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Nuclear receptors as novel regulators that modulate cancer radiosensitivity and normal tissue radiotoxicity

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Abstract

Nuclear receptors (NRs) are a superfamily of transcription factors that are involved in various pathophysiological processes. The human genome contains 48 types of nuclear receptors, including steroid hormone receptors (e.g., estrogen receptor [ER] and vitamin D receptor [VDR]), nonsteroid hormone receptors (e.g. peroxisome proliferator-activated receptor [PPAR] and retinoic acid receptor [RAR]), and orphan nuclear receptors (e.g. neuron-derived clone 77 [Nur77] and testicular nuclear receptor 4 [TR4]) and certain nuclear receptors are specifically overexpressed in tumor cells or surrounding normal tissues. Radiotherapy is one of the main methods of tumor treatment, but radioresistance in tumors and radiotoxicity to normal tissues strongly affect radiotherapy efficacy. Accumulating evidence has indicated the critical role of nuclear receptor modulators (including agonists and antagonists) as promising radiosensitizers in radiotherapy through various mechanisms. In addition, several nuclear receptors and their agonists alleviate normal tissue toxicity during radiotherapy. Thus, nuclear receptors serve as novel targets for tumor radiosensitization and for protecting of normal tissues from radiation damage. This review summarizes the research progress of nuclear receptors and highlights a promising synergistic strategy in radiotherapy.

Keywords Nuclear receptor (NR), Ionizing radiation, Radiosensitivity, Radioprotection

Introduction

Cancer remains a leading cause of mortality despite of significant breakthroughs in therapies. According to statistics, 4,824,700 new cancer cases and 2,574,200 cancer deaths are estimated to have occurred in China in 2022, and 2,001,140 new cancer cases and 611,720 cancer deaths were expected to have occurred in the US in 2024 [1, 2]. Current cancer treatments include surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapy, etc., and a number of factors need to be considered when choosing a specific treatment. While most treatments kill or destroy cancer cells directly, others cause cancer cells to die by stimulating the body's own defenses, such as immune checkpoint blockade targeting T cell surface proteins including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 receptor (PD-1), adoptive cell therapy utilizing natural

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killer (NK) cells, cytokine-induced killer (CIK) cells, and natural killer T (NKT) cells isolated from patients; or by affecting signals related to tumor survival, such as epidermal growth factor receptor (EGFR)-related pathways, phosphatidylinositol 3-Kinase (PI3 K)/Akt, and the Wnt/β-catenin pathway [3–7]. Nevertheless, radiotherapy is one of the most important treatments for patients with tumors, with two-thirds of patients needing to undergo radiotherapy. Radiotherapy uses the ionizing radiation effects of high-energy rays to kill cancer cells. The principle is to damage the DNA of cancer cells directly or indirectly through radiation, thus inhibiting their growth or killing them.

Despite the increasing precision of radiotherapy techniques, certain normal tissues are more or less inevitably damaged by irradiation. The mechanism of cell killing from radiation is not selective for tumor cells, thus simply increasing the radiation dose is likely to exert many adverse effects on normal tissues, referred to as radiotherapy toxicity. Radiotherapy can cause cardiotoxicity, neurotoxicity, gastrointestinal toxicity, hematological toxicity, dermatotoxicity, osteotoxicity, pulmonary toxicity, urological toxicity and many other types of damage to the organs and functions of the human body, potentially even developing into a factor leading to the discontinuation of radiotherapy or even the death of the patient [8–10]. Therefore, there is an urgent need to address how to increase the sensitivity of tumor tissues to radiotherapy and reduce the degree of radiation damage to normal tissues.

However, results from studies on new targets and mechanisms of radiosensitization and radioprotection are still not clear and comprehensive, and thus, further studies are warranted. In recent years, studies have shown that a variety of nuclear receptors and their ligands are involved in the resistance of tumors to radiotherapy as well as in normal tissue radioprotection. In this review, the research progress on the role of nuclear receptors and their related ligands in radiosensitivity is summarized and discussed.

