

The role of NR2F2 in cancer (Review)

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Abstract. The incidence and mortality rates of tumors continue to show an annual upward trend. Since its discovery in 1986, nuclear receptor subfamily 2, group F, member 2 (NR2F2) has been shown to serve a key role in the transcriptional regulation of various genes. Furthermore, NR2F2 has a notable impact on the progression of tumors; however, its role in tumor progression is not yet fully understood. Multi-omics can illuminate the paradoxical roles of NR2F2 across various malignancies, where it functions as either an oncogenic driver or tumor suppressor in a context-dependent manner. The present review discusses the determinant influence of NR2F2 in modulating disease advancement and mechanisms in heterogeneous types of cancer, including its effects on tumor proliferation, apoptosis and epithelial-mesenchymal transition. The aim was to assess the role and mechanisms of NR2F2 in various tumors, identify its clinical utility in targeted cancer therapy and thereby provide a novel therapeutic option for overcoming cancer.

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1. Introduction

Global epidemiological surveillance data have indicated that ~20% of adults will receive a diagnosis of cancer during their lifespan, with sex-specific mortality differentials demonstrating that 11.1% of men and 8.3% of women ultimately succumb to neoplastic diseases (1). Contemporary epidemiological analyses have revealed that while refinements in cancer prevention strategies and therapeutic advancements have improved survival rates, the increasing incidence of numerous types of cancer alongside the ageing population, is leading to an increase in the number of cancer cases and cancer-associated mortalities (2-4). Therefore, cancer remains a global problem that requires an urgent solution.

Nuclear receptor subfamily 2, group F, member 2 (NR2F2), also known as COUP-TF II or ARPI, was discovered in 1986 (5). It belongs to the steroid/thyroid hormone receptor superfamily (6) and serves a role in the transcriptional regulation of various genes (7). At present, its natural ligand has not been found, thus it is called an 'orphan nuclear receptor'. NR2F2 has an important role in early embryonic development in humans and mice, and its expression decreases shortly after birth and is expressed at a very low basal level in mature individuals (8,9). NR2F2 has emerged as a molecule of translational significance in contemporary oncology; however, its oncogenic duality (context-dependent tumor promotion/suppression) remains mechanistically ambiguous.

The references for the present review were systematically retrieved from the following databases: PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Web of Science (<https://www.webof-science.com/wos/woscc/basic-search>). The core search terms were: 'NR2F2' or 'COUP-TFII' or 'ARPI' and ('cancer' or 'tumor' or 'tumor lesion') and ('proliferation' or 'cell apoptosis' or 'extracellular matrix remodeling' or 'microRNA' or 'long non-coding RNA'). The current study reviewed the study results regarding the role and mechanisms of NR2F2 in various tumors (Fig. 1), with the aim of identifying the clinical application of NR2F2 in targeted cancer therapy, which could provide a novel strategy to overcome cancer.

2. Mechanism of NR2F2 affecting proliferation and apoptosis

In most types of cancer, the pathways limiting the normal cellular proliferative response are disturbed, and

mutations required for tumor development act by shortening the normal external mitogenic signals of somatic cells (10). Cyclin-dependent kinases (CDKs) are closely associated with the regulation of cell cycle progression and have been identified as kinases that can promote cell division (11). Tumors are diverse and heterogeneous, but they all have the ability to break through normal tissue growth restrictions and to initiate abnormal proliferation. Uncontrolled cell proliferation and the mandatory compensatory mechanism of inhibiting cell apoptosis work together to provide the necessary microenvironment for tumor progression (12). Previous studies (13-19) have demonstrated that NR2F2 can affect the proliferation, programmed death and cell cycle changes of various tumor cells (Table I).

NR2F2 serves an important role in maintaining venous properties (6,20). In immortalized human lung microvascular endothelial cells, NR2F2 regulates cell proliferation and migration, thereby promoting the regeneration and repair of vascular endothelial cells. NR2F2 promotes vascular endothelial proliferation by directly binding to cyclin D1, and it directly activates the VEGFA/neuropilin 1/VEGFR2 signaling pathway and promotes cell migration (21). Cyclin D1 is a cell cycle protein, which belongs to the D-type cell cycle protein family; this protein serves a crucial role in the G₁ phase of the cell cycle. By forming complexes with CDK4 and CDK6, it promotes the transition of cells from the G₁ phase to the S phase. Mesenchymal stem cells (MSCs) isolated from Wharton's jelly (WJ) are highly proliferative and have a wide range of differentiation potentials (22). Notably, knockdown of NR2F2 in WJ-MSCs can decrease the expression of proliferation-related factors cyclin D1 and CDK4, increase the expression of IL-6 and IL-8 and slow cell proliferation (13). When WJ-MSCs with NR2F2 knockdown are co-cultured with other cells, the expression levels of cyclin D1, CDK4 and inflammatory factors are upregulated in the human fibroblast-like synovial cell line MH7A, whereas in HepG2 hepatoma cells, the levels of p53, a key regulator of apoptosis, are elevated, BCL-expression is decreased and the apoptosis rate increases (13). Therefore, NR2F2 could be considered a key regulator of the cell cycle.

In healthy ovaries, NR2F2 is stably expressed in the stroma but lowly expressed or not expressed in epithelial cells; however, this expression pattern is disrupted in ovarian cancer, where the expression levels in the stroma and ectopic epithelium are decreased (14). Notably, upregulating NR2F2 in ovarian cancer cell lines stimulates cell death while also increasing cell proliferation. Nucleolar and spindle-associated protein 2 (NEK2) is a serine/threonine kinase that can phosphorylate centrosomal proteins, driving centrosome separation and assembly of the mitotic spindle, thus accelerating the cell cycle process. Specifically, NR2F2 influences ovarian cancer progression by modulating cell cycle-related genes, including NEK2 and retinoic acid induced 14; NR2F2 directly binds to the promoter of NEK2, thereby promoting its transcriptional expression. In OVCAR-3 cells, overexpression of NR2F2 can increase the mRNA levels of NEK2, resulting in an increase in the proportion of S-phase cells from 25 to 44%. Furthermore, overexpression of NR2F2 in OVCAR-3 cells leads to an increase in Bim protein levels, resulting in a 37% decrease in mitochondrial membrane potential and activation of caspase-3,

ultimately inducing cell apoptosis. This contradictory effect is regulated by the PI3K/Akt pathway: When Akt phosphorylates the Ser194 site of NR2F2, the binding ability of NR2F2 to the Bim promoter is reduced; at this time, the proliferative effect dominates. However, in a state of low Akt activity, NR2F2 preferentially binds to the Bim promoter, and the pro-apoptotic effect is notable (13,14,23).

In renal cell carcinoma (RCC), the mRNA expression levels of NR2F2 are markedly higher compared with those in adjacent non-cancerous tissues, and elevated NR2F2 levels are associated with worse clinical outcomes in patients (24). When NR2F2 is knocked down in RCC cells, it hinders cell proliferation, enhances programmed cell death and causes cell cycle disruption. This mechanism also triggers the mitochondrial-mediated apoptotic pathway, thereby effectively inhibiting tumor growth *in vivo* (25). Knockdown of NR2F2 in RCC cells also markedly upregulates breast cancer 1, early onset (BRCA1) expression (2.3-fold increase in protein level), accompanied by enhanced DNA damage repair and apoptosis. Conversely, co-knockdown of BRCA1 and NR2F2 partially rescues the proliferation inhibition caused by NR2F2 depletion, indicating that NR2F2 suppresses BRCA1 transcription via direct binding to its promoter region. This mechanism aligns with the observation that high NR2F2 levels in RCC tissues are associated with reduced BRCA1 expression and worse patient survival (15).

In uterine fibroids, NR2F2 and the cell proliferation-related factor β -catenin are abnormally highly expressed, and both have strong vascular-specific localization characteristics (16).

In colorectal cancer (CRC), knockout of NR2F2 can activate the Akt/GSK-3 β / β -catenin pathway and upregulate FOXC1, thereby promoting cell proliferation and invasion (17). Overexpression of NR2F2 in SNU-C4, a human CRC cell line, strongly impairs cell multiplication and colony generation. Furthermore, it has been shown that p53 is necessary for inhibiting cell proliferation; on the other hand, the decreased expression of phosphorylated (p)-Akt enhances the inhibitory effect of NR2F2 on cell proliferation and invasion (18). These findings provide new therapeutic ideas for metastatic CRC.

By exogenous overexpression of NR2F2 in the breast cancer cell line MDA-MB-435, the cell growth rate can be decreased; at the same time, NR2F2 can increase the expression of cyclin D1 and p21 in MDA-MB-435 cells (13). Notably, NR2F2 transduction does not affect the speed of G₁-S phase progression but leads to a prolonged G₂/M phase compared with control cells. Compared with in parental cells, the CDK2 activity necessary for G₂/M transition is reduced in NR2F2 overexpressing cells (19). Therefore, NR2F2 may influence the cell cycle progression of breast cancer cells, thereby exerting regulatory effects on cell proliferation and apoptosis.

Cancer stem cells (CSCs) are a small subset of cells in tumors that possess the characteristics of self-renewal and continuous proliferation. These cells can cause the occurrence and metastasis of tumors, and maintain the heterogeneity of tumors (26). Notably, CSCs may evade immune recognition and attack by innate immune cells and adaptive immune cells (27,28). CSCs have been demonstrated to be one of the essential conditions for successful cancer metastasis (29-31); therefore, targeting CSCs may be an opportunity for treating metastatic diseases. Yes-associated protein 1 (YAP1) positively

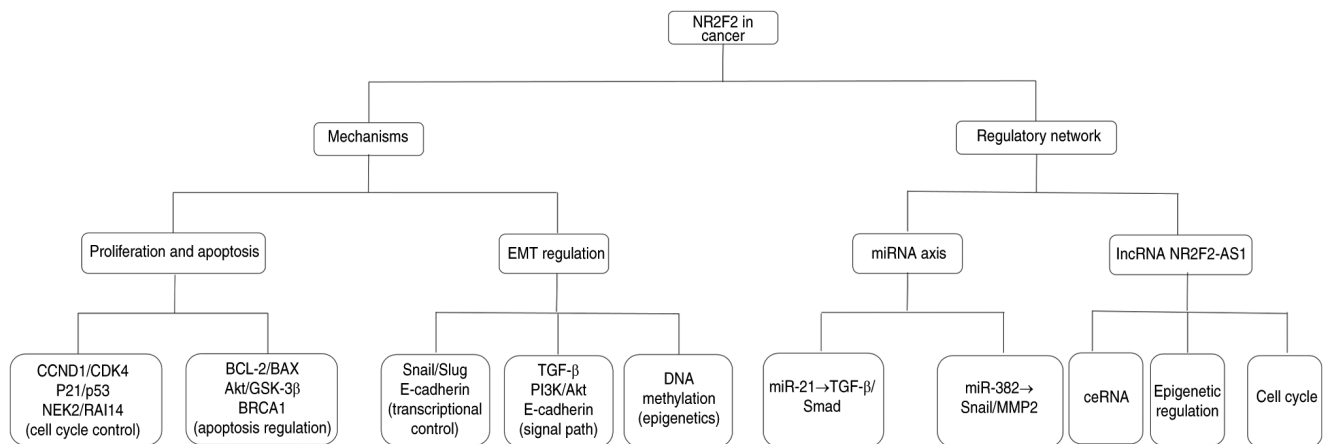


Figure 1. The mechanism and regulatory network through which NR2F2 exerts its functions in cancer development and progression. NR2F2, nuclear receptor subfamily 2, group F, member 2; CCND1, cyclin D1; NEK2, nucleolar and spindle-associated protein 2; RAI14, retinoic acid induced 14; EMT, epithelial-mesenchymal transition; miRNA/miR, microRNA; ceRNA, competing endogenous RNA; lncRNA, long non-coding RNA; AS1, antisense 1.

regulates numerous genes related to CSCs and lipid metabolism, and YAP1 is overexpressed in enzalutamide-resistant (EnzaR) CSCs (28). NR2F2 functions in transcriptional regulation and mediates the expression of YAP1 induced by enzalutamide, and interacts with itself to form a transcriptional complex. Therefore, YAP1 and NR2F2 can be detected in extracellular vesicles isolated from EnzaR cells and prostate cancer patient serum, indicating the therapeutic potential of NR2F2 in cancer (32,33). Mauri *et al* (24) performed a comparative analysis of the transcriptional profiles of CSCs in benign tumors and malignant cutaneous squamous cell carcinoma (SCC) using microarray technology. The results revealed that NR2F2 was highly expressed in malignant SCC, and that NR2F2 promoted the malignant tumor state by controlling the tumor stemness and maintenance of SCC in mice and humans. Furthermore, NR2F2 is directly regulated by microRNA (miRNA/miR)-302, which suppresses the promoter activity of OCT4, weakening the mutual reinforcement between OCT4 and miR-302; through this mechanism, miR-302 indirectly elevates OCT4 levels, promoting pluripotency (34). This indicates that NR2F2 is a key regulatory factor for the function of malignant CSCs, which can promote tumor renewal and inhibit differentiation, thereby maintaining the state of malignant tumors.

3. NR2F2 and epithelial-mesenchymal transition (EMT)

The most critical factor that accelerates the deterioration of the prognosis of patients with cancer is metastasis, which refers to the migration and invasion of cancer cells and their settlement and continued growth in specific locations outside the primary tumor site (35). Metastasis can occur through the EMT pathway. During EMT, tumor cells undergo a phenotypic shift from epithelial to mesenchymal characteristics. Key changes include the downregulation of membrane-bound E-cadherin (leading to weakened cell adhesion) and upregulation of N-cadherin (enhancing cell migration) (36). The EMT pathway mainly involves the remodeling of the cell surface proteome, which is closely associated with EMT transcriptional regulation and intermediate filament structural

changes, to meet the migration and invasion requirements of cancer cells during metastasis. When cells exhibit a mesenchymal phenotype, this change (EMT and its reverse process, mesenchymal-epithelial transition) is particularly notable, and during the colonization process at distant metastatic sites, cells regain an epithelial phenotype. These plastic events are driven by metabolic conversion combined with direct transcriptional regulation by TGF- β , but the ability of TGF- β to induce cell apoptosis is inhibited (37). Studies have reported that NR2F2 participates in regulating the EMT process through multiple signaling pathways; however, differences exist among the research results (Table II).

NR2F2 is increased in CRC cells, and is associated with cancer metastasis and a shorter patient survival time (38). Notably, NR2F2 serves a crucial role in the onset and progression of CRC, and it drives the EMT process in CRC through two mechanisms: i) The upregulation of NR2F2 promotes the EMT of CRC cells, manifested as a decrease in E-cadherin and an increase in N-cadherin and vimentin; and ii) NR2F2 activates the expression of miR-21 through transcription and inhibits the expression of Smad7, thereby promoting activation of the TGF- β signaling pathway. The activated TGF- β signaling pathway further promotes EMT of CRC cells, enhancing cell migration and invasion (39). Furthermore, in CRC tissues, the elevated expression of NR2F2 is associated with Snail upregulation; NR2F2 directly targets the promoter of Snail1 to regulate the transcription and expression of Snail1, and also regulates the expression of adhesion molecules such as tight junction protein 1, E-cadherin and β -catenin, thereby promoting the metastasis of CRC (40). Therefore, NR2F2 is considered a biomarker associated with the survival and metastasis of patients with colon cancer, and may be a new therapeutic target for CRC.

The formation of metastatic melanoma begins with the dedifferentiation of transformed melanocytes, resulting in the formation of migratory and invasive melanoma cells with the characteristics of neural crest cells (NCCs) and EMT. NR2F2 isoform 2 (NR2F2-Iso2) drives the progression of metastatic melanoma by regulating the functional activity of full-length NR2F2 (isoform 1) on EMT and NCC-related

Table I. Regulatory axis of NR2F2 in proliferation and apoptosis.

Cancer	Role	Axis	(Refs.)
Liver cancer	Unknown	NR2F2↓ → p53↑, BCL-2↓ → apoptosis↑	(13)
Ovarian cancer	Unknown	NR2F2↑ → NEK2, RAI14↑, proliferation↑, apoptosis↑	(13,14)
Renal cell carcinoma	Oncogene	NR2F2 → BRCA1↓	(15)
Uterine fibroids	Oncogene	NR2F2 and CTNNB1 high expression co-localization	(16)
Colorectal cancer	Oncogene suppressor	NR2F2↓ → Akt/GSK-3β/β-catenin↑ → FOXC1↑ → proliferation↑	(17)
		NR2F2↑ → p53↑, PTEN↑ → Akt phosphorylation↓ → proliferation↓	(18)
Breast cancer	Oncogene suppressor	NR2F2 → cyclin D1↑, p21↑, CDK2↓ → G ₂ /M arrest	(19)

↑, promotion; ↓, inhibition; NR2F2, nuclear receptor subfamily 2, group F, member 2; NEK2, nucleolar and spindle-associated protein 2; RAI14, retinoic acid induced 14; BRCA1, breast cancer 1; CTNNB1, catenin b 1; CDK2, cyclin-dependent kinase 2; PTEN, phosphatase and tensin homolog.

Table II. Regulatory axis of NR2F2 in EMT.

Cancer	Role	Axis	(Refs.)
Colorectal cancer	Oncogene	NR2F2 → activation of the transcription of miR-21 → TGF-β↑ → EMT↑	(39)
		NR2F2 → Snail↑ → ZO-1↑, E-cadherin↑, β-catenin↑	(40)
Metastatic melanoma	Oncogene	DNA methylation → increased activity of NR2F2 → melanocytes acquire the characteristics of NCC and EMT	(41)
Intrahepatic cholangiocarcinoma	Oncogene	PI3K/AKT↑ → NR2F2↑ → Snail↑ → EMT↑	(42)
Gastric cancer	Oncogene	Fbxo21 → NR2F2↓ → EMT↓	(43)
Prostate cancer	Oncogene	NR2F2 → TGF-β↓	(6)
Breast cancer	Oncogene	NR2F2 → TGF-β↓ → EMT↓	(47)
	suppressor		
	Oncogene	Insulin → NR2F2↑ → EMT↑	(48)
Type A ductal carcinoma of the breast	Oncogene suppressor	NR2F2-ERα	(40)

↑, promotion; ↓, inhibition; NR2F2, nuclear receptor subfamily 2, group F, member 2; ZO-1, tight junction protein 1; NCC, neural crest cell; Fbxo21, F-box protein 21; ER, estrogen receptor; EMT, epithelial-mesenchymal transition.

target genes (41). During this process, DNA methylation has a crucial role; its regulation of NR2F2 activity enables transformed melanocytes to exhibit characteristics similar to NCCs and EMT. This epigenetic regulation-induced transcriptional plasticity promotes the transformation and metastatic spread of cells (41).

The research results of Lang *et al* (42) indicate that in intrahepatic cholangiocarcinoma (ICC) cells, the expression of NR2F2 is excessively expressed at the protein level, but not at the mRNA level. This suggests that the factors and/or signaling pathways that promote the development of ICC may have upregulated the expression of NR2F2 in ICC cells at the post-transcriptional level. They speculate that the PI3K/Akt signaling pathway may be the main mechanism leading to the upregulation of NR2F2 protein expression in ICC (42). Higher NR2F2 expression levels in ICC are associated with enhanced tumor growth, lymph node spread and reduced survival. Moreover, the activation of PI3K/Akt signaling can promote

the upregulation of NR2F2 protein expression in ICC, and NR2F2 promotes EMT in ICC cells through Snail upregulation. These findings suggest that NR2F2 promotes EMT and metastasis in ICC, indicating that NR2F2 could be a potential target for adjuvant therapy in these patients (42).

In gastric cancer, F-box protein 21 (Fbxo21) inhibits EMT by downregulating NR2F2. The expression levels of Fbxo21 are negatively associated with those of NR2F2 in gastric cancer tissues and cell lines (43).

Analysis of samples from patients with prostate cancer has also demonstrated the biological importance of NR2F2 in the development of prostate cancer. Notably, the expression levels of NR2F2 have a notable association with tumor recurrence and disease advancement, exhibiting a negative association with TGF-β signaling (44). These findings indicate that the disruption of TGF-β-dependent barriers by NR2F2 is crucial for the development of phosphatase and tensin homolog (PTEN)-mutant prostate cancer into a life-threatening disease,

and support NR2F2 as a potential drug target for the intervention of metastatic human prostate cancer (6).

Certain studies have predicted that NR2F2 is negatively associated with genes related to EMT and TGF- β signaling pathways (45,46). The expression of NR2F2 inhibits TGF- β -induced EMT and suppresses breast cancer metastasis; this has been supported by observing changes in EMT-like morphology, alongside a decrease in E-cadherin and an increase in Slug expression, which are known EMT markers (45). Table III provides a detailed description of the functional heterogeneity of NR2F2 in different breast cancer subtypes. After being treated with insulin, the expression levels of NR2F2 are increased in breast cancer cells (MCF-7 and MDA-MB-231), and the high expression of NR2F2 promotes the invasion and migration of breast cancer cells, accompanied by a decrease in E-cadherin expression and an increase in N-cadherin and vimentin expression (45). Some authors have also proposed that it is inappropriate to generalize all subtypes of breast cancer. In specific breast cancer subgroups, such as in patients with type A ductal carcinoma of the breast, higher expression of NR2F2 is associated with improved survival rates. Chromatin immunoprecipitation and high-throughput sequencing methods have been used to map the genomic NR2F2 and estrogen receptor (ER) α binding sites in type A ductal breast carcinoma cells, revealing that most NR2F2 overlaps with ER α . Transcriptome analysis of breast cancer cells with low NR2F2 expression has shown that NR2F2 is associated with endocrine therapy resistance and has confirmed that NR2F2 is a target gene of ER α . This indicates that NR2F2 may serve a key role in ER α -mediated transcription and could provide a potential therapeutic target for patients with luminal A-type breast cancer (7).

As well as in cancer, pulmonary fibrosis is also closely related to EMT of type II alveolar epithelial cells (AECII). The long non-coding RNA (lncRNA)-ASLNC12002 is highly expressed in the AECII of patients with sepsis-induced acute respiratory distress syndrome, and the enhanced expression of ASLNC12002 leads to inactivation of the NR2F2/miR-128-3p/Snail1 pathway, thereby enabling the EMT progression of AECII in patients with sepsis-induced acute respiratory distress syndrome (40). This study suggests that NR2F2 may have a universal role in EMT regulation across different diseases, providing a cross-system reference basis for understanding the universal function of NR2F2 in cell phenotypic transformation.

4. NR2F2 and miRNA

miRNAs are a type of non-coding RNA that are 18-22 nucleotides long. By interacting with the 3'UTR of mRNA, miRNAs reduce the stability of mRNA or inhibit its translation efficiency, thereby suppressing gene expression at the post-transcriptional level (45). To date, a large number of miRNAs have been recognized as either oncogenes or tumor suppressor genes, and they have been extensively studied in the field of cancer diagnosis and treatment (46-49). NR2F2 also interacts with miRNAs (Table IV).

Increased NR2F2 expression is associated with unfavorable survival rates in patients with CRC. Notably, in CRC NR2F2 can promote TGF- β -induced EMT by transactivating

miR-21 (39). Some researchers have also discovered that when NR2F2 is upregulated, it reduces the suppressive impact of miR-382 on the proliferation, migration and invasiveness of CRC cells (50). Furthermore, the tumor suppressor miR-34a is negatively associated with NR2F2 expression, and NR2F2 promotes EMT by inhibiting the expression of miR-34a in CRC (51).

The Oncomine (<https://www.oncomine.org>) and Kaplan-Meier plotter (<http://kmplot.com/analysis>) databases indicate that NR2F2 is upregulated in gastric cancer and is associated with a lower survival rate. Furthermore, miR-27b can bind to the 3'UTR region of NR2F2 mRNA and inhibit its expression; knockdown of NR2F2 reduces the migration and invasion abilities of gastric cancer cells. These results indicate that miR-27b suppresses gastric cancer metastasis through targeting NR2F2 (52).

Upregulation of miR-382 expression can markedly inhibit the proliferation, migration and invasion of prostate cancer cells (53). The results of dual luciferase reporter assay, reverse transcription-quantitative polymerase chain reaction and western blot analysis have confirmed that NR2F2 is a direct target of miR-382. Notably, the expression of downstream genes of NR2F2 (such as Snail and matrix metalloproteinase 2) is inhibited by miR-382. miR-382 can inhibit the proliferation and metastasis of prostate cancer cells by suppressing NR2F2, providing crucial insights into how prostate cancer develops and suggesting a new molecular target for potential treatments (53).

5. lncRNA NR2F2 antisense RNA 1 (NR2F2-AS1)

In previous years, lncRNAs have drawn considerable interest in cancer research owing to their crucial functions in this disease (54,55). NR2F2-AS1 is a lncRNA, and its gene is located in the antisense direction of the NR2F2 gene. It is located in the chromosomal region 15q26.2 and contains 12 exons. Previous studies have shown that NR2F2-AS1 serves a notable role in the occurrence and progression of various types of cancer (Table V) (41,46,56-65).

lncRNA NR2F2-AS1 was initially identified as being anomalously high expressed in non-small cell lung cancer (NSCLC). Downregulation of lncRNA NR2F2-AS1 can regulate the miR-320b/BMI1 proto-oncogene, polycomb ring finger mechanism, promote apoptosis of A549 and SPC-A-1 cells, and inhibit cell proliferation and invasion (66). Furthermore, in NSCLC tissues and cells, in addition to high expression of lncRNA NR2F2-AS1, c-Met, biliverdin reductase (BVR) and activating transcription factor 2 (ATF-2) are also highly expressed, whereas miR-545-5p is downregulated. The results of a previous study have shown that knocking down NR2F2-AS1 or upregulating the expression levels of miR-545-5p can notably inhibit the proliferation, migration, invasion and EMT process of NSCLC cells. After lncRNA NR2F2-AS1 inhibits miR-545-5p, it activates the EMT process through the c-Met/BVR/ATF-2 axis, thereby promoting the development of NSCLC. Studies have shown that regulating NR2F2-AS1 and miR-545-5p may be an effective method for improving the treatment of NSCLC (66,67).

lncRNA NR2F2-AS1 is highly expressed in prostate carcinoma and is positively associated with CDK4 expression.

Table III. Functional differences and mechanisms of NR2F2 in different subtypes of breast cancer.

Subtypes	Role	Axis	(Refs.)
Luminal A (ER ⁺ /HER2 ⁻)	Suppressor	NR2F2 + ER α $\rightarrow$ cyclin D1 $\downarrow$ p53-PTEN $\uparrow$ -p-Akt $\downarrow$	(7,45)
HER2 ⁺ (ER ⁻ /HER2 ⁺)	Oncogene	ERK1/2 $\rightarrow$ p-NR2F2 $\rightarrow$ binding with β -catenin $\uparrow$ $\rightarrow$ EMT $\uparrow$ N-cadherin $\uparrow$	(47)
Triple-negative breast cancer	Bidirectional regulation	Mut-p53: NR2F2 $\rightarrow$ YAP1 $\uparrow$ $\rightarrow$ stemness $\uparrow$	(7,47)
Luminal B (ER ⁺ /HER2 ⁺)	Mixed-effects	Estrogen $\downarrow$: NR2F2 + ER α $\rightarrow$ proliferation $\downarrow$ Insulin $\uparrow$: p-NR2F2 $\rightarrow$ migration $\uparrow$	(7,47)

$\uparrow$, promotion; $\downarrow$, inhibition; NR2F2, nuclear receptor subfamily 2, group F, member 2; ER α , estrogen receptor α ; PTEN, phosphatase and tensin homolog; HER2, human epidermal growth factor receptor 2; mut, mutated; p, phosphorylated; EMT, epithelial-mesenchymal transition.

Table IV. Regulatory axis of NR2F2 and miRNAs.

Cancer	Role	Axis	(Refs.)
Colorectal cancer	Oncogene	NR2F2 $\rightarrow$ miR-21 $\uparrow$ $\rightarrow$ TGF- β $\uparrow$ $\rightarrow$ EMT $\uparrow$	(39)
		NR2F2 $\rightarrow$ miR-382 $\downarrow$ $\rightarrow$ proliferation, migration, invasion $\uparrow$	(53)
		NR2F2 $\rightarrow$ miR-34a $\downarrow$ $\rightarrow$ EMT $\uparrow$	(54)
Gastric cancer	Oncogene	NR2F2 $\rightarrow$ miR-27b $\downarrow$ $\rightarrow$ tumor metastasis $\uparrow$	(55)
Prostate cancer	Oncogene	miR-382 $\rightarrow$ NR2F2 $\downarrow$ $\rightarrow$ Snail $\downarrow$, MMP2 $\downarrow$ $\rightarrow$ proliferation, migration, invasion $\downarrow$	(67)

$\uparrow$, promotion; $\downarrow$, inhibition; MMP2, matrix metalloproteinase 2; NR2F2, nuclear receptor subfamily 2, group F, member 2; miR/miRNA, microRNA; EMT, epithelial-mesenchymal transition.

NR2F2 promotes the proliferation of prostate carcinoma cells and serves a positive role in the cell cycle (68).

In human osteosarcoma (OS), the lncRNA NR2F2-AS1 exhibits high expression levels and is associated with an unfavorable prognosis. Furthermore, elevated levels of NR2F2-AS1 can enhance the proliferation and invasive capabilities of OS cells, while also suppressing their apoptosis (56). By acting as a sponge for miR-425-5p, NR2F2-AS1 increases high mobility group box 2 (HMGB2) expression, facilitating OS development. Therefore, the lncRNA NR2F2-AS1/miR-425-5p/HMGB2 regulatory axis is considered to be a promising target for the treatment of human OS (56).

The expression levels of NR2F2-AS1 are increased in CRC and its upregulation is associated with a reduced overall survival rate among patients with CRC. Cyclin D1 is also upregulated, and there is a positive association between cyclin D1 and NR2F2-AS1 (57). Small interfering RNA (siRNA)-mediated silencing of NR2F2-AS1 leads to decreased cyclin D1 levels and the occurrence of G₀/G₁ phase arrest, whereas the overexpression of cyclin D1 can reverse the G₀/G₁ phase arrest caused by the siRNA-induced silencing of NR2F2-AS1 (57). Compared with in normal tissues in The Cancer Genome Atlas (<https://portal.gdc.cancer.gov>), CRC tissues exhibit a marked increase in miR-106b expression levels. Notably, the direct interaction between miR-106b and NR2F2-AS1/pleckstrin homology domain containing O2 (PLEKHO2) has been confirmed using dual luciferase reporter experiments. Additionally, as a competing endogenous RNA (ceRNA), NR2F2-AS1 can

absorb miR-106b through the 'sponge' effect and thereby regulate the expression levels of PLEKHO2. By affecting the MAPK signaling axis, NR2F2-AS1 and PLEKHO2 serve a key role in driving CRC progression. Therefore, the miR-106b/lncRNA NR2F2-AS1/PLEKHO2/MAPK signaling axis may have potential therapeutic effects in CRC (58).

Elevated expression levels of lncRNA NR2F2-AS1 have been detected in both cervical cancer cells and tissues. NR2F2-AS1 induces cell proliferation, migration, invasion and the EMT process by regulating the miR-4429/methyl-CpG binding domain protein 1 axis, and induces cell apoptosis to accelerate the progression of cervical cancer (59).

The expression levels of NR2F2-AS1 are also increased in clear cell RCC (ccRCC), and its high expression in ccRCC tissues is associated with an unfavorable prognosis. Notably, NR2F2-AS1 may enhance the CSC characteristics of ccRCC by upregulating Rac1 (60).

In nasopharyngeal carcinoma (NPC), the expression of NR2F2-AS1 is negatively associated with that of PTEN. NR2F2-AS1 inhibits the proliferation of nasopharyngeal cancer cells and induces apoptosis by regulating the expression of PTEN. Therefore, the upregulation of NR2F2-AS1 expression and the downregulation of PTEN expression indicate a worse survival prognosis for patients with NPC (61).

Unlike in other types of cancer, NR2F2-AS1 is lowly expressed in gastric cancer cells. As a ceRNA, NR2F2-AS1 absorbs miR-320b to downregulate the expression of programmed cell death 4 (PDCD4),

Table V. Regulatory axis of the long non-coding RNA NR2F2-AS1 in cancer.

Cancer	Role	Axis	(Refs.)
Non-small cell lung cancer	Oncogene	NR2F2-AS1↓ → miR-320b/BMI1 → apoptosis↑	(56)
Prostate carcinoma	Oncogene	NR2F2-AS1↑ → miR-545-5p↓ → c-Met/BVR/ATF-2↑ → EMT↑	(57)
Osteosarcoma	Oncogene	NR2F2-AS1↑ → CDK4↑ → proliferation↑	(58)
Colorectal cancer	Oncogene	NR2F2-AS1 → miR-425-5p↓ → HMGB2↑ → proliferation, growth, invasion and inhibition of apoptosis↑	(59)
Cervical cancer	Oncogene	NR2F2-AS1↓ → cyclin D1↓ → G ₀ /G ₁ arrest	(60)
		miR-106b/NR2F2-AS1/PLEKHO2/MAPK	(61)
Clear cell Renal cell carcinoma	Oncogene	NR2F2-AS1↑ → miR-4429/MBD1↑ → proliferation, growth, invasion and inhibition of apoptosis↑	(62)
Nasopharyngeal carcinoma	Oncogene	NR2F2-AS1↑ → Rac1↑ → stem cell characteristics↑	(63)
Gastric cancer	Oncogene suppressor	NR2F2-AS1↑ → PTEN↓ → proliferation↑ apoptosis↓	(64)
Oral squamous cell carcinoma cells	Oncogene suppressor	NR2F2-AS1↓ → miR-320b↓ → PDCD4↓	(65)
		NR2F2-AS1↑ → miR-494↑ → miR-494 methylation↓ → proliferation↓	(41)
		NR2F2-AS1↑ → miR-32-5p/SEMA3A → HUVECs↓, tumor metastasis↓	(45)

↑, promotion; ↓, inhibition; BMI1, BMI1 proto-oncogene, polycomb ring finger; BVR, biliverdin reductase; ATF-2, activating transcription factor 2; CDK4, cyclin-dependent kinase 4; HMGB2, high mobility group box 2; PLEKHO2, pleckstrin homology domain containing O2; MBD1, methyl-CpG binding domain protein 1; PTEN, phosphatase and tensin homolog; PDCD4, programmed cell death 4; SEMA3A, semaphorin 3A; HUVECs, human umbilical vein endothelial cells; NR2F2, nuclear receptor subfamily 2, group F, member 2; miR/miRNA, microRNA.

thereby inhibiting the development of gastric cancer. The NR2F2-AS1/miR-320b/PDCD4 pathway suggests a new therapeutic route for gastric cancer treatment (62).

In oral SCC (OSCC) cells, NR2F2-AS1 may weaken the metastatic ability of OSCC cells through the miR-32-5p/sema- phorin 3A axis, inhibit the angiogenesis of human umbilical vein endothelial cells, suppress tumor growth and metastasis in mice (63) and regulate the proliferation of OSCC cells by inhibiting miR-494 methylation (64).

6. Expression, regulatory mechanisms and prospects of targeting NR2F2 in tumors

The expression characteristics and functional heterogeneity of NR2F2 in tumors. NR2F2 is broadly expressed across various tissues in the human body; however, its expression in different tumors exhibits species-specific and tissue-specific characteristics (65). Drawing from the aforementioned existing research, NR2F2 has been extensively investigated in the context of prostate cancer and seems to exert a carcinogenic effect (6,53,68). In CRC, although NR2F2 inhibits the proliferation of tumor cells (17,18), it promotes the EMT process (39,40) and also interacts with miRNAs (39,50,51). In gastric cancer, NR2F2 promotes the EMT process (43) and interacts with miRNAs (52), but the lncRNA NR2F2-AS1 inhibits the development of gastric cancer (62). The function of NR2F2 in breast cancer remains highly debated. On the one hand, the expression of NR2F2 inhibits breast cancer proliferation and metastasis (19,45); however, on the other hand,

NR2F2 expression levels are increased in insulin-treated breast cancer cells, and the high expression of NR2F2 promotes breast cancer cell invasion and migration (45). Currently, the research on NR2F2 in NSCLC, OS, cervical cancer, RCC, uterine leiomyoma, ccRCC, NPC, metastatic melanoma and ICC remains limited. The limited studies available generally indicate that NR2F2 may serve a role in promoting tumor progression (15,16,41,42,56,59-61,66). Furthermore, the function of NR2F2 in liver cancer and ovarian cancer is still largely unclear (13,69). Fig. 2 visually presents the multi-level regulatory network of NR2F2 in tumors, covering the interactions among non-coding RNA regulation, cell cycle regulation, EMT regulation and epigenetic regulation pathways.

NR2F2 exhibits both tumor suppressor and oncogenic functions in different types of cancer and at different stages of the same cancer, and there are complex molecular mechanisms underlying this. The influence of the tissue microenvironment on the function of NR2F2 is crucial. In breast cancer, the synergistic effect of ER α and NR2F2 is the core of functional differentiation. In luminal A-type breast cancer, NR2F2 binds to ER α to form a transcriptional complex, which activates p53 and PTEN to inhibit cell proliferation, demonstrating a tumor suppressive effect (7). In insulin-stimulated breast cancer cells, the activation of the insulin-PI3K/Akt pathway leads to phosphorylation of NR2F2 (at Ser294 site), causing it to bind to β -catenin and promote EMT. At this time, NR2F2 acts as a carcinogenic factor to promote metastasis (51). In the gastric cancer microenvironment, the absence of Fbxo21 ubiquitin

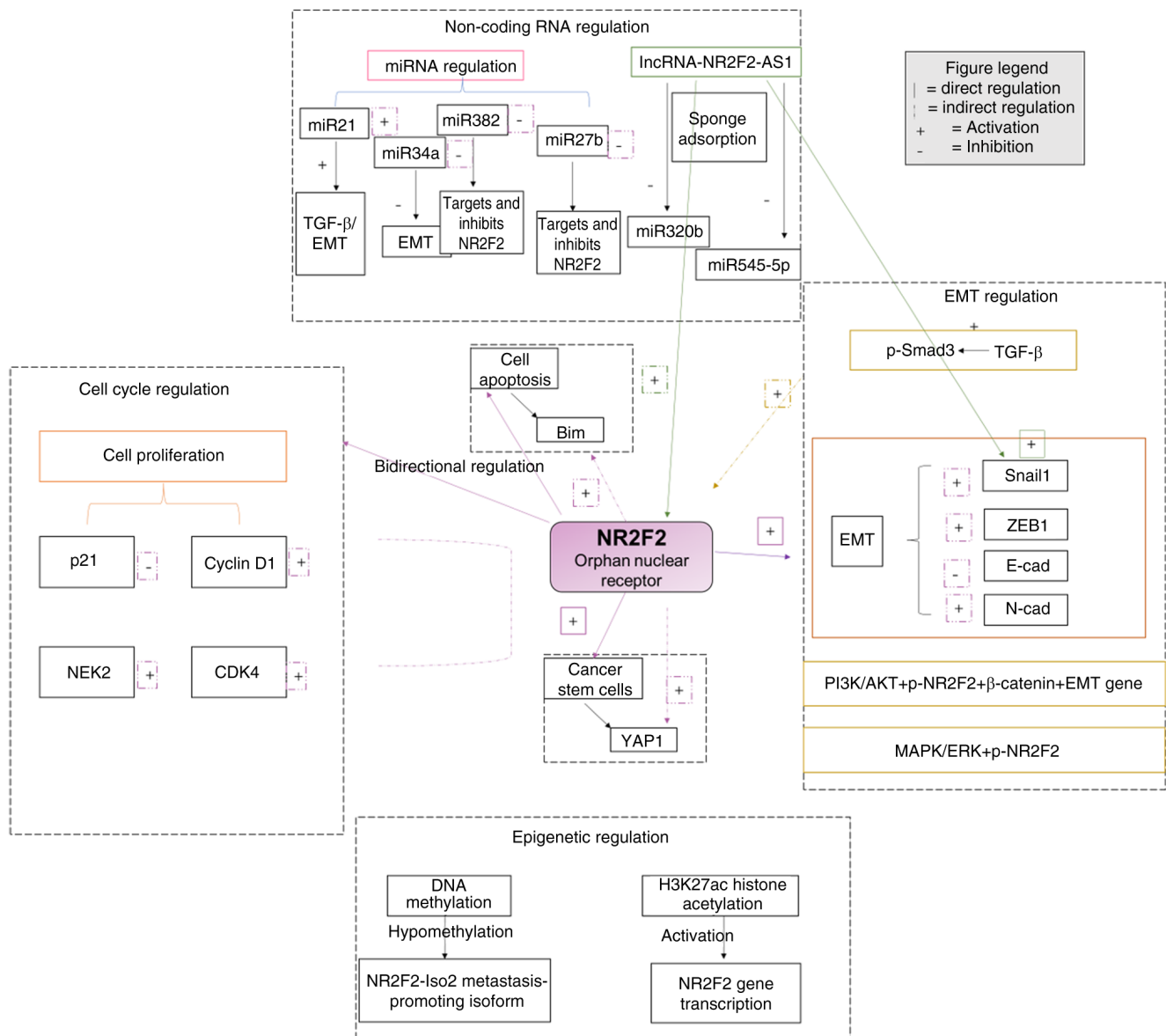


Figure 2. Panoramic model of the core regulatory network of NR2F2. NR2F2, nuclear receptor subfamily 2, group F, member 2; EMT, epithelial-mesenchymal transition; miRNA/miR, microRNA; lncRNA, long non-coding RNA; NEK2, nucleolar and spindle-associated protein 2; ZEB1, zinc finger E-box-binding homeobox 1; cad, cadherin; p, phosphorylated; CDK4, cyclin dependent kinase; AS1, antisense 1; Iso, isoform.

ligase leads to a reduction in ubiquitination and degradation of NR2F2, and the abnormal accumulation of NR2F2 activates Snail to promote EMT, exerting a carcinogenic effect (43).

The regulatory mechanisms of NR2F2 (including transcriptional isoforms, upstream and downstream regulation, and epigenetic modifications). At the same time, NR2F2 has multiple transcriptional isoforms, and these distinct isoforms may have differences in structure and function. The expression levels of these isoforms vary in different tissues or cellular environments, which may lead to the diversity of the functions of NR2F2. For example, in metastatic melanoma, NR2F2-Iso2 competitively binds to the target genes of Iso1 (such as the EMT-related gene Snail1), thereby relieving the inhibitory effect of Iso1 on metastasis and driving tumor progression (41). Post-translational modifications are also important factors in regulating the function of NR2F2.

Studies have shown that post-translational modifications of other nuclear receptors, such as phosphorylation and acetylation, can notably affect their activity, stability and interactions with other molecules (70). In CRC, low methylation of the NR2F2 promoter is notably associated with its high expression, and the increased levels of H3K27 acetylation in the promoter region further enhances its transcriptional activity (39). Given the limited scope of tumor types and the small number of samples examined, the conclusions regarding the role of NR2F2 in the development of various tumors remain inconsistent. Thus, the complete role of NR2F2 in cancer still requires further investigation.

The upstream regulatory factors of NR2F2 are complex. In breast cancer, an NRAS proto-oncogene, GTPase mutation activates ERK1/2, phosphorylates the Ser294 site of NR2F2 and enhances its binding with β -catenin to promote EMT (45). In CRC, TGF- β activates NR2F2 through Smad3

phosphorylation, and thereby promote the transcription of miR-21. Meanwhile, miR-21, by targeting and binding to the 3'UTR of Smad7 mRNA, inhibits its translation process, ultimately leading to a decrease in the level of Smad7 protein (34,71). Regarding downstream effectors, in ER-positive breast cancer, NR2F2 regulates ER-dependent transcription programs through multiple mechanisms, influencing the expression of a series of downstream genes. For example, NR2F2 inhibits the transcriptional program of ER by redistributing the binding sites of ER, altering the balance of transcriptional co-regulators, and modifying chromatin accessibility (72). In lung cancer cell lines, NR2F2 can regulate immune-related pathways and cell cycle-related proteins (such as cyclin D3, cyclin A2, CDK inhibitor 1A and TP53), and affect the immune function and cell cycle progression of the cells (13).

Epigenetic modifications also serve a role in the functional regulation of NR2F2. Epigenetic modifications, such as DNA methylation and histone modifications, can affect gene expression. In the endometrium, NR2F2 mainly occupies genomic regions with H3K27ac and H3K4me1 histone modifications, which are closely associated with the activation state of the genes (73). In melanoma, the expression of the NR2F2 isoform NR2F2-Iso2 is regulated by DNA methylation. When the promoter region of NR2F2-Iso2 undergoes low methylation, its expression is upregulated, thereby promoting the metastasis of melanoma (41). In terms of co-transcription factors, NR2F2 interacts with a series of transcriptional co-regulatory factors in breast cancer, such as histone deacetylase 1/2 (HDAC1/2), nuclear receptor co-repressor 1/2 (NCOR1/2), CREB-binding protein (CBP) and FOXA1. These factors work in synergy with NR2F2 to jointly regulate the transcriptional activity of ER (7). In other cancer types, there may also be different co-transcription factors that cooperate with NR2F2 to participate in the occurrence and development process of tumors; however, further in-depth research in this area is still needed.

Research progress on targeted inhibitors of NR2F2. Currently, while the specific ligand for NR2F2 has yet to be identified, small-molecule compounds that can suppress its activity have been discovered (74). Moreover, reducing NR2F2 expression in the normal tissues of adults does not result in notable damage to the organism (75). Therefore, implementing targeted therapy focused on NR2F2 is likely to offer a promising option for the treatment of malignant tumors.

At present, research on small molecule inhibitors targeting NR2F2 has made some progress. Researchers have developed inhibitors, such as Z021, for the ligand-binding domain (LBD) of NR2F2. Through thermal shift experiments, it has been confirmed that Z021 can directly bind to NR2F2 ($\Delta T_m = 2^\circ\text{C}$). Moreover, in cell lines and patient-derived xenograft models, Z021 combined with fulvestrant can completely eliminate neurofibromin 1-knockout tumors and markedly inhibit tumor growth in three different drug-resistant patient-derived xenograft models (72,76).

Challenges and practical obstacles in the treatment based on targeting NR2F2. However, there are still numerous challenges in targeting NR2F2 for treatment in cancer therapy. Firstly, NR2F2 is also expressed at a certain level in normal

tissues. How to achieve specific inhibition of NR2F2 in tumor cells while minimizing the side effects on normal tissues has become an urgent issue to be addressed. Secondly, the functions of NR2F2 vary in different cancer types and at different stages of the same cancer. For example, in breast cancer, NR2F2 can mediate endocrine therapy resistance through mechanisms such as interaction with ER in the ER⁺ tumor microenvironment and exert carcinogenic effects (72). In some lung cancer cell lines, upregulation of NR2F2 can inhibit cell cycle-related signaling pathways and exert tumor suppressor functions (77). Moreover, the current understanding of the interaction networks between NR2F2 and other molecules is not comprehensive. NR2F2 not only interacts with a series of transcriptional co-regulators (such as HDAC1/2, NCOR1/2, CBP and FOXA1) to regulate gene transcription (7), but may also affect cell functions through unknown molecular pathways. This may affect the full effectiveness of small molecule inhibitors. Despite the challenges, targeted NR2F2 therapy also holds great potential. NR2F2 serves a crucial role in the occurrence and development of various types of cancer, especially in some drug-resistant cancer subtypes. For example, in the case of endocrine therapy resistance in ER⁺ breast cancer, NR2F2 is a key regulatory factor (72). Developing effective NR2F2 inhibitors is expected to provide novel treatment options for these refractory cancers. Moreover, as the research on NR2F2 continues, the understanding of its structure, function and mechanism of action will be more comprehensive, providing a solid theoretical basis for the design of more efficient and specific small molecule inhibitors.

The practical obstacles to targeting NR2F2, such as the absence of specific ligands and potential off-target effects, include: i) As an 'orphan nuclear receptor', the natural ligand of NR2F2 has not yet been identified. This has led to the lack of a clear target for traditional small molecule inhibitors based on ligand design. Currently developed inhibitors (such as Z021) mainly target the hydrophobic pocket of the LBD, but this region has a homology of up to 68% with other nuclear receptors (such as COUP-TF1 and retinoid X receptor α), which may cause off-target effects. For example, *in vitro* experiments have shown that the IC_{50} value of Z021 on COUP-TF1 was only 2.3x higher compared with that on NR2F2, suggesting a potential risk of hepatotoxicity (72,73). ii) Single-cell sequencing has revealed that the proportion of NR2F2-expressing cells within the same tumor could range from 12 to 79% (for example, primary tumor vs. metastatic tumor), resulting in the 'targeting gap' phenomenon. Residual highly-expressing cells may trigger recurrence (7). iii) The oral bioavailability of the reported NR2F2 inhibitors is generally low, and their distribution in tumor tissues is uneven. Although nanocarrier delivery systems (such as poly lactic-co-glycolic acid nanoparticles encapsulating Z021) can increase tumor accumulation, they may cause immunogenicity issues (72).

Future research directions of NR2F2 based on cutting-edge technologies. Focusing on cutting-edge technologies, such as single-cell analysis and organoid models, the present review discusses the future research directions of NR2F2. Using single-cell RNA sequencing (scRNA-seq) technology to analyze the heterogeneous expression of NR2F2 in tumor cell subpopulations (such as stem cells and drug-resistant cells)

and the microenvironment (immune cells and fibroblasts), a cell interaction map could be constructed to reveal the mechanism of functional differences (78). For example, in the field of tumor research, scRNA-seq can be utilized to finely classify NR2F2-positive cells in tumor tissues. Analyzing the co-expression gene networks of NR2F2 in different subpopulations, the specific functions of NR2F2 in key tumor phenotypes, such as proliferation, migration and immune escape, can be clarified. In CRC, a study has investigated how NR2F2-positive tumor cells interact with tumor-associated macrophages to influence the polarization state of macrophages and thereby alter the immunosuppressive characteristics of the tumor microenvironment (79). Using tumor organoids derived from patients to simulate the physiological environment, the regulatory effect of NR2F2 on tumor growth and invasion can be verified, which may be used for high-throughput screening of targeted inhibitors. Combined with gene expression profiles, personalized treatment markers can be developed. For example, in the research on liver cancer, tumor tissues from patients have been used to construct organoids. Through gene editing technology, the expression of NR2F2 was regulated to observe its effects on the growth, differentiation and invasion of the organoids (13). In the study of endocrine therapy resistance in breast cancer, organoids with high expression of NR2F2 and endocrine therapy resistance were constructed. Small molecule inhibitors that could reverse resistance were screened, and at the same time, gene expression profiling analysis was combined to search for biomarkers that predict drug sensitivity (72). This may help provide more precise personalized treatment plans for patients and improve the clinical efficacy of NR2F2-targeted therapy.

7. Conclusion

NR2F2 exhibits complex dual functions in various cancers, functioning as both a tumor suppressor gene and a tumor promoter gene. Its function is regulated by various factors such as the tissue microenvironment, differences in transcriptional isoforms and post-translational modifications. Although there have been certain studies on the role of NR2F2 in some cancers, its function remains unclear in numerous cancer types, and the existing research conclusions show inconsistencies across different tumors. Moreover, the upstream regulatory factors and downstream effector molecules of NR2F2 are diverse, and their interactions with epigenetic modifications and co-transcription factors also affect its function.

Currently, targeted therapy targeting NR2F2 has shown certain potential, such as the positive role of the small molecule inhibitor Z021 in reversing the resistance of breast cancer to endocrine therapy. However, it still faces practical challenges such as the lack of specific ligands, potential off-target effects, tumor internal expression heterogeneity and drug delivery efficiency. In the future, combining cutting-edge technologies such as scRNA-seq and organoid models to deeply analyze the heterogeneous functional mechanisms of NR2F2 in different tumor subtypes and microenvironments and to develop more efficient and more specific targeted drugs and delivery systems, will provide new ideas and strategies for the precise treatment of NR2F2-related tumors.

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Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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