receptors

MDPI

Review

Exploring Nuclear Receptor Functions in Multipotent Mesenchymal Stromal Stem Cell Differentiation

Alivia Dougherty and Bruce Blumberg *

Department of Developmental and Cell Biology, University of California, Irvine, CA 92697, USA; aldoughe@uci.edu
* Correspondence: blumberg@uci.edu

Abstract

Multipotent mesenchymal stromal stem cells have captivated the scientific community in recent years due to their ability to differentiate into multiple adult cell types. Central to this potential are many members of the nuclear hormone receptor superfamily, comprising 48 ligand-modulated transcription factors involved in key biological processes such as metabolism, physiology, embryonic development, and reproduction. These transcription factors influence cellular fate by regulating gene expression networks critical for MSC specification, commitment, and differentiation. This review explores the role of nuclear receptors in MSC development, focusing on interactions with chromatin structure, co-regulatory complexes, and responsiveness to extracellular stimuli such as hormones, metabolic cues, and endocrine-disrupting chemicals. We conclude with a discussion of the dangers posed by exogenous and aberrant signaling through nuclear receptors.

Keywords: MSC; mesenchymal stem cell; EDC; endocrine disruptor; nuclear receptor

1. Introduction

Multipotent mesenchymal stromal stem cells, also called mesenchymal stem cells (MSCs), are a unique class of embryonic and adult stem cells that are notable for their ability to differentiate into multiple adult tissues. MSCs give rise to adipocytes, osteoblasts, chondrocytes, myoblasts, fibroblasts, and several neural cell types [1]. MSC lineages also express some of the key markers typical of endothelial cells, neuron-like cells, and cardiomyocytes [1]. Recent research has linked members of the nuclear hormone receptor superfamily (NR) in processes governing MSC commitment, differentiation, and function [2]. These ligand-activated transcription factors serve as molecular sensors that translate extracellular signals into precise gene expression programs, thereby influencing the fate and function of cells such as MSCs. This review will first explore the integral role of nuclear receptors within MSCs, beginning with an examination of their structure, followed by a brief discussion of the mechanisms by which nuclear receptors direct gene expression, with a focus on ligand-binding, dimerization, and chromatin remodeling [1,2]. We next discuss specific nuclear receptors that are known or thought to be involved in steering MSC differentiation. Finally, we address how exogenous cell signaling, including the influence of endocrine disruptors, can impact nuclear receptor activity in MSCs.

Academic Editor: Stephen H. Safe

Received: 22 August 2025
Revised: 17 October 2025
Accepted: 13 January 2026
Published: 19 January 2026

2. NRs and MSC Biology

2.1. MSC Biology

It is important to note that the terminology surrounding MSCs can be convoluted and inconsistent. The terms "mesenchymal stromal cells", "multipotent mesenchymal stromal stem cells", and "mesenchymal stem cells" are often used interchangeably, although they refer to distinct cell types that differ in terms of functional specificity and "stemness." Mesenchymal stromal cells are heterogeneous populations of adult cells that can be found in various tissues throughout the body, such as bone marrow, adipose tissue, and umbilical cord tissue [3]. This grouping of stromal cells is a broader category, including various mesenchymal cells with self-renewing and immunomodulatory properties. Mesenchymal stem cells (MSCs) are a specific subset of the larger mesenchymal stromal cell grouping that retain the ability to act as self-renewing progenitor cells and can differentiate into various cell types, such as adipocytes, osteoblasts, and chondrocytes [4]. These stem cells are often isolated and characterized in vitro through their expression of specific surface markers (e.g., CD73, CD90, and CD105) and their trilineage differentiation potential (adipogenic, chondrogenic, and osteogenic). However, due to the overlapping functions and phenotypes of these cells, especially when cultured outside of their native environment, the distinction between MSC types can become blurred in experimental and clinical contexts. Therefore, it has been recommended that multipotent MSCs be further identified by their tissue of origin for the sake of clarity [4]. For example, human bone marrow-derived MSCs would be designated hBM-MSCs. For the sake of clarity and consistency, the term MSCs in the remainder of this review will refer broadly to the mesenchymal stromal stem cell population, which includes both multipotent stem cells akin to bona fide mesenchymal stem cells and their more lineage-committed counterparts that still retain multilineage potential.

MSC potential is typically restricted by their respective niches via the limited selection of growth factors and cell signals in their surrounding microenvironment. This enforces a tissue-specific differentiation pattern to the cells in vivo, although this limitation is not present in vitro when cells are cultured outside of their normal niches [5,6]. The local microenvironment exerts a tightly regulated control over MSC fate through a specific array of extracellular signals, including soluble growth factors, cytokines, and mechanical cues, that limit cellular access to the full range of lineage options observed in vitro. For example, MSCs in the bone marrow niche are predominantly involved in maintaining bone homeostasis and supporting hematopoietic stem cells, and thus are biased toward osteogenic and stromal fates. In contrast, when BM-MSCs are removed from these environmental constraints and cultured ex vivo, they encounter an artificially permissive milieu that allows for broader differentiation capacity. Under optimized culture conditions, supplemented with lineage-specific differentiation cocktails, BM-MSCs can even differentiate into neuron-like cells. This discrepancy emphasizes that while MSCs may possess inherent multipotency, their true functional potential is highly dependent on the surrounding context [1].

2.2. Nuclear Receptor-Directed Gene Regulation

Nuclear receptors are a specialized superfamily of ligand-modulated transcription factors that translate extracellular cues into gene expression. NRs operate through a complex multi-step mechanism. In their unliganded state, many nuclear receptors are already bound to chromatin, where they may associate with co-repressor proteins [7,8]. Upon ligand binding, NRs experience a conformational change within their ligand-binding domains [8]. This change involves a reorientation of alpha-helices, including those that form the activation function-2 (AF-2) region [9,10]. This repositioning displaces present co-repressors and creates a binding surface environment favorable to the recruitment of co-activators [10]. Co-activator proteins such as CBP/p300 typically possess histone

acetyltransferase (HAT) activity [11]. Acetylation reduces the positive charge on histone tails, loosening their hold on DNA and opening the chromatin structure to facilitate transcription. Conversely, positioning of AF-2 can also recruit corepressors and associated histone deacetylases to blunt gene expression [10]. Various nuclear receptors (e.g., VDR, RARs, and TRs) are often associated with corepressor proteins such as NCoR or SMRT [12]. Corepressors recruit histone deacetylases (HDACs), which keep the chromatin in a largely inactive state [9]. This regulation of gene expression through varying chromatin interactions is a recurring theme within the NR superfamily. Maintaining balance between the association of co-repressors/histone deacetylases and recruitment of co-activators allows NRs to integrate hormonal and metabolic signals within the local chromatin environment. This functions to maintain controlled gene expression patterns in response to changing extracellular conditions.

NR signaling is also intricately balanced by post-translational modifications such as phosphorylation and ubiquitination [13]. These post-translational modifications impact receptor stability, localization, and interaction with co-regulatory complexes [13]. This mosaic of chromatin interactions ensures that the receptors integrate extracellular signals such as hormonal fluctuations or metabolic changes with intracellular transcriptional responses. The ligand-induced conformational shift dictates the switch between repression and activation [10] and also defines the broader framework of chromatin remodeling and transcription factor assembly.

3. NRs and MSC Commitment and Differentiation

Figure 1 shows a schematic overview of which NRs function in MSC differentiation to specific mature cell types, and Table 1 highlights the essential roles of each NR in MSC differentiation together with the standard and common names. Because NRs are regulators of gene expression, much has been learned via transcriptomic studies of gene expression in response to stimulation or blockade of receptor action with specific ligands, together with gain- and loss-of-function studies in cultured cells and in transgenic animal models.

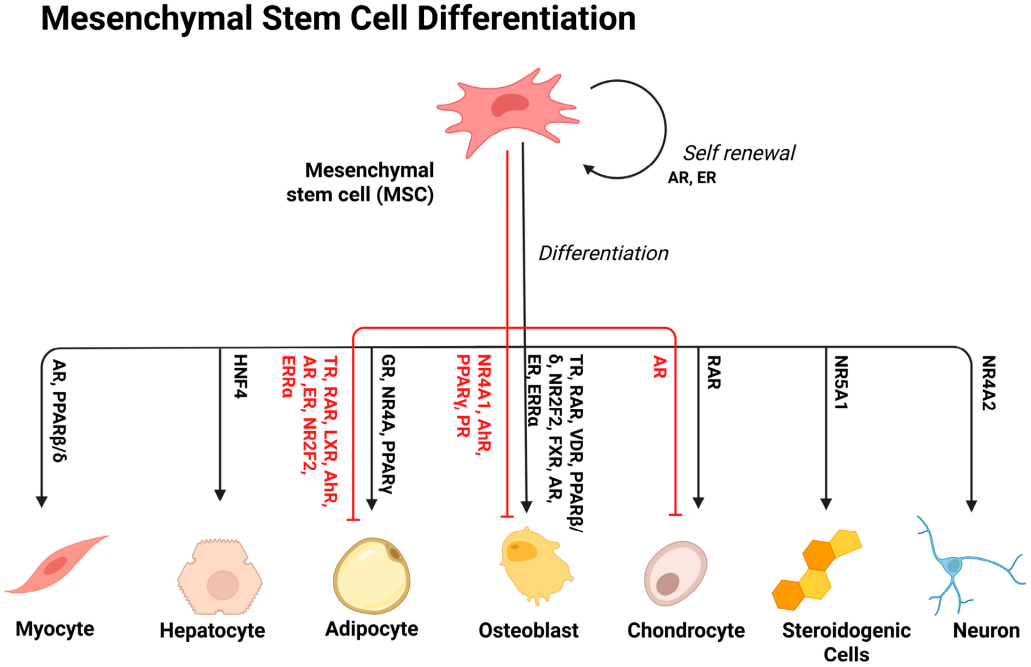

Figure 1. Mesenchymal stem cell differentiation and corresponding nuclear receptor signaling pathways. Black arrows correspond to nuclear receptors that positively control MSC differentiation, and red inhibitory arrows indicate nuclear receptors that negatively impact MSC differentiation into their respective cell types.

Table 1. Major functions of NHRs in MSC differentiation.

Standard Name	Common Name	Role in MSCs
NR3C4	AR	Inhibits adipogenesis, promotes myogenesis, blocks chondrogenesis and suppression enhances MSC self-renewal
NR3A1,2	ERα,β	Suppresses adipogenesis, promotes osteogenesis, enhances MSC proliferation
NR3B1,2,3	ERRα,β,γ	ERRγ antagonizes osteogenis, ERRα increases brown fat differentiation, ERRα overexpression increases osteoblastic differentiation, while silencing led to less osteoblastic differentiation. ERRα also mitigates senescence in MSCs
NR1H	FXR	Positive regulator of osteogenesis in MSCs by increasing Wnt/β-catenin signaling at the expense of adipogenesis
NR3C1	GR	Promotes adipogenesis in MSCs at the expense of osteogenesis
NR2A1, 2	HNF4α, β	Directs MSCs toward hepatocyte fate
NR1H1,2	LXRα,β	Overexpression of LXRα in mouse BM-MSCs increased Wnt signaling and bone marker expression while inhibiting expression of adipogenic markers. Also led to differentiation of juxtaglomerular cells in mouse BM-MSCs
NR1F1,2,3	RORα,β,γ	RORα up-regulation in MSCs led to increased osteogenic differentiation. RORγ expression in MSCs could influence inflammatory phenotypes depending on context, may regulate immunomodulation.
NR2F1, 2	COUP-TFI, COUP-TFII	NR2F1 knockdown inhibited osteogenesis. Overexpression of NR2F2 increased PPARγ expression and decreased bone marker genes. Silencing diminished lipid accumulation and adipogenic gene expression while promoting osteogenic markers.
NR4A1,2,3	Nur77, Nurr1, NOR1	Nur77 acts as a negative regulator of osteogenic differentiation, knockdown increased expression of osteogenic markers in MSCs and reduced adipogenic differentiation. Nurr1 overexpression in MSCs led to expression of dopaminergic neuron markers
NR5A1,2	SF-1, LRH-1	Forced expression of SF-1 or SF-1+LRH-1 produced steroidogenic cells after implantation into adrenal-insufficient mice.
NR1C1,2,3	PPARα,β/δ, γ	PPARγ expression and activation in MSCs leads to adipogenic differentiation and suppression of osteogenic pathways. PPARβ/δ can promote osteogenesis in MSCs.
NR3C3	PR	Actively restrains osteogenic differentiation while promoting osteoclast recruitment and bone resorption.
NR1B1,2,3	RARα,β,γ	RA signaling promotes neural identity, increases osteogenesis and inhibits adipogenesis in MSCs. RARγ activation in MSCs promotes chondrogenesis and inhibition inhibits chondrogenesis, and increases ossification
NR2B1,2,3	RXRα,β,γ	Partner for FXR, LXR, PPARs, RARs, TR, VDR and other NHRs. Can also act as homodimers. RXR activation in MSCs promotes adipogenic commitment at the expense of bone.
NR1A1,2	TRα,β	Early TR activation in MSCs enhances osteogenic differentiation and inhibits adipocyte proliferation while later activation promotes expression of adipogenic genes and later the differentiation of thermogenic adipocytes
NR1I1	VDR	Activation promotes expression of bone markers and substrate adhesion and also reduces senescence in MSCs
	AhR	AhR activation suppresses adipogenesis and osteogenesis, while increasing inflammation. Also supports MSC multipotency by inhibiting lineage commitment

3.1. Androgen Receptor (AR, NR3C4)

The androgen receptor (AR, NR3C4) [8] is a steroid receptor that acts as a homodimer to regulate gene expression. Like other steroid receptors discussed below, AR has non-genomic actions on gene regulation that are less well-studied than its genomic actions as a transcription factor. AR is largely sequestered in the cytoplasm until ligand binding stimulates its nuclear

transport [8]. AR plays a critical role in MSC lineage commitment by inhibiting adipogenesis and promoting myogenic differentiation in males. AR signaling suppresses adipocyte formation by downregulating adipogenic regulators such as PPARγ and C/EBPα [14,15]. In contrast, AR activation facilitates skeletal muscle differentiation through transcriptional induction of myogenic factors, including MyoD and Myf5, installing AR as a necessary enhancer of myogenesis in MSC populations [16,17]. In harmony with these sentiments, genetic ablation of AR led to increased adiposity and concurrent reductions in bone and muscle mass [18,19]. These findings are consistent with an important role for AR as a balancing factor in MSC lineage determination, at least in males. Emerging evidence also suggests that AR antagonism may enhance chondrogenic potential, positioning AR as a negative regulator of cartilage formation in male rabbits [20]. Somewhat paradoxically, AR suppression has also been associated with enhanced MSC self-renewal [14]. This may result from AR action relieving constraints on stemness-associated transcriptional programs. AR signaling clearly plays a larger role in MSC fate, regulating musculoskeletal homeostasis and self-renewal.

3.2. The Estrogen Receptors (ERs, NR3A)

The estrogen receptors (ERα, NR3A1 and Erβ, as well as NR3A2) [8] are activated by several endogenous estrogens, notably 17β-estradiol, as well as 17α-estradiol, estrone, and estriol [21,22]. ERs remain largely in the cytoplasm where, similar to GR, ligand binding results in the release of a multiprotein complex and translocation into the nucleus [22,23]. ERs then dimerize and bind to estrogen response elements (EREs) in the DNA. However, ER has an alternate repressive binding pathway, one where the homodimer exists in the nucleus prior to ligand binding. Upon ligand binding in the nucleus, the ER releases coactivators (CBP/P300, etc.) and recruits corepressors SMRT and NcoR1 to inhibit transcription [23]. It is one of the few steroid-binding receptors to interact with co-repressors [24]. ERs also have a non-genomic pathway of action where they are tethered to the cell membrane and act via G-protein coupled mechanisms [25].

ERs are primary mediators of estrogen's effects on MSCs, particularly in bone formation and skeletal homeostasis. ERα and ERβ polymorphisms have been shown to correlate with bone mass in humans [22]. ERα and ERβ are also expressed in immune cells, such as T cells and monocytes [26], which are important in bone regulation. Simultaneously, ER signaling suppresses adipogenic differentiation by downregulating transcriptional regulators of adipogenesis, including PPARγ and C/EBPα. This shows a pattern of shifting MSC lineage commitment away from adipogenesis and towards more osteogenic fates. Activation of ERs by xenoestrogens such as bisphenol S [27] or dichlorodiphenyltrichloroethane [28] was shown to inhibit MSC self-renewal. Estrogen receptor signaling also interacts with other signaling pathways, including those involved in metabolic and growth factor responses [29]. ER activation has also been associated with enhanced MSC proliferation, suggesting a broader role in maintaining progenitor cell pools.

3.3. The Estrogen-Related Receptors (ERRs, NR3B)

The estrogen-related receptors (ERRs, NR3B) comprise a family of three members: ERRα (NR3B1), ERRβ (NR3B2), and ERRβγ (NR3B3) [8]. ERRs are key players in osteogenesis, although their specific roles depend on the presence of coactivator proteins. In contrast to ERs, members of the estrogen-related receptor (ERR) family, particularly ERRγ (NR3B3), have been shown to antagonize osteogenic differentiation under certain conditions [30]. ERRγ may exert these effects by interfering with Wnt/β-catenin signaling and/or by repressing osteogenic transcriptional networks. ERRα targeted deletion in adipocytes was also shown to promote osteogenesis and vascular formation in mouse bone marrow [31].

Similarly, knockdown of ERRα in BM-MSCs abolished the anti-senescence effects of the phytoestrogen genistein in rats, establishing a role for ERRα in MSC senescence [32].

ERRα increases brown fat differentiation from MSCs [33]. ERRα silencing in hMSCs led to increased osteoblastic differentiation in one study [34], whereas in another, BM-MSCs from ERRα knockout mice showed reduced proliferation as well as less osteoblastic differentiation [35]. In contrast, overexpression of ERRα in MC3T3-E1 pre-osteoblast cells increased expression of osteoblastic markers and accumulation of calcium. These results could be at least partly resolved by showing that the presence of coactivator proteins such as PGC-1α led to increased Wnt signaling and bone differentiation, whereas ERRα knockout also enhanced Wnt signaling and increased osteoblastic differentiation [36].

3.4. The Farnesoid X Receptor (FXRs, NR1H4,5)

The farnesoid X receptors (FXRα, NR1H4 and FXRβ, as well as NR1H5) [8] are receptors for bile acids and lanosterols, respectively. While NR1H5 is a pseudogene in primates, it is a lanosterol receptor in rodents [37]. It has no described role in MSCs. FXRα was shown to be a positive regulator of osteogenic differentiation in MSCs [38]. Bone tissue contains bile acid, accumulated from serum and released into the bone microenvironment. FXR activation in bone enhances osteogenesis by promoting the expression of osteogenic transcription factors RUNX2 and osterix, as well as matrix mineralization genes osteocalcin and alkaline phosphatase [39,40]. The mechanism by which FXR influences osteogenesis is through pressure on Wnt/β-catenin signaling pathways. Activation of FXR not only increases nuclear β-catenin accumulation but also upregulates Wnt target genes, thus driving osteoblast differentiation at the expense of adipogenesis [38]. These findings are particularly relevant in the context of age-related bone loss and osteoporosis, as FXR signaling may be harnessed to maintain bone homeostasis. FXR remains an emerging NR in the direction of lineage specification in MSCs.

3.5. The Glucocorticoid Receptor (GR, NR3C1)

The glucocorticoid receptor (GR, NR3C1) is a high-affinity receptor for endogenous glucocorticoids such as cortisol in humans and corticosterone in rodents [8]. In its native state, GR resides in the cytoplasm bound to heat shock proteins [41]. GR remains in the cytoplasm held in its inactive state by a multiprotein complex composed of Hsp90, Hsp70, and P23 [41]. Upon binding its ligand, GR dissociates from this complex and undergoes a conformational change that allows it to dimerize and translocate to the nucleus [41]. Once in the nucleus, GR binds to glucocorticoid response elements (GREs) [41], and this interaction recruits transcriptional coactivators, resulting in regulation of gene expression [41]. The effects of GR signaling are highly context-dependent, with evidence that GR signaling tilts the differentiation balance of MSCs away from osteogenesis toward adipogenesis [42]. GR has been implicated in the loss of regulation of bone density during the aging process and contributes to pathological conditions like osteoporosis and marrow adiposity. In one study, GR conditional knockout mice demonstrated a significant reduction in both cortical and trabecular bone as compared to GR-wild type controls [43]. This phenotype was even more pronounced at 21 weeks of age, indicating the importance of GR in maintenance during development and also throughout aging [43]. Similarly, it was previously reported that conditional deletion of the GR in Runx2-expressing osteoblasts reduced trabecular bone mass in the spine of young mice [44]. GR-mediated transcriptional networks also interact with signaling pathways such as Wnt and BMP, contributing to the strong effects of GR on the balance between osteogenesis and adipogenesis.

3.6. Hepatocyte Nuclear Factor 4 (HNF4, NR2A)

Hepatocyte nuclear factor 4 comprises a family of two genes, HNF4α (NR2A1) and HNF4γ (NR2A2) [8]. Both have apparent constitutive activity that results from tight binding of 14-18 carbon fatty acids [45]. HNF4 comprises a family of regulators of fatty acid oxidation and storage in the liver. HNF4α is a regulator of hepatic differentiation [46] and directs MSCs toward a hepatocyte-like fate. Ectopic expression of HNF4α in adipose-derived MSCs initiates a transcriptional cascade that activates liver-enriched genes, including albumin, α-fetoprotein, and cytochrome P450 enzymes. This cascade and following activation promote the acquisition of hepatocytic morphology and function [47]. The mechanism by which HNF4α carries out this process is through its function as a transcriptional hub. HNF4α cooperates with other hepatic transcription factors such as HNF1α and C/EBPα to remodel chromatin and establish a hepatic gene expression program [48]. In recent studies, integrative epigenomic analyses have revealed that HNF4α activation in adipose-derived MSCs leads to widespread enhancer reprogramming and histone modification changes that parallel those observed during normal liver development [49]. Thus, HNF4α is the most notable inducer of hepatogenic differentiation in MSCs.

3.7. The Liver X Receptors (LXR, NR1H)

The Liver X Receptor (LXR) is another emerging NR in the context of MSC differentiation and cell identity. There are two LXR genes, LXRα (NR1H3) and LXRβ (NR1H2) [8]. These two receptors share a high degree of amino acid similarity and are activated by similar oxysterol and synthetic ligands, but differ in their localization [50]. LXRα was first identified in the liver and other metabolically active tissues such as the kidney, intestine, adipose tissue, and macrophages [34]. Conversely, LXRβ is ubiquitously expressed [50]. Both receptors operate through the classic heterodimer nuclear receptor mechanism with RXR [51]. LXR plays a variety of roles in metabolic and immune health, and most research on the receptor has been primarily implicated in atherosclerosis and cardiovascular disease.

Recent studies have investigated LXRs in metabolic disorders [52,53]. Its identified role as a cholesterol regulator directed much of this research toward adipogenesis and obesity related disorders [54]. LXR contributions to lipogenesis also implicated the receptor in the regulation of MSC fate. LXRα overexpression in mouse BM-MSCs led to increased Wnt signaling and expression of Wnt1, Wnt5a, and Wnt 10b, together with blunted expression of adipogenic markers such as PPARγ and fatty acid synthase [55]. In contrast, knockout of LXRα in MSCs led to decreased Wnt signaling and expression of Wnts 1, 5a, and 10b and correspondingly increased expression of PPARγ, fatty acid synthase, lipid droplet accumulation, and adipocyte differentiation [55].

LXRα activation in mouse BM-MSCs or human BM-MBCs was also shown to induce differentiation into a juxtaglomerular cell type that could express marker genes such as renin and smooth muscle actin [56]. While it is unclear whether this type of differentiation occurs in vivo, it could be related to increased renin production in the context of obesity.

3.8. Retinoic Acid Receptor-Related Orphan Receptor (RORs, NR1F)

RORs comprise a family of three genes: the NR1F family RORα (NR1F1), RORβ (NR1F2), and RORγ (NR1F3) [8]. RORα was shown to play important roles in chondrogenic differentiation of MSCs, in vitro [57]. Up-regulation of RORα promoter activity after depletion of DNA methyltransferase 1 increased expression of osteogenic genes in MSCs [58].

RORγ is best known for its role in the development and function of Th17 cells through the regulation and expression of pro-inflammatory cytokines IL-17A and IL-22 [59]. In the context of MSCs, RORγ may utilize its influence over proinflammatory cytokines to control cytokine secretion and shape T cell responses. MSCs can express RORγ under inflamma-

tory stimuli, possibly contributing to their context-dependent pro- or anti-inflammatory phenotypes [60]. Inhibition of RORγ has been shown to attenuate Th17-mediated immune responses, which could be leveraged to enhance immunosuppressive properties of MSCs in a therapeutic setting [61]. Currently, the direct mechanisms by which RORγ functions in the context of MSCs remain uncertain; however, there is some evidence that it may serve as a transcriptional node that links NR signaling and MSC-mediated immunomodulation [62].

3.9. The COUP-TF Family (NR2F)

The NR2F family comprises a family of three genes: COUP-TFI (NR2F1), COUP-TFII (NR2F2), and EAR1 (NR2F3) [8]. The NR2F family member COUP-TFI (Chicken Ovalbumen Upstream Promoter-Transcription Factor I, NR2F1) was shown to be highly expressed in osteoblast differentiation from MSCs, and knockdown of NR2F1 mRNA expression inhibited osteogenesis [63]. Overexpression of COUP-TFII in hMSCs led to increased *PPARγ* expression and decreased levels of *osteocalcin* [64]. In contrast, knockdown of COUP-TFII significantly reduced adipocyte formation and enhanced osteoblast differentiation, revealing a repressive influence on osteogenic programming [63]. Silencing *COUP-TFII* in bone marrow-derived MSCs not only diminished lipid accumulation and adipogenic gene expression but also upregulated osteogenic markers such as *RUNX2* and *ALP* [63]. This suggests a reciprocal regulatory mechanism. Beyond adipogenesis and osteogenesis, COUP-TFII may also contribute to MSC chondrogenesis. Gao et al. (2017) showed that COUP-TFII is expressed during early chondrogenic differentiation [65]. COUP-TFII enhances the expression of cartilage-specific genes, including *SOX9*, *COL2A1*, and *ACAN*, furthering chondrogenic maturation [65]. These studies establish COUP-TFII as a lineage-instructive nuclear receptor in MSCs.

3.10. The NR4A Family

The NR4A family of orphan nuclear receptors is composed of NR4A1 (Nur77), NR4A2 (Nurr1), and NR4A3 (NOR1) [8]. As a family, these receptors have been implicated in balancing osteogenic, adipogenic, and neurogenic potential. NR4A1 acts as a negative regulator of osteogenic differentiation; knockdowns of NR4A1 in MSCs led to increased expression of *SLP* (secreted phosphoprotein 1/osteopontin) and elevated calcium deposition [66]. These changes indicate enhanced calcification and osteogenesis. The same study demonstrated that NR4A1 knockdown reduced adipogenic differentiation, while overexpression enhanced lipid accumulation and upregulated adipogenic markers such as *PPARγ* and *C/EBPα* [66]. This adipogenic effect was found to be mediated, at least in part, through modulation of Notch signaling. This implicates NR4A1 as a pro-adipogenic and anti-osteogenic factor in MSC lineage fate. However, other recent data support a more context-dependent impact; NR4A1 may under some conditions promote osteogenesis and bone healing while suppressing adipogenesis [67].

NR4A family members are not entirely limited to differentiation into bone, fat, or cartilage. Beyond its role in skeletal tissues, NR4A2 (Nurr1) has been implicated as a key regulator of dopaminergic neuron production [68] as well as promoting neurogenic differentiation of umbilical cord-derived MSCs [69]. It was also reported that ectopic expression of NR4A2 in human MSCs induced dopaminergic characteristics, including elevated expression of *tyrosine hydroxylase* and *dopamine transporter* [70].

3.11. The NR5A Family

The NR5A comprises two members, steroidogenic factor-1 (SF-1; NR5A1) and liver receptor homolog 1 (LRH-1, NR5A2) [8]. NR5A1/SF-1 was identified for its steroidogenic lineage specification from mesenchymal stem cells (MSCs), primarily in the context of adrenal and gonadal cell fate. SF-1 functions as a transcriptional regulator of steroidogenic

gene expression, including *CYP11A1*, *STAR*, and *CYP17A1*. All of these are essential for the biosynthesis of steroid hormones. Forced expression of SF-1, or SF-1 together with LRH-1 in human MSCs was sufficient to induce a steroidogenic program, leading to upregulation of steroid biosynthetic enzymes and accumulation of cortisol and other steroid metabolites in vitro [71,72]. Furthermore, overexpression of SF-1 in MSCs and their subsequent implantation into adrenal insufficient mice led to steroid synthesis, in vivo [73]. Umbilical cord-derived MSCs were superior to BM-MSCs in their steroidogenic response to SF-1 overexpression as measured by production of steroidogenic genes [74]. Taken together, these results indicate that overexpression of NR5A genes is sufficient to reprogram MSCs into functional steroidogenic-like cells.

3.12. The Peroxisome Proliferator-Activated Receptors (PPARs, NR1C)

The peroxisome proliferator-activated receptor (PPAR) family includes PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3) [8,29]. PPARγ, in particular, is an integral player in the receptor family and serves as an important regulator in both stem cell differentiation and endocrine signaling [75]. Indeed, it is considered to be the "master regulator" of adipogenesis [75]. Structurally, PPARγ is composed of distinct modular domains that provide isoform-specific functions [75–77]. PPARγ1 primarily directs the function of MSCs toward an adipogenic lineage and away from the osteogenic lineage [78]. Loss-of-function studies revealed that sclerostin production downstream of PPARγ mediated this phenotype [79]. PPARγ2 activation drives the commitment of MSCs toward adipocytes by inducing a transcriptional program favoring lipid metabolism, insulin sensitivity, and terminal adipocyte differentiation [75]. This process is interwoven with the suppression of alternative differentiation pathways such as osteogenesis. PPARγ acts as an integrative node that links extracellular cues to gene regulation in MSC lineage commitment. Circulating ligands, from dietary fatty acids to hormonally regulated lipid mediators, bind to PPARγ and attune its activity in response to changes in metabolic state [80]. Most critically, PPARγ engages in crosstalk with other nuclear receptors and transcription factors, including the glucocorticoid and estrogen receptors in multiple tissues and physiological processes [81]. This allows cells to integrate multiple hormonal inputs to regulate multiple metabolic programs in a cohesive manner. PPARγ is involved in the recruitment of co-activators and chromatin remodeling to influence longer-term adipogenic-osteogenic balances. Co-activators such as CBP/p300, SRC-1, and PGC-1α, acetylate histones and open chromatin at adipogenic loci [82]. PPARγ can also recruit chromatin remodeling complexes to repress osteogenic targets.

PPARβ/δ is primarily involved in metabolic regulation and promotes fatty acid oxidation and mitochondrial biogenesis in progenitor cells [83]. PPARβ/δ can promote osteogenesis in MSCs by modulating both cell fate and their immunosuppressive properties [84]. Some evidence also supports a role for PPARβ/δ ligands in alleviating diabetic osteoporosis [85]. PPARβ/δ has also been shown to support myogenic lineage differentiation and proliferation of progenitor cells in satellite cells, although this capacity has not yet been tested in MSCs [86,87]. PPARα remains relatively uninfluential with regard to direct modulation of MSC differentiation. PPARα functions largely in lipid metabolism and immune function, although its effects on inflammatory processes may influence MSC fate indirectly.

3.13. The Progesterone Receptor (PR, NR3C3)

The progesterone receptor (PR, NR3C3) [8] is a specific receptor for progesterone, but, like other steroid receptors, it has some non-genomic activities that are not yet well understood. PR is most well-studied in reproductive tissues, but also plays a significant role in influencing both mesenchymal stem cell (MSC) differentiation and bone remodeling dynamics. Global [88] or osteoprogenitor-specific [89] PR knockout (PRKO) mice exhibited increased trabecular

bone mass and bone formation rates, accompanied by reduced osteoclast number and surface area. This suggests that PR signaling contributes to bone loss, potentially by enhancing osteoclastogenesis. This osteoprotective phenotype in PR-deficient mice was observed across both sexes, although it was more pronounced in females. Transcriptomal and epigenetic evidence revealed that PR modulated osteoprogenitor function through direct chromatin binding and regulation of gene networks associated with osteogenesis and inflammation [90]. PR deletion in osterix-expressing osteoprogenitors altered the expression of genes involved in osteoblast maturation and organization of extracellular matrices [90]. PR appears to actively restrain osteogenic differentiation while indirectly promoting osteoclast recruitment. This highlights a dual role for PR in skeletal tissue as both a modulator of the osteoblast lineage and as an upstream regulator of bone-resorptive activity.

3.14. The Retinoic Acid Receptors (RARs, NR1B)

Retinoic acid receptors (RARs) are another main point of interest in NR influence on MSC fate. RARS comprise a family of three genes: RARα (NR1B1), RARβ (NR1B2), and RARγ (NR1B3) [8]. RAR is well-studied for its extensive role in embryonic development. RA and RARs have been associated with the differentiation of various cell types. In the developing nervous system, for example, RA signaling is vital for the induction of neuronal phenotypes [91]. It drives the expression of genes that promote neuronal identity and other transcription factors, including NeuroD and Pax6 [91], both of which are key in neuronal lineage specification and the maturation of neural precursors. Similarly, in MSCs, RA/RARs regulate gene networks that balance stem cell lineage commitment. For instance, RA signaling impacts the expression of transcription factors such as Runx2 as well as genes linked to adipogenesis like PPARγ and C/EBP family members; however, its specific role can vary with cellular context and differentiation stage [92,93]. Ligand binding to RAR triggers a displacement of corepressors and a recruitment of coactivators to the already chromatin-bound receptor heterodimer [94]. This mechanism is essential in directing stem cell differentiation for processes such as osteogenesis and chondrogenesis.

Activation of RARγ has been shown to influence osteoblast differentiation [92]. Studies involving RARγ-deficient mice demonstrated alterations in bone structure, suggesting that RARγ is essential for normal osteoblast function and skeletal homeostasis [95]. During early chondrogenic differentiation, suppression of RAR activity is crucial for the expression of pro-chondrogenic genes like *SOX9* [96]. Interestingly, in an opposite fashion, activation of RARs by ligands such as *all-trans* retinoic acid can inhibit chondrogenesis and promote hypertrophic differentiation, leading to ossification [97]. Pharmacological inhibition of RARs using inverse agonists (e.g., BMS204493) was shown to attenuate hypertrophy in chondrogenically differentiated MSCs, stabilizing engineered cartilage tissues [98].

3.15. The Retinoid X Receptors (RXRs, NR2B)

Retinoid X Receptors (RXR) comprise a family of three genes encoding RXRα (NR2B1), RXRβ (NR2B2), and RXRγ (NR2B3) [8]. RXRs play a key role in nuclear receptor signaling since they are obligate heterodimeric partners for a large group of receptors, including RARs, TRs, VDR, PPARs, PXR, FXR, and LXR [99]. RXRs can also signal as homodimers. RXR can form permissive heterodimers in which the RXR half can be activated by ligand and non-permissive heterodimers wherein the RXR is silent [99]. RXR homodimers allow for the integration of signals from different ligands and pathways, giving them a broad role in physiology [99]. In MSCs, RXR-containing heterodimers integrate signals that drive lineage-specific differentiation [100]. RXR activation in MSCs promotes de-repression of genes required for adipogenic commitment, pushing the MSCs to the adipogenic lineage at the expense of bone [100]. Intriguingly, activation of RXR during MSC differentiation into adipocytes leads

to the production of dysfunctional adipocytes with impaired glucose uptake, blunted expression of the antidiabetic hormone adiponectin, and elevated expression of proinflammatory and profibrotic genes [101]. Loss of RXR signaling in hematopoietic stem cells leads to the production of dysfunctional osteoclasts, which results in increased bone mass in male and female mice [102]. Overall, it is now clear that RXR plays a key role in bone remodeling both via its action in RXR homodimers and through a variety of heterodimers [103].

3.16. The Thyroid Hormone Receptors (TR, NR1A)

The thyroid hormone receptors TRα (NR1A1) and TRβ (NR1A2) [8] are important regulators of metabolism [104]. The thyroid hormone, through TRs, has multiple functions in MSC biology. Early TR activation enhances osteogenic differentiation by upregulating Runx2 and osterix to promote bone formation and mineralization [105]. Thyroid hormone also potentiates the action of bone morphogenetic protein 9 on the induction of BM-MSCs into osteocytes [106]. TR signaling exerts an inhibitory effect on the proliferation of adipocytes while at the same time being an important factor in the expression of adipogenic genes [107]. Thyroid hormone is also an important factor in the differentiation and function of thermogenic brown and beige adipocytes [107,108].

3.17. The Vitamin D Receptor (VDR, NR1I1)

The Vitamin D Receptor (VDR, NR1I1) [8] finds its place in MSC differentiation in the regulation of osteogenesis [109]. VDR is activated by the ligand 1,25-dihydroxyvitamin D3, a hormonal form of vitamin D3, and functions as a heterodimer with RXR to bind DNA and regulate gene expression [8]. The liganded VDR up-regulates expression of osteocyte marker genes such as alkaline phosphatase, osteopontin, and osteocalcin [109]. Vitamin D3 also stimulates adhesion of MSCs to the substrate, which is a key factor in commitment to the osteogenic lineage [110]. VDR is also important for bone remodeling after differentiation [111]. Lastly, vitamin D3 was recently shown to reduce senescence in BM-MSCs by stimulating pluripotency markers, as well as those important for osteogenic differentiation potential [112].

3.18. Aryl Hydrocarbon Receptor (AhR)

The aryl hydrocarbon receptor (AhR) is not a canonical nuclear receptor but is often grouped with NRs when discussing gene regulation because it functions as a ligand-modulated transcription factor in response to exogenous signals. AhR plays a complex regulatory role in MSC fate. AhR exerts pro-inflammatory effects, promoting the maintenance of multipotency, and activation of AhR by endogenous or exogenous ligands was shown to inhibit both adipogenesis and osteogenesis. This is accomplished by suppression of lineage-specific transcription factors such as PPARγ and RUNX2, which are essential for adipocyte and osteoblast differentiation, respectively [113,114]. These inhibitions have been investigated using multiple AhR ligands, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), resulting in disruption of osteogenic differentiation in human bone-derived MSCs (hBM-MSCs) in vitro [113]. There have been reports of AhR influencing chondrogenic differentiation as well, although this has been discordant in the scientific literature [115,116]. Additionally, AhR is heavily implicated in immune function and specifically macrophage differentiation. AhR activation elicits increased expression of inflammatory cytokines IL-6 and TNF-α, creating an inflammatory microenvironment likely to influence MSC immune responsiveness [114]. AhR signaling also supports preservation of MSC multipotency by blocking lineage commitment. This helps to maintain stemness and allows cells to remain in an undifferentiated state.

4. The Danger of Exogenous Signaling

As ligand-modulated transcription factors that bind small molecules, nuclear receptors are susceptible to their signaling being disrupted by small molecules with similar properties to their ligands, such as dietary and xenobiotic chemicals [117]. Endocrine-disrupting chemicals (EDCs) were first defined as those that could disrupt signaling through estrogen-, androgen-, or thyroid hormone-related pathways. This definition was formalized to include nuclear receptor signaling in general, and the effects of such EDCs have been discussed in numerous review articles. Of particular note are an exhaustive report by the United Nations Environmental Program/World Health Organization [118], two by the Endocrine Society [119,120], and another by an expert working group that delineated the key characteristics (KCs) of EDCs [117]. KCs are particularly useful in discussing the effects of chemicals and other agents that may disrupt various physiological pathways because they are agnostic toward a particular pathway of action, and most EDCs and other types of disruptive chemicals target multiple pathways. EDCs mimic endogenous ligands and can derail endocrine signaling in a variety of ways, including increasing activity, decreasing activity, and/or exerting effects at the wrong time or place during development or physiology. These disturbances endanger both tissue homeostasis and various functional developmental processes. Recent years have seen an increase in studies about the epigenetic effects of EDCs [121,122] and that their effects may be transmitted to future generations without further exposure [123]. The fact that the effects of EDC exposure can be passed down the generations to unexposed offspring presents a particularly difficult public health concern.

Before considering the effects of EDCs on MSCs, it is useful to consider the concept that EDCs and other agents can influence metabolism in a variety of ways that may be detrimental to the organism. These were termed "metabolism disrupting agents", and a recent position paper delineated the key characteristics of these metabolism-disrupting agents [124]. Metabolism-disrupting agents disrupt various aspects of metabolism, and an important subset of these, the obesogens, are pertinent to our discussion. Obesogens are agents (mostly EDCs) that elicit obesity, or a predisposition to obesity in exposed individuals or their offspring [125–127]. One obesogen that has been well-studied with respect to its effects in vitro and in vivo is tributyltin (TBT), a common environmental contaminant. TBT disrupts nuclear receptor signaling by aberrantly activating both PPARγ and RXR [128–131]. When pregnant mouse dams were exposed to low, environmentally relevant doses of TBT throughout pregnancy or pregnancy and lactation, male descendants through at least the F4 generation were predisposed to obesity and insulin intolerance when dietary fat was increased modestly (13% to 21% Kcal from fat) [132–134]. When TBT enters the cell, it diffuses into the nucleus and binds directly to the ligand-binding domains of RXR and PPARγ [128,135]. This misdirected activation forces MSCs to favor adipogenic differentiation over osteogenic differentiation [100,136]. Therefore, TBT exposure alters MSC fate by diverting cells toward the adipogenic pathway at the expense of bone. As noted above, RXR activation in MSCs promotes de-repression of genes required for adipogenic commitment [100] and favors the development of dysfunctional adipocytes with impaired glucose uptake, blunted expression of the antidiabetic hormone adiponectin, and elevated expression of proinflammatory and profibrotic genes [101]. Male mice whose ancestral dams were exposed to TBT throughout pregnancy and lactation show gene expression pathways indicative of similar alterations in MSC fate and do not respond to fasting by mobilizing stored fat compared with controls [132]. A variety of cell-based assays are being developed to test the effects of obesogens on MSCs and other cells [126], but we argue that future studies directed toward identifying other agents that alter MSC lineage commitment, specification, and differentiation are warranted and will be important.

5. Conclusions and Future Directions

In this review, we have defined a central role for nuclear receptors in steering MSC differentiation and touched on how these factors coordinate the complex process of MSC lineage commitment and differentiation. Together, these findings emphasize the importance of understanding nuclear receptor function in both normal physiology and in the context of external perturbations. While the concept of endocrine disruption is important, the endocrine system has many signaling pathways not mediated by nuclear receptors (e.g., insulin and other peptide hormones), and any disruption of endocrine disruption should also consider these other pathways. Beyond the endocrine system, in principle, any ligand-mediated signaling pathway (e.g., growth factor signaling) is susceptible to disruption by agents that alter the signaling pathway. This has been termed "signal toxicity" and is a widely underappreciated field of study [137]. There are hundreds of "druggable" receptors that are targets for clinically useful drugs, and drugs are nothing more than chemicals that have been identified as being useful to treat a particular medical condition. Studies aiming at identifying the effects of drugs, natural and xenobiotic chemicals on MSC potential will have broad implications for understanding disease and for efforts in regenerative medicine to exploit the multi-lineage potential of MSCs for tissue engineering.

Author Contributions: Writing—original draft preparation, A.D.; writing—review and editing, B.B. All authors have read and agreed to the published version of the manuscript.

Funding: Supported by grants from the NIH to B.B. (ES023316, ES031139).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created in the writing of this paper.

Conflicts of Interest: B.B. is a named inventor on patents related to nuclear receptors. A.D. declares no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

NR	Nuclear Receptor
MSCs	Multipotent Mesenchymal Stromal Stem Cells—Mesenchymal Stem Cells
AF-2	Activation function-2
Ahr	Aryl Hydrocarbon Receptor
AR	Androgen Receptor
ER	Estrogen Receptor
ERR	Estrogen Related Receptor
FXR	Farnesoid X receptor
GR	Glucocorticoid Receptor
HNF-4	Hepatocyte Nuclear Factor 4
LXR	Liver X Receptor
NR2F2	Nuclear Receptor Subfamily 2, Group F
NR4A	Nuclear Receptor Subfamily 4, Group A
NR5A	Nuclear Receptor Subfamily 5, Group A
PPAR	Peroxisome Proliferator-Activated Receptor
PR	Progesterone Receptor
RXR	Retinoid X Receptor
TR	Thyroid Hormone Receptor
VDR	Vitamin D Receptor

ROR	RAR-related Orphan Receptor
FDA	Food and Drug Administration
EDCs	Endocrine-Disrupting Chemicals

References

1. Pittenger, M.F.; Discher, D.E.; Peault, B.M.; Phinney, D.G.; Hare, J.M.; Caplan, A.I. Mesenchymal stem cell perspective: Cell biology to clinical progress. *NPJ Regen. Med.* **2019**, *4*, 22. [CrossRef]
2. Walewska, A.; Janucik, A.; Tynecka, M.; Moniuszko, M.; Eljaszewicz, A. Mesenchymal stem cells under epigenetic control—The role of epigenetic machinery in fate decision and functional properties. *Cell Death Dis.* **2023**, *14*, 720. [CrossRef]
3. Benayahu, D. Mesenchymal stem cell differentiation and usage for biotechnology applications: Tissue engineering and food manufacturing. *Biomater. Transl.* **2022**, *3*, 17–23. [CrossRef]
4. Viswanathan, S.; Shi, Y.; Galipeau, J.; Krampera, M.; Leblanc, K.; Martin, I.; Nolta, J.; Phinney, D.G.; Sensebe, L. Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell committee position statement on nomenclature. *Cytotherapy* **2019**, *21*, 1019–1024. [CrossRef]
5. Klimczak, A.; Kozlowska, U. Mesenchymal Stromal Cells and Tissue-Specific Progenitor Cells: Their Role in Tissue Homeostasis. *Stem Cells Int.* **2016**, *2016*, 4285215. [CrossRef] [PubMed]
6. Liu, J.; Gao, J.; Liang, Z.; Gao, C.; Niu, Q.; Wu, F.; Zhang, L. Mesenchymal stem cells and their microenvironment. *Stem Cell Res. Ther.* **2022**, *13*, 429. [CrossRef]
7. Evans, R.M. The nuclear receptor superfamily: A rosetta stone for physiology. *Mol. Endocrinol.* **2005**, *19*, 1429–1438. [CrossRef]
8. Germain, P.; Staels, B.; Dacquet, C.; Spedding, M.; Laudet, V. Overview of nomenclature of nuclear receptors. *Pharmacol. Rev.* **2006**, *58*, 685–704. [CrossRef]
9. Kilu, W.; Merk, D.; Steinhilber, D.; Proschak, E.; Heering, J. Heterodimer formation with retinoic acid receptor RXRalpha modulates coactivator recruitment by peroxisome proliferator-activated receptor PPARgamma. *J. Biol. Chem.* **2021**, *297*, 100814. [CrossRef] [PubMed]
10. MacTavish, B.S.; Zhu, D.; Shang, J.; Shao, Q.; He, Y.; Yang, Z.J.; Kamenecka, T.M.; Kojetin, D.J. Ligand efficacy shifts a nuclear receptor conformational ensemble between transcriptionally active and repressive states. *Nat. Commun.* **2025**, *16*, 2065. [CrossRef] [PubMed]
11. Xu, W.; Fukuyama, T.; Ney, P.A.; Wang, D.; Rehg, J.; Boyd, K.; van Deursen, J.M.; Brindle, P.K. Global transcriptional coactivators CREB-binding protein and p300 are highly essential collectively but not individually in peripheral B cells. *Blood* **2006**, *107*, 4407–4416. [CrossRef]
12. Frigo, D.E.; Bondesson, M.; Williams, C. Nuclear receptors: From molecular mechanisms to therapeutics. *Essays Biochem.* **2021**, *65*, 847–856. [CrossRef]
13. Jin, P.; Duan, X.; Huang, Z.; Dong, Y.; Zhu, J.; Guo, H.; Tian, H.; Zou, C.-G.; Xie, K. Nuclear receptors in health and disease: Signaling pathways, biological functions and pharmaceutical interventions. *Signal Transduct. Target. Ther.* **2025**, *10*, 228. [CrossRef]
14. Huang, C.K.; Tsai, M.Y.; Luo, J.; Kang, H.Y.; Lee, S.O.; Chang, C. Suppression of androgen receptor enhances the self-renewal of mesenchymal stem cells through elevated expression of EGFR. *Biochim. Biophys. Acta* **2013**, *1833*, 1222–1234. [CrossRef]
15. Huang, C.K.; Luo, J.; Lee, S.O.; Chang, C. Concise review: Androgen receptor differential roles in stem/progenitor cells including prostate, embryonic, stromal, and hematopoietic lineages. *Stem Cells* **2014**, *32*, 2299–2308. [CrossRef] [PubMed]
16. Sakai, H.; Imai, Y. Cell-specific functions of androgen receptor in skeletal muscles. *Endocr. J.* **2024**, *71*, 437–445. [CrossRef] [PubMed]
17. Sakai, H.; Uno, H.; Yamakawa, H.; Tanaka, K.; Ikedo, A.; Uezumi, A.; Ohkawa, Y.; Imai, Y. The androgen receptor in mesenchymal progenitors regulates skeletal muscle mass via Igf1 expression in male mice. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2407768121. [CrossRef]
18. Russell, P.K.; Mangiafico, S.; Fam, B.C.; Clarke, M.V.; Marin, E.S.; Andrikopoulos, S.; Wiren, K.M.; Zajac, J.D.; Davey, R.A. The androgen receptor in bone marrow progenitor cells negatively regulates fat mass. *J. Endocrinol.* **2018**, *237*, 15–27. [CrossRef]
19. Ucer, S.; Iyer, S.; Bartell, S.M.; Martin-Millan, M.; Han, L.; Kim, H.N.; Weinstein, R.S.; Jilka, R.L.; O'Brien, C.A.; Almeida, M.; et al. The Effects of Androgens on Murine Cortical Bone Do Not Require AR or ERα Signaling in Osteoblasts and Osteoclasts. *J. Bone Miner. Res.* **2015**, *30*, 1138–1149. [CrossRef] [PubMed]
20. Hui, L.; Shoumei, X.; Zhoujing, Z.; Kuang, G.; Duohong, Z.; Jiacai, H.; Yong, Z. Effects of Androgen Receptor Overexpression on Chondrogenic Ability of Rabbit Articular Chondrocytes. *Tissue Eng. Regen. Med.* **2021**, *18*, 641–650. [CrossRef]
21. Chhabra, A.; Tripathi, A.; Rizvi, S.; Tyagi, R.K. Ligand-independent homo-/hetero-dimerization events of ERα and ERβ occur in the cytoplasmic compartment: Evidences from receptor dynamics in live cells. *J. Steroid Biochem. Mol. Biol.* **2025**, *247*, 106668. [CrossRef]
22. Khalid, A.B.; Krum, S.A. Estrogen receptors alpha and beta in bone. *Bone* **2016**, *87*, 130–135. [CrossRef]
23. Fuentes, N.; Silveyra, P. Estrogen receptor signaling mechanisms. *Adv. Protein Chem. Struct. Biol.* **2019**, *116*, 135–170. [CrossRef]

24. Ritter, M.J.; Amano, I.; Imai, N.; Soares De Oliveira, L.; Vella, K.R.; Hollenberg, A.N. Nuclear Receptor CoRepressors, NCOR1 and SMRT, are required for maintaining systemic metabolic homeostasis. *Mol. Metab.* **2021**, *53*, 101315. [CrossRef] [PubMed]
25. Mauvais-Jarvis, F.; Lange, C.A.; Levin, E.R. Membrane-Initiated Estrogen, Androgen, and Progesterone Receptor Signaling in Health and Disease. *Endocr. Rev.* **2022**, *43*, 720–742. [CrossRef] [PubMed]
26. Harding, A.T.; Heaton, N.S. The Impact of Estrogens and Their Receptors on Immunity and Inflammation during Infection. *Cancers* **2022**, *14*, 909. [CrossRef] [PubMed]
27. Li, M.; Li, T.; Yin, J.; Xie, C.; Zhu, J. Evaluation of toxicological effects of bisphenol S with an in vitro human bone marrow mesenchymal stem cell: Implications for bone health. *Toxicology* **2023**, *484*, 153408. [CrossRef]
28. Strong, A.L.; Shi, Z.; Strong, M.J.; Miller, D.F.; Rusch, D.B.; Buechlein, A.M.; Flemington, E.K.; McLachlan, J.A.; Nephew, K.P.; Burow, M.E.; et al. Effects of the endocrine-disrupting chemical DDT on self-renewal and differentiation of human mesenchymal stem cells. *Environ. Health Perspect.* **2015**, *123*, 42–48. [CrossRef]
29. Xiao, Z.; Liu, H. The estrogen receptor and metabolism. *Women's Health* **2024**, *20*, 17455057241227362. [CrossRef]
30. Kim, E.J.; Kang, I.H.; Lee, J.W.; Jang, W.G.; Koh, J.T. MiR-433 mediates ERRgamma-suppressed osteoblast differentiation via direct targeting to Runx2 mRNA in C3H10T1/2 cells. *Life Sci.* **2013**, *92*, 562–568. [CrossRef]
31. Huang, T.; Lu, Z.; Wang, Z.; Cheng, L.; Gao, L.; Gao, J.; Zhang, N.; Geng, C.A.; Zhao, X.; Wang, H.; et al. Targeting adipocyte ESRRA promotes osteogenesis and vascular formation in adipocyte-rich bone marrow. *Nat. Commun.* **2024**, *15*, 3769. [CrossRef]
32. Li, M.; Yu, Y.; Xue, K.; Li, J.; Son, G.; Wang, J.; Qian, W.; Wang, S.; Zheng, J.; Yang, C.; et al. Genistein mitigates senescence of bone marrow mesenchymal stem cells via ERRalpha-mediated mitochondrial biogenesis and mitophagy in ovariectomized rats. *Redox Biol.* **2023**, *61*, 102649. [CrossRef]
33. Morganstein, D.L.; Wu, P.; Mane, M.R.; Fisk, N.M.; White, R.; Parker, M.G. Human fetal mesenchymal stem cells differentiate into brown and white adipocytes: A role for ERRalpha in human UCP1 expression. *Cell Res.* **2010**, *20*, 434–444. [CrossRef]
34. Delhon, I.; Gutzwiller, S.; Morvan, F.; Rangwala, S.; Wyder, L.; Evans, G.; Studer, A.; Kneissel, M.; Fournier, B. Absence of estrogen receptor-related-alpha increases osteoblastic differentiation and cancellous bone mineral density. *Endocrinology* **2009**, *150*, 4463–4472. [CrossRef]
35. Rajalin, A.M.; Pollock, H.; Aarnisalo, P. ERRalpha regulates osteoblastic and adipogenic differentiation of mouse bone marrow mesenchymal stem cells. *Biochem. Biophys. Res. Commun.* **2010**, *396*, 477–482. [CrossRef]
36. Auld, K.L.; Berasi, S.P.; Liu, Y.; Cain, M.; Zhang, Y.; Huard, C.; Fukayama, S.; Zhang, J.; Choe, S.; Zhong, W.; et al. Estrogen-related receptor alpha regulates osteoblast differentiation via Wnt/beta-catenin signaling. *J. Mol. Endocrinol.* **2012**, *48*, 177–191. [CrossRef]
37. Otte, K.; Kranz, H.; Kober, I.; Thompson, P.; Hoefer, M.; Haubold, B.; Remmel, B.; Voss, H.; Kaiser, C.; Albers, M.; et al. Identification of farnesoid X receptor beta as a novel mammalian nuclear receptor sensing lanosterol. *Mol. Cell. Biol.* **2003**, *23*, 864–872. [CrossRef] [PubMed]
38. Zhao, X.; Liang, M.; Li, X.; Qiu, X.; Cui, L. Identification of key genes and pathways associated with osteogenic differentiation of adipose stem cells. *J. Cell. Physiol.* **2018**, *233*, 9777–9785. [CrossRef] [PubMed]
39. Dong, Q.; Fu, H.; Li, W.; Ji, X.; Yin, Y.; Zhang, Y.; Zhu, Y.; Li, G.; Jia, H.; Zhang, H.; et al. Nuclear farnesoid X receptor protects against bone loss by driving osteoblast differentiation through stabilizing RUNX2. *Bone Res.* **2025**, *13*, 20. [CrossRef] [PubMed]
40. Fujimori, K.; Iguchi, Y.; Yamashita, Y.; Gohda, K.; Teno, N. FXR Activation Accelerates Early Phase of Osteoblast Differentiation Through COX-2-PGE_2-EP4 Axis in BMP-2-Induced Mouse Mesenchymal Stem Cells. *Molecules* **2024**, *30*, 58. [CrossRef]
41. Scheschowitsch, K.; Leite, J.A.; Assreuy, J. New Insights in Glucocorticoid Receptor Signaling-More Than Just a Ligand-Binding Receptor. *Front. Endocrinol.* **2017**, *8*, 16. [CrossRef] [PubMed]
42. Han, L.; Wang, B.; Wang, R.; Gong, S.; Chen, G.; Xu, W. The shift in the balance between osteoblastogenesis and adipogenesis of mesenchymal stem cells mediated by glucocorticoid receptor. *Stem Cell Res. Ther.* **2019**, *10*, 377. [CrossRef] [PubMed]
43. Pierce, J.L.; Sharma, A.K.; Roberts, R.L.; Yu, K.; Irsik, D.L.; Choudhary, V.; Dorn, J.S.; Bensreti, H.; Benson, R.D., Jr.; Kaiser, H.; et al. The Glucocorticoid Receptor in Osterix-Expressing Cells Regulates Bone Mass, Bone Marrow Adipose Tissue, and Systemic Metabolism in Female Mice During Aging. *J. Bone Miner. Res.* **2022**, *37*, 285–302. [CrossRef]
44. Rauch, A.; Seitz, S.; Baschant, U.; Schilling, A.F.; Illing, A.; Stride, B.; Kirilov, M.; Mandic, V.; Takacz, A.; Schmidt-Ullrich, R.; et al. Glucocorticoids suppress bone formation by attenuating osteoblast differentiation via the monomeric glucocorticoid receptor. *Cell Metab.* **2010**, *11*, 517–531. [CrossRef]
45. Wisely, G.B.; Miller, A.B.; Davis, R.G.; Thornquest, A.D., Jr.; Johnson, R.; Spitzer, T.; Sefler, A.; Shearer, B.; Moore, J.T.; Miller, A.B.; et al. Hepatocyte nuclear factor 4 is a transcription factor that constitutively binds fatty acids. *Structure* **2002**, *10*, 1225–1234. [CrossRef]
46. Sladek, F.M. Orphan receptor HNF-4 and liver-specific gene expression. *Receptor* **1994**, *4*, 64.
47. Taléns-Visconti, R.; Bonora, A.; Jover, R.; Mirabet, V.; Carbonell, F.; Castell, J.V.; Gómez-Lechón, M.J. Hepatogenic differentiation of human mesenchymal stem cells from adipose tissue in comparison with bone marrow mesenchymal stem cells. *World J. Gastroenterol.* **2006**, *12*, 5834–5845. [CrossRef]

48. Alizadeh, E.; Akbarzadeh, A.; Eslaminejad, M.B.; Barzegar, A.; Hashemzadeh, S.; Nejati-Koshki, K.; Zarghami, N. Up regulation of liver-enriched transcription factors HNF4a and HNF6 and liver-specific microRNA (miR-122) by inhibition of let-7b in mesenchymal stem cells. *Chem. Biol. Drug Des.* **2015**, *85*, 268–279. [CrossRef]
49. Jahnavi, S.; Garg, V.; Vasandan, A.B.; SundarRaj, S.; Kumar, A.; Prasanna, S.J. Lineage reprogramming of human adipose mesenchymal stem cells to immune modulatory i-Heps. *Int. J. Biochem. Cell Biol.* **2022**, *149*, 106256. [CrossRef]
50. Korach-Andre, M.; Archer, A.; Barros, R.P.; Parini, P.; Gustafsson, J.A. Both liver-X receptor (LXR) isoforms control energy expenditure by regulating brown adipose tissue activity. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 403–408. [CrossRef] [PubMed]
51. Kojetin, D.J.; Matta-Camacho, E.; Hughes, T.S.; Srinivasan, S.; Nwachukwu, J.C.; Cavett, V.; Nowak, J.; Chalmers, M.J.; Marciano, D.P.; Kamenecka, T.M.; et al. Structural mechanism for signal transduction in RXR nuclear receptor heterodimers. *Nat. Commun.* **2015**, *6*, 8013. [CrossRef]
52. Dixon, E.D.; Nardo, A.D.; Claudel, T.; Trauner, M. The Role of Lipid Sensing Nuclear Receptors (PPARs and LXR) and Metabolic Lipases in Obesity, Diabetes and NAFLD. *Genes* **2021**, *12*, 645. [CrossRef]
53. Hua, X.; Wei, X. Liver X receptors: From pharmacology to nanoparticle-based drug delivery. *Eur. J. Pharmacol.* **2023**, *956*, 175953. [CrossRef]
54. da Silva Pereira, J.A.; de Souza, G.P.; Virgilio-da-Silva, J.V.; Prodonoff, J.S.; de Castro, G.; Pimentel, L.F.; Mousovich-Neto, F.; Davanzo, G.G.; Aguiar, C.F.; Breda, C.N.S.; et al. LXR regulation of adipose tissue inflammation during obesity is associated with dysregulated macrophage function. *Obesity* **2025**, *33*, 78–90. [CrossRef]
55. Matsushita, K.; Morello, F.; Zhang, Z.; Masuda, T.; Iwanaga, S.; Steffensen, K.R.; Gustafsson, J.A.; Pratt, R.E.; Dzau, V.J. Nuclear hormone receptor LXRalpha inhibits adipocyte differentiation of mesenchymal stem cells with Wnt/beta-catenin signaling. *Lab. Investig.* **2016**, *96*, 230–238. [CrossRef] [PubMed]
56. Matsushita, K.; Morello, F.; Wu, Y.; Zhang, L.; Iwanaga, S.; Pratt, R.E.; Dzau, V.J. Mesenchymal stem cells differentiate into renin-producing juxtaglomerular (JG)-like cells under the control of liver X receptor-alpha. *J. Biol. Chem.* **2010**, *285*, 11974–11982. [CrossRef]
57. Liang, T.; Li, P.; Liang, A.; Zhu, Y.; Qiu, X.; Qiu, J.; Peng, Y.; Huang, D.; Gao, W.; Gao, B. Identifying the key genes regulating mesenchymal stem cells chondrogenic differentiation: An in vitro study. *BMC Musculoskelet. Disord.* **2022**, *23*, 985. [CrossRef]
58. Tao, C.; Liu, J.; Li, Z.; Lai, P.; Zhang, S.; Qu, J.; Tang, Y.; Liu, A.; Zou, Z.; Bai, X.; et al. DNMT1 is a negative regulator of osteogenesis. *Biol. Open* **2022**, *11*, bio058534. [CrossRef] [PubMed]
59. Nalbant, A.; Eskier, D. Genes associated with T helper 17 cell differentiation and function. *Front. Biosci.* **2016**, *8*, 427–435. [CrossRef] [PubMed]
60. Baharlou, R.; Rashidi, N.; Ahmadi-Vasmehjani, A.; Khoubyari, M.; Sheikh, M.; Erfanian, S. Immunomodulatory Effects of Human Adipose Tissue-derived Mesenchymal Stem Cells on T Cell Subsets in Patients with Rheumatoid Arthritis. *Iran. J. Allergy Asthma Immunol.* **2019**, *18*, 114–119. [CrossRef]
61. Ma, D.; Xu, K.; Zhang, G.; Liu, Y.; Gao, J.; Tian, M.; Wei, C.; Li, J.; Zhang, L. Immunomodulatory effect of human umbilical cord mesenchymal stem cells on T lymphocytes in rheumatoid arthritis. *Int. Immunopharmacol.* **2019**, *74*, 105687. [CrossRef] [PubMed]
62. Najar, M.; Fayyad-Kazan, H.; Faour, W.H.; Merimi, M.; Sokal, E.M.; Lombard, C.A.; Fahmi, H. Immunological modulation following bone marrow-derived mesenchymal stromal cells and Th17 lymphocyte co-cultures. *Inflamm. Res.* **2019**, *68*, 203–213. [CrossRef]
63. Manikandan, M.; Abuelreich, S.; Elsafadi, M.; Alsalman, H.; Almalak, H.; Siyal, A.; Hashmi, J.A.; Aldahmash, A.; Kassem, M.; Alfayez, M.; et al. NR2F1 mediated down-regulation of osteoblast differentiation was rescued by bone morphogenetic protein-2 (BMP-2) in human MSC. *Differentiation* **2018**, *104*, 36–41. [CrossRef]
64. Wang, S.H.; Gou, G.H.; Wu, C.C.; Shen, H.C.; Lin, L.C.; Pan, R.Y. Increased COUP-TFII Expression Mediates the Differentiation Imbalance of Bone Marrow-Derived Mesenchymal Stem Cells in Femoral Head Osteonecrosis. *Biomed. Res. Int.* **2019**, *2019*, 9262430. [CrossRef]
65. Gao, G.; Zhang, X.F.; Hubbell, K.; Cui, X. NR2F2 regulates chondrogenesis of human mesenchymal stem cells in bioprinted cartilage. *Biotechnol. Bioeng.* **2017**, *114*, 208–216. [CrossRef]
66. Jin, Y.; Son, Y.; Song, I.; Chung, Y.S.; Choi, Y.J. Orphan nuclear receptor NR4A1 regulates both osteoblastogenesis and adipogenesis in human mesenchymal stem cells. *Mol. Med. Rep.* **2025**, *31*, 3. [CrossRef]
67. Gao, Y.; Zou, Y.; Sokolowskei, D.; Xing, X.; Tower, R.J.; Lai, Z.; Shi, J.; Zhu, L.; Zheng, Q.; James, A.W.; et al. Nr4a1 enhances Wnt4 transcription to promote mesenchymal stem cell osteogenesis and alleviates inflammation-inhibited bone regeneration. *Mol. Ther.* **2024**, *32*, 1479–1496. [CrossRef]
68. Zetterstrom, R.H.; Solomin, L.; Jansson, L.; Hoffer, B.J.; Olson, L.; Perlmann, T. Dopamine neuron agenesis in Nurr1-deficient mice. *Science* **1997**, *276*, 248–250. [CrossRef]
69. Ko, T.L.; Fu, Y.Y.; Shih, Y.H.; Lin, Y.H.; Ko, M.H.; Fu, T.W.; Lin, T.Y.; Hsiao, H.S.; Chu, P.M.; Fu, Y.S. A high-efficiency induction of dopaminergic cells from human umbilical mesenchymal stem cells for the treatment of hemiparkinsonian rats. *Cell Transplant.* **2015**, *24*, 2251–2262. [CrossRef] [PubMed]

70. Park, J.S.; Yang, H.N.; Woo, D.G.; Jeon, S.Y.; Do, H.J.; Huh, S.H.; Kim, N.H.; Kim, J.H.; Park, K.H. Exogenous Nurr1 gene expression in electrically-stimulated human MSCs and the induction of neurogenesis. *Biomaterials* **2012**, *33*, 7300–7308. [CrossRef] [PubMed]
71. Yazawa, T.; Inanoka, Y.; Mizutani, T.; Kuribayashi, M.; Umezawa, A.; Miyamoto, K. Liver receptor homolog-1 regulates the transcription of steroidogenic enzymes and induces the differentiation of mesenchymal stem cells into steroidogenic cells. *Endocrinology* **2009**, *150*, 3885–3893. [CrossRef] [PubMed]
72. Yazawa, T.; Kawabe, S.; Inaoka, Y.; Okada, R.; Mizutani, T.; Imamichi, Y.; Ju, Y.; Yamazaki, Y.; Usami, Y.; Kuribayashi, M.; et al. Differentiation of mesenchymal stem cells and embryonic stem cells into steroidogenic cells using steroidogenic factor-1 and liver receptor homolog-1. *Mol. Cell. Endocrinol.* **2011**, *336*, 127–132. [CrossRef] [PubMed]
73. Aoyagi, C.; Tanaka, T.; Haga, N.; Yanase, T.; Kodama, S. Differentiation of human adipose tissue-derived mesenchymal stromal cells into steroidogenic cells by adenovirus-mediated overexpression of NR5A1 and implantation into adrenal insufficient mice. *Cytotherapy* **2023**, *25*, 866–876. [CrossRef]
74. Wei, X.; Peng, G.; Zheng, S.; Wu, X. Differentiation of umbilical cord mesenchymal stem cells into steroidogenic cells in comparison to bone marrow mesenchymal stem cells. *Cell Prolif.* **2012**, *45*, 101–110. [CrossRef]
75. Tontonoz, P.; Spiegelman, B.M. Fat and beyond: The diverse biology of PPARgamma. *Annu. Rev. Biochem.* **2008**, *77*, 289–312. [CrossRef]
76. Hu, W.; Jiang, C.; Kim, M.; Xiao, Y.; Richter, H.J.; Guan, D.; Zhu, K.; Krusen, B.M.; Roberts, A.N.; Miller, J.; et al. Isoform-specific functions of PPARgamma in gene regulation and metabolism. *Genes. Dev.* **2022**, *36*, 300–312. [CrossRef]
77. Kroker, A.J.; Bruning, J.B. Review of the Structural and Dynamic Mechanisms of PPARgamma Partial Agonism. *PPAR Res.* **2015**, *2015*, 816856. [CrossRef]
78. Akune, T.; Ohba, S.; Kamekura, S.; Yamaguchi, M.; Chung, U.I.; Kubota, N.; Terauchi, Y.; Harada, Y.; Azuma, Y.; Nakamura, K.; et al. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J. Clin. Investig.* **2004**, *113*, 846–855. [CrossRef]
79. Kim, S.P.; Seward, A.H.; Garcia-Diaz, J.; Alekos, N.; Gould, N.R.; Aja, S.; Stains, J.P.; Wolfgang, M.J.; Riddle, R.C. Peroxisome proliferator activated receptor-gamma in osteoblasts controls bone formation and fat mass by regulating sclerostin expression. *iScience* **2023**, *26*, 106999. [CrossRef] [PubMed]
80. Grygiel-Gorniak, B. Peroxisome proliferator-activated receptors and their ligands: Nutritional and clinical implications—A review. *Nutr. J.* **2014**, *13*, 17. [CrossRef]
81. Vallee, A.; Lecarpentier, Y. Crosstalk Between Peroxisome Proliferator-Activated Receptor Gamma and the Canonical WNT/beta-Catenin Pathway in Chronic Inflammation and Oxidative Stress During Carcinogenesis. *Front. Immunol.* **2018**, *9*, 745. [CrossRef] [PubMed]
82. Rosen, E.; MacDougald, O. Adipocyte differentiation from the inside out. *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 885–896. [CrossRef] [PubMed]
83. Bevilacqua, A.; Franco, F.; Lu, Y.T.; Rahiman, N.; Kao, K.C.; Chuang, Y.M.; Zhu, Y.; Held, W.; Xie, X.; Gunsalus, K.C.; et al. PPARbeta/delta-orchestrated metabolic reprogramming supports the formation and maintenance of memory CD8(+) T cells. *Sci. Immunol.* **2024**, *9*, eadn2717. [CrossRef]
84. Djouad, F.; Ipseiz, N.; Luz-Crawford, P.; Scholtysek, C.; Kronke, G.; Jorgensen, C. PPARbeta/delta: A master regulator of mesenchymal stem cell functions. *Biochimie* **2017**, *136*, 55–58. [CrossRef]
85. Chen, M.; Lin, W.; Ye, R.; Yi, J.; Zhao, Z. PPARbeta/delta Agonist Alleviates Diabetic Osteoporosis via Regulating M1/M2 Macrophage Polarization. *Front. Cell Dev. Biol.* **2021**, *9*, 753194. [CrossRef]
86. Angione, A.R.; Jiang, C.; Pan, D.; Wang, Y.X.; Kuang, S. PPARdelta regulates satellite cell proliferation and skeletal muscle regeneration. *Skelet. Muscle* **2011**, *1*, 33. [CrossRef]
87. Lee, S.J.; Go, G.Y.; Yoo, M.; Kim, Y.K.; Seo, D.W.; Kang, J.S.; Bae, G.U. Peroxisome proliferator-activated receptor β/δ (PPARβ/δ) activates promyogenic signaling pathways, thereby promoting myoblast differentiation. *Biochem. Biophys. Res. Commun.* **2016**, *470*, 157–162. [CrossRef] [PubMed]
88. Yao, W.; Dai, W.; Shahnazari, M.; Pham, A.; Chen, Z.; Chen, H.; Guan, M.; Lane, N.E. Inhibition of the progesterone nuclear receptor during the bone linear growth phase increases peak bone mass in female mice. *PLoS ONE* **2010**, *5*, e11410. [CrossRef]
89. Kot, A.; Zhong, Z.A.; Zhang, H.; Lay, Y.E.; Lane, N.E.; Yao, W. Sex dimorphic regulation of osteoprogenitor progesterone in bone stromal cells. *J. Mol. Endocrinol.* **2017**, *59*, 351–363. [CrossRef]
90. Ruiz Magaña, M.J.; Puerta, J.M.; Martínez-Aguilar, R.; Llorca, T.; Blanco, O.; Muñoz-Fernández, R.; Olivares, E.G.; Ruiz-Ruiz, C. Endometrial and decidual stromal precursors show a different decidualization capacity. *Reproduction* **2020**, *160*, 83–91. [CrossRef]
91. Janesick, A.; Wu, S.C.; Blumberg, B. Retinoic acid signaling and neuronal differentiation. *Cell. Mol. Life Sci.* **2015**, *72*, 1559–1576. [CrossRef]

92. Hisada, K.; Hata, K.; Ichida, F.; Matsubara, T.; Orimo, H.; Nakano, T.; Yatani, H.; Nishimura, R.; Yoneda, T. Retinoic acid regulates commitment of undifferentiated mesenchymal stem cells into osteoblasts and adipocytes. *J. Bone Miner. Metab.* **2013**, *31*, 53–63. [CrossRef]
93. Cao, J.; Ma, Y.; Yao, W.; Zhang, X.; Wu, D. Retinoids Regulate Adipogenesis Involving the TGFbeta/SMAD and Wnt/beta-Catenin Pathways in Human Bone Marrow Mesenchymal Stem Cells. *Int. J. Mol. Sci.* **2017**, *18*, 842. [CrossRef] [PubMed]
94. Minucci, S.; Pelicci, P.G. Retinoid receptors in health and disease: Co-regulators and the chromatin connection. *Semin. Cell Dev. Biol.* **1999**, *10*, 215–225. [CrossRef] [PubMed]
95. Green, A.C.; Rudolph-Stringer, V.; Straszkowski, L.; Tjin, G.; Crimeen-Irwin, B.; Walia, M.; Martin, T.J.; Sims, N.A.; Purton, L.E. Retinoic Acid Receptor gamma Activity in Mesenchymal Stem Cells Regulates Endochondral Bone, Angiogenesis, and B Lymphopoiesis. *J. Bone Miner. Res.* **2018**, *33*, 2202–2213. [CrossRef]
96. Weston, A.D.; Rosen, V.; Chandraratna, R.A.; Underhill, T.M. Regulation of skeletal progenitor differentiation by the BMP and retinoid signaling pathways. *J. Cell Biol.* **2000**, *148*, 679–690. [CrossRef] [PubMed]
97. Zhang, W.; Deng, Z.L.; Chen, L.; Zuo, G.W.; Luo, Q.; Shi, Q.; Zhang, B.Q.; Wagner, E.R.; Rastegar, F.; Kim, S.H.; et al. Retinoic acids potentiate BMP9-induced osteogenic differentiation of mesenchymal progenitor cells. *PLoS ONE* **2010**, *5*, e11917. [CrossRef]
98. Riedl, M.; Witzmann, C.; Koch, M.; Lang, S.; Kerschbaum, M.; Baumann, F.; Krutsch, W.; Docheva, D.; Alt, V.; Pfeifer, C. Attenuation of Hypertrophy in Human MSCs via Treatment with a Retinoic Acid Receptor Inverse Agonist. *Int. J. Mol. Sci.* **2020**, *21*, 1444. [CrossRef]
99. Evans, R.M.; Mangelsdorf, D.J. Nuclear Receptors, RXR, and the Big Bang. *Cell* **2014**, *157*, 255–266. [CrossRef]
100. Shoucri, B.M.; Martinez, E.S.; Abreo, T.J.; Hung, V.T.; Moosova, Z.; Shioda, T.; Blumberg, B. Retinoid X Receptor Activation Alters the Chromatin Landscape To Commit Mesenchymal Stem Cells to the Adipose Lineage. *Endocrinology* **2017**, *158*, 3109–3125. [CrossRef]
101. Shoucri, B.M.; Hung, V.T.; Chamorro-Garcia, R.; Shioda, T.; Blumberg, B. Retinoid X Receptor Activation During Adipogenesis of Female Mesenchymal Stem Cells Programs a Dysfunctional Adipocyte. *Endocrinology* **2018**, *159*, 2863–2883. [CrossRef] [PubMed]
102. Menendez-Gutierrez, M.P.; Roszer, T.; Fuentes, L.; Nunez, V.; Escolano, A.; Redondo, J.M.; De Clerck, N.; Metzger, D.; Valledor, A.F.; Ricote, M. Retinoid X receptors orchestrate osteoclast differentiation and postnatal bone remodeling. *J. Clin. Investig.* **2015**, *125*, 809–823. [CrossRef] [PubMed]
103. Menendez-Gutierrez, M.P.; Ricote, M. The multi-faceted role of retinoid X receptor in bone remodeling. *Cell. Mol. Life Sci.* **2017**, *74*, 2135–2149. [CrossRef]
104. Obregon, M.J. Thyroid hormone and adipocyte differentiation. *Thyroid* **2008**, *18*, 185–195. [CrossRef]
105. Xing, W.; Cheng, S.; Wergedal, J.; Mohan, S. Epiphyseal chondrocyte secondary ossification centers require thyroid hormone activation of Indian hedgehog and osterix signaling. *J. Bone Miner. Res.* **2014**, *29*, 2262–2275. [CrossRef]
106. Chen, X.; Hu, Y.; Jiang, T.; Xia, C.; Wang, Y.; Gao, Y. Triiodothyronine Potentiates BMP9-Induced Osteogenesis in Mesenchymal Stem Cells Through the Activation of AMPK/p38 Signaling. *Front. Cell Dev. Biol.* **2020**, *8*, 725. [CrossRef]
107. Obregon, M.J. Adipose tissues and thyroid hormones. *Front. Physiol.* **2014**, *5*, 479. [CrossRef]
108. Bianco, A.C.; McAninch, E.A. The role of thyroid hormone and brown adipose tissue in energy homoeostasis. *Lancet Diabetes Endocrinol.* **2013**, *1*, 250–258. [CrossRef]
109. Lou, Y.-R.; Toh, T.C.; Tee, Y.H.; Yu, H. 25-Hydroxyvitamin D3 induces osteogenic differentiation of human mesenchymal stem cells. *Sci. Rep.* **2017**, *7*, 42816. [CrossRef]
110. Posa, F.; Di Benedetto, A.; Cavalcanti-Adam, E.A.; Colaianni, G.; Porro, C.; Trotta, T.; Brunetti, G.; Lo Muzio, L.; Grano, M.; Mori, G. Vitamin D Promotes MSC Osteogenic Differentiation Stimulating Cell Adhesion and αVβ3 Expression. *Stem Cells Int.* **2018**, *2018*, 6958713. [CrossRef]
111. Mori, T.; Horibe, K.; Koide, M.; Uehara, S.; Yamamoto, Y.; Kato, S.; Yasuda, H.; Takahashi, N.; Udagawa, N.; Nakamichi, Y. The Vitamin D Receptor in Osteoblast-Lineage Cells Is Essential for the Proresorptive Activity of 1alpha,25(OH)2D3 In Vivo. *Endocrinology* **2020**, *161*, bqaa178. [CrossRef] [PubMed]
112. Borojević, A.; Jauković, A.; Kukolj, T.; Mojsilović, S.; Obradović, H.; Trivanović, D.; Živanović, M.; Zečević, Ž.; Simić, M.; Gobeljić, B.; et al. Vitamin D3 Stimulates Proliferation Capacity, Expression of Pluripotency Markers, and Osteogenesis of Human Bone Marrow Mesenchymal Stromal/Stem Cells, Partly through SIRT1 Signaling. *Biomolecules* **2022**, *12*, 323. [CrossRef]
113. Kakutani, H.; Yuzuriha, T.; Akiyama, E.; Nakao, T.; Ohta, S. Complex toxicity as disruption of adipocyte or osteoblast differentiation in human mesenchymal stem cells under the mixed condition of TBBPA and TCDD. *Toxicol. Rep.* **2018**, *5*, 737–743. [CrossRef]
114. Abney, K.K.; Galipeau, J. Aryl hydrocarbon receptor in mesenchymal stromal cells: New frontiers in AhR biology. *FEBS J.* **2021**, *288*, 3962–3972. [CrossRef]
115. Skalny, A.V.; Aschner, M.; Zhang, F.; Guo, X.; Buha Djordevic, A.; Sotnikova, T.I.; Korobeinikova, T.V.; Domingo, J.L.; Farsky, S.H.P.; Tinkov, A.A. Molecular mechanisms of environmental pollutant-induced cartilage damage: From developmental disorders to osteoarthritis. *Arch. Toxicol.* **2024**, *98*, 2763–2796. [CrossRef]

116. Wang, X.; Zhao, Y.; Li, S.; Wang, Y.; Jia, C.; Yang, X.; Li, S.; Zhang, B.; Wei, W.; Chang, Y. Activation of the kynurenine-aryl hydrocarbon receptor axis impairs the chondrogenic and chondroprotective effects of human umbilical cord-derived mesenchymal stromal cells in osteoarthritis rats. *Hum. Cell* **2023**, *36*, 163–177. [CrossRef]
117. La Merrill, M.A.; Vandenberg, L.N.; Smith, M.T.; Goodson, W.; Browne, P.; Patisaul, H.B.; Guyton, K.Z.; Kortenkamp, A.; Cogliano, V.J.; Woodruff, T.J.; et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat. Rev. Endocrinol.* **2020**, *16*, 45–57. [CrossRef] [PubMed]
118. WHO/UNEP. *State of the Science of Endocrine Disrupting Chemicals—2012; United Nations Environmental Program*; World Health Organization: Geneva, Switzerland, 2013; p. 260.
119. Diamanti-Kandarakis, E.; Bourguignon, J.P.; Giudice, L.C.; Hauser, R.; Prins, G.S.; Soto, A.M.; Zoeller, R.T.; Gore, A.C. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. *Endocr. Rev.* **2009**, *30*, 293–342. [CrossRef]
120. Gore, A.C.; Chappell, V.A.; Fenton, S.E.; Flaws, J.A.; Nadal, A.; Prins, G.S.; Toppari, J.; Zoeller, R.T. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr. Rev.* **2015**, *36*, E1–E150. [CrossRef] [PubMed]
121. Alavian-Ghavanini, A.; Rüegg, J. Understanding Epigenetic Effects of Endocrine Disrupting Chemicals: From Mechanisms to Novel Test Methods. *Basic. Clin. Pharmacol. Toxicol.* **2018**, *122*, 38–45. [CrossRef]
122. Van Cauwenbergh, O.; Di Serafino, A.; Tytgat, J.; Soubry, A. Transgenerational epigenetic effects from male exposure to endocrine-disrupting compounds: A systematic review on research in mammals. *Clin. Epigenetics* **2020**, *12*, 65. [CrossRef]
123. Skinner, M.K. Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. *Genome Biol. Evol.* **2015**, *7*, 1296–1302. [CrossRef]
124. La Merrill, M.A.; Smith, M.T.; McHale, C.M.; Heindel, J.J.; Atlas, E.; Cave, M.C.; Collier, D.; Guyton, K.Z.; Koliwad, S.; Nadal, A.; et al. Consensus on the key characteristics of metabolism disruptors. *Nat. Rev. Endocrinol.* **2025**, *21*, 245–261. [CrossRef] [PubMed]
125. Heindel, J.J.; Howard, S.; Agay-Shay, K.; Arrebola, J.P.; Audouze, K.; Babin, P.J.; Barouki, R.; Bansal, A.; Blanc, E.; Cave, M.C.; et al. Obesity II: Establishing causal links between chemical exposures and obesity. *Biochem. Pharmacol.* **2022**, *199*, 115015. [CrossRef]
126. Kassotis, C.D.; Vom Saal, F.S.; Babin, P.J.; Lagadic-Gossmann, D.; Le Mentec, H.; Blumberg, B.; Mohajer, N.; Legrand, A.; Munic Kos, V.; Martin-Chouly, C.; et al. Obesity III: Obesogen assays: Limitations, strengths, and new directions. *Biochem. Pharmacol.* **2022**, *199*, 115014. [CrossRef]
127. Lustig, R.H.; Collier, D.; Kassotis, C.; Roepke, T.A.; Kim, M.J.; Blanc, E.; Barouki, R.; Bansal, A.; Cave, M.C.; Chatterjee, S.; et al. Obesity I: Overview and molecular and biochemical mechanisms. *Biochem. Pharmacol.* **2022**, *199*, 115012. [CrossRef] [PubMed]
128. Grun, F.; Watanabe, H.; Zamanian, Z.; Maeda, L.; Arima, K.; Cubacha, R.; Gardiner, D.M.; Kanno, J.; Iguchi, T.; Blumberg, B. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol. Endocrinol.* **2006**, *20*, 2141–2155. [CrossRef] [PubMed]
129. Li, X.; Ycaza, J.; Blumberg, B. The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes. *J. Steroid Biochem. Mol. Biol.* **2011**, *127*, 9–15. [CrossRef]
130. Baker, A.H.; Watt, J.; Huang, C.K.; Gerstenfeld, L.C.; Schlezinger, J.J. Tributyltin engages multiple nuclear receptor pathways and suppresses osteogenesis in bone marrow multipotent stromal cells. *Chem. Res. Toxicol.* **2015**, *28*, 1156–1166. [CrossRef]
131. Yanik, S.C.; Baker, A.H.; Mann, K.K.; Schlezinger, J.J. Organotins are potent activators of PPARgamma and adipocyte differentiation in bone marrow multipotent mesenchymal stromal cells. *Toxicol. Sci.* **2011**, *122*, 476–488. [CrossRef]
132. Chamorro-Garcia, R.; Diaz-Castillo, C.; Shoucri, B.M.; Kach, H.; Leavitt, R.; Shioda, T.; Blumberg, B. Ancestral perinatal obesogen exposure results in a transgenerational thrifty phenotype in mice. *Nat. Commun.* **2017**, *8*, 2012. [CrossRef] [PubMed]
133. Chamorro-Garcia, R.; Poupin, N.; Tremblay-Franco, M.; Canlet, C.; Egusquiza, R.; Gautier, R.; Jouanin, I.; Shoucri, B.M.; Blumberg, B.; Zalko, D. Transgenerational metabolomic fingerprints in mice ancestrally exposed to the obesogen TBT. *Environ. Int.* **2021**, *157*, 106822. [CrossRef] [PubMed]
134. Chang, R.C.; Huang, Y.; To, K.; Whitlock, R.S.; Nguyen, K.U.; Joemon, M.C.; Lopez, M.; Deeprompt, K.G.; Shioda, T.; Blumberg, B. Transgenerational Effects of the Obesogen Tributyltin on Metabolic Health in Mice: Interactions With a Western Diet. *Endocrinology* **2025**, *166*, bqaf063. [CrossRef] [PubMed]
135. le Maire, A.; Grimaldi, M.; Roecklin, D.; Dagnino, S.; Vivat-Hannah, V.; Balaguer, P.; Bourguet, W. Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. *EMBO Rep.* **2009**, *10*, 367–373. [CrossRef]
136. Kirchner, S.; Kieu, T.; Chow, C.; Casey, S.; Blumberg, B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol. Endocrinol.* **2010**, *24*, 526–539. [CrossRef]
137. Kanno, J. Introduction to the concept of signal toxicity. *J. Toxicol. Sci.* **2016**, *41*, SP105–SP109. [CrossRef]