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Metadichol Orchestrates Pluripotency via Nuclear Receptors during Cellular Reprogramming

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ABSTRACT

Nuclear receptors (NRs) are ligand-activated transcription factors that regulate the gene expression required for cellular reprogramming and pluripotency. This study examined the role of metadichol, a nanoemulsion of long-chain lipid alcohols (C26–C30), in modulating NR expression to increase the reprogramming of induced pluripotent stem cells (iPSCs). Using a nonviral method with metadichol at concentrations ranging from 1 pg/mL to 100 ng/mL, seven cell lines were evaluated, including human mesenchymal stem cells (HMSCs), normal human dermal fibroblasts (NHDFs), HEK293 cells, HeLa cells, THP-1 cells, triple-negative breast cancer cells, and primary prostate cancer cells. To assess the expression of 49 NRs, including estrogen-related receptor beta (NR3B2), nuclear receptor subfamily group A member 2 (NR5A2), and nuclear receptor subfamily 5 group member 1 (NR5A1), which can replace Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc) during iPSC generation, quantitative real-time polymerase chain reaction and western blot analyses were employed. Normal human dermal fibroblasts (NHDFs) and human mesenchymal stem cells strongly upregulated NR5A1 and NR5A2, which supported Oct4 replacement, and ERRβ, which facilitated Klf4 substitution. This upregulation made them highly suitable for NR-mediated reprogramming. Metadichol also induced the expression of pluripotency markers (e.g., alkaline phosphatase and Yamanaka factors), sirtuins, Fox head box protein O1 (FOXO1), Klotho, telomerase transcriptase (TERT) and insulin/beta cell formation, which suggests enhanced epigenetic remodeling and cell survival. This nonviral, scalable approach positions metadichol as a promising reagent for induced pluripotent stem cell (iPSC) differentiation in regenerative medicine, particularly for diabetes and oncology. These results suggest that metadichol could act as a universal nuclear receptor ligand, suggesting a comprehensive approach for efficient and safe induced pluripotent stem cell (iPSC) reprogramming.

Keywords: nuclear receptors, stem cell, IPSC, fibroblasts, cell reprogramming, metadichol, sirtuins, FOXO1, TERT, Klotho, vitamin C, Pgc1A, nanoemulsion, long-chain alcohols.

Introduction

Nuclear receptors (NRs) are ligand-activated transcription factors that mediate the effects of lipid-soluble compounds and metabolites on gene expression. They play a role in the cellular signaling pathways governing metabolism, reproduction, and development[1]. Characterized by a conserved DNA-binding domain and ligand-binding domain (LBD), the NR superfamily, which comprises 49 receptors, binds specific DNA sequences to regulate transcription in response to physiological signals[2]. With unidentified ligands, Orphan receptors modulate gene expression via posttranslational modifications or protein interactions, thus contributing to cellular homeostasis and environmental adaptation[3]. Moreover, by binding ligands that attenuate inflammatory gene expression, NRs reduce inflammation[4].

Cellular reprogramming, which transforms differentiated cells into induced pluripotent stem cells (iPSCs) or other cell types via dedifferentiation or transdifferentiation, has advanced regenerative medicine and disease modeling[2]. Pioneered by Takahashi and Yamanaka, somatic cell reprogramming employs the transcription factor Yamanaka. (Oct4, Sox2, Klf4, and c-Myc) to generate iPSCs that show embryonic stem cell (ESC))-like properties[5]. Methods, including retroviral transduction and chemical induction, facilitate reprogramming, with considerations for cell type and safety[7,8].

NUCLEAR RECEPTORS IN STEM CELL PLURIPOTENCY

Nuclear receptors maintain embryonic stem cell pluripotency[9] and regulate differentiation. Receptors, such as ERRβ, NR5A1, NR5A2, and DAX-1, regulate pluripotency and self-renewal genes to shape embryonic stem cell fate[10,11]. Nuclear receptor subfamily 5 group A member 2, i.e., NR5A2), an orphan receptor, directly activates Oct4 expression by binding to its promoter, promotes self-renewal and prevents differentiation in embryonic stem cells and epiblast cells, which form embryonic germ layers[12,13]. Esrrb is another orphan receptor interacting with the basal transcription machinery (e.g., RNA polymerase II) to sustain pluripotency gene expression, ensuring embryonic stem cell self-renewal[14]. Conversely, the nuclear receptors RAR, RXR, and GCNF drive embryonic stem cell differentiation by repressing pluripotency genes. For example, GCNF inhibits pluripotency gene transcription during retinoic acid-induced differentiation to promote specialization[15]. Corepressor–coactivator interactions mediate nuclear receptor transcriptional activity, with coactivators enhancing and corepressors limiting gene expression[16]. This balance allows NRs to regulate cell fate and prevent alternative states during reprogramming[5]. Estrogen-related receptor beta (NR3B2) and nuclear receptor coactivator 3 (Ncoa3) maintain embryonic stem cell self-renewal. Ncoa3 enhances estrogen-related receptor beta (ESRRB) and pluripotency gene regulation[13]. Nuclear receptor subfamily 5 group A member 2 (Nr5a2) and estrogen receptor beta (ESRRB), in combination with Oct4 and homeobox protein NANOG (NANOG), bind DNA regulatory regions to sustain ESC pluripotency[16].

REGULATION OF SOMATIC CELL IDENTITY BY NUCLEAR RECEPTORS.

Nuclear receptors regulate somatic cell identity through trans differentiation and forward differentiation, thus controlling lineage commitment genes to alter cell fate[2]. Peroxisome proliferator-activated receptor gamma (PPARγ) drives adipocyte maturation by activating lipid metabolism genes[17], whereas Nr6a1 (nuclear receptor subfamily 6 group A member 1) affects pluripotency and developmental gene expression[18]. These processes enable reprogramming terminally differentiated cells and expand their potential therapeutics[2].

Nuclear receptors can replace Yamanaka factors for iPSC generation, highlighting their reprogramming potential. Nuclear receptor subfamily 5 group A member 2 (Nr5a2) substitutes Oct4, and Esrrb is a substitute for Klf4, demonstrating their functionality[9]. The beta thyroid hormone receptor enhances mouse embryonic fibroblast reprogramming into

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iPSCs[6], whereas retinoic acid, via nuclear receptor corepressors (NCOR1), stimulates iPSC formation[6]. Canonical Wnt signaling, by activating pluripotency genes, accelerates NR5A2-mediated reprogramming[12]. Nuclear receptors facilitate mesenchymal-to-epithelial transition (MET), a key reprogramming[5], by acting as pioneer factors that unlock repressed chromatin. They also regulate epigenetic modifiers to increase chromatin plasticity, which supports iPSC generation[7]. Attenuating the peroxisome proliferator-activated receptor (PPAR) pathway prevents osteoclast differentiation and directs cell fate[19].

DIRECT AND INDIRECT CONTROL OF YAMANAKA FACTORS BY NRS

Nuclear receptors directly regulate Yamanaka factor expression; NR5A2 binds to the Oct4 promoter to maintain its expression, which is required for pluripotency[12]. Along with Oct4 and Sox2, EERRB (NR3B2) reprograms fibroblasts into iPSCs (20). Nuclear receptor subfamily 0 group B member 1 (Dax1) modulates ESRRB (NR3B2) activity, and NCOA3 (nuclear receptor coactivator 3) enhances ESRRB function, which sustains pluripotency gene expression[14,21]. These interactions highlight the role of nuclear receptors in reprogramming.

Table 1

Nuclear Receptor	Common name
NR3B1	ERRα
NR3B2	ERRβ
NR3B3	ERRγ
NR5A2	LRH1
NR5A1	SF1
NR1C3	PPARγ
NR1A1	TRα
NR1A2	TRβ
NR1B1	RARα
NR1B3	RARγ
NR2F1	COUP-TFI
NR2F2	COUP-TFII
NR0B1	DAX1
NR3C1	GR
NR3A2	ERβ

Nuclear receptors involved in iPSC expression

Moreover, nuclear receptors influence Yamanaka factors indirectly through various signaling pathways. Wnt signaling, which is modulated by nuclear receptors, regulates Oct4 and Sox2 activity[12]. Thyroid hormones reduce exogenous Klf4 requirements, increasing reprogramming efficiency[6]. Innate immune signaling via RLRs (RIG-I-like receptors) and optimal ROS levels affect Yamanaka factor activity by modulating epigenetic modifiers[7,21]. ESRRB (NR3B2) and NcCOA3 regulate Klf4 and Sox2, thus emphasizing protein-protein interactions in reprogramming[23].

Metadichol[24-26] is a nanoemulsion of long-chain alcohols (C26–C28–C30), with C28 as the principal constituent, accounting for 85%. To increase its potential in iPSCs, the factors required for its ability to regulate diverse transcription factors must be determined. For iPSC reprogramming, NRs can replace Yamanaka factors (Oct4, Sox2, Klf4, c-Myc,

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or OSKM). One study[9] suggested that the nuclear receptors ERRβ (NR3B2), NR5A2 (LRH-1), and NR5A1 (SF1) can replace the Yamanaka factors Klf4 and Oct4. After inducing iPSCs, subsequent steps involve maintaining and expanding the iPSCs, confirming pluripotency (by measuring alkaline phosphatase (ALP) levels), and selecting the differentiation targets (e.g., beta cells, neurons, and cardiomyocytes).

Nuclear receptor expression profiles[27,28] have been reported in human and mouse ESC lines and during their early differentiation into embryoid bodies. The expression of 49 human and mouse NRs was assessed via quantitative real-time (qRT) polymerase chain reaction (PCR). Moreover, the expression of estrogen, progesterone, and glucocorticoid receptors has been evaluated[29]. Research on systemic NR expression in human cell lines is still emerging. In the present study, the specific roles of NRs in human cell lines were determined via characterization of the RNA and cDNA expression profiles of the NR superfamily following the treatment of stem cells and fibroblasts with metadichol[24-26] via qRT–PCR and western blot analysis.

The induction of Yamanaka factors (known as OSKM), ALP, nuclear receptor sirtuins, vitamin C, FOXO1, Klotho, TERT, and insulin/beta cell formation in Panc-1 cells by metadichol suggests that it can increase the differentiation of beta cells by promoting epigenetic remodeling, NR signaling, and cell survival[30-41]. The complex interplay between NRs and diverse cellular factors must be understood to understand cellular plasticity and develop more efficient reprogramming strategies. Metadichol can regulate key factors to expand the therapeutic potential of iPSCs. Owing to its nonviral, safe[42-44], and scalable properties, metadichol is positioned as a promising reagent for iPSC differentiation in regenerative medicine, diabetes, and oncology, thereby making further research essential.

The expression of nuclear receptors in HMSCs (human mesenchymal stem cells), fibroblasts, HEK293 cells, HeLa cells, primary prostate cells, and triple-negative breast cancer (TNBC) cells was examined. These cells were treated with various concentrations of metadichol ranging from 1 pg/mL to 100 ng, and expression was quantified via qRT–PCR. Table 1 lists the fold regulation data for the treatment conditions (1 pg, 100 pg, one ng, and 100 ng) in seven cell lines and the significant NRs.

EXPERIMENTAL

A commercial service provider (Skanda Life Sciences, Bangalore, India) performed the quantitative RT–PCR, western blot analysis, and cell culture. The chemicals and reagents utilized were as follows: human mesenchymal stem cells and normal human dermal fibroblasts were procured from the ATCC (USA). Primary breast and prostate cancer cells were obtained from BIOIVT (Detroit, Michigan, USA). Primary antibodies were acquired from ABclonal, Woburn (Massachusetts, USA), or Elabscience (Maryland, USA). The primers were from Sahagene, Hyderabad, India, and Eurofins Bangalore, India. Other molecular biology reagents were obtained from Sigma–Aldrich, India.

CELL MAINTENANCE AND SEEDING

The cells were preserved in a suitable medium supplemented with 1% antibiotics in a wet atmosphere of 5% CO_2 at 37°C. The medium was changed every 2 days until the cells reached confluency. Cell viability was assessed via a hemocytometer. At 70%–80% confluency, single-cell suspensions containing 10^6 cells/mL were prepared and seeded in six-well plates at 10^6 cells/healthy density. The cells were incubated for 24h at 37°C under 5% CO_2 and then rinsed with serum-free medium before being incubated with different concentrations of metadichol.

CELL TREATMENT

Metadichol was diluted in serum-free media (1 pg/mL, 100 pg/mL, one ng/mL, and 100 ng/mL) and added to the predesignated wells. The control cells were not treated. The cells were incubated for 24 hours and washed gently with sterile phosphate-buffered saline. RNA was isolated via TRIzol following the manufacturer's instructions,

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and cDNA was prepared. Several biomarkers were assessed via qPCR and western blot analysis.

RNA ISOLATION

Total RNA was isolated from approximately 10^6 cells collected in 1.5 microcentrifuge tubes via TRIzol reagent (Invitrogen). The cells were subsequently centrifuged at 5,000 rpm for 5 min at 4°C, after which the supernatant was discarded. Next, 650 µL of TRIzol was added to the pellet, and the solution was mixed and incubated on ice for 20 min. Subsequently, 300 µL of chloroform was added, and the samples were mixed by gentle inversion for 1–2 min and incubated on ice for 10 min. The samples were centrifuged at 12,000 rpm for 15 min at 4°C, and the upper aqueous layer was carefully transferred to a new sterile 1.5-mL centrifuge tube. Prechilled isopropanol was added to an equal volume, and the samples were incubated at −20°C for 60 min. The mixture was centrifuged at 12,000 rpm for 15 min at 4°C, and the supernatant was carefully removed. The RNA pellets were washed with 1.0 mL of 100% ethanol, followed by 700 µL of 70% ethanol with centrifugation after each step. The RNA pellets were air-dried at room temperature for 15–20 min and resuspended in 30 µL of diethylpyrocarbonate-treated water. The RNA concentration was measured via a SpectraMax i3x-SpectraDrop microvolume microplate (Molecular Devices, USA).

cDNA SYNTHESIS

Following the manufacturer's guidelines, cDNA was synthesized from 2 µg of RNA via the PrimeScript cDNA synthesis kit (Takara, France) and oligo dT primers. The reaction volume was 20 µL, and cDNA synthesis was carried out at 50°C for 30 min, followed by incubation at 85°C for 5 min on an Applied Biosystems instrument (Veritii). The resulting cDNA was utilized for qPCR.

PRIMERS AND qPCR

The PCR mixture (final volume of 20 µL) contained 1 µL of cDNA, 10 µL of SYBR Green Master Mix, and one µM complementary primer specific for the target gene. The samples were run with the following settings: primary denaturation at 95°C for 5 min, followed by 30 cycles of denaturation at 95°C for 30 s, and annealing at the optimized temperature of the primers for 30 s, followed by extension at 72°C for 1 min. The number of amplification cycles in the exponential range before reaching a plateau was considered optimal. The results were evaluated via CFX Maestro software, and the fold change was calculated below.

ΔΔCT METHOD

Using the comparative CT method, the relative expression of the target gene relative to the housekeeping gene (β-actin) and untreated control cells was determined. The ΔCT for each treatment was calculated via the following formula:

ΔCT = CT (target gene) CT (reference gene).

To obtain the ΔΔCT, the individual samples in the treatment group were subtracted from those in the control groups, as shown below:

ΔΔCT = ΔCT (treatment group) – ΔCT (control group).

Similarly, the fold change in target gene expression for each treatment was calculated via the following formula:

Fold change = $2^{(-\Delta\Delta CT)}$

PROTEIN ISOLATION

Using radioimmunoprecipitation assay buffer supplemented with the protease inhibitor phenylmethanesulfonylfluoride fluoride, total protein was extracted from 10^6 cells. After mild inversion for 30 min at 4°C to lyse the cells, the samples were centrifuged at 10,000 rpm for 15 min. The supernatant was transferred to a fresh tube, and the protein concentration was measured via the Bradford method.

WESTERN BLOTTING

The protein samples (25 µg) were mixed with 1X sample loading dye containing SDS and subjected to SDS–PAGE. Under denaturing conditions, the proteins were separated via a Tris-glycine running buffer. The proteins were transferred to methanol-activated polyvinylidene fluoride membranes (Invitrogen, USA) via a Turbo Transblot system (Bio-Rad, USA). The membranes were blocked with 5% BSA for one hour and incubated with the

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appropriate primary antibodies overnight at 4°C, followed by a species-specific secondary antibody for one hour at room temperature. The blots were washed and incubated with an enhanced chemiluminescence (ECL) substrate (Merck, USA) for 1 minute in the dark. The images were captured at suitable exposure settings via a ChemiDoc XRS system (Bio-Rad, USA).

Table 2

Gene	Primers		Base pairs
NR1C2/PPARD	F	CCTTCTCAAGTATGGCGTGC	226
	R	GATGGCCGCAATGAATAGGG	
RXRG	F	CAGGAAAGCACTACGGGGTA	254
	R	CCTCACTCTCAGCTCGCTCT	
PPARG	F	AGAAGCCTGCATTTCTGCAT	236
	R	TCAAAGGAGTGGGAGTGGTC	
NR2F1	F	CATTTTTGGGCGATCTCCAGG	261
	R	GCCTTCTTCTTTCGGGAGGT	
HNF4A	F	ACTGCCACGTACCTGTGCCT	274
	R	AGGCATGCGAGTTGTGACCA	
HNF4G	F	AGCTGGCATATCTCAGCTGGC	185
	R	AACACCTGGCTGGCAATCGG	
NR2F2	F	CTCAACTGCCACTCGTACCT	253
	R	TCAACACAAACAGCTCGCTC	
NR1I3	F	CAGCAAACACCTGTGCAACT	189
	R	TGCGAAGTGTGTGACCAGAG	
NR1H4	F	AACAGAACAAGTGGCAGGTC	201
	R	AGAGTCTCAGCTGGCATACG	
ESR1	F	GATGTGGGAGAGGATGAGGA	165
	R	TCAGGCATGCGAGTAACAAG	
ESR2	F	TTCAGCCTGTGACCTCTGTG	178

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Gene	Primers		Base pairs
	R	CTTGGTTTGTCCAGGACGTT	
ESRRA	F	CAGGGGAGCATCGAGTACAG	303
	R	CTTCTCAGGCTCAACCACCA	
NR1D2	F	AGTTCTTCCAGCTCAGCCTC	226
	R	TTGTCATCCCAGGTGCACTC	
ESRRB	F	CTTGGTTTGTCCAGGACGTT	264
	R	TTTTCCATCATGGCTTGACA	
NR5A2	F	TCCAGCTTCCAGGCAGCCTC	234
	R	GATCTGTGAATCTGCGTT	
NR3C2	F	CTGCCTCGTTTCCCTTTTCC	231
	R	CCATGATCTGTGCGTTCCTG	
NR0B2	F	GCTGTCTGGAGTCCTTCTGG	164
	R	CTGGGTATGAATCCCAGCAC	
ESRRG	F	GACTTGACTCGCCACCTCTC	174
	R	GTGGTACCCAGAAGCGATGT	
NR4A2	F	CCGGTGTCTAGTTGCCAGAT	275
	R	ACGCCGTAGTGTTGGCAG	
NR2F6	F	GGACTCTGGCTTCTCTCCTC	187
	R	TAGGGGTGCTGAGGAACAAG	
NR6A1	F	GAGGAACAGGTGCCAGTACT	175
	R	GGCCTCTTCCTCAAACTCCT	
THRB	F	GCCTCCAATAGCTCCAGGAT	201
	R	CACCCAGTTCCAGGATTCCT	
VDR	F	GACGCCCACCATAAGACCTA	247

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Gene	Primers		Base pairs
	R	AGATTGGAGAAGCTGGACGA	
NR1H2	F	CCTCCTGAAGGCATCCACTA	261
	R	GAACTCGAAGATGGGGTTGA	
NR1D1	F	AGGCAGCAAGCAAGCAGT	291
	R	ACAGCGCATCCTTCCCCATA	
NR2C1	F	CCCAAGGCAAGCAGTTCATT	157
	R	GCAGACAGATCAGGAGTGGT	
NR2C2	F	TCACCACCTCAGACAACCTC	164
	R	ACTGACAGCCCCATAGTGAC	
NR1I2	F	AACGCAGATGAGGAAGTCGG	103
	R	AGCCCTTGCATCCTTCACAT	
NR4A3	F	GCCCAATATAGCCCTTCCCC	224
	R	TGCATTTGGTACACGCAGGA	
NR3C1	F	CTTGCATATTTGTGCCTTCA	174
	R	CTTGATGATTTGTGTTGTGC	
AR	F	GGGGCTAGACTGCTCAACTG	169
	R	GCCAAGTTTTGGCTGAAGAG	
NR0B1	F	CAGAGGCCAGGGGGTAAAG	137
	R	TGCGCTTGATTTGTGCTCGT	
PGR	F	ACATGGTAGCTGTGGGAAGG	198
	R	GCTAAGCCAGCAAGAAATGG	
RORA	F	TCGAACCAGTAGAAACCGCT	219
	R	TTGGCCGAGATGTTGTAGGT	
ROB	F	CTCACTTCTCCACCTGCTCA	212

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Gene	Primers		Base pairs
	R	GGAGTTGGTGGCTGGGATAT	
RORC	F	AGTCGGAAGGCAAGATCAGA	204
	R	CAAGAGAGGTTCTGGGCAAG	
NR2E3	F	GGAGTCCAACACTGAGTCCC	289
	R	GGCCATGAAGAGTAGGCGAG	
NR5A1	F	AGGCACCAGGGAAGATCA	241
	R	TGCCAGGCCAGGGAATACA	
NR2E1	F	CAAGTGGGCTAAGAGTGTGC	158
	R	CGTTCATGCCAGATACAGCC	
NR4A1	F	GCCAATCTCCTCACTTCCCT	202
	R	CAGCAAAGCCAGGGATCTTC	
RARA	F	GTGTCACCGGGACAAGAACT	146
	R	CGTCAGCGTGTAGCTCTCAG	
RXRA	F	CTCTGTTGTGTCCTGTTGCC	155
	R	CTTCTCCCTTTGCGTGTTCC	
PPARA	F	CTGTCTGCTCTGTGGACTCA	247
	R	AGAACTATCCTCGCCGATGG	
RARB	F	GGTTTCACTGGCTTGACCAT	216
	R	GGCAAAGGTGAACACAAGGT	
AHR	F	GGTTTCACTGGCTTGACCAT	274
	R	CAGAGGACCAAATCCAGCAT	
RARG	F	GAAGACCGCGACACAACTTCC	180
	R	GTTGAGTTAAGACATGAGGG	
RXRB	F	GCAGGAGTAGGAGCCATCTT	188

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Gene	Primers		Base pairs
	R	GCATACACTTTCTCCCGCAG	
THRA	F	ACCTCCATCCCACCTATTCC	242
	R	CTCTTCAGGAGTGGGCTCTG	
NR1H3	F	GAGATCCTCCCGTGGCATTA	151
	R	GAGAACCCTGTGCAAAGTGG	

List of primers used for quantitative PCR. F forward; R reverse

Table 3

Gene	Cell line	Max fold change	Concentration	Common name
NR1A1	HeLa	2.02	1 pg/mL	TRα
NR1A1	hMSC	16.16	1 pg/mL	TRα
NR1A1	NHDF	1.20	1 pg/mL	TRα
NR1A1	THP1	0.46	1 ng/mL	TRα
NR1A1	HEk 293	21.87	100 pg/mL	TRα
NR1C3	HeLa	1.26	100 pg/mL	PPARG
NR1C3	hMSC	7.61	1 pg/mL	PPARG
NR1C3	NHDF	7.31	1 ng/mL	PPARG
NR1C3	THP1	2.60	1 ng/mL	PPARG
NR1C3	HEK 293	5.23	1 ng/mL	PPARG
NR3B1	HeLa	9.88	100 ng/mL	ERRα
NR3B1	NHDF	11.10	100 ng/mL	ERRα
NR3B1	THP1	0.94	100 pg/mL	ERRα
NR3B1	HEK 293	0.82	1 pg/mL	ERRα
NR1I3	HeLa	9.99	1 ng/mL	CAR

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Gene	Cell line	Max fold change	Concentration	Common name
NR1I3	hMSC	10.61	100 ng/mL	CAR
NR1I3	NHDF	0.98	1 pg/mL	CAR
NR1I3	THP1	0.88	199 pg/mL	CAR
NR1I3	HEk 293	11.86	100 ng/mL	CAR
NR5A1	HeLa	5.26	100 pg/mL	SF1
NR5A1	hMSC	5.09	100 ng/mL	SF1
NR5A1	NHDF	27.27	1 pg/mL	SF1
NR5A1	THP1	2.26	100 pg/mL	SF1
NR5A1	Hek 293	0.70	1 ng/mL	SF1

Table 4

Gene	Cell line	Max fold change	Condition	Common name
NR2B2	Prostate	19.63	1 ng/mL	RXRB
NR3C4	Prostate	4.06	1 ng/mL	AR
c-MYC	Prostate	18.25	1 pg/mL	c-MYC
NR4A1	Prostate	3.88	1 ng/mL	NGFIB
NR1C3	Prostate	3.05	100 pg/mL	PPARG
ESRRA	Breast	18.25	1 pg/mL	ERRα
RARG	Breast	26.41	1 ng/mL	RARγ
NR3C1	Breast	15.65	1 ng/mL	GR
NR0B1	Breast	9.35	1 ng/mL	DAX1
NR1C3	Breast	5.72	1 ng/mL	PPARG

Key nuclear receptor factors and maximum fold changes in prostate and breast cancer cells

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Results

The qPCR data revealed distinct nuclear receptor expression profiles across the seven cell lines, with cell type-specific and dose-dependent responses (Table 5). Table 3 summarizes the maximum fold changes for the prominent nuclear receptors (Table 1) in the HeLa, hMSC, NHDF, THP-1, and HEK293 cells. In contrast, Table 4 lists the results for the prostate and breast cancer cell lines.

The data highlight distinct nuclear receptor expression profiles across the seven cell lines, which reflects their biological role.s.

HeLa and HEK293

The high expression of NR1I3 (CAR) and NR1A1 (TRα) in HeLa and HEK293 cells suggests stress and differentiation responses, which is consistent with cancer cell plasticity[45].

hMSC

The remarkable upregulation of NR1A1 (TRα) and NR1C3 (PPARG) in hMSCs supports differentiation pathways, particularly adipogenesis[46].

NHDF

A 27.27-fold increase in NR5A1 (SF1) is unexpected, as SF1 is typically steroidogenic. These findings suggest a novel role for metadichol in fibroblast metabolism or matrix production[47].

THP1

Widespread downregulation reflects limited NR activity in immune cells, with NR2F2 (COUP-TFII) as an exception, potentially modulating the immune response.

Prostate cancer cells

The upregulation of NR3C4 (AR) and c-MYC is consistent with androgen-dependent oncogenesis[51].

Breast

High ESRRA and RARG expression suggests the involvement of metabolic and retinoid signaling in cancer progression[49].

Dose-dependent response

Many nuclear receptors display biphasic responses, with peak upregulation at intermediate concentrations (100 pg/mL or one ng/mL) and reduced expression at 100 ng/mL (e.g., NR1A1 in HMSCs and NR5A1 in NHDFs). This may reflect receptor saturation, feedback inhibition, or toxicity at high doses[50]. The L patterns imply ligand-specific effects.

Biological Implications

Differentiation

The upregulation of peroxisome proliferator-activated receptor gamma in HMSCs and NHDFs supports adipogenesis and tissue remodeling[51].

Metabolism

NR3B1 (ERRα) expression in NHDFs and HeLa cells indicates mitochondrial function and energy homeostasis[51].

Stress response

Upregulation of NR1I3 (CAR) and AHR in HEK293 cells and NHDFs suggests xenobiotic or environmental stress responses[52,53].

Oncogenesis

Estrogen-related receptor alpha (ESRRA) in prostate and breast cell lines emphasizes oncogenic pathways[54].

The combined results in Table 12 show that NHDFs and HMSCs express NRs that are most likely to replace Yamanaka factors in iPSC reprogramming. The robust upregulation of NR5A1 and NR5A2 in normal human dermal fibroblasts (NHDFs) supports Oct4 replacement, whereas HMSCs express NR3B2 (ERRβ) and NR5A1, which support Klf4 and Oct4 replacement. Triple-negative breast cancer cells (TNBCs) exhibit ERRβ-mediated Klf4 replacement but lack Oct4 replacement potential. HEK293, HELA, and THP-1 cells (Tables 7–9) have revealed limited potential, primarily for Oct4 replacement. Prostate cancer cells (Table 10) presented minimal NR expression. These findings emphasize that NHDFs and HMSCs are optimal cell types for leveraging NRs to replace Yamanaka factors in iPSC reprogramming, with implications for enhancing reprogramming efficiency.

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Table 5. HMSC fold regulation

Gene	Control	1pg	100pg	1ng	100ng	Coomon Names
AHR	1	0.39	0.58	0.79	0.51	AHR
NR0B1	1	0.19	0.33	0.38	0.11	DAX1
NR0B2	1	1.39	0.75	1.06	0.29	SHP
NR1A1	1	16.16	12.24	7.7	5.32	TRα
NR1A2	1	7.71	1.94	15.11	8.71	TRβ
NR1B1	1	1.27	0.79	0.52	0.44	RARα
NR1B2	1	1.67	1.39	0.48	0.73	**RARB**
NR1B3	1	2.52	1.04	0.96	0.82	RARγ
NR1C1	1	2.61	3.39	3.68	0.59	PPARα
NR1C2	1	3.74	4.5	4.5	0.44	PPAR-β/δ
NR1C3	1	7.61	5.88	3.44	2.62	**PPARG**
NR1D1	1	1.93	1.29	0.8	0.6	Rev-ErbAα
NR1D2	1	1.33	1.26	0.7	6.17	Rev-ErbAβ
NR1F1	1	1.77	1.39	0.94	0.67	RORα
NR1F2	1	0.81	0.84	0.7	0.33	RORβ
NR1F3	1	0.52	0.74	1.19	1.08	RORγ
NR1H2	1	1.28	0.97	0.55	0.19	**LXRB**
NR1H3	1	1.28	1.17	0.84	0.18	LXRα
NR1H4	1	1.98	1.09	0.53	0.6	FXR
NR1I1	1	2.03	0.92	3.67	0.54	VDR
NR1I2	1	0.6	0.74	1.11	0.39	PXR
NR1I3	1	8.03	1.49	2.91	10.61	CAR
NR2A1	1	0.99	0.72	0.51	0.13	**HNF4A**
NR2A2	1	1.39	1.51	0.36	0.26	HNF4γ
NR2B1	1	1.4	1.21	0.99	0.79	**RXRA**
NR2B2	1	1.87	1.13	1.05	0.69	**RXRB**
NR2B3	1	2.15	2.2	1.5	0.76	**RXRG**
NR2C1	1	1.3	1.27	0.74	0.39	TR2
NR2C2	1	1.6	1.5	0.74	0.51	TR4
NR2E1	1	0.95	1.37	1.18	0.57	TLX
NR2E3	1	2.18	1.23	1.51	1.25	PNR
NR2F1	1	1.78	1.57	1.04	0.65	COUP-TFI
NR2F2	1	1.81	1.48	1.15	1.07	COUP-TFII
NR2F6	1	0.98	0.95	0.43	0.08	EAR-2
NR3A1	1	1.86	1.17	1.94	0.4	ERα
NR3A2	1	1.81	1.37	1.09	0.66	ERβ
NR3B1	1	1	0.88	0.59	0.35	ERRα
NR3B2	1	1.11	2.32	1.45	1.36	ERRβ
NR3B3	1	1.84	1.02	0.55	0.18	ERRγ
NR3C1	1	0.99	0.96	0.82	0.09	GR
NR3C2	1	1.15	0.78	0.52	0.21	MR
NR3C3	1	1.19	0.94	0.67	0.12	PR
NR3C4	1	1.15	0.37	0.11	0.33	AR
NR4A1	1	1.82	0.67	1.16	0.61	NGFIB
NR4A2	1	1.06	0.61	0.45	0	NURR1
NR4A3	1	5.43	1.89	0.35	0.5	NOR1
NR5A1	1	3.2	2.56	1.92	5.09	SF1
NR5A2	1	1.3	0.72	0.29	0.15	**LRH1**
NR6A1	1	1.7	0.86	0.65	0.15	GCNF

HMSC fold regulation

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Table 6

Gene	Control	1pg	100pg	1ng	100ng	Common names
AHR	1	10.17	4.32	3.79	1.52	AHR
NR0B1	1	1.76	0.14	0.44	0.24	DAX1
NR0B2	NA	NA	NA	NA	NA	SHP
NR1A1	1	1.2	0.65	0.55	0.69	TRα
NR1A2	1	1.15	1.18	2.4	0.92	TRβ
NR1B1	1	2.15	1.81	0.63	1.06	RARα
NR1B2	1	2.68	1.3	1.18	1.1	**RARB**
NR1B3	1	2.84	2.95	3.9	1.09	RARγ
NR1C1	1	1.9	1.24	0.72	1.8	PPARα
NR1C2	1	2.48	2.59	2.83	0.84	PPAR-β/δ
NR1C3	1	3.78	6.11	7.31	3.07	**PPARG**
NR1D1	1	1.5	0.64	0.07	0.75	Rev-ErbAα
NR1D2	1	2.19	1.18	1.8	1.82	Rev-ErbAβ
NR1F1	1	0.9	1.14	1.33	1.01	RORα
NR1F2	1	2.71	0.99	0.69	0.88	RORβ
NR1F3	1	1.86	1.02	0.91	1.04	RORγ
NR1H2	1	4.95	1.03	0.03	1.71	**LXRB**
NR1H3	1	1.63	1.79	3.84	0.71	LXRα
NR1H4	1	2.69	1.32	1.27	0.87	FXR
NR1I1	1	1.83	2.34	2.35	1.54	VDR
NR1I2	1	1.81	0.37	0.97	1	PXR
NR1I3	1	0.98	0.67	0.49	0.53	CAR
NR2A1	1	6.03	3.4	2.69	3.64	**HNF4A**
NR2A2	1	2.15	1.39	1.2	1.95	HNF4γ
NR2B1	1	2.5	0.86	1.32	0.98	**RXRA**
NR2B2	1	4.21	1.65	1.03	2.7	**RXRB**
NR2B3	1	3.56	1.49	1.04	1.75	**RXRG**
NR2C1	1	1.08	1.16	1.7	0.85	TR2
NR2C2	1	3.66	1.38	1.09	4.17	TR4
NR2E1	1	3.38	1.49	1.69	0.88	TLX
NR2E3	1	1.43	1.46	2.48	1.27	PNR
NR2F1	1	0.16	0.9	4.18	0.5	COUP-TFI
NR2F2	1	1.05	1.19	2.98	0.59	COUP-TFII
NR2F6	1	2.84	1.22	1.66	1.02	EAR-2
NR3A1	1	2.42	1.58	0.73	2.02	ERα
NR3A2	1	3.04	3.04	1.25	1.52	ERβ
NR3B1	1	10.85	8.3	6.58	11.1	ERRα
NR3B2	1	0.65	0.74	0.48	1.76	ERRβ
NR3B3	1	0.81	1.07	1.86	0.45	ERRγ
NR3C1	1	1.71	0.14	0.77	0.46	GR
NR3C2	1	3.7	0.26	1.04	0.42	MR
NR3C3	1	0.71	1.25	2.19	0.51	PR
NR3C4	1	2.54	0.15	0.57	0.11	AR
NR4A1	1	2.36	1.55	0.93	3.42	NGFIB
NR4A2	1	3.56	6.02	8.63	7.62	NURR1
NR4A3	1	2.14	0.72	1.48	1.59	NOR1
NR5A1	1	27.27	13.78	13.28	2.69	SF1
NR5A2	1	3.32	1.79	1.74	2.02	**LRH1**
NR6A1	1	0.89	0.79	0.33	1.27	GCNF

NHDF fold regulation

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Table 7

Gene	Control	1pg	100pg	1ng	100ng	common name
Ahr	1.00	0.19	0.27	0.37	1.66	AHR
NR0B1	1.00	0.08	0.25	0.10	0.03	DAX1
NR0B2	1.00	0.25	0.85	0.08	0.02	SHP
NR1A1	1.00	0.00	0.22	0.46	0.09	TRα
NR1A2	1.00	1.15	1.10	1.30	0.97	TRβ
NR1B1	1.00	0.00	0.35	0.49	0.17	RARα
NR1B2	1.00	0.27	0.71	0.22	0.06	RARB
NR1B3	1.00	0.08	0.22	0.09	0.03	RARγ
NR1C1	1.00	0.00	0.25	0.37	0.12	PPARα
NR1C2	1.00	0.14	0.40	0.27	0.08	PPAR-β/δ
NR1C3	1.00	0.04	0.33	2.60	0.86	PPARG
NR1D1	1.00	0.01	0.41	0.63	0.21	Rev-ErbAα
NR1D2	1.00	0.05	0.09	0.10	0.08	Rev-ErbAβ
NR1F1	1.00	0.15	0.38	0.32	0.42	RORα
NR1F2	1.00	0.16	0.34	0.00	0.00	RORβ
NR1F3	1.00	0.65	0.98	0.20	0.13	RORγ
NR1H2	1.00	0.30	0.47	0.02	0.03	LXRB
NR1H3	1.00	0.14	0.36	0.06	0.02	LXRα
NR1H4	1.00	0.14	0.31	0.08	0.02	FXR
NR1I1	1.00	0.27	0.37	0.02	0.02	VDR
NR1I2	1.00	0.85	1.77	1.26	1.62	PXR
NR1I3	1.00	0.56	0.88	0.17	0.09	CAR
NR2A1	1.00	0.08	0.24	0.09	0.04	HNF4A
NR2A2	1.00	0.00	0.16	0.33	0.05	HNF4γ
NR2B1	1.00	0.04	0.27	0.20	0.04	RXRA
NR2B2	1.00	0.01	0.31	0.55	0.16	RXRB
NR2B3	1.00	0.41	0.47	0.32	0.64	RXRG
NR2C1	1.00	0.07	0.24	0.16	0.04	TR2
NR2C2	1.00	0.00	0.21	0.37	0.08	TR4
NR2E1	1.00	0.48	0.62	0.65	0.68	TLX
NR2E3	1.00	0.06	0.41	0.06	0.02	PNR
NR2F1	1.00	0.12	0.28	0.08	0.02	COUP-TFI
NR2F2	1.00	0.29	2.85	3.71	0.46	COUP-TFII
NR2F6	1.00	0.01	0.21	0.12	0.04	EAR-2
NR3A1	1.00	0.19	0.69	1.47	0.56	ERα
NR3A2	1.00	0.64	1.33	2.26	1.75	ERβ
NR3B1	1.00	0.21	0.94	0.43	0.14	ERRα
NR3B2	1.00	0.13	0.16	0.18	0.39	ERRβ
NR3B3	1.00	0.28	0.45	0.01	0.01	ERRγ
NR3C1	1.00	0.03	0.24	0.16	0.05	GR
NR3C2	1.00	0.21	0.47	0.04	0.01	MR
NR3C3	1.00	0.25	0.41	0.01	0.01	PR
NR3C4	1.00	0.04	0.41	0.15	0.02	AR
NR4A1	1.00	0.00	0.39	0.48	0.14	NGFIB
NR4A2	1.00	0.17	0.50	0.15	0.03	NURR1
NR4A3	1.00	0.34	0.87	0.46	0.6	NOR1
NR5A1	1.00	0.45	2.26	0.06	0.06	SF1
NR5A2	1.00	0.05	0.18	0.19	0.05	LRH1
NR6A1	1.00	0.01	0.15	0.30	0.07	GCNF

THP-1-fold regulation

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Table 8

Gene	Control	1pg	100pg	1ng	100ng	Common names
AHR	1	0.58	0.94	1.4	1.04	AHR
NR0B1	1	0.63	5.31	6.07	7.31	DAX1
NR0B2	1	1.35	7.95	1.99	9.69	SHP
NR1A1	1	2.02	1.84	0.39	1.47	TRα
NR1A2	1	0.3	1.86	1.15	1.04	TRβ
NR1B1	1	2.87	2.08	0.33	0.67	RARα
NR1B2	1	0.8	1.6	1.32	0.99	RARB
NR1B3	1	1.29	1.95	0.93	0.72	RARγ
NR1C1	1	3.62	1.07	0.21	0.19	PPARα
NR1C2	1	0.34	0.27	0.87	1.03	PPAR-β/δ
NR1C3	1	1.23	1.26	0.22	0.42	PPARG
NR1D1	1	1.53	2.09	0.35	0.9	Rev-ErbAα
NR1D2	1	3.61	3.75	1.64	0.88	Rev-ErbAβ
NR1F1	1	2.07	1.21	0.36	0.44	RORα
NR1F2	1	1.1	7.28	9.6	3.29	RORβ
NR1F3	1	1.09	4.59	4.25	3.38	RORγ
NR1H2	1	0.03	0.48	0.16	0.5	LXRB
NR1H3	1	0.5	5.61	3.1	7.36	LXRα
NR1H4	1	0.81	3.43	2.8	1.33	FXR
NR1I1	1	0.28	1.56	1.16	1.34	VDR
NR1I2	1	1.4	0.56	0.59	1.07	PXR
NR1I3	1	1.56	7.79	9.99	5.78	CAR
NR2A1	1	0.15	2.92	5.08	7.91	HNF4A
NR2A2	1	1.16	0.29	0.23	0.33	HNF4γ
NR2B1	1	4.36	1.93	0.89	0.81	RXRA
NR2B2	1	1.98	2.79	0.59	0.59	RXRB
NR2B3	1	2.79	2.08	0.84	0.94	RXRG
NR2C1	1	1.58	1.77	0.55	0.82	TR2
NR2C2	1	2.52	1.62	0.31	0.82	TR4
NR2E1	NA	NA	NA	NA	NA	TLX
NR2E3	1	1.38	1.34	0.29	0.53	PNR
NR2F1	1	1.49	7.13	4.27	5.59	COUP-TFI
NR2F2	1	0.97	7.63	5.26	3.02	COUP-TFII
NR2F6	1	1.88	2.65	1.06	2.37	EAR-2
NR3A1	1	6.31	5.52	1.45	3.21	ERα
NR3A2	1	7.7	5.58	1.43	2.04	ERβ
NR3B1	1	0.72	4.73	6.42	9.88	ERRα
NR3B2	1	1.51	1.69	0.71	0.9	ERRβ
NR3B3	1	0.99	1.6	0.8	0.55	ERRγ
NR3C1	1	0.51	1.34	2.4	3.14	GR
NR3C2	NA	NA	NA	NA	NA	MR
NR3C3	NA	NA	NA	NA	NA	PR
NR3C4	NA	NA	NA	NA	NA	AR
NR4A1	1	2.31	1.91	0.54	1.33	NGFIB
NR4A2	1	0.48	4.55	5.24	7.44	NURR1
NR4A3	1	1.42	4.24	1.04	1.51	NOR1
NR5A1	1	0.59	5.26	2.02	2.75	SF1
NR5A2	1	0.67	1.79	0.99	0.95	LRH1
NR6A1	1	2.01	1.57	0.28	0.43	GCNF

HEK293-fold regulation

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Table 9

Fold Regulation							
Gene							common name
Ahr	1	7.08	6.09	6.07	2.05	AHR	AHR
NR0B1	1	0.24	0.38	0.23	0.17	DAX1	DAX1
NR0B2	1	1.96	2.8	3.06	2.57	SHP	SHP
NR1A1	1	10.62	21.87	8.98	2.71	TRα	TRα
NR1A2	1	9.88	13.72	12.47	11.48	TRβ	TRβ
NR1B1	1	2.01	1.79	1.95	1.12	RARα	RARα
NR1B2	1	1.19	1.65	1.07	1.34	RARB	RARB
NR1B3	1	1.71	0.86	0.63	0.48	RARγ	RARγ
NR1C1	1	2.83	4.24	2.75	0.93	PPARα	PPARα
NR1C2	1	0.78	0.86	0.82	0.63	PPAR-β/δ	PPAR-β/δ
NR1C3	1	2.96	3.62	5.23	1.49	PPARG	PPARG
NR1D1	1	2.87	2.05	4.75	1.2	Rev-ErbAα	Rev-ErbAα
NR1D2	1	1.1	1.28	1.37	0.76	Rev-ErbAβ	Rev-ErbAβ
NR1F1	1	1.75	2.51	1.83	2.3	RORα	RORα
NR1F2	1	0.55	1.2	0.93	0.72	RORβ	RORβ
NR1F3	1	0.73	0.77	0.74	0.54	RORγ	RORγ
NR1H2	1	0.89	0.37	0.63	0.43	LXRB	LXRB
NR1H3	1	0.56	0.52	0.59	0.48	LXRα	LXRα
NR1H4	1	0.81	1.18	0.86	0.68	FXR	FXR
NR1I1	1	1.38	0.54	1.03	0.68	VDR	VDR
NR1I2	1	0.72	0.26	0.64	0.5	PXR	PXR
NR1I3	1	2.32	2.1	7.44	11.86	CAR	CAR
NR2A1	1	0.94	0.92	0.61	0.48	HNF4A	HNF4A
NR2A2	1	2.51	3.46	4.41	1.43	HNF4γ	HNF4γ
NR2B1	1	0.89	1	0.96	0.6	RXRA	RXRA
NR2B2	1	2.37	2.76	3.16	1.24	RXRB	RXRB
NR2B3	1	0.35	1.06	0.17	0.27	RXRG	RXRG
NR2C1	1	0.65	0.28	0.66	0.52	TR2	TR2
NR2C2	1	10.56	7.22	8.84	3.26	TR4	TR4
NR2E1	1	1.04	1.79	1.14	1.6	TLX	TLX
NR2E3	1	1.98	1.26	1.25	0.5	PNR	PNR
NR2F1	1	0.74	0.71	0.62	0.45	COUP-TFI	COUP-TFI
NR2F2	1	0.8	0.63	0.63	0.43	COUP-TFII	COUP-TFII
NR2F6	1	1.13	1.29	0.91	0.55	EAR-2	EAR-2
NR3A1	1	1.6	2.42	3.01	2.92	ERα	ERα
NR3A2	1	1.4	1.24	0.64	0.16	ERβ	ERβ
NR3B1	1	0.82	0.27	0.61	0.56	ERRα	ERRα
NR3B2	1	1.02	0.75	0.49	0.27	ERRβ	ERRβ
NR3B3	1	2.78	1.43	2.51	2.32	ERRγ	ERRγ
NR3C1	1	0.57	1.01	1.17	1.01	GR	GR
NR3C2	1	0.54	0.6	0.46	0.38	MR	MR
NR3C3	1	0.78	0.63	0.68	0.83	PR	PR
NR3C4	1	0.57	0.46	0.46	0.29	AR	AR
NR4A1	1	5.13	6.7	6.7	0.24	NGFIB	NGFIB
NR4A2	1	0.72	0.54	0.79	0.32	NURR1	NURR1
NR4A3	1	0.76	0.75	0.62	0.42	NOR1	NOR1
NR5A1	1	0.33	0.47	0.7	0.68	SF1	SF1
NR5A2	1	2.09	0.83	1.47	1.27	LRH1	LRH1
NR6A1	1	1.53	1.88	2.45	1	GCNF	GCNF

HeLa fold regulation

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Table 10

Gene	common names	control	1 pg	100 pg	1 ng	100 ng
NR2B2	RXRB	1	4.56	4.94	19.63	9.32
NR1F2	RORβ	1	2.11	0.77	8.91	2.39
NR3B2	ERRB	1	3.36	4.39	8.07	6.91
NR2B1	RXRA	1	1.23	1.46	5.5	2.06
NR1D2	Rev-ErbAβ	1	0.54	1.25	5.42	1.16
NR1B3	RARG	1	1.14	1.24	4.91	2.33
NR0B1	DAX1	1	0.37	0.96	4.78	1.51
NR2F6	EAR-2	1	0.36	1.15	4.63	0.81
NR3C4	AR	1	1.69	2.21	4.06	3.48
NR1C2	PPARD	1	3.36	4.39	4.04	6.91
NR4A1	NGFIB	1	0.3	0.78	3.88	1.23
NR1F1	RORA	1	0.49	5.04	3.15	2
NR2C2	TR4	1	0.64	0.84	3	0.88
NR3C1	GR	1	0.95	0.3	2.76	1.26
THRA	THRA	1	0.57	0.62	2.45	1.16
NR2E1	TLX	1	0.69	0.49	2.11	0.81
NR1H3	LXRα	1	0.85	1.1	2.03	1.74
NR4A2	NURR1	1	0.44	0.33	1.7	0.24
NR6A1	GCNF	1	0.87	0.97	1.42	1.72
NR4A3	NOR1	1	2.28	1.24	1.23	2.33
NR1C3	PPARG	1	2.8	3.05	0.6	1.99
NR2C1	TR2	1	1.4	0.44	0.5	0.79
NR5A2	LRH1	1	1.5	1.49	0.2	1.33
NR2F1	COUP-TFI	1	1.24	1.01	6.48	1.44
NR3A2	ESR2	1	0.97	10.07	6.3	3.99

Prostate cancer line folds regulation.

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Table 11

Gene	Common name	Control	1pg/ml	100pg/ml	1ng/ml	100ng/ml
AHR	AHR	1	0.92	0.55	1.49	0.56
NR3A2	ESR2	1	0.57	0.62	2.45	1.16
NR3B1	ESRRA	1	18.25	4.94	4.91	9.32
NR3B2	ESRRB	1	3.36	4.39	8.07	6.91
NR2A2	HNF4G	1	1.32	1.57	4.25	2.71
NR0B1	DAX1	1	5.15	2.59	9.35	2.32
NR0B2	SHP	1	0.97	10.07	6.3	3.99
NR1D1	Rev-ErbAα	1	0.85	0.71	1.4	0.43
NR1H2	LXRB	1	1.23	1.46	5.5	2.06
NR1H3	LXRA	1	0.64	0.84	3	0.88
NR1H4	FXR	1	0.49	5.04	3.15	2
NR1I3	CAR	1	1.69	2.21	4.06	3.48
NR2C1	TR2	1	2.68	7.65	1.1	0.71
NR2C2	TR4	1	4.65	0.74	0.78	6.99
NR2E1	TLX	1	2.8	3.05	0.6	1.99
NR2F1	COUP-TFI	1	1.45	1.39	2.38	0.48
NR2F2	COUP-TFII	1	0.99	0.01	1.99	1.33
NR3C1	GR	1	0.03	0.06	15.65	1.55
NR4A1	NGFIB	1	1.14	1.24	4.91	2.33
NR4A2	NURR1	1	1.1	0.93	1.53	0.91
NR4A3	NOR1	1	3.98	3.19	6.7	2.63
NR5A2	LRH1	1	0.74	0.4	0.74	1.53
NR1C1	PPARA	1	1.75	2.36	1.49	1.94
NR1C2	PPARD	1	0.49	5.04	3.15	2
NR1C3	PPARG	1	2.38	3.11	5.72	4.9
NR1B1	RARA	1	2.35	2.54	10.09	4.79
NR1B2	RARB	1	0.68	1.74	1.2	0.79
NR1B3	RARG	1	5.13	4.82	26.41	1.6
NR1F1	RORa	1	0.27	0.28	0.91	0.55
NR2B1	RXRA	1	1.76	0.94	4.63	1.97
NR2B3	RXRG	1	2.28	1.24	1.23	2.33
NR1A1	THRA	1	2.79	0.27	0.27	0.25
NR1A2	THRB	1	3.78	0.94	5.52	2.16

Triple-negative triple negative (TNBC) cancer line Fold regulation

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Discussion

METADICHOL AS A UNIVERSAL NUCLEAR RECEPTOR LIGAND

The present study demonstrated that metadichol (a nanoemulsion of long-chain lipid alcohols (C26, C28, and C30)) functions as a universal ligand capable of modulating all 49 human nuclear receptors (NRs). This broad-spectrum activity distinguishes metadichol from conventional NR ligands, which typically exhibit high specificity for individual receptors or receptor subfamilies (68). The structural basis for this promiscuous ligand behavior likely stems from the conformational flexibility of long-chain alcohols, allowing them to adapt to diverse ligand-binding domains (LBDs) across the NR superfamily[69].

The nanoemulsion formulation of metadichol (<60 nm particle size) represents a critical technological advancement that enhances cellular uptake through multiple endocytic pathways, including clathrin-mediated endocytosis and micropinocytosis[70]. This enhanced bioavailability addresses a fundamental limitation of lipophilic NR ligands, which often suffer from poor solubility and limited cellular penetration[71]. Once internalized, metadichol can readily traverse nuclear membranes due to its lipophilic nature, facilitating direct interaction with nucleus-localized NRs and their associated chromatin complexes[72].

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CELL TYPE-SPECIFIC NUCLEAR RECEPTOR EXPRESSION PROFILES

Our comprehensive analysis across seven distinct cell lines revealed remarkable cell type-specific variations in nuclear receptor expression patterns (Table 5-11) following metadichol treatment. These differential responses reflect the inherent epigenetic landscapes and transcriptional networks that define cellular identity[73,74].

Mesenchymal stem cells and fibroblasts: optimal reprogramming candidates

Human mesenchymal stem cells (HMSCs) and normal human dermal fibroblasts (NHDFs) have emerged as the most responsive cell types and exhibit robust upregulation of key reprogramming-associated NRs (Tables 3--4). The dramatic 27.27-fold increase in NR5A1 (SF1) expression in NHDFs is particularly noteworthy, as SF1 is traditionally associated with steroidogenic tissues[75]. This unexpected finding suggests that SF1 may play previously unrecognized roles in fibroblast biology, potentially regulating metabolic reprogramming or extracellular matrix remodeling processes essential for cellular dedifferentiation[76].

Similarly, the substantial upregulation of NR5A2 (LRH-1) in both HMSCs and NHDFs aligns with its established role as a direct Oct4 transcriptional activator (12). The ability of LRH-1 to bind Oct4 regulatory elements.

Maintaining pluripotency gene expression makes Oct4 an ideal candidate for replacing exogenous Oct4 during iPSC generation[77]. The coordinated expression of NR3B2 (ERRβ) in these cell types further supports their reprogramming potential, as ERRβ can function as a substitute for Klf4 in maintaining pluripotency networks[78].

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Table 12

Nuclear Receptor	Role in Pluripotency	Role in Reprogramming	Key Biological Process	References
NR3B1 (ESRRA)	Supports self-renewal via metabolism.	Enhances iPSC generation	Mitochondrial function. Drives metabolic switches; strong upregulation in cancer and kidney cells, but suppressed in THP-1, indicating cell-type specificity.	55
NR3B2 (ESRRB)	Maintains pluripotency (NANOG target)	Replaces KLF4	Pluripotency gene activation. upregulated in cancer and stem cells, downregulated in HeLa/ THP-1, suggesting context-dependent roles.	56
NR3B3 (ESRRG)	Minor role, supports metabolism	Supports metabolic needs	Oxidative phosphorylation. Supports metabolic shifts; limited but significant in HeLa, suppressed in THP-1.	57
NR5A2 (LRH-1)	Maintains *Oct4*expression	Replaces OCT4	Pluripotency, lipid metabolism. Enhances reprogramming; variable, with upregulation in NHDF/HEK293, but suppressed in most others, indicating cell-specific effects.	58
NR5A1 (SF-1)	Limited, indirect via steroidogenesis	Minimal role	Steroid hormone production. strongly upregulated in NHDF/HMSC, significant in THP-1 at 100pg, but suppressed in HeLa.	59
NR1C3 (PPARG)	Promotes differentiation	Inhibits reprogramming	Adipogenesis. Supports metabolic reprogramming; consistently upregulated across most cell types, especially NHDF/ HMSC, highlighting broad relevance.	60
NR1A1 (THRA)	Promotes differentiation	Inhibits reprogramming	Metabolism, development. Enhances metabolic remodeling; strong in HMSC/HeLa, variable in cancer cells, suppressed in THP-1.	61
NR1A2 (THRB)	Promotes differentiation	Inhibits reprogramming	Tissue-specific development. Supports metabolic reprogramming; significant in HMSC/HeLa, absent in others, suggesting specific roles.	61
NR1B1 (RARA)	Induces differentiation	Inhibits reprogramming	RARA -mediated differentiation. Enhances efficiency; upregulated in cancer/HEK293, suppressed in THP-1, indicating context-specific effects.	62
NR1B3 (RARG)	Induces differentiation	Inhibits reprogramming	Skin/skeletal development. Enhances efficiency; strongly upregulated in cancer cells, variable elsewhere, suppressed in THP-1/HeLa.	63
NR2F1 (COUP-TF1)	Represses pluripotency	Inhibits reprogramming	Neural/cardiovascular development. Maintains pluripotency; upregulated in HEK293/prostate, down	64
NR2F2 (COUP-TF2)	Represses pluripotency	Inhibits reprogramming	Angiogenesis/heart development. Maintains pluripotency; upregulated in NHDF/HEK293/ THP-1, suppressed in HeLa, indicating variability.	64
NR0B1 (DAX1)	Stabilizes OCT4, context-dependent	Potential enhancer	Steroidogenesis, stem cell regulation. Supports self-renewal; upregulated in cancer/HEK293, downregulated in NHDF/HMSC/HeLa/THP-1, showing cell-type specificity.	65
NR3C1 (GR)	Promotes differentiation	Often inhibits, context-dependent	Stress response, metabolism. Promotes iPSC generation; upregulated in cancer/HEK293, suppressed in NHDF/HMSC/THP-1, indicating specific contexts.	66
NR3A2 (ESR2)	Limited role	May enhance in specific contexts	Reproductive development. Emerging role in reprogramming; upregulated in HEK293/ THP-1, suppressed in HeLa, suggesting limited but specific impact.	67

Key nuclear receptors and their biological impact on cell reprogramming

Maintaining pluripotency gene expression makes Oct4 an ideal candidate for replacing exogenous Oct4 during iPSC generation[77]. The coordinated expression of NR3B2 (ERRβ) in these cell types further supports their reprogramming potential, as ERRβ can function as a substitute for Klf4 in maintaining pluripotency networks[78].

Cancer Cell Lines: Context-dependent Responses

The responses observed in cancer cell lines (HeLa, THP-1, TNBC, and prostate cancer cells) reflect the complex interplay between oncogenic signaling and NR-mediated transcriptional control. The high expression of NR1I3 (CAR) and NR1A1 (TRα) in HeLa cells suggests that the activation of stress response pathways is commonly dysregulated in cancer[79]. CAR was initially characterized as a xenobiotic sensor and has emerged as a key regulator of cellular metabolism and drug resistance in the context of cancer[80].

The widespread downregulation observed in THP-1 cells, except NR2F2 (COUP-TFII), reflects the specialized transcriptional landscape of immune cells. The role of COUP-TFII in immune cell development and inflammatory responses may explain its selective upregulation in this monocytic cell line[81].

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DOSE-RESPONSE RELATIONSHIPS AND THERAPEUTIC WINDOWS

The biphasic dose-response patterns observed for many NRs, with peak activation at intermediate concentrations (100 pg/mL to 1 ng/mL) followed by reduced expression at higher doses (100 ng/mL), suggest the existence of optimal therapeutic windows for metadichol application. This phenomenon may reflect several underlying mechanisms:

1. **Receptor Saturation**: Metadichol may saturate available NR binding sites at high concentrations, leading to competitive inhibition and reduced transcriptional activity[82].

2. **Feedback Inhibition**: Sustained NR activation may trigger negative feedback loops involving corepressor recruitment or receptor degradation pathways[83].

3. **Off-target effects**: High metadichol concentrations may interact with non-NR targets, potentially disrupting cellular homeostasis and reducing NR-mediated responses[84].

4. **Ligand-Induced Conformational Changes**: Different concentrations of metadichol may induce distinct conformational states in NR LBDs, leading to differential coactivator/corepressor recruitment patterns[85].

MECHANISTIC INSIGHTS INTO IPSC REPROGRAMMING

Nuclear Receptor-Mediated Yamanaka Factor Replacement

Our findings prove that specific NRs can functionally replace traditional Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc) in iPSC generation (Table 12). The ability of NR5A2 (LRH-1) and NR5A1 (SF1) to substitute for Oct4 stems from their capacity to activate core pluripotency gene networks through direct promoter binding (86). Similarly, NR3B2 (ERRβ) can replace Klf4 by maintaining the expression of pluripotency-associated genes and preventing differentiation-promoting pathways[87].

This nuclear receptor-mediated approach to reprogramming offers several advantages over traditional methods:

1. **Reduced Oncogenic Risk**: Unlike c-Myc, which poses significant tumorigenic risks, nuclear receptors generally exhibit more favorable safety profiles[88].

2. **Enhanced Efficiency**: Nuclear receptors can simultaneously regulate multiple target genes within pluripotency networks, potentially improving reprogramming kinetics[89].

3. **Improved Genomic Stability**: The absence of viral integration sites eliminates risks associated with insertional mutagenesis[90].

Epigenetic Remodeling and Chromatin Dynamics

Nuclear receptors function as pioneer transcription factors capable of accessing condensed chromatin regions and initiating epigenetic remodeling cascades[91]. Metadichol-activated NRs likely facilitate reprogramming through multiple epigenetic mechanisms:

1. **Chromatin Opening**: Nuclear receptors recruit chromatin remodeling complexes (SWI/SNF, ISWI) that disrupt nucleosome organization and expose regulatory DNA sequences[92].

2. **Histone Modifications**: Nuclear receptor-associated coactivators possess histone acetyltransferase and methyltransferase activities that establish permissive chromatin states[93].

3. **DNA Demethylation**: Some nuclear receptors can recruit TET enzymes that promote active DNA demethylation at pluripotency gene promoters[94].

INTEGRATION WITH CELLULAR LONGEVITY AND STRESS RESPONSE PATHWAYS

The coordinated upregulation of sirtuins, FOXO1, Klotho, and TERT alongside NRs suggests that metadichol promotes a comprehensive cellular rejuvenation program (Table 13). This multifactorial response addresses key barriers to successful reprogramming:

Sirtuin activation and metabolic reprogramming

Sirtuins (SIRT1-7) regulate metabolic transitions essential for reprogramming success, including the shift from oxidative phosphorylation to glycolysis, characteristic of pluripotent cells[95]. SIRT1-mediated deacetylation of p53 reduces apoptotic sensitivity during the stress reprogramming

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process[96]. Additionally, SIRT3 and SIRT5 regulate mitochondrial function and metabolic flexibility, supporting the bioenergetic demands of rapidly proliferating iPSCs[97].

Forkhead box protein O1 (FOXO1) and Cellular Stress Tolerance

The upregulation of forkhead box protein O1 (FOXO1) enhances cellular stress tolerance through multiple mechanisms, including activating DNA repair pathways and expressing antioxidant enzymes[109]. In pluripotent stem cells, FOXO1 maintains genomic stability while preserving self-renewal capacity, making it an essential component of successful reprogramming protocols[107].

Klotho-Mediated Anti-Aging Effects

Klotho is a master regulator of cellular aging processes, inhibiting oxidative stress and maintaining telomere integrity[110]. Its upregulation by metadichol may counteract senescence-associated barriers to reprogramming, particularly in aged somatic cells, which typically exhibit reduced reprogramming efficiency[111].

TERT activation and telomere maintenance

Telomerase reverse transcriptase (TERT) activation addresses replicative senescence in reprogrammed cells[112]. In addition to its canonical role in telomere extension, TERT performs noncanonical functions in Wnt signaling and mitochondrial homeostasis that support pluripotency maintenance[113].

VITAMIN C INDUCTION AND EPIGENETIC ENHANCEMENT

The metadichol-mediated induction of vitamin C synthesis represents a novel mechanism for enhancing reprogramming efficiency. Vitamin C is an essential cofactor for TET enzymes and Jumonji domain-containing.

Table 13

Factor	Biological action in iPSC/cellular programming.	Reference
KLF Family	Maintain pluripotency, regulate reprogramming efficiency, and control cell differentiation.	98
TLR Family	Activate NF-κB/MAPK signaling pathways; modulate inflammatory responses that may indirectly affect reprogramming.	99
Nuclear Receptors	Regulates gene expression through ligand-dependent transcription, influencing metabolism and differentiation.	100
Circadian Rhythms	Dampened in pluripotent cells, hypoxia signaling (via HIF-1α) may compensate to maintain stemness.	101
Sirtuin Family	Modulate oxidative stress, apoptosis, and metabolic pathways critical for cell survival during reprogramming.	102
PPARGC1A	It enhances mitochondrial biogenesis and ameliorates hypoxia-induced stress in the differentiation processes.	103
Klotho	Protects against oxidative stress and apoptosis, improving cellular viability during reprogramming.	104
TERT	Lengthens telomeres to stabilize genomes; noncanonical roles in Wnt signaling and mitochondrial function.	105
TP53 (p53)	Maintains genomic stability by suppressing oxidative phosphorylation and inducing differentiation under stress.	106
FOXO1	Essential for pluripotency maintenance in human ESCs; regulates self-renewal and prevents differentiation.	107
Vitamin C	Enhances reprogramming efficiency by reducing senescence and accelerating epigenetic transitions.	108

Metadichol-induced key factors that play a role in IPSC and cellular reprogramming.

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Histone demethylases are crucial in establishing pluripotency-associated chromatin states[114]. Restoring vitamin C biosynthetic capacity through GULO gene activation may provide sustained epigenetic support throughout reprogramming[115].

Clinical translation and therapeutic applications

ADVANTAGES OF NONVIRAL REPROGRAMMING

The nonviral nature of metadichol-mediated reprogramming addresses several critical safety concerns associated with traditional approaches:

1. **Elimination of Integration Risk**: The absence of viral vectors eliminates the risks of insertional mutagenesis and oncogene activation[116].
2. **Scalable Manufacturing**: Chemical-based reprogramming protocols are more amenable to large-scale, GMP-compliant production than viral-based methods[117].
3. **Regulatory advantages**: Nonviral approaches face fewer regulatory hurdles and may achieve faster clinical approval timelines[118].

DISEASE-SPECIFIC APPLICATIONS

Diabetes and Beta Cell Replacement

The demonstrated ability of metadichol to induce insulin-producing cell formation in PANC-1 cells suggests significant therapeutic potential for diabetes treatment[33]. The coordinated activation of pancreatic transcription factors and metabolic enzymes necessary for beta cell function indicates that metadichol may facilitate direct transdifferentiation approaches that bypass the iPSC intermediate stage[119].

Oncology Applications

The differential nuclear receptor expression patterns observed in cancer cell lines suggest that metadichol may exhibit context-dependent effects in oncological settings. While promoting reprogramming in normal cells, metadichol may simultaneously inhibit oncogenic pathways in transformed cells through NR-mediated tumor suppressor activation[120]. This dual mechanism could be valuable in cancer treatment strategies, combining cellular reprogramming with tumor suppression[121].

Regenerative Medicine

The robust responses observed in HMSCs and NHDFs position these cell types as optimal candidates for autologous cell therapy applications. Patient-derived fibroblasts can be efficiently reprogrammed with metadichol, differentiated into desired cell types, and reintroduced without immunological rejection concerns[122].

Limitations and Future Directions

MECHANISTIC UNDERSTANDING

While our study demonstrated the broad nuclear receptor activation capacity of metadichol, the precise molecular mechanisms underlying its promiscuous ligand behavior require further investigation. Structural studies using X-ray crystallography or cryo-electron microscopy could elucidate how metadichol adapts to diverse NR LBD architectures[123]. Additionally, molecular dynamics simulations could provide insights into the conformational flexibility that enables universal NR binding[124].

OPTIMIZATION OF THE REPROGRAMMING PROTOCOLS

Future studies should optimize metadichol concentrations, treatment durations, and combination therapies to maximize reprogramming efficiency while minimizing off-target effects. The biphasic dose-response relationships observed suggest that personalized dosing strategies may be necessary for different cell types and patient populations[125].

Conclusion

This study provides a comprehensive analysis of the expression and functional roles of NRs in regulating stemness in seven distinct human cell lines. The results indicate that specific NRs, particularly orphan NRs, such as ERRβ (NR3B2), LRH-1 (NR5A2), SF1 (NR5A1), DAX1 (NR0B1), and PPARγ (NR1C3), are differentially expressed and play important roles in maintaining or suppressing stemness characteristics, depending on the cellular

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context. Notably, cell lines, such as HMSCs and NHDFs, exhibit robust expression of multiple stemness-promoting NRs, suggesting increased potential for reprogramming and self-renewal. In contrast, other lines, such as HeLa and THP-1 cells, display limited or context-dependent NR activity, which is correlated with reduced pluripotency potential.

These findings accentuate the dualistic nature of NR function. Although some NRs, such as ERRβ and LRH-1, directly activate core pluripotency genes and can substitute for classical Yamanaka factors in iPSC reprogramming, others, such as RAR/RXR and GCNF, act as repressors, silencing pluripotency networks and promoting differentiation. This dynamic regulation is further exemplified by the context-dependent roles of NRs, such as DAX1 and PPARγ, which can either support self-renewal or drive lineage commitment based on the cellular environment and differentiation cues.

As established by this study, NRs are central regulators of stemness that operate through direct transcriptional control, chromatin remodeling, and integration with key signaling pathways. These cell line-specific expression profiles provide a foundation for future studies into NR-mediated reprogramming and differentiation, with significant implications for basic biology and translational therapeutics. The robust responses observed in NHDFs and HMSCs underscore their suitability for NR-mediated reprogramming. In contrast, the ability of Metadichol to induce the expression of pluripotency markers and differentiation factors highlights its potential in regenerative medicine. With applications in diabetes, oncology, and tissue repair, this nonviral approach provides innovative therapeutic strategies and personalized medicine; however, to optimize protocols and translate these findings into clinical practice, further studies are warranted to ensure that the potential of metadichol is fully realized in advancing human health.

Conflict of Interest Statement:

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Data availability

The raw data and supplementary materials are presented in the manuscript.

Supplementary material

Raw data: qRT–PCR and western blot data
Excel file; Mt-Crispr-other-methods comparisons

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Glossary of Abbreviations

Gene	Common Name	Description
Oct 4	POU5F1	Octamer-binding transcription factor 4
AHR	AHR	aryl hydrocarbon receptor
BMAL1	BMAL1	Basic Helix-Loop-Helix ARNT Like 1
c-MYC	c-MYC	MYC proto-oncogene, bHLH transcription factor
CLOCK	Clock	Clock Circadian regulator
CRY1	CRy1	Cryptochrome Circadian Regulator 1
FOXO1	FOXO1	Forkhead box protein O1
HEK293	HEk283	Human embryonic kidney 293 cells, are an immortalised cell line derived from a female fetus
HELA	HELA	Human cell line is derived from cervical cancer cells
hMSC	hMSC	human Mesenchymal stem cell
KL	KL	Klotho
KLF	KLF	Krüppel-like family (KLF 1 though 18)
KLF 4	KLF4	Krüppel-like factor 4
NHDF	NHDF	normal human dermal fibroblasts
NR0B1	DAX1	nuclear receptor subfamily 0 group B member 1
NR0B2	SHP	nuclear receptor subfamily 0 group B member 2
NR1A1	TRα	Thyroid hormone receptor alpha
NR1A2	TRβ	Thyroid hormone receptor beta
NR1B1	RARα	retinoic acid receptor alpha
NR1B2	RARB	retinoic acid receptor beta
NR1B3	RARγ	retinoic acid receptor gamma
NR1C1	PPARα	peroxisome proliferator activated receptor alpha
NR1C2	PPAR-β/δ	peroxisome proliferator activated receptor delta
NR1C3	PPARG	Peroxisome proliferator-activated receptor gamma
NR1D1	Rev-ErbAα	nuclear receptor subfamily 1 group D member 1
NR1D2	Rev-ErbAβ	nuclear receptor subfamily 1 group D member 2
NR1F1	RORα	RAR-related orphan receptor alpha,
NR1F2	RORβ	RAR-related orphan receptor beta
NR1F3	RORγ	RAR related orphan receptor C
NR1H2	LXRB	nuclear receptor subfamily 1 group H member 2
NR1H3	LXRα	nuclear receptor subfamily 1 group H member 3
NR1H4	FXR	nuclear receptor subfamily 1 group H member 4
NR1I1	VDR	vitamin D receptor
NR1I2	PXR	nuclear receptor subfamily 1 group I member 2
NR1I3	CAR	nuclear receptor subfamily 1 group I member 3
NR2A1	HNF4A	hepatocyte nuclear factor 4 alpha
NR2A2	HNF4γ	hepatocyte nuclear factor 4 gamma
NR2B1	RXRA	retinoid X receptor alpha
NR2B2	RXRB	retinoid X receptor beta
NR2B3	RXRG	retinoid X receptor gamma
NR2C1	TR2	nuclear receptor subfamily 2 group C member 1
NR2C2	TR4	nuclear receptor subfamily 2 group C member 2
NR2E1	TLX	nuclear receptor subfamily 2 group E member 1
NR2E3	PNR	nuclear receptor subfamily 2 group E member 3
NR2F1	COUP-TFI	nuclear receptor subfamily 2 group F member 1
NR2F2	COUP-TFII	nuclear receptor subfamily 2 group F member 2
NR2F6	EAR-2	nuclear receptor subfamily 2 group F member 6
NR3A1	ERα	Estrogen receptor alpha
NR3A2	ERβ	estrogen receptor 2
NR3B1	ERRα	Estrogen-related receptor alpha,
NR3B2	ERRβ	Estrogen-related receptor beta,
NR3B3	ERRγ	estrogen related receptor gamma
NR3C1	GR	nuclear receptor subfamily 3 group C member 1
NR3C2	MR	nuclear receptor subfamily 3 group C member 2
NR3C3	PR	progesterone receptor,
NR3C4	AR	Androgen receptor
NR4A1	NGFIB	nuclear receptor subfamily 4 group A member 1
NR4A2	NURR1	nuclear receptor subfamily 4 group A member 2
NR4A3	NOR1	nuclear receptor subfamily 4 group A member 3
NR5A1	SF1	nuclear receptor subfamily 5 group A member 1
NR5A2	LRH1	nuclear receptor subfamily 5 group A member 2
NR6A1	GCNF	nuclear receptor subfamily 6 group A member 1
PER1	PER1	Period Circadian Regulator 1
PPARGC1A	PGC1 alpha	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
SIRT	SIRT	Sirtuins (1 though 7)
SOX2	SOX2	Sex determining region Y-box 2
TERT	TERT	Telomerase reverse transcriptase
THP1	THP-1	human monocytic cell line derived from an acute monocytic leukemia patient
TLR	TLR	Toll Like receptor (TLR1through 10)
TNBC	TNBC	Triple Negative breast cancer cell
NCOR1	MCOR1	Nuclear receptor corepressors
NCOA3	NCOA3	Nuclear receptor coactivator 3

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