Role of ionizing radiation

Biological effects of ionizing radiation

After Wilhelm Conrad Röntgen discovered X-rays in 1895, physicians began to pioneer the development of ionizing radiation in disease diagnosis and therapy [11]. Over the past century, the applications of ionizing radiation in disease treatment have greatly expanded. DNA damage is one of the molecular biological effects caused by ionizing radiation, directly or indirectly. Different types of ionizing radiation trigger different types and proportions of direct DNA damage. X-rays, γ-rays and electron beams radiation produce DNA damage including single-strand breaks (SSBs), basal damage, DNA–protein cross-links and small amount of double-strand breaks (DSBs) in the genomic DNA. In contrast, proton and heavy ion radiation are more likely to cause direct DNA damage than photon irradiation (X-rays and γ-rays) [12]. Proton and heavy ion radiation create up to four times more DSBs at the same dose and cause clustered DNA damage to multiple base-pairs, which are more difficult to repair [13]. Another major mechanism of radiotherapy is the indirect damage to macromolecules caused by free radicals. When a water molecule receives ionizing radiation, positively charged water ions (H_2O^+) and free electrons are produced. H_2O^+ is unstable and rapidly dissociates into hydrogen ions and hydroxyl radicals (·OH), and the free electrons trigger secondary ionization. ·OH is a type of reactive oxygen species (ROS) with an oxidative stress effect, that can cause damage to the DNA of tumor cells, induce cell death, and promote cell damage mediated by lipid peroxidation [14]. In addition, according to the oxygen fixation hypothesis, when these radicals encounter molecular oxygen they form a peroxyl radical, $RO_2^{\bullet}$, rendering radical-induced DNA damage more difficult or impossible to repair, thus enhancing the damaging effects of radiation [15].

Through a series of biochemical and signaling processes, ionizing radiation finally induces cellular effects, including cell cycle changes, senescence, bystander effects, radiation-induced rescue effects (RIREs), and various types of cell death (including apoptosis, pyroptosis, autophagy, necroptosis and/or ferroptosis) [16, 17]. The cellular effect of radiation varies according to various factors, such as quality of ionizing radiation, radiation dose, dose rate and the intrinsic radiosensitivity of the cells.

The development of clinical radiotherapy

Ionizing radiation is classified as photon radiation (e.g., X-rays and γ-rays) and particle radiation (e.g., proton, neutron and heavy ions). Radiation levels are quantified through absorbed dose measurements expressed in grays (Gy) and although both deliver the same physical dose (1 Gy), protons and heavy ions like carbon ion beams produce greater biological effects than X-rays [18]. By comparison, particle therapy has the advantages of fast speed, high energy, and precise irradiation. And due to the unique physical properties of particles, i.e., the aforementioned Bragg peak, particle therapy introduces a lower entry dose and eliminates dose deposit beyond the target volume compared to photon therapy, resulting in fewer toxic side effects [12].

Since the late nineteenth century when several major discoveries related to ionizing radiation were made, external beam radiotherapy (EBRT) has been used to increase ray energy, and during this period, many studies have been conducted to improve the controllability of local tumor irradiation. With the development of computer technology and medical imaging technology such as computed tomography (CT), radiotherapy has gradually transitioned from two-dimensional to three-dimensional, such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT). Four-dimensional computed tomography (4D-CT) has led the way to the emergence of image-guided radiation therapy (IGRT) and supported radiotherapy techniques, such as adaptive therapy (ART), which optimizes radiotherapy planning during treatment, and the positioning accuracy of the target area and surrounding organs is becoming more and more accurate [19, 20].

In recent years, FLASH radiotherapy (FLASH-RT), which can achieve ultrahigh-dose rate irradiation with an average dose rate of more than 40 Gy/s in less than 200 ms of delivery time by a linear electron accelerator, has attracted increasing attention. FLASH-RT has the characteristics of instantaneous, ultrahigh dose, one-time irradiation, which can effectively shorten the radiotherapy treatment time, improve the tolerance of normal tissues, and have high therapeutic efficacy [21, 22]. In 2019, FLASH-RT was used for the first time in clinical care in a patient with multiresistant T-cell cutaneous lymphoma [23]. A non-randomized clinical study of proton FLASH-RT was carried out in 2023 for the treatment of bone metastases, supporting the application of FLASH-RT in the clinical treatment [24]. Studies indicate that FLASH-RT induces less ROS and promotes the preservation of mitochondrial integrity and function, which helps attenuating apoptotic pathways in normal tissues, attenuating damage [25, 26]. However, the molecular radiobiology underlying FLASH effect is not fully illustrated and further experiments are necessary to understand the biological response.

Resistance to and toxicity of radiotherapy

Theoretically, radiotherapy is effective for all tumor cells, but many cells are radiation-resistant, resulting in a weakened or ineffective radiotherapy effect. Biological factors affecting the therapeutic effect of radiotherapy have evolved from the “4R” to the “6R” theory, which includes the following aspects: repair, redistribution, repopulation, reoxygenation, radiosensitivity and reactivation of the immune system [27–29]. There are many mechanisms of radioresistance, including radiation-induced DNA damage repair, antioxidant response, cell cycle regulation, apoptosis escape, the abundance of cancer stem cells, modification of cancer cells and their microenvironment and metabolic reprogramming [30].

The DNA damage response (DDR) senses DNA damage through fast and accurate signaling pathways and activates repair mechanisms to maintain genomic integrity and stability, and alterations in the DDR are associated with tumor development [31]. The ataxia telangiectasia mutated and Rad3-related (ATR)-checkpoint kinase 1 (CHK1) pathway is a major regulator of the DDR and the level of activation of this pathway is directly related to radioresistance [32, 33]. DSBs are the most lethal form of DNA damage induced by ionizing radiation, and are repaired mainly by two mechanisms: non-homologous end joining (NHEJ) and homologous recombination (HR) [34, 35]. DNA-dependent protein kinase catalytic subunit (DNA-PKcs) is a key component of NHEJ and has been shown to be a possible predictive marker of recurrence after radiotherapy, and an increase in DNA-PKcs levels is associated with late cancer development [36, 37]. Radiation resistance in tumor cells is associated with the dysregulation of DNA repair factors thereby promoting DNA repair, related molecular such as zinc finger E-box binding homeobox 1 (ZEB1) and the homologous recombination repair protein RAD51 recombinase (RAD51) [38].

The Inhibition of apoptosis is one of the fundamental mechanisms by which cancer cells evade cell death and develop radioresistance, a process that involves complex molecular interactions and the dysregulation of apoptotic pathways. The B-cell lymphoma-2 (Bcl-2) protein family plays a central role in the regulation of apoptosis. Both increased Bcl-2 expression and decreased Bcl-2 associated X (BAX) expression inhibit apoptosis [39, 40]. In addition, the inhibition of the p53 pathway, enhancement of nuclear factor kappa B (NF-κB) expression, and inhibition of the caspase pathway cause apoptosis evasion and thus radioresistance [40, 41]. Radioresistance can also be addressed by promoting other modes of cell death such as iron death and cellular pyroptosis. In studies of various cancers such as lung, nasopharyngeal, colorectal and breast cancers, numerous proteins have been found to inhibit radiation-induced cellular juxtaposition and iron death through different signaling pathways to produce radioresistance [42–46]. Iron death inducers (FIN) have been shown to have radiosensitizing effects as well [47, 48].

Cell cycle regulation is one of the most important determinants of cellular sensitivity to ionizing radiation. ATM and ATR are two important protein kinases involved in cell cycle checkpoint regulation that sense injury and activate downstream response elements and signaling pathways [49]. The G2 and M phases of the cell cycle are the more radiation-sensitive phases, followed by the G1 and S phases. Therefore, blocking cells in the G2/M phase can increase radiosensitivity.

In addition to the tumor cells themselves, which develop radiation resistance, the tumor microenvironment (TME) is also associated with radiosensitivity. The environment around tumor cells is an ecosystem composed of non-cancerous cells, such as immune cells and fibroblasts, extracellular matrix (ECM), and a variety of non-cytokines in the immediate vicinity of the tumor. Radiotherapy can lead to changes in the TME and thus cause tumors to become radioresistant. Involvement of TME components such as cancer associated fibroblasts (CAFs) in radiotherapy resistance has been widely reported [50, 51].

Radiotherapy toxicities are categorized as acute, subacute, or delayed; acute effects are usually inflammatory or reflected in a reduction in epithelial cell populations, and delayed effects usually reflect fibrosis, vascular damage, or progressive parenchymal damage that may reduce overall organ function [52–54]. Because of the different anatomical characteristics of the organs and tissues involved, the mechanisms and clinical manifestations of toxic side effects vary. For example, radiotherapy may lead to atrophy and thinning of the skin in the radiation area, fibrosis of the soft tissues, dilation of capillaries and radiation dermatitis, which will lead to gradual degeneration, necrosis of the skin, and even cancer [55–57]. Studying the mechanisms affecting the radiosensitivity of tumor cells and exploring safe and effective radiation sensitization strategies for tumor treatment are essential.

Overview of nuclear receptors

Nuclear receptors are a ligand-dependent superfamily of transcription factors, that can bind directly to lipophilic ligands. The human genome contains 48 types of nuclear receptors, which are involved in a variety of pathophysiological processes such as development, metabolism, circadian rhythms, immunoregulation, proliferation and differentiation [58]. Approximately 14% of the drugs used in clinical practice target nuclear receptors, most of these drugs are receptor agonists, targeting glucocorticoid receptor (GR), progesterone receptor (PR), androgen receptor (AR), estrogen receptor (ER), peroxisome proliferator-activated receptor (PPAR), vitamin D receptor (VDR), retinoic acid X receptor (RXR), retinoic acid receptor (RAR), mineralocorticoid receptor (MR) and farnesol X receptor (FXR), and some are antagonists, targeting AR, ER, GR, MR and PR, or modulators, targeting ER and PR [59, 60]. Common medications include dexamethasone, flutamide and tamoxifen.

The study of nuclear receptors began with the exploration of the mechanisms of action of lipid-soluble hormones such as steroids, retinoids, and thyroid hormones. Unlike water-soluble hormones, which bind to receptors on the surface of the cell membrane, lipid-soluble hormones enter the cytoplasm by simple diffusion across the lipid bilayer of the cell membrane. The development of radionuclide-labeled ligands at the end of the 1970 s initially revealed the mechanism of nuclear receptor activation, which involves lipid-soluble hormones entering the cytoplasm and translocating into the nucleus by binding to specific receptor proteins to modulate gene transcription [61].

Since 1985, researchers have used molecular cloning techniques to reveal the high degree of similarity in the structure of nuclear receptors. The primary structure of a nuclear receptor consists of 5–6 regions from the amino terminus to the carboxy terminus, denoted by A to F (Fig. 1). The A/B region constitutes a highly variable amino-terminal structural domain (NTD), which includes ligand-independent activation of the transcription functional region (AF-1); the C region is highly conserved and contains a centrally located DNA-binding structural domain (DBD) with two zinc-finger binding sequences; the D region, known as the hinge region, contains the major nuclear localization sequence (NLS) and is a highly variable and flexible hinge region that binds to heat shock proteins (HSPs) and stabilizes the function of the C region; and the E/F region is a moderately conserved C-terminal ligand-binding structural domain (LBD) and another transcriptional activation region (AF-2). The E region is usually involved in dimerization, whereas the F region contains an additional short, variable carboxy-terminal structural domain (CTD). Among them, the LBD is the largest and most targeted structural domain in nuclear receptors and plays an important role in the transcriptional regulation of classical nuclear receptors [62–64]. An exception is the NR0 family, the members of which do not contain a DNA-binding domain.

Nuclear receptor families are continuously discovered, and are categorized into three groups on the basis of their ligands: steroid hormone receptors, nonsteroid hormone receptors, and orphan nuclear receptors, for which endogenous ligands have not yet been identified. These families of nuclear receptors are involved in a variety of pathophysiological processes with different modes of action (Fig. 2). Before binding to ligands, members of the steroid hormone receptor family generally form complexes with co-repressors (e.g., HSPs) in the cytoplasm. Upon binding to ligands, ligand-receptor complexes detach from and translocate into the nucleus, where they form homodimers that bind to the corresponding hormone response elements (HREs) of target genes, recruiting co-activators and regulating the transcription of target genes. Prior to ligand binding, members of the non-steroidal hormone receptor family generally bind to the retinoid X receptor (RXR) in the form of a heterodimer in the nucleus and serve as a co-inhibitor. When a non-steroid hormone receptor family member binds to a ligand, the ligand-heterodimer complex frees and forms a

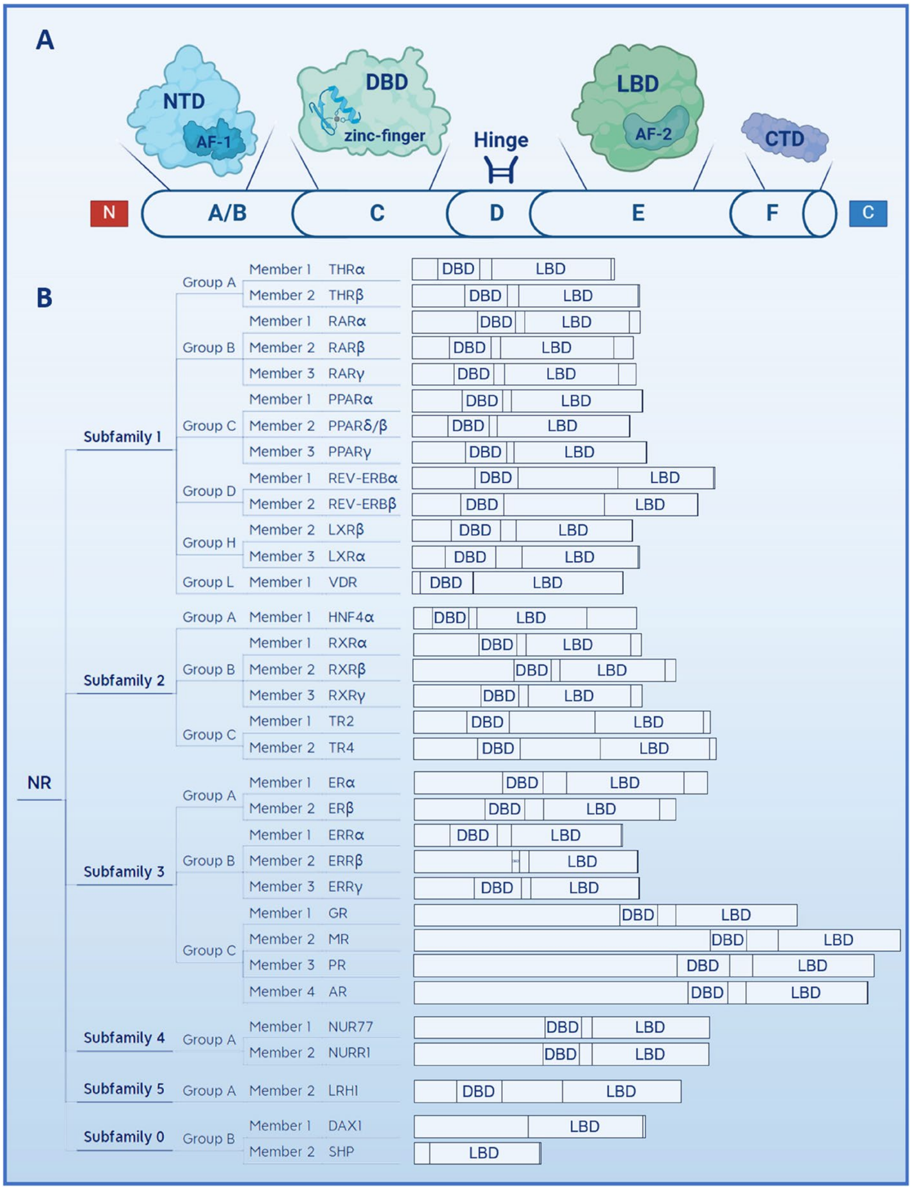

Fig. 1 General structure and nomenclature of nuclear receptors [65]. **A** The basic molecular composition of nuclear receptors can be categorized into 5–6 (A F) regions with structural domains that perform different actions. (Created with bioRender.com). **B** The nomenclature of the nuclear receptors mentioned in this paper and a schematic diagram of their functional domains (choose the MANE SELECT protein set from NCBI), with the A/B structural domain being the most varied region and the DBD and LBD structural domains being highly conserved

complex with a co-inactivator to bind to the corresponding hormone-responsive element to regulate the expression of target genes. Orphan nuclear receptor family members do not have a clear endogenous ligand and generally bind to the hormone response element of a target gene as a monomer or homodimer to activate the transcription of the corresponding target gene. In general, nuclear receptors have two dimerization sites, one in the DBD and the other in the LBD, the latter of which is considered the major dimerization site of nuclear receptors. Ligand binding alters the conformation of the LBD and promotes the dimerization of nuclear receptors [64].

Nuclear receptors and tumor radiosensitivity

The aberrant expression of nuclear receptors may be one of the key factors in tumorigenesis as well as in the development of radiation resistance in tumors. Long and Campbell analyzed breast tissue data from 1905 patients with breast cancer in situ and 113 healthy subjects in The Cancer Genome Atlas (TCGA) database, and

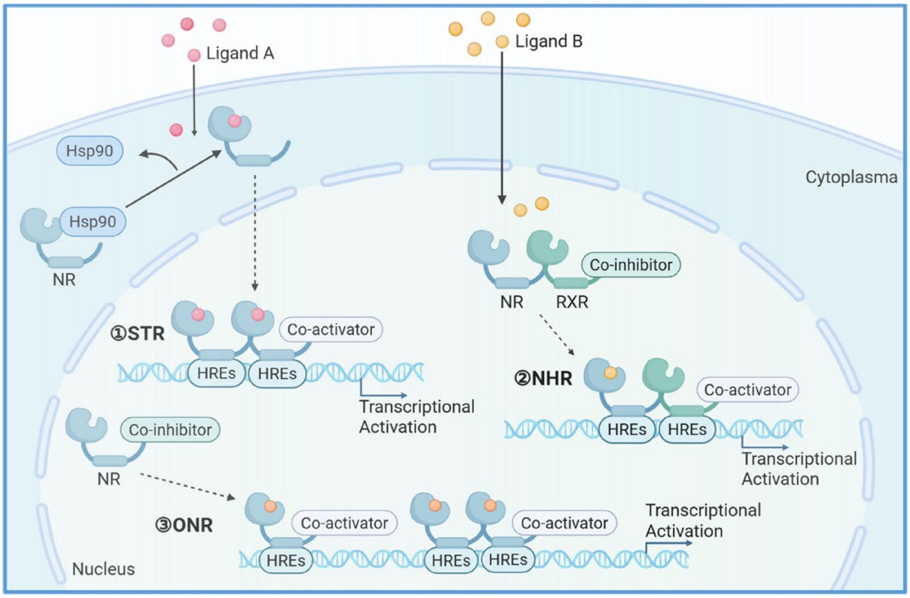

Fig. 2 Three transcriptional activation patterns of nuclear receptors [63]. (1) Steroid hormone receptor (STR): Upon ligand A activation, nuclear receptors translocate into the nucleus to facilitate transcription. (2) Nonsteroid hormone receptor (NHR): Ligand B enters the nucleus and activates nuclear receptors originally localized in the nucleus to promote transcription. (3) Orphan nuclear receptor (ONR): Radiation promotes or inhibits nuclear receptor action. NR, nuclear receptor; RXR, retinoid X receptor; HREs, hormone response elements. (Created with bioRender.com)

reported that, compared with normal tissues, there were 42 nuclear receptors with abnormal expression in tumors [66]. Their concurrent analysis of data from bladder, colorectal, head and neck, liver and prostate cancers yielded similar results with tissue specificity (Table 1 and Fig. 3).

Thus, the activation or inhibition of nuclear receptors may be a potential strategy for tumor suppression. Specifically, targeted regulation of nuclear receptor expression in tumor tissues may significantly enhance radiosensitivity, as will be comprehensively discussed in the subsequent section (Table 2 and Fig. 4).

Steroid hormone receptors and tumor radiosensitivity

Estrogen receptor (ER)

ER is a member of the steroid hormone receptor family that binds specifically to estrogen and regulates gene transcription through estrogen response elements (EREs). ER contains two classical nuclear receptor isoforms ERα and ERβ, which differ greatly in their NTD sequences, whereas the LBD sequences are essentially identical [182]. The tissue distribution and expression of these two genes are relatively different. ERα is expressed mainly in the female reproductive system, such as the ovary and mammary glands, and in brain regions related to reproduction, whereas ERβ is expressed mainly in bone tissue, the central nervous system, the digestive system, and the cardiovascular system. ERα is highly expressed in many early stage tumors to promote the growth and proliferation of cancer cells, whereas ERβ is reduced or absent in tumors, and its re-expression can inhibit the proliferation and promote the apoptosis of tumor cells. The expression of ERα and ERβ suggests that high ERα expression and the absence of ERβ expression may be related to tumorigenesis [100–102, 183, 184].

Tamoxifen, a selective estrogen receptor modulator (SERM), can competitively bind to ER and block ER signaling-mediated transcriptional activation by preventing the recruitment of coactivator molecules via the LBD structural domain of ER. Studies have suggested that the ER receptor agonist estradiol (E2) impedes the inhibitory effect of ionizing radiation on breast cancer cell proliferation, potentially reducing cellular sensitivity to radiation, and can be blocked by SERMs; however, other studies have suggested that radiosensitivity is affected by overall estrogen availability and that tamoxifen has a slight radioprotective effect on ER +breast cancer cells, whereas exogenous E2 can be used to attenuate these effects [103, 104].

Fulvestrant is a selective ERα inhibitor that can competitively inhibit the binding of endogenous estrogen to ER, degrade ER proteins, and block the ER signaling pathway, thus exerting antitumor effects; moreover, it has good inhibitory effects against hormone-dependent breast cancer, and is a first-line option for ER-positive menopausal patients with advanced breast cancer [105, 106]. Some researchers have explored the effect of fulvestrant on the radiosensitivity of the human breast cancer

Table 1 Names and expression distribution of tumor-associated nuclear receptors

Nuclear receptor	Head and neck	Esophagus	Mammary gland	Lung	Liver	Kidney	Colorectum	Cervix	Bladder	Prostate gland	Skin
ERα	+	#	+	#	#	#	#	+	+	#	#
ERβ	#	#	#	#	#	#	−	−	#	#	#
AR	+	#	−	+	#	#	#	#	+/−	+	#
PR	#	#	+	#	#	#	#	−	#	#	#
GR	#	#	+/−	#	#	#	#	#	#	−	#
PPARα/β	#	#	#	#	#	−	#	#	#	#	#
PPARγ	−	#	#	−	+	−	−	#	#	#	−
VDR	−	#	#	+	−	#	−	#	−	#	#
RXRα/β	#	#	−	#	#	#	−	#	#	#	−
RXRγ	#	#	−	−	#	#	−	#	#	#	−
RARα	−	#	−	#	#	#	−	#	#	#	−
RARβ/γ	−	#	#	#	#	#	−	#	#	#	−
LXRα	#	#	−	#	#	#	#	#	#	#	#
LXRβ	#	#	−	#	#	#	#	#	#	#	−
FXR	#	+	#	#	−	#	#	#	#	#	#
LRH1	#	#	+	#	#	#	+	#	#	#	#
SHP	#	#	#	#	−	−	#	#	#	#	#
HNF4α	#	#	#	#	#	#	+/−	#	#	#	#
NUR77	#	#	#	#	#	+	#	#	−	#	#
NURR1	#	#	#	#	#	#	#	#	−	+	#
ERRα	#	#	#	#	#	#	#	+	#	#	#
ERRγ	#	#	#	#	#	#	#	−	#	−	#
DAX1	#	#	#	#	#	#	#	#	#	−	#
TR2	#	#	#	#	#	#	#	#	#	−	#
THRα	−	#	#	#	#	−	−	#	#	#	−

ER Estrogen receptor, *AR* Androgen receptor, *PR* Progesterone receptor, *GR* Glucocorticoid receptor, *PPAR* Peroxisome proliferator-activated receptor, *VDR* Vitamin D receptor, *RXR* Retinoic acid X receptor, *RAR* Retinoic acid receptor, *LXR* Hepatic X receptor, *FXR* Farnesol X receptor, *LRH1* Hepatic receptor homology 1, *SHP* Small heterodimeric chaperone receptor, *HNF4α* Hepatocyte nuclear factor 4α, *Nur77* Neuron-derived clone 77, *Nurr1* Nuclear receptor-associated protein 1, *ERR* Estrogen-associated receptor, *DAX1* Dosage-sensitive sex transition syndrome adrenal hypoplasia gene on the X chromosome, gