deletion. The continued expression of NR4A3 in peripheral Tregs suggests these cells maintain aspects of this signalling program even after thymic egress [71].

Notably, NR4A3 exhibits several unique regulatory features that make it particularly valuable for studying T-cell activation. Along with NR4A1, it is rapidly induced by TCR engagement and ERK signalling [71], but its expression dynamics provide superior resolution of strong versus weak activation compared to conventional markers like CD69 [59,70]. These properties, combined with its specific association with Treg development, make NR4A3 both a critical functional mediator and a sensitive reporter of high-affinity TCR interactions throughout T-cell maturation.

4.1.2. CD8+ T-Cells

CD8+ T-cells are essential for combating intracellular infections and cancer. Once activated, they become effector cells that secrete cytokines (e.g., IFN- γ , TNF- α) and cytolytic molecules (e.g., perforin, granzymes) to kill infected or malignant cells. During chronic antigen exposure—as in persistent infections or cancer—they can become exhausted, losing function and upregulating inhibitory receptors like PD-1 and LAG-3. CD8+ T-cells also form memory subsets: central memory (TCM) for self-renewal, effector memory (TEM) for rapid response, and tissue-resident memory (TRM) for local protection. Their differentiation and function are regulated by transcription factors (e.g., T-bet, EOMES, NR4A1), metabolic programs, and environmental signals, ensuring effective yet controlled immunity [29,73].

NR4A1

NR4A1 orchestrates CD8+ T-cell responses through stage-specific functions. During initial TCR activation, NR4A1 expression peaks rapidly (1–3 h post-stimulation), with single-cell RNA sequencing demonstrating its transcription levels directly correlate with TCR signal strength [74]. This immediate-early response supports initial T-cell activation while simultaneously establishing regulatory checkpoints. Under conditions of chronic antigen exposure, NR4A1 undergoes functional switching—upregulating the pro-apoptotic factor BIM to trigger mitochondrial apoptosis of overactivated clones, thereby preventing immunopathology [29]. This dual role as both activation promoter and termination signal is evidenced in NR4A1-deficient models, which exhibit enhanced antitumor activity but also dysregulated T-cell expansion [13,57].

Furthermore, NR4A1 regulates CD8+ T-cell function and homeostasis through two key transcriptional mechanisms. First, it directly suppresses Interferon Regulatory Factor 4 (IRF4); in its absence, uncontrolled IRF4 expression drives T-cell hyperproliferation, aberrant differentiation into short-lived effector cells (SLECs), heightened cytokine production, and accelerated exhaustion [29,75]. Second, NR4A1 controls CD8+ T-cell development by recruiting the CoREST corepressor to repress Runx3 expression. Loss of NR4A1 leads to increased Runx3 levels, which subsequently increase the frequency and total number of intrathymic and peripheral CD8+ T-cells [76,77]. Thus, NR4A1 is a critical transcriptional regulator that maintains the balance between effective immunity and pathological T-cell activation.

Another important function of NR4A1 is the promotion of immune tolerance by inducing T-cell exhaustion (Figure 2). This state is maintained by a balance of signals, where dominant co-inhibitory pathways like PD-1 enforce tolerance by driving T-cell dysfunction. This correlates with suppressed effector function, notably a reduction in IFN γ production from CD8 $^{+}$ T-cells. Conversely, NR4A1 deletion enhances proliferative capacity and cytokine secretion (IL-2, IFN γ), establishing its role as a transcriptional mediator of exhaustion [51,78]. These findings establish NR4A1 as a central transcriptional mediator of T-cell exhaustion.

Further supporting the role of NR4A1 in exhaustion, studies in the tumour microenvironment demonstrated that NR4A1 promotes surface expression of exhaustion markers PD-1 and TIM-3 on CD8 $^{+}$ T-cells, as well as reduces effector cytokine production. Furthermore, its expression correlates with exhaustion-associated gene signatures in tumour-infiltrating lymphocytes [79]. The therapeutic implications of NR4A1 modulation are substantial. Genetic deletion of NR4A1 in T-cells enhances antitumor responses, increasing IL-2 and IFN γ production, together with a reduced PD-1 expression and improving T-cell persistence [51,80]. Strikingly, adoptive transfer of triple NR4A knockout CAR-T-cells in murine solid tumour models resulted in complete tumour eradication and improved survival [79], highlighting the therapeutic potential of targeting this pathway to enhance T-cell function in cancer immunotherapy.

NR4A2

NR4A2 also participates in CD8 $^{+}$ T-cell exhaustion. A recent work of Srirat et al. demonstrated that genetic deletion of NR4A2 in CD8 $^{+}$ T-cells reduced tumour size, with the double-knockout in NR4A1/2 showing a strong antitumoral response [81].

Regarding its participation in memory response, studies evaluating the heterogeneity of TRM cells following LCMV infection by scRNA-Seq have revealed that the highly functional CD28 $^{+}$ subset of CD8 $^{+}$ TRM cells is particularly enriched in NR4A1-3 and that knockdown of NR4A2 specifically decreased the proportion of these CD28 $^{+}$ TRM cells [29,73].

NR4A3

While NR4A1 and NR4A3 share overlapping expression patterns, accumulating evidence reveals their distinct functional roles in T-cell biology. NR4A3 serves as a specific marker for thymocytes receiving strong TCR signals during negative selection, with NR4A3 deficiency impairing the deletion of autoreactive clones [55]. Their differential expression patterns further highlight this functional divergence—NR4A1 responds to both positive and negative selection signals (albeit more strongly to the latter), while NR4A3 induction occurs exclusively in response to high-affinity TCR engagement [29]. These findings fundamentally challenge the concept of complete redundancy between these nuclear receptor family members.

In CD8 $^{+}$ T-cell differentiation, NR4A3 plays unique regulatory roles through epigenetic mechanisms. During early activation, it restricts chromatin accessibility at bZIP transcription factor binding sites (including Fos/Jun family motifs), thereby suppressing memory-promoting programs while favouring short-lived effector cell (SLEC) differentiation [29,74]. This explains why NR4A3 deficiency enhances central memory (TCM) formation, demonstrating its specialised role in balancing effector and memory fates [74]. The restriction of bZIP factor binding represents a key mechanism through which NR4A family members coordinate T-cell responses.

The NR4A receptors exhibit stage-specific modulation of CD8 $^{+}$ T-cell responses during immune challenges. While both NR4A1 and NR4A3 suppress cytokine production dur-

ing the effector phase, only NR4A3 actively promotes SLEC differentiation [29]. Notably, NR4A3 shows differential regulation from NR4A1, as it remains unresponsive to tonic signalling in both T- and B-cells—a property confirmed by early TCR stimulation sequencing data [29,74]. This suggests NR4A3's effects on differentiation occur independently of tonic signalling pathways.

In thymocyte development, NR4A1 and NR4A3 demonstrate both shared and specialised functions. Both receptors are sharply upregulated during negative selection and cooperate with BIM to eliminate self-reactive clones through dual mechanisms: transcriptional activation of pro-apoptotic genes and direct mitochondrial targeting of BCL-2 to expose its BH3 domain [29]. Despite this functional overlap in clonal deletion, they maintain distinct expression dynamics and activation thresholds that tailor their responses to different TCR signal strengths.

Beyond thymic selection, the NR4A family plays an indispensable role in regulatory T-cell (Treg) biology. Complete deletion of NR4A1 and NR4A3 (with or without NR4A2) leads to near-total Treg loss and severe autoimmunity in mice. These receptors reinforce Foxp3 expression in thymic Treg precursors and maintain peripheral Treg stability by suppressing inflammatory cytokine production while preserving suppressive function. Their coordinated activity links strong self-antigen recognition to Treg lineage commitment while preventing aberrant Th1/Th2 differentiation in conventional CD4⁺ T-cells, highlighting their central role in maintaining immune tolerance at multiple levels.

In summary, NR4A receptors emerge as central regulators of T-cell function and biology, with their diverse actions schematized in Figure 2.

4.2. NR4A Receptors Function in B-Cell Responses

B-cells are essential for adaptive immunity, particularly for antibody production and memory generation. Following antigen encounter in lymphoid organs, they differentiate into plasma or memory cells—a process dependent on BCR signalling and T-cell help. Like T-cells, B-cells rapidly upregulate NR4A receptors upon BCR activation. NR4A1 is most highly expressed (both basally and after activation), followed by NR4A3, whereas NR4A2 is minimally expressed [58].

During the GC response, B-cell clones compete for entry and dominance, with selection typically favouring those expressing high-affinity B-cell receptors (BCRs). However, GCs are not exclusively dominated by high-affinity clones; they can sustain a heterogeneous population, including low-affinity B-cells, over extended periods. This suggests the presence of regulatory mechanisms that prevent early monopolisation by dominant clones. Recent studies highlight NR4A1 as a key negative regulator in this process. Upon BCR-antigen engagement, this receptor is rapidly induced, forming a negative feedback loop that curbs B-cell proliferation and restricts the early expansion of high-affinity clones [82].

NR4A1 and NR4A3 jointly restrain B-cell survival and proliferation when signal 1 (antigen) is received in the absence of signal 2 (co-stimulation via T-cell help or presence of Pathogen-Associated Molecular Patterns). However, strong signal 2 overrides this suppression. Notably, NR4As also inhibit BCR-induced upregulation of key interaction molecules CD86 (critical for CD28 co-stimulation), CCL3/CCL4 (which recruit T-cells via CCR5), and ICAM1/2 (essential for T-B-cell conjugation)—all of which are required for efficient B-cell expansion in T-dependent responses [83]. This suppression confers a competitive disadvantage on NR4A-deficient B-cells in competing for scarce T-cell help [64].

Functionally, NR4A receptors temper the early dominance of high-affinity clones in polyclonal immune responses, enabling the participation of lower-affinity or subdominant clones [82]. This mechanism may safeguard lower-affinity but potentially neutralising antibody responses elicited during infection. Acting as a negative feedback loop in B-cells,

NR4As help maintain clonal diversity in the GC reaction, which could ultimately optimise long-term affinity maturation [64].

In summary, these findings reveal a molecular pathway that restrains immunodominance and preserves clonal diversity during humoral responses. This regulation may prevent gaps in the post-immune repertoire that pathogens could exploit while enhancing the affinity maturation of long-lived plasma cells [82].

While NR4A2 shows minimal expression and no apparent role in B-cell signalling, NR4A3 functions redundantly with NR4A1 despite its lower expression levels [83].

4.3. NKT Cell

Natural Killer T (NKT) cells are a unique T lymphocyte subset that bridges innate and adaptive immunity by recognising lipid antigens via CD1d. They express both T-cell receptors and NK cell markers, enabling rapid cytokine secretion upon activation. Classified into type I (invariant TCR) and type II (diverse TCR) subsets, NKT cells modulate immune responses—including tumour surveillance, antimicrobial defence, and autoimmunity—through swift production of Th1, Th2, or Th17 cytokines. Their distinct antigen recognition and rapid effector functions make them essential to immune homeostasis [84].

iNKT cells develop in the thymus from double-positive precursors. Their lineage commitment is triggered by recognition of CD1d-presented self-lipids through their semi-invariant TCR, along with IL-7 and IL-15 signalling. This induces a unique transcriptional program involving NR4A1, a critical checkpoint in iNKT development, tolerance, and function [59,64,84]. NR4A1 reinforces self-tolerance via two mechanisms: caspase-3-mediated apoptosis during thymic negative selection and induction of peripheral hyporesponsiveness. These roles distinguish iNKT regulation from conventional T-cells. To prevent autoimmunity, excessive activation is restrained by a Nur77-dependent feedback loop, where strong TCR or cytokine signals upregulate NR4A1 to limit iNKT activity [84].

5. NR4A Receptors at the Immune-Neuroendocrine Interface

The expression of the NR4A family was first documented in the brain, together with their stress-induced nature [85–87]. Their role in the stress response was further elucidated by the discovery of both NBRE and NurRE sequence binding motifs in the promoter of the POMC gene (the precursor for ACTH, α -MSH, and β -Endorphin) [15,88,89]. By binding this element, NR4A1 and NR4A2 regulate POMC transcription, thereby mediating the neuroendocrine response of the HPA axis. This leads to the release of ACTH, which subsequently stimulates glucocorticoids (Gc) synthesis indirectly via the cAMP pathway and activation of transcription factors for steroidogenic enzymes [87,90].

Within the adrenal glands, NR4A1 is a key mediator of ACTH-induced gene expression, directly translating hormonal signals into increased steroid production. This is demonstrated by NR4A1 binding to and activating functional NBRE and NurRE binding sites in the promoters of steroidogenic enzymes including P450c21 [91]. Conversely, in the anterior pituitary, NR4A1 also mediates the stimulatory effect of CRH and, at least partially, the inhibitory feedback of glucocorticoids (Gc) on POMC transcription [92]. The glucocorticoid receptor (GR) can directly interact with NR4A proteins and is recruited to the promoter of the POMC gene. There, it antagonises the activity of NR4A1 (which binds as a homo- or heterodimer). The relative concentrations of NR4A1 and GR therefore determine the net effect on the promoter. This reveals a unique transrepression mechanism between GR and NR4A1, which is quite similar to the proposed transrepression between GR and other factors like AP-1 or NF- κ B [93].

Inflammation serves a dual role: it is a vital defence mechanism that can also become harmful when misregulated. GCs help control this process by binding GR and

reprogramming the expression of inflammatory genes. This occurs through both genomic mechanisms—like DNA binding, tethering to transcription factors, and altering cofactor recruitment—and non-genomic signalling, combined with tissue-specific regulation of GC availability. The overall balance of these actions determines whether the result is net anti- or pro-inflammatory. Notably, NR4A1 supports this anti-inflammatory outcome both centrally, via POMC neurons, and locally in the adrenal gland by promoting GC production, aligning with its direct immune-suppressing effects.

NR4As also participate in metabolism regulation. In the arcuate hypothalamus, leptin acting on POMC neurons is a fundamental mechanism for regulating energy balance and glucose homeostasis. Binding to the leptin receptor activates JAK2-STAT3 and PI3K-Akt signalling, which suppresses appetite and promotes energy expenditure through melanocortin pathways [94]. Crucially, the nuclear receptor NR4A1 is a key modulator of this leptin signal. NR4A1 facilitates the acetylation of STAT3, enhancing its transcriptional activity and the expression of the anorexigenic peptide POMC. This role is physiologically significant, as NR4A1 deficiency induces severe leptin resistance, characterised by hyperphagia, reduced energy expenditure, and hyperleptinemia [95].

Furthermore, there is evidence indicating that NR4A1 is a critical regulator of β -cell function and fuel metabolism. Glucose concentration regulates its expression through the cAMP/PKA/CREB pathway, enabling NR4A1 to modulate the expression of GLUT2 and other genes involved in glucose uptake and metabolism. This regulation is necessary for the machinery of glucose-stimulated insulin secretion [96]. Beyond this metabolic role, NR4A1 also provides a protective function. During chronic hyperglycaemia and hyperlipidaemia, which induce β -cell apoptosis via ER stress, ROS, and JNK activation, NR4A1 counteracts this process by reducing phosphorylated JNK levels, thus promoting β -cell survival [97].

The regulatory influence of NR4A receptors extends to critical endocrine axes. The ubiquitous expression of NR4A1 underscores its fundamental role in maintaining physiological homeostasis. Crucially, a principal function of these receptors is to promote the resolution of inflammation and maintain a non-inflammatory state. This is powerfully demonstrated by the severe inflammatory pathologies that emerge from their dysregulation.

6. NR4A Receptors in Pathology

NR4A receptors have key physiological roles (besides immunological ones), including proliferation, apoptosis, DNA repair, cellular stress, memory, endocrinology, neuronal signalling, and hematopoietic, immune and metabolic processes, all of which have been demonstrated in many cell types. Moreover, these receptors are involved in the onset and progression of numerous diseases, such as obesity, atherosclerosis, inflammation and cancer (Table 1) [98]. In autoimmune diseases, NR4A1–3 modulate immune cell function and tolerance, particularly by influencing Th17 differentiation and NF- κ B signalling. These receptors act as early regulators of inflammation, with aberrant expression linked to immune-mediated rheumatic diseases (IMRDs), where they are found in inflamed synovial tissue (e.g., in arthritis) and psoriatic lesions [10,12,40,99]. NR4A2, for instance, promotes TNF- α production in synovial cells [86,87], while in multiple sclerosis (MS), it governs IL-17 expression. Silencing NR4A2 in experimental autoimmune encephalomyelitis (EAE) mitigates disease severity [100], whereas NR4A1 deficiency exacerbates EAE via enhanced CNS macrophage infiltration [33].

Parkinson's disease (PD) is the world's second most common neurodegenerative disorder. Existing treatments only address symptoms and lose effectiveness as dopaminergic neurons are lost, with no disease-modifying therapies currently available. Microglia-driven neuroinflammation and oxidative stress are key drivers of PD pathology. Research shows

that NR4A1 exerts anti-inflammatory and antioxidant stress effects by inhibiting I κ B- α phosphorylation expression in a Parkinson's cell model [101] and activating the receptor with an agonist like Cytosporone B (CnsB) suppresses pro-inflammatory genes in microglia, while inhibiting it exacerbates inflammation [102]. Separately, NR4A2 is crucial for maintaining dopaminergic neuron function by regulating metabolic enzymes [103]. Due to these dual roles in curbing neuroinflammation and supporting neuronal health, both NR4A receptors are promising therapeutic targets for PD.

In hematologic malignancies, the expression and function of NR4A receptors have been studied in lymphomas, where decreased nuclear levels of NR4A1 and NR4A3 were observed in follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) compared to their normal cell counterparts. Reduced NR4A1 expression was associated with more aggressive disease and poorer patient survival, whereas NR4A2 was inconsistently detected and showed no significant difference between tumour and non-tumour tissues. Notably, NR4A3 overexpression was linked to a favourable response to chemotherapy in DLBCL patients, suggesting a potential tumour-suppressive role in these malignancies. Evidence also indicates that the loss of NR4A1 and NR4A3 may contribute to the development and progression of certain leukaemias and lymphomas [17,104–106].

Conversely, in solid tumours—including breast, lung, pancreatic, ovarian, and colon cancers—NR4A receptors often play oncogenic roles. NR4A1 in particular promotes tumour growth, and its elevated expression is linked to poor survival, highlighting a tissue-specific functional duality compared to its protective role in blood cancers. Although less extensively studied, NR4A2 may also support tumourigenesis in solid tissues. Taken together, these findings illustrate the context-dependent behaviour of NR4A receptors across cancer types [17,80,107].

NR4A receptors are crucial regulators of energy metabolism, influencing obesity and diabetes through their roles in glucose and lipid homeostasis. They modulate insulin sensitivity, gluconeogenesis, and mitochondrial function, with tissue-specific effects: promoting glucose utilisation in muscle and fat while stimulating hepatic glucose production and reducing lipid accumulation in muscle. However, their impacts on liver and adipose tissue metabolism remain incompletely understood, and their effects on insulin secretion and resistance vary across experimental models. While NR4As participate in organ-specific metabolic control, their systemic coordination of whole-body energy balance through inter-organ communication remains unresolved [108].

Although NR4As do not rely on endogenous ligands for their transcriptional activity and regulation, several modulators have been identified. These include potential endogenous ligands such as prostaglandins and tryptophan/indolic metabolites, as well as exogenous ligands like CnsB, celastrol, and bis-indole-derived compounds [22,109–113]. Both agonists and antagonists—particularly those selective for specific NR4A family members—could have broad applications in autoimmunity, inflammatory diseases, cancer, transplantation, and vaccine development.

Given their role as transcription regulators of key immune processes (inflammation, exhaustion, T-cell differentiation), these nuclear receptors present a unique therapeutic opportunity to simultaneously modulate tolerance pathways across both myeloid and lymphoid cell lineages. Unlike targeting a single surface receptor, modulating NR4A activity could reprogram the broader immunosuppressive microenvironment that characterises chronic disease. Such strategies may prove especially valuable in settings like autoimmunity or persistent infection, where sustained immune dysregulation disrupts homeostasis. Consequently, further research to delineate NR4A functions and identify their endogenous ligands or synthetic modulators will be crucial for developing novel, targeted immunotherapies.

Table 1. Overview of the NR4A Nuclear Receptor Subfamily in homeostasis and pathology.

Feature	NR4A1 (Nur77)	NR4A2 (Nurr1)	NR4A3 (NOR1)
Gene Symbol/Synonyms	<i>NR4A1</i> /Nur77, TR3, NGFI-B	<i>NR4A2</i> /Nurr1, NOT, RNR1	<i>NR4A3</i> /NOR1, TEC, MINOR, CHN
Expression Type	Immediate early gene	Immediate early gene	Immediate early gene
DNA Binding	Monomer (NBRE), homodimer or heterodimer (NurRE), RXR dimerization [114,115]	Monomer (NBRE), homodimer or heterodimer (NurRE), RXR dimerization [86,115]	Monomer (NBRE); low affinity for NurRE; does not dimerise with RXR [116]
Ligand Binding Domain (LBD)	Atypical, constitutively active; binds synthetic ligands [19,109]	Atypical but dynamic; binds Docosaehaenoic Acid (DHA, Anandamide (AEA), and synthetic molecules [16,22]	Atypical; potential interaction with unsaturated fatty acids and prostaglandins [19,117]
Tissue Expression	Broad (thymus, spleen, liver, brain, immune cells) [118,119]	CNS (midbrain dopaminergic neurons), cartilage, and immune tissues [8,44,103]	Heart, skeletal muscle, immune cells, CNS [119]
Canonical Functions	Apoptosis regulation, T-cell development, inflammation modulation [55]	Dopaminergic neuron maintenance, anti-inflammatory roles, immune regulation [42,69,120]	Vascular remodeling, metabolic regulation, immune homeostasis [56]
Role in Immune Response	Suppresses NF- κ B signalling, regulates T-cell activation and macrophage polarization [36,38,39,121]	Restricts DC immunogenicity, promotes anti-inflammatory macrophage phenotypes [21,65]	Modulates DC migration, neutrophil survival, anti-inflammatory effects in monocytes/macrophages [46,49,50]
Neurological Role	Neuroprotective; expressed in cortex and hippocampus [28,33,122,123]. Mediates depressive behaviour in chronic stress [124]	Essential for dopaminergic neuron development; mutations linked to Parkinson's disease [41,125]	Implicated in hippocampal development, inner ear formation, depressive behaviour [126,127]
Cardiovascular Involvement	Attenuates vascular inflammation, promotes endothelial homeostasis [128]	Limited but protective role in atherosclerosis [27]	Regulates Vascular Smooth Muscle Cells (VSMC) proliferation, modulates atherosclerosis progression, promotes cardiac hypertrophy [45]
Cancer-Related Functions	Dual role: tumor suppressor or promoter depending on context; modulates immune microenvironment [80,81,105,128]	Tumor suppressor; may inhibit angiogenesis and inflammatory gene expression [31,81]	Tumour suppressor in Acute Myeloid Leukaemia (AML); involved in oncogenic fusion proteins (e.g., Ewing Sarcoma Breakpoint EWS–NR4A3 in sarcomas) [104,129]
Metabolic Regulation	Modulates glucose and lipid metabolism, mitochondrial function [13,97,130,131]	Regulates insulin gene expression and β -cell function [13]	Controls lipid/glucose homeostasis in skeletal muscle, insulin secretion [130]

Table 1. Cont.

Feature	NR4A1 (Nur77)	NR4A2 (Nurr1)	NR4A3 (NOR1)
Modulators/Ligands	CsnB, 6-mercaptopurine, Phorbol-Diester [19,107,110,113,132]	AEA, DHA, CsnB, prostaglandins (PG) [22,103,133,134]	6-mercaptopurine, Arachidonic acid, PGA1/PGA2, synthetic fatty acids [117,135]
Therapeutic Potential	Immunotherapy, cancer, inflammation, cardiovascular disease, osteoarthritis [81,107,118,128,136–138]	Parkinson’s disease, rheumatoid arthritis, sepsis, inflammatory disorders [42,103,139–141]	Cardiovascular disease, AML, metabolic syndrome, neurodegeneration [104,130,142]

7. Concluding Remarks

The NR4A subfamily of nuclear receptors has emerged as a central node in the regulation of systemic homeostasis, functioning as inducible transcriptional sensors that integrate diverse metabolic, endocrine, and inflammatory signals. As detailed throughout this review, these receptors are indispensable modulators of both innate and adaptive immunity. In myeloid cells, NR4As exert multifaceted control over macrophage and dendritic cell function, polarising responses toward resolution and tolerance by repressing NF-κB-driven inflammation and regulating immunometabolic programs. In lymphoid cells, they act as critical rheostats of activation: directing thymic selection, constraining effector T-cell responses, promoting regulatory T-cell differentiation, driving exhaustion in chronic environments, and modulating B-cell receptor signalling to maintain clonal diversity. Their non-redundant roles are evident across cellular lineages and organ systems, reflecting their broad involvement in physiological and pathological processes.

Therapeutic targeting of NR4A receptors holds significant promise, though it remains an evolving landscape. While no drugs are currently approved that explicitly target NR4As as their primary mechanism, several established agents—including anti-diabetic thiazolidinediones and statins—mediate part of their benefits through NR4A-dependent pathways. A new generation of selective ligands is now under active investigation. NR4A1 agonists are being developed to treat atherosclerosis, inflammatory diseases, and diabetes by leveraging their anti-inflammatory and metabolic actions, whereas antagonists may offer benefit in certain hematologic malignancies. Meanwhile, NR4A2 has emerged as a highly compelling target for neurodegenerative disorders, particularly Parkinson’s disease, where agonists aim to provide neuroprotection by restoring dopaminergic function. The ongoing delineation of NR4A-specific mechanisms—and their complex interplay in different tissues and disease contexts—will be essential for translating these insights into targeted therapies that can modulate immune and metabolic pathways with precision and efficacy.

Author Contributions: Writing—original draft preparation, Figures and table preparation, Conceptualisation, Writing—review & editing S.L.F.; Conceptualisation, Funding acquisition, Writing—original draft, Figures preparation, Writing—review & editing N.S. All authors have read and agreed to the published version of the manuscript.

Funding: The authors declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from Funds for Scientific and Technological Research-FONCyT-(PICT-2019-00044) and the contribution of Facultad de Ciencias Medicas, Universidad Nacional de Rosario, Rosario, Argentina.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: During the preparation of this manuscript, the authors used DeepSeek and Grammarly in their free versions for the purposes of grammar and spelling correction. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Volle, D.H. Nuclear Receptors in Physiology and Pathophysiology. *Mol. Asp. Med.* **2021**, *78*, 100956. [[CrossRef](#)] [[PubMed](#)]
2. Xu, P. Nuclear Receptors in Health and Diseases. *Int. J. Mol. Sci.* **2023**, *24*, 9153. [[CrossRef](#)] [[PubMed](#)]
3. Sever, R.; Glass, C.K. Signaling by Nuclear Receptors. *Cold Spring Harb. Perspect. Biol.* **2013**, *5*, a016709. [[CrossRef](#)]
4. Volle, D.H. Nuclear Receptors as Pharmacological Targets, Where Are We Now? *Cell Mol. Life Sci.* **2016**, *73*, 3777–3780. [[CrossRef](#)] [[PubMed](#)]
5. Kiss, M.; Czimmerer, Z.; Nagy, L. The Role of Lipid-Activated Nuclear Receptors in Shaping Macrophage and Dendritic Cell Function: From Physiology to Pathology. *J. Allergy Clin. Immunol.* **2013**, *132*, 264–286. [[CrossRef](#)]
6. Fan, R.; Pineda-Torra, I.; Venticlef, N. Editorial: Nuclear Receptors and Coregulators in Metabolism and Immunity. *Front. Endocrinol.* **2021**, *12*, 10–12. [[CrossRef](#)]
7. Milbrandt, J. Nerve Growth Factor Induces a Gene Homologous to the Glucocorticoid Receptor Gene. *Neuron* **1988**, *1*, 183–188. [[CrossRef](#)]
8. Law, S.W.; Conneely, O.M.; DeMayo, F.J.; O'Malley, B.W. Identification of a New Brain-Specific Transcription Factor, NURR1. *Mol. Endocrinol.* **1992**, *6*, 2129–2135. [[CrossRef](#)]
9. Ohkura, N.; Hijikuro, M.; Yamamoto, A.; Miki, K. Molecular Cloning of a Novel Thyroid/Steroid Receptor Superfamily Gene from Cultured Rat Neuronal Cells. *Biochem. Biophys. Res. Commun.* **1994**, *205*, 1959–1965. [[CrossRef](#)]
10. Murphy, E.P.; Crean, D. Molecular Interactions between NR4A Orphan Nuclear Receptors and NF- κ B Are Required for Appropriate Inflammatory Responses and Immune Cell Homeostasis. *Biomolecules* **2015**, *5*, 1302–1318. [[CrossRef](#)]
11. Crean, D.; Murphy, E.P. Targeting NR4A Nuclear Receptors to Control Stromal Cell Inflammation, Metabolism, Angiogenesis, and Tumorigenesis. *Front. Cell Dev. Biol.* **2021**, *9*, 589770. [[CrossRef](#)]
12. Ranhotra, H.S. The NR4A Orphan Nuclear Receptors: Mediators in Metabolism and Diseases. *J. Recept. Signal Transduct.* **2015**, *35*, 184–188. [[CrossRef](#)] [[PubMed](#)]
13. Herring, J.A.; Elison, W.S.; Tessem, J.S. Function of Nr4a Orphan Nuclear Receptors in Proliferation, Apoptosis and Fuel Utilization across Tissues. *Cells* **2019**, *8*, 1373. [[CrossRef](#)] [[PubMed](#)]
14. Yu, X.; He, Y.; Kamenecka, T.M.; Kojetin, D.J. Towards a Unified Molecular Mechanism for Liganddependent Activation of NR4A-RXR Heterodimers. *bioRxiv* **2025**. [[CrossRef](#)]
15. Maira, M.; Martens, C.; Philips, A.; Drouin, J. Heterodimerization between Members of the Nur Subfamily of Orphan Nuclear Receptors as a Novel Mechanism for Gene Activation. *Mol. Cell. Biol.* **1999**, *19*, 7549–7557. [[CrossRef](#)]
16. De Vera, I.M.S.; Munoz-Tello, P.; Zheng, J.; Dharmarajan, V.; Marciano, D.P.; Matta-Camacho, E.; Giri, P.K.; Shang, J.; Hughes, T.S.; Rance, M.; et al. Defining a Canonical Ligand-Binding Pocket in the Orphan Nuclear Receptor Nurr1. *Structure* **2019**, *27*, 66–77.e5. [[CrossRef](#)]
17. Safe, S.; Karki, K. The Paradoxical Roles of Orphan Nuclear Receptor 4A (NR4A) in Cancer. *Mol. Cancer Res.* **2021**, *19*, 180–191. [[CrossRef](#)]
18. Boulet, S.; Le Corre, L.; Odagiu, L.; Labrecque, N. Role of NR4A Family Members in Myeloid Cells and Leukemia. *Curr. Res. Immunol.* **2022**, *3*, 23–36. [[CrossRef](#)]
19. Kurakula, K.; Koenis, D.S.; van Tiel, C.M.; de Vries, C.J.M. NR4A Nuclear Receptors Are Orphans but Not Lonesome. *Biochim. Biophys. Acta (BBA)-Mol. Cell Res.* **2014**, *1843*, 2543–2555. [[CrossRef](#)]
20. Zárraga-Granados, G.; Muciño-Hernández, G.; Sánchez-Carbente, M.R.; Villamizar-Gálvez, W.; Peñas-Rincón, A.; Arredondo, C.; Andrés, M.E.; Wood, C.; Covarrubias, L.; Castro-Obregón, S. The Nuclear Receptor NR4A1 Is Regulated by SUMO Modification to Induce Autophagic Cell Death. *PLoS ONE* **2020**, *15*, e0222072. [[CrossRef](#)]
21. McMorro, J.P.; Murphy, E.P. Inflammation: A Role for NR4A Orphan Nuclear Receptors? *Biochem. Soc. Trans.* **2011**, *39*, 688–693. [[CrossRef](#)] [[PubMed](#)]
22. Munoz-Tello, P.; Lin, H.; Khan, P.; De Vera, I.M.S.; Kamenecka, T.M.; Kojetin, D.J. Assessment of NR4A Ligands That Directly Bind and Modulate the Orphan Nuclear Receptor Nurr1. *J. Med. Chem.* **2020**, *63*, 15639–15654. [[CrossRef](#)] [[PubMed](#)]
23. Liu, Z.G.; Smith, S.W.; McLaughlin, K.A.; Schwartz, L.M.; Osborne, B.A. Apoptotic Signals Delivered through the T-Cell Receptor of a T-Cell Hybrid Require the Immediate-Early Gene Nur77. *Nature* **1994**, *367*, 281–284. [[CrossRef](#)] [[PubMed](#)]
24. Woronicz, J.D.; Calnan, B.; Ngo, V.; Winoto, A. Requirement for the Orphan Steroid Receptor Nur77 in Apoptosis of T-Cell Hybridomas. *Nature* **1994**, *367*, 277–281. [[CrossRef](#)]

25. Hiwa, R.; Brooks, J.F.; Mueller, J.L.; Nielsen, H.V.; Zikherman, J. NR4A Nuclear Receptors in T and B Lymphocytes: Gatekeepers of Immune Tolerance. *Immunol. Rev.* **2022**, *307*, 116–133. [\[CrossRef\]](#)
26. Sekiya, T.; Kashiwagi, I.; Yoshida, R.; Fukaya, T.; Morita, R.; Kimura, A.; Ichinose, H.; Metzger, D.; Chambon, P.; Yoshimura, A. Nr4a Receptors Are Essential for Thymic Regulatory T Cell Development and Immune Homeostasis. *Nat. Immunol.* **2013**, *14*, 230–237. [\[CrossRef\]](#)
27. Bonta, P.I.; Van Tiel, C.M.; Vos, M.; Pols, T.W.H.; Van Thienen, J.V.; Ferreira, V.; Arkenbout, E.K.; Seppen, J.; Spek, C.A.; Van Der Poll, T.; et al. Nuclear Receptors Nur77, Nurr1, and NOR-1 Expressed in Atherosclerotic Lesion Macrophages Reduce Lipid Loading and Inflammatory Responses. *Arter. Thromb. Vasc. Biol.* **2006**, *26*, 2288–2294. [\[CrossRef\]](#)
28. Jeanneteau, F.; Barrère, C.; Vos, M.; De Vries, C.J.M.; Rouillard, C.; Levesque, D.; Dromard, Y.; Moisan, M.P.; Duric, V.; Franklin, T.C.; et al. The Stress-Induced Transcription Factor NR4a1 Adjusts Mitochondrial Function and Synapse Number in Prefrontal Cortex. *J. Neurosci.* **2018**, *38*, 1335–1350. [\[CrossRef\]](#)
29. Odagiu, L.; May, J.; Boulet, S.; Baldwin, T.A.; Labrecque, N. Role of the Orphan Nuclear Receptor NR4A Family in T-Cell Biology. *Front. Endocrinol.* **2021**, *11*, 624122. [\[CrossRef\]](#)
30. Raveney, B.J.E.; Oki, S.; Yamamura, T. Nuclear Receptor NR4A2 Orchestrates Th17 Cell-Mediated Autoimmune Inflammation via IL-21 Signalling. *PLoS ONE* **2013**, *8*, e56595. [\[CrossRef\]](#)
31. Hibino, S.; Chikuma, S.; Kondo, T.; Ito, M.; Nakatsukasa, H.; Omata-Mise, S.; Yoshimura, A. Inhibition of Nr4a Receptors Enhances Antitumor Immunity by Breaking Treg-Mediated Immune Tolerance. *Cancer Res.* **2018**, *78*, 3027–3040. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Bandukwala, H.S.; Rao, A. ‘Nurr’ishing Treg Cells: Nr4a Transcription Factors Control Foxp3 Expression. *Nat. Immunol.* **2013**, *14*, 201–203. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Wang, L.M.; Zhang, Y.; Li, X.; Zhang, M.L.; Zhu, L.; Zhang, G.X.; Xu, Y.M. Nr4a1 Plays a Crucial Modulatory Role in Th1/Th17 Cell Responses and CNS Autoimmunity. *Brain Behav. Immun.* **2018**, *68*, 44–55. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Seo, H.; Chen, J.; González-Avalos, E.; Samaniego-Castruita, D.; Das, A.; Wang, Y.H.; López-Moyado, I.F.; Georges, R.O.; Zhang, W.; Onodera, A.; et al. TOX and TOX2 Transcription Factors Cooperate with NR4A Transcription Factors to Impose CD8⁺ T Cell Exhaustion. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 12410–12415. [\[CrossRef\]](#)
35. Tan, C.; Mueller, J.L.; Noviski, M.; Huizar, J.; Lau, D.; Dubinin, A.; Molofsky, A.; Wilson, P.C.; Zikherman, J. Nur77 Links Chronic Antigen Stimulation to B Cell Tolerance by Restricting the Survival of Self-Reactive B Cells in the Periphery. *J. Immunol.* **2019**, *202*, 2907–2923. [\[CrossRef\]](#)
36. Koenis, D.S.; Medzikovic, L.; van Loenen, P.B.; van Weeghel, M.; Huveneers, S.; Vos, M.; Evers-van Gogh, I.J.; Van den Bossche, J.; Speijer, D.; Kim, Y.; et al. Nuclear Receptor Nur77 Limits the Macrophage Inflammatory Response through Transcriptional Reprogramming of Mitochondrial Metabolism. *Cell Rep.* **2018**, *24*, 2127–2140.e7. [\[CrossRef\]](#)
37. Ryan, D.G.; O’Neill, L.A.J. Krebs Cycle Rewired for Macrophage and Dendritic Cell Effector Functions. *FEBS Lett.* **2017**, *591*, 2992–3006. [\[CrossRef\]](#)
38. Li, L.; Liu, Y.; Chen, H.Z.; Li, F.W.; Wu, J.F.; Zhang, H.K.; He, J.P.; Xing, Y.Z.; Chen, Y.; Wang, W.J.; et al. Impeding the Interaction between Nur77 and P38 Reduces LPS-Induced Inflammation. *Nat. Chem. Biol.* **2015**, *11*, 339–346. [\[CrossRef\]](#)
39. Hanna, R.N.; Shaked, I.; Hubbeling, H.G.; Punt, J.A.; Wu, R.; Herrley, E.; Zaugg, C.; Pei, H.; Geissmann, F.; Ley, K.; et al. NR4A1 (Nur77) Deletion Polarizes Macrophages toward an Inflammatory Phenotype and Increases Atherosclerosis. *Circ. Res.* **2012**, *110*, 416–427. [\[CrossRef\]](#)
40. Murphy, E.P.; Crean, D. NR4A1-3 Nuclear Receptor Activity and Immune Cell Dysregulation in Rheumatic Diseases. *Front. Med.* **2022**, *9*, 874182. [\[CrossRef\]](#)
41. Saijo, K.; Winner, B.; Carson, C.T.; Collier, J.G.; Boyer, L.; Rosenfeld, M.G.; Gage, F.H.; Glass, C.K. A Nurr1/CoREST Pathway in Microglia and Astrocytes Protects Dopaminergic Neurons from Inflammation-Induced Death. *Cell* **2009**, *137*, 47–59. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Mahajan, S.; Saini, A.; Chandra, V.; Nanduri, R.; Kalra, R.; Bhagyaraj, E.; Khatir, N.; Gupta, P. Nuclear Receptor Nr4a2 Promotes Alternative Polarization of Macrophages and Confers Protection in Sepsis. *J. Biol. Chem.* **2015**, *290*, 18304–18314. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Solís-Barbosa, M.A.; Santana, E.; Muñoz-Torres, J.R.; Segovia-Gamboa, N.C.; Patiño-Martínez, E.; Meraz-Ríos, M.A.; Samaniego, R.; Sánchez-Mateos, P.; Sánchez-Torres, C. The Nuclear Receptor Nurr1 Is Preferentially Expressed in Human Pro-Inflammatory Macrophages and Limits Their Inflammatory Profile. *Int. Immunol.* **2024**, *36*, 111–128. [\[CrossRef\]](#) [\[PubMed\]](#)
44. De Paoli, F.; Eeckhoutte, J.; Copin, C.; Vanhoutte, J.; Duhem, C.; Derudas, B.; Dubois-Chevalier, J.; Colin, S.; Zawadzki, C.; Jude, B.; et al. The Neuron-Derived Orphan Receptor 1 (NOR1) Is Induced upon Human Alternative Macrophage Polarization and Stimulates the Expression of Markers of the M2 Phenotype. *Atherosclerosis* **2015**, *241*, 18–26. [\[CrossRef\]](#)
45. Zhao, Y.; Howatt, D.A.; Gizard, F.; Nomiya, T.; Findeisen, H.M.; Heywood, E.B.; Jones, K.L.; Conneely, O.M.; Daugherty, A.; Bruemmer, D. Deficiency of the NR4A Orphan Nuclear Receptor NOR1 Decreases Monocyte Adhesion and Atherosclerosis. *Circ. Res.* **2010**, *107*, 501–511. [\[CrossRef\]](#)

46. Boulet, S.; Daudelin, J.F.; Odagiu, L.; Pelletier, A.N.; Yun, T.J.; Lesage, S.; Cheong, C.; Labrecque, N. The Orphan Nuclear Receptor NR4A3 Controls the Differentiation of Monocyte-Derived Dendritic Cells Following Microbial Stimulation. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 15150–15159. [\[CrossRef\]](#)
47. Tel-Karthaous, N.; Kers-Rebel, E.D.; Looman, M.W.; Ichinose, H.; de Vries, C.J.; Ansems, M. Nuclear Receptor Nur77 Deficiency Alters Dendritic Cell Function. *Front. Immunol.* **2018**, *9*, 1797. [\[CrossRef\]](#)
48. Saini, A.; Mahajan, S.; Gupta, P. Nuclear Receptor Expression Atlas in BMDCs: Nr4a2 Restricts Immunogenicity of BMDCs and Impedes EAE. *Eur. J. Immunol.* **2016**, *46*, 1842–1853. [\[CrossRef\]](#)
49. Park, K.; Mikulski, Z.; Seo, G.Y.; Andreyev, A.Y.; Marcovecchio, P.; Blatchley, A.; Kronenberg, M.; Hedrick, C.C. The Transcription Factor NR4A3 Controls CD103⁺ Dendritic Cell Migration. *J. Clin. Investig.* **2016**, *126*, 4603–4615. [\[CrossRef\]](#)
50. Nagaoka, M.; Yashiro, T.; Uchida, Y.; Ando, T.; Hara, M.; Arai, H.; Ogawa, H.; Okumura, K.; Kasakura, K.; Nishiyama, C. The Orphan Nuclear Receptor NR4A3 Is Involved in the Function of Dendritic Cells. *J. Immunol.* **2017**, *199*, 2958–2967. [\[CrossRef\]](#)
51. Liu, X.; Wang, Y.; Lu, H.; Li, J.; Yan, X.; Xiao, M.; Hao, J.; Alekseev, A.; Khong, H.; Chen, T.; et al. Genome-Wide Analysis Identifies NR4A1 as a Key Mediator of T Cell Dysfunction. *Nature* **2019**, *567*, 525–529. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Dejean, A.S.; Joulia, E.; Walzer, T. The Role of Eomes in Human CD4 T Cell Differentiation: A question of context. *Eur. J. Immunol.* **2019**, *49*, 38–41. [\[CrossRef\]](#)
53. Savino, W.; Mendes-Da-Cruz, D.A.; Lepletier, A.; Dardenne, M. Hormonal Control of T-Cell Development in Health and Disease. *Nat. Rev. Endocrinol.* **2016**, *12*, 77–89. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Hamburg, J.P.V.; Tas, S.W. Molecular Mechanisms Underpinning T Helper 17 Cell Heterogeneity and Functions in Rheumatoid Arthritis. *J. Autoimmun.* **2018**, *87*, 69–81. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Boulet, S.; Odagiu, L.; Dong, M.; Lebel, M.-È.; Daudelin, J.-F.; Melichar, H.J.; Labrecque, N. NR4A3 Mediates Thymic Negative Selection. *J. Immunol.* **2021**, *207*, 1055–1064. [\[CrossRef\]](#)
56. Nielsen, H.V.; Yang, L.; Mueller, J.L.; Ritter, A.J.; Hiwa, R.; Proekt, I.; Rackaityte, E.; Aylard, D.; Gupta, M.; Scharer, C.D.; et al. Nr4a1 and Nr4a3 Redundantly Control Clonal Deletion and Contribute to an Anergy-like Transcriptome in Auto-Reactive Thymocytes to Impose Tolerance in Mice. *Nat. Commun.* **2025**, *16*, 784. [\[CrossRef\]](#)
57. Fujii, Y.; Matsuda, S.; Takayama, G.; Koyasu, S. ERK5 Is Involved in TCR-Induced Apoptosis through the Modification of Nur77. *Genes Cells* **2008**, *13*, 411–419. [\[CrossRef\]](#)
58. Liebmman, M.; Hücke, S.; Koch, K.; Eschborn, M.; Ghelman, J.; Chasan, A.I.; Glander, S.; Schädlich, M.; Kuhlencord, M.; Daber, N.M.; et al. Nur77 Serves as a Molecular Brake of the Metabolic Switch during T Cell Activation to Restrict Autoimmunity. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E8017–E8026. [\[CrossRef\]](#)
59. Moran, A.E.; Holzapfel, K.L.; Xing, Y.; Cunningham, N.R.; Maltzman, J.S.; Punt, J.; Hogquist, K.A. T Cell Receptor Signal Strength in Treg and INKT Cell Development Demonstrated by a Novel Fluorescent Reporter Mouse. *J. Exp. Med.* **2011**, *208*, 1279–1289. [\[CrossRef\]](#)
60. Hiwa, R.; Nielsen, H.V.; Mueller, J.L.; Mandla, R.; Zikherman, J. NR4A Family Members Regulate T Cell Tolerance to Preserve Immune Homeostasis and Suppress Autoimmunity. *JCI Insight* **2021**, *6*, e151005. [\[CrossRef\]](#)
61. Sekiya, T.; Kondo, T.; Shichita, T.; Morita, R.; Ichinose, H.; Yoshimura, A. Suppression of Th2 and Tfh Immune Reactions by Nr4a Receptors in Mature T Reg Cells. *J. Exp. Med.* **2015**, *212*, 1623–1640. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Yoshimura, A.; Ito, M.; Mise-Omata, S.; Ando, M. SOCS: Negative Regulators of Cytokine Signaling for Immune Tolerance. *Int. Immunol.* **2021**, *33*, 711–716. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Ashouri, J.F.; Weiss, A. Endogenous Nur77 Is a Specific Indicator of Antigen Receptor Signaling in Human T and B Cells. *J. Immunol.* **2017**, *198*, 657–668. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Bending, D.; Zikherman, J. Nr4a Nuclear Receptors: Markers and Modulators of Antigen Receptor Signaling. *Curr. Opin. Immunol.* **2023**, *81*, 102285. [\[CrossRef\]](#)
65. Park, T.Y.; Jang, Y.; Kim, W.; Shin, J.; Toh, H.T.; Kim, C.H.; Yoon, H.S.; Leblanc, P.; Kim, K.S. Chloroquine Modulates Inflammatory Autoimmune Responses through Nurr1 in Autoimmune Diseases. *Sci. Rep.* **2019**, *9*, 15559. [\[CrossRef\]](#)
66. Won, H.Y.; Shin, J.H.; Oh, S.; Jeong, H.; Hwang, E.S. Enhanced CD25⁺Foxp3⁺ Regulatory T Cell Development by Amodiaquine through Activation of Nuclear Receptor 4A. *Sci. Rep.* **2017**, *7*, 16946. [\[CrossRef\]](#)
67. Ogawa, C.; Tone, Y.; Tsuda, M.; Peter, C.; Waldmann, H.; Tone, M. TGF- β -Mediated Foxp3 Gene Expression Is Cooperatively Regulated by Stat5, Creb, and AP-1 through CNS2. *J. Immunol.* **2014**, *192*, 475–483. [\[CrossRef\]](#)
68. Takahashi, H.; Tsuboi, H.; Asashima, H.; Hirota, T.; Kondo, Y.; Moriyama, M.; Matsumoto, I.; Nakamura, S.; Sumida, T. CDNA Microarray Analysis Identifies NR4A2 as a Novel Molecule Involved in the Pathogenesis of Sjögren's Syndrome. *Clin. Exp. Immunol.* **2017**, *190*, 96–109. [\[CrossRef\]](#)
69. Zhang, W.; Cao, X.; Zhong, X.; Wu, H.; Feng, M.; Gwack, Y.; Noah, I.; Sun, Z. Steroid Nuclear Receptor Coactivator 2 Controls Immune Tolerance by Promoting Induced Treg Differentiation via Up-Regulating Nr4a2. *Sci. Adv.* **2022**, *8*, eabn7662. [\[CrossRef\]](#)

70. Bending, D.; Martín, P.P.; Paduraru, A.; Ducker, C.; Marzaganov, E.; Laviron, M.; Kitano, S.; Miyachi, H.; Crompton, T.; Ono, M. A Timer for Analyzing Temporally Dynamic Changes in Transcription during Differentiation in Vivo. *J. Cell Biol.* **2018**, *217*, 2931–2950. [\[CrossRef\]](#)
71. Jennings, E.; Elliot, T.A.E.; Thawait, N.; Kanabar, S.; Yam-Puc, J.C.; Ono, M.; Toellner, K.M.; Wraith, D.C.; Anderson, G.; Bending, D. Nr4a1 and Nr4a3 Reporter Mice Are Differentially Sensitive to T Cell Receptor Signal Strength and Duration. *Cell Rep.* **2020**, *33*, 108328. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Scott-Browne, J.P.; López-Moyado, I.F.; Trifari, S.; Wong, V.; Chavez, L.; Rao, A.; Pereira, R.M. Dynamic Changes in Chromatin Accessibility Occur in CD8⁺ T Cells Responding to Viral Infection. *Immunity* **2016**, *45*, 1327–1340. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Kurd, N.S.; He, Z.; Louis, T.L.; Milner, J.J.; Omilusik, K.D.; Jin, W.; Tsai, M.S.; Widjaja, C.E.; Kanbar, J.N.; Olvera, J.G.; et al. Early Precursors and Molecular Determinants of Tissue-Resident Memory CD8⁺ T Lymphocytes Revealed by Single-Cell RNA Sequencing. *Sci. Immunol.* **2020**, *5*, eaaz6894. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Odagiu, L.; Boulet, S.; de Sousa, D.M.; Daudelin, J.F.; Nicolas, S.; Labrecque, N. Early Programming of CD8⁺ T Cell Response by the Orphan Nuclear Receptor NR4A3. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 24392–24402. [\[CrossRef\]](#)
75. Nowyhed, H.N.; Huynh, T.R.; Thomas, G.D.; Blatchley, A.; Hedrick, C.C. Cutting Edge: The Orphan Nuclear Receptor Nr4a1 Regulates CD8⁺ T Cell Expansion and Effector Function through Direct Repression of Irf4. *J. Immunol.* **2015**, *195*, 3515–3519. [\[CrossRef\]](#)
76. Nowyhed, H.N.; Huynh, T.R.; Blatchley, A.; Wu, R.; Thomas, G.D.; Hedrick, C.C. The Nuclear Receptor Nr4a1 Controls CD8 T Cell Development Through Transcriptional Suppression of Runx3. *Sci. Rep.* **2015**, *5*, 9059. [\[CrossRef\]](#)
77. Woolf, E.; Xiao, C.; Fainaru, O.; Lotem, J.; Rosen, D.; Negreanu, V.; Bernstein, Y.; Goldenberg, D.; Brenner, O.; Berke, G.; et al. Runx3 and Runx1 Are Required for CD8 T Cell Development during Thymopoiesis. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7731–7736. [\[CrossRef\]](#)
78. Chen, J.; López-Moyado, I.F.; Seo, H.; Lio, C.W.J.; Hempleman, L.J.; Sekiya, T.; Yoshimura, A.; Scott-Browne, J.P.; Rao, A. NR4A Transcription Factors Limit CAR T Cell Function in Solid Tumours. *Nature* **2019**, *567*, 530–534. [\[CrossRef\]](#)
79. Lith, S.C.; van Os, B.W.; Seijkens, T.T.P.; de Vries, C.J.M. 'Nur'turing Tumor T Cell Tolerance and Exhaustion: Novel Function for Nuclear Receptor Nur77 in Immunity. *Eur. J. Immunol.* **2020**, *50*, 1643–1652. [\[CrossRef\]](#)
80. Kleberg, J.; Nataraj, A.; Xiao, Y.; Podder, B.R.; Jin, Z.; Tithi, T.I.; Zheng, G.; Smalley, K.S.M.; Moser, E.K.; Safe, S.; et al. Targeting Lineage-Specific Functions of NR4A1 for Cancer Immunotherapy. *Int. J. Mol. Sci.* **2025**, *26*, 5266. [\[CrossRef\]](#)
81. Srirat, T.; Hayakawa, T.; Mise-Omata, S.; Nakagawara, K.; Ando, M.; Shichino, S.; Ito, M.; Yoshimura, A. NR4a1/2 Deletion Promotes Accumulation of TCF1⁺ Stem-like Precursors of Exhausted CD8⁺ T Cells in the Tumor Microenvironment. *Cell Rep.* **2024**, *43*, 113898. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Brooks, J.F.; Tan, C.; Mueller, J.L.; Hibiya, K.; Hiwa, R.; Vykunta, V.; Zikherman, J. Negative Feedback by NUR77/Nr4a1 Restrains B Cell Clonal Dominance during Early T-Dependent Immune Responses. *Cell Rep.* **2021**, *36*, 109645. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Tan, C.; Hiwa, R.; Mueller, J.L.; Vykunta, V.; Hibiya, K.; Noviski, M.; Huizar, J.; Brooks, J.F.; Garcia, J.; Heyn, C.; et al. NR4A Nuclear Receptors Restrain B Cell Responses to Antigen When Second Signals Are Absent or Limiting. *Nat. Immunol.* **2020**, *21*, 1267–1279. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Kumar, A.; Hill, T.M.; Gordy, L.E.; Suryadevara, N.; Wu, L.; Flyak, A.I.; Bezbradica, J.S.; Van Kaer, L.; Joyce, S. Nur77 Controls Tolerance Induction, Terminal Differentiation, and Effector Functions in Semi-Invariant Natural Killer T Cells. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 17156–17165. [\[CrossRef\]](#)
85. Honkaniemi, J.; Kononen, J.; Kainu, T.; Pyrkönen, I.; Peltö-Huikko, M. Induction of Multiple Immediate Early Genes in Rat Hypothalamic Paraventricular Nucleus after Stress. *Mol. Brain Res.* **1994**, *25*, 234–241. [\[CrossRef\]](#)
86. Fernandez, P.M.; Brunel, F.; Jimenez, M.A.; Saez, J.M.; Cereghini, S.; Zakin, M.M. Nuclear Receptors Nor1 and NGFI-B/Nur77 Play Similar, Albeit Distinct, Roles in the Hypothalamo-Pituitary-Adrenal Axis. *Endocrinology* **2000**, *141*, 2392–2400. [\[CrossRef\]](#)
87. Helbling, J.C.; Minni, A.M.; Pallet, V.; Moisan, M.P. Stress and Glucocorticoid Regulation of NR4A Genes in Mice. *J. Neurosci. Res.* **2014**, *92*, 825–834. [\[CrossRef\]](#)
88. Jiang, L.; Wei, H.; Yan, N.; Dai, S.; Li, J.; Qu, L.; Chen, X.; Guo, M.; Chen, Z.; Chen, Y. Structural Basis of NR4A1 Bound to the Human Pituitary Proopiomelanocortin Gene Promoter. *Biochem. Biophys. Res. Commun.* **2020**, *523*, 1–5. [\[CrossRef\]](#)
89. Murphy, E.P.; Conneely, O.M. Neuroendocrine Regulation of the Hypothalamic Pituitary Adrenal Axis by the Nurr1/Nur77 Subfamily of Nuclear Receptors. *Mol. Endocrinol.* **1997**, *11*, 39–47. [\[CrossRef\]](#)
90. Zhang, D.; Heaney, A.P.; Zhang, D.; Heaney, A.P. Nuclear Receptors as Regulators of Pituitary Corticotroph Pro-Opiomelanocortin Transcription. *Cells* **2020**, *9*, 900. [\[CrossRef\]](#)
91. Wilson, T.E.; Mouw, A.R.; Weaver, C.A.; Milbrandt, J.; Parker, K.L. The Orphan Nuclear Receptor NGFI-B Regulates Expression of the Gene Encoding Steroid 21-Hydroxylase. *Mol. Cell. Biol.* **1993**, *13*, 861–868. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Philips, A.; Maira, M.; Mullick, A.; Chamberland, M.; Lesage, S.; Hugo, P.; Drouin, J. Antagonism between Nur77 and Glucocorticoid Receptor for Control of Transcription. *Mol. Cell. Biol.* **1997**, *17*, 5952–5959. [\[CrossRef\]](#) [\[PubMed\]](#)

93. Martens, C.; Bilodeau, S.; Maira, M.; Gauthier, Y.; Drouin, J. Protein-Protein Interactions and Transcriptional Antagonism between the Subfamily of NGFI-B/Nur77 Orphan Nuclear Receptors and Glucocorticoid Receptor. *Mol. Endocrinol.* **2005**, *19*, 885–897. [[CrossRef](#)] [[PubMed](#)]
94. Lavoie, O.; Michael, N.J.; Caron, A. A Critical Update on the Leptin-Melanocortin System. *J. Neurochem.* **2023**, *165*, 467–486. [[CrossRef](#)]
95. Chen, Y.; Wu, R.; Chen, H.Z.; Xiao, Q.; Wang, W.J.; He, J.P.; Li, X.X.; Yu, X.W.; Li, L.; Wang, P.; et al. Enhancement of Hypothalamic STAT3 Acetylation by Nuclear Receptor Nur77 Dictates Leptin Sensitivity. *Diabetes* **2015**, *64*, 2069–2081. [[CrossRef](#)]
96. Herring, J.A.; Crabtree, J.E.; Hill, J.T.; Tessem, J.S. Loss of Glucose-Stimulated β -Cell Nr4a1 Expression Impairs Insulin Secretion and Glucose Homeostasis. *Am. J. Physiol. Cell Physiol.* **2024**, *327*, C1111–C1124. [[CrossRef](#)]
97. Pu, Z.Q.; Liu, D.; Lobo Mouguegue, H.P.P.; Jin, C.W.; Sadiq, E.; Qin, D.D.; Yu, T.F.; Zong, C.; Chen, J.C.; Zhao, R.X.; et al. NR4A1 Counteracts JNK Activation Incurred by ER Stress or ROS in Pancreatic β -Cells for Protection. *J. Cell. Mol. Med.* **2020**, *24*, 14171–14183. [[CrossRef](#)]
98. Chen, L.; Fan, F.; Wu, L.; Zhao, Y. The Nuclear Receptor 4A Family Members: Mediators in Human Disease and Autophagy. *Cell. Mol. Biol. Lett.* **2020**, *25*, 48. [[CrossRef](#)]
99. Safe, S.; Jin, U.-H.; Morpurgo, B.; Abdayyeh, A.; Singh, M.; Tjalkens, R.B. Nuclear Receptor 4A (NR4A) Family—Orphans No More. *J. Steroid Biochem. Mol. Biol.* **2016**, *157*, 48–60. [[CrossRef](#)]
100. Doi, Y.; Oki, S.; Ozawa, T.; Hohjoh, H.; Miyake, S.; Yamamura, T. Orphan Nuclear Receptor NR4A2 Expressed in T Cells from Multiple Sclerosis Mediates Production of Inflammatory Cytokines. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 8381–8386. [[CrossRef](#)]
101. Yan, J.; Huang, J.; Wu, J.; Fan, H.; Liu, A.; Qiao, L.; Shen, M.; Lai, X. Nur77 Attenuates Inflammatory Responses and Oxidative Stress by Inhibiting Phosphorylated I κ B- α in Parkinson's Disease Cell Model. *Aging* **2020**, *12*, 8107–8119. [[CrossRef](#)] [[PubMed](#)]
102. Liu, T.Y.; Yang, X.Y.; Zheng, L.T.; Wang, G.H.; Zhen, X.C. Activation of Nur77 in Microglia Attenuates Proinflammatory Mediators Production and Protects Dopaminergic Neurons from Inflammation-Induced Cell Death. *J. Neurochem.* **2017**, *140*, 589–604. [[CrossRef](#)] [[PubMed](#)]
103. Hammond, S.L.; Safe, S.; Tjalkens, R.B. A Novel Synthetic Activator of Nurr1 Induces Dopaminergic Gene Expression and Protects against 6-Hydroxydopamine Neurotoxicity in Vitro. *Neurosci. Lett.* **2015**, *607*, 83–89. [[CrossRef](#)] [[PubMed](#)]
104. Deutsch, A.J.A.; Rinner, B.; Pichler, M.; Prochazka, K.; Pansy, K.; Bischof, M.; Fechter, K.; Hatzl, S.; Feichtinger, J.; Wenzl, K.; et al. NR4A3 Suppresses Lymphomagenesis through Induction of Proapoptotic Genes. *Cancer Res.* **2017**, *77*, 2375–2386. [[CrossRef](#)]
105. Fechter, K.; Feichtinger, J.; Prochazka, K.; Unterluggauer, J.J.; Pansy, K.; Steinbauer, E.; Pichler, M.; Haybaeck, J.; Prokesch, A.; Greinix, H.T.; et al. Cytoplasmic Location of NR4A1 in Aggressive Lymphomas Is Associated with a Favourable Cancer Specific Survival. *Sci. Rep.* **2018**, *8*, 14528. [[CrossRef](#)]
106. Li, Q.X.; Ke, N.; Sundaram, R.; Wong-Staal, F. NR4A1, 2, 3—An Orphan Nuclear Hormone Receptor Family Involved in Cell Apoptosis and Carcinogenesis. *Histol. Histopathol.* **2006**, *21*, 533–540. [[CrossRef](#)]
107. Wang, J.R.; Gan, W.J.; Li, X.M.; Zhao, Y.Y.; Li, Y.; Lu, X.X.; Li, J.M.; Wu, H. Orphan Nuclear Receptor Nur77 Promotes Colorectal Cancer Invasion and Metastasis by Regulating MMP-9 and E-Cadherin. *Carcinogenesis* **2014**, *35*, 2474–2484. [[CrossRef](#)]
108. Zhang, C.; Zhang, B.; Zhang, X.; Sun, G.; Sun, X. Targeting Orphan Nuclear Receptors NR4As for Energy Homeostasis and Diabetes. *Front. Pharmacol.* **2020**, *11*, 587457. [[CrossRef](#)]
109. Safe, S.; Shrestha, R.; Mohankumar, K. Orphan Nuclear Receptor 4A1 (NR4A1) and Novel Ligands. *Essays Biochem.* **2021**, *65*, 877–886. [[CrossRef](#)]
110. Lee, M.; Upadhyay, S.; Mariyam, F.; Martin, G.; Hailemariam, A.; Lee, K.; Jayaraman, A.; Chapkin, R.S.; Lee, S.O.; Safe, S. Flavone and Hydroxyflavones Are Ligands That Bind the Orphan Nuclear Receptor 4A1 (NR4A1). *Int. J. Mol. Sci.* **2023**, *24*, 8152. [[CrossRef](#)]
111. Hu, M.; Luo, Q.; Alitongbieke, G.; Chong, S.; Xu, C.; Xie, L.; Chen, X.; Zhang, D.; Zhou, Y.; Wang, Z.; et al. Celastrol-Induced Nur77 Interaction with TRAF2 Alleviates Inflammation by Promoting Mitochondrial Ubiquitination and Autophagy. *Mol. Cell* **2017**, *66*, 141–153.e6. [[CrossRef](#)] [[PubMed](#)]
112. Safe, S. Natural Products and Synthetic Analogs as Selective Orphan Nuclear Receptor 4A (NR4A) Modulators. *Histol. Histopathol.* **2023**, *39*, 543–556. [[CrossRef](#)]
113. Zhan, Y.; Du, X.; Chen, H.; Liu, J.; Zhao, B.; Huang, D.; Li, G.; Xu, Q.; Zhang, M.; Weimer, B.C.; et al. Cytosporone B Is an Agonist for Nuclear Orphan Receptor Nur77. *Nat. Chem. Biol.* **2008**, *4*, 548–556. [[CrossRef](#)] [[PubMed](#)]
114. Philips, A.; Lesage, S.; Gingras, R.; Maira, M.-H.; Gauthier, Y.; Hugo, P.; Drouin, J. Novel Dimeric Nur77 Signaling Mechanism in Endocrine and Lymphoid Cells. *Mol. Cell. Biol.* **1997**, *17*, 5946–5951. [[CrossRef](#)] [[PubMed](#)]
115. Perlmann, T.; Jansson, L. A Novel Pathway for Vitamin A Signaling Mediated by RXR Heterodimerization with NGFI-B and NURR1. *Genes Dev.* **1995**, *9*, 769–782. [[CrossRef](#)]
116. Zetterström, R.H.; Solomin, L.; Mitsiadis, T.; Olson, L.; Perlmann, T. Retinoid X Receptor Heterodimerization and Developmental Expression Distinguish the Orphan Nuclear Receptors NGFI-B, Nurr1, and Nor1. *Mol. Endocrinol.* **1996**, *10*, 1656–1666. [[CrossRef](#)]

117. Kagaya, S.; Ohkura, N.; Tsukada, T.; Miyagawa, M.; Sugita, Y.; Tsujimoto, G.; Matsumoto, K.; Saito, H.; Hashida, R. Prostaglandin A2 Acts as a Transactivator for NOR1 (NR4A3) within the Nuclear Receptor Superfamily. *Biol. Pharm. Bull.* **2005**, *28*, 1603–1607. [\[CrossRef\]](#)
118. Maxwell, M.A.; Muscat, G.E.O. The NR4A Subgroup: Immediate Early Response Genes with Pleiotropic Physiological Roles. *Nucl. Recept. Signal.* **2006**, *4*, e002. [\[CrossRef\]](#)
119. Safe, S. NR4A1 Acts as a Nutrient Sensor That Inhibits the Effects of Aging. *Nutrients* **2025**, *17*, 2709. [\[CrossRef\]](#)
120. Sekiya, T.; Kashiwagi, I.; Inoue, N.; Morita, R.; Hori, S.; Waldmann, H.; Rudensky, A.Y.; Ichinose, H.; Metzger, D.; Chambon, P.; et al. The Nuclear Orphan Receptor Nr4a2 Induces Foxp3 and Regulates Differentiation of CD4⁺ T Cells. *Nat. Commun.* **2011**, *2*, 269. [\[CrossRef\]](#)
121. Pei, L.; Castrillo, A.; Tontonoz, P. Regulation of Macrophage Inflammatory Gene Expression by the Orphan Nuclear Receptor Nur77. *Mol. Endocrinol.* **2006**, *20*, 786–794. [\[CrossRef\]](#)
122. Shaked, I.; Hanna, R.N.; Shaked, H.; Chodaczek, G.; Nowyhed, H.N.; Tweet, G.; Tacke, R.; Basat, A.B.; Mikulski, Z.; Togher, S.; et al. Transcription Factor Nr4a1 Couples Sympathetic and Inflammatory Cues in CNS-Recruited Macrophages to Limit Neuroinflammation. *Nat. Immunol.* **2015**, *16*, 1228–1234. [\[CrossRef\]](#)
123. Rothe, T.; Ipseiz, N.; Faas, M.; Lang, S.; Perez-Branguli, F.; Metzger, D.; Ichinose, H.; Winner, B.; Schett, G.; Krönke, G. The Nuclear Receptor Nr4a1 Acts as a Microglia Rheostat and Serves as a Therapeutic Target in Autoimmune-Driven Central Nervous System Inflammation. *J. Immunol.* **2017**, *198*, 3878–3885. [\[CrossRef\]](#) [\[PubMed\]](#)
124. Trudler, D.; Levy-Barazany, H.; Nash, Y.; Samuel, L.; Sharon, R.; Frenkel, D. Alpha Synuclein Deficiency Increases CD4⁺ T-Cells pro-Inflammatory Profile in a Nurr1-Dependent Manner. *J. Neurochem.* **2020**, *152*, 61–71. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Pönniö, T.; Conneely, O.M. Nor-1 Regulates Hippocampal Axon Guidance, Pyramidal Cell Survival, and Seizure Susceptibility. *Mol. Cell. Biol.* **2004**, *24*, 9070–9078. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Hong, H.; Su, J.; Huang, C.; Lu, X.; Cui, Z. Comprehensive Insights into the Function and Molecular and Pharmacological Regulation of Neuron-Derived Orphan Receptor 1, an Orphan Receptor. *Front. Pharmacol.* **2022**, *13*, 981490. [\[CrossRef\]](#)
127. Lu, L.; Jang, S.; Zhu, J.; Qin, Q.; Sun, L.; Sun, J. Nur77 Mitigates Endothelial Dysfunction through Activation of Both Nitric Oxide Production and Anti-Oxidant Pathways. *Redox Biol.* **2024**, *70*, 103056. [\[CrossRef\]](#)
128. Jin, M.; Wang, Y.; Song, M.; Guo, W.; Li, S.; Pu, Z. Targeting the Nuclear Orphan Receptor NR4A1: A Key Target in Lung Cancer Progression and Therapeutic Resistance. *Front. Oncol.* **2025**, *15*, 1566598. [\[CrossRef\]](#)
129. Mullican, S.E.; Zhang, S.; Konopleva, M.; Ruvolo, V.; Andreeff, M.; Milbrandt, J.; Conneely, O.M. Abrogation of Nuclear Receptors Nr4a3 AndNr4a1 Leads to Development of Acute Myeloid Leukemia. *Nat. Med.* **2007**, *13*, 730–735. [\[CrossRef\]](#)
130. Veum, V.L.; Dankel, S.N.; Gjerde, J.; Nielsen, H.J.; Solsvik, M.H.; Haugen, C.; Christensen, B.J.; Hoang, T.; Fadnes, D.J.; Busch, C.; et al. The Nuclear Receptors NUR77, NURR1 and NOR1 in Obesity and during Fat Loss. *Int. J. Obes.* **2012**, *36*, 1195–1202. [\[CrossRef\]](#)
131. Kim, B.Y.; Kim, H.; Cho, E.J.; Youn, H.D. Nur77 Upregulates HIF-Alpha by Inhibiting PVHL-Mediated Degradation. *Exp. Mol. Med.* **2008**, *40*, 71–83. [\[CrossRef\]](#)
132. Ismaiel, M.; Murphy, B.; Aldhafiri, S.; Giffney, H.E.; Thornton, K.; Mukhopadhyay, A.; Keogh, C.E.; Fattah, S.; Mohan, H.M.; Cummins, E.P.; et al. The NR4A Agonist, Cyclosporine B, Attenuates pro-Inflammatory Mediators in Human Colorectal Cancer Tissue Ex Vivo. *Biochem. Biophys. Res. Commun.* **2021**, *554*, 179–185. [\[CrossRef\]](#) [\[PubMed\]](#)
133. Willems, S.; Kilu, W.; Ni, X.; Chaikuad, A.; Knapp, S.; Heering, J.; Merk, D. The Orphan Nuclear Receptor Nurr1 Is Responsive to Non-Steroidal Anti-Inflammatory Drugs. *Commun. Chem.* **2020**, *3*, 85. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Teichmann, T.; Pflüger-Müller, B.; Giménez, V.M.M.; Sailer, F.; Dirks, H.; Zehr, S.; Warwick, T.; Brettner, F.; Munoz-Tello, P.; Zimmer, A.; et al. The Endocannabinoid Anandamide Mediates Anti-Inflammatory Effects through Activation of NR4A Nuclear Receptors. *Br. J. Pharmacol.* **2025**, *182*, 1164–1182. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Wansa, K.D.S.A.; Harris, J.M.; Yan, G.; Ordentlich, P.; Muscat, G.E.O. The AF-1 Domain of the Orphan Nuclear Receptor NOR-1 Mediates Trans-Activation, Coactivator Recruitment, and Activation by the Purine Anti-Metabolite 6-Mercaptopurine. *J. Biol. Chem.* **2003**, *278*, 24776–24790. [\[CrossRef\]](#)
136. Moyer, C.L.; Brown, P.H. Targeting Nuclear Hormone Receptors for the Prevention of Breast Cancer. *Front. Med.* **2023**, *10*, 1200947. [\[CrossRef\]](#)
137. Chen, Z.; Zhang, D.; Yan, S.; Hu, C.; Huang, Z.; Li, Z.; Peng, S.; Li, X.; Zhu, Y.; Yu, H.; et al. SAR Study of Celastrol Analogs Targeting Nur77-Mediated Inflammatory Pathway. *Eur. J. Med. Chem.* **2019**, *177*, 171–187. [\[CrossRef\]](#)
138. Xiong, Y.; Ran, J.; Xu, L.; Tong, Z.; Adel Abdo, M.S.; Ma, C.; Xu, K.; He, Y.; Wu, Z.; Chen, Z.; et al. Reactivation of NR4A1 Restrains Chondrocyte Inflammation and Ameliorates Osteoarthritis in Rats. *Front. Cell Dev. Biol.* **2020**, *8*, 158. [\[CrossRef\]](#)
139. Ralph, J.A.; Ahmed, A.U.; Santos, L.L.; Clark, A.R.; McMorro, J.; Murphy, E.P.; Morand, E.F. Identification of NURR1 as a Mediator of MIF Signaling during Chronic Arthritis: Effects on Glucocorticoid-Induced MKP1. *Am. J. Pathol.* **2010**, *177*, 2366–2378. [\[CrossRef\]](#)

140. Murphy, E.P.; McEvoy, A.; Conneely, O.M.; Bresnihan, B.; Fitzgerald, O. Involvement of the Nuclear Orphan Receptor NURR1 in the Regulation of Corticotropin-Releasing Hormone Expression and Actions in Human Inflammatory Arthritis. *Arthritis Rheum.* **2001**, *44*, 782–793. [[CrossRef](#)]
141. Mix, K.S.; McMahon, K.; McMorrow, J.P.; Walkenhorst, D.E.; Smyth, A.M.; Petrella, B.L.; Gogarty, M.; Fearon, U.; Veale, D.; Attur, M.G.; et al. Orphan Nuclear Receptor NR4A2 Induces Synoviocyte Proliferation, Invasion, and Matrix Metalloproteinase 13 Transcription. *Arthritis Rheum.* **2012**, *64*, 2126–2136. [[CrossRef](#)]
142. Paillasse, M.R.; de Medina, P. The NR4A Nuclear Receptors as Potential Targets for Anti-Aging Interventions. *Med. Hypotheses* **2015**, *84*, 135–140. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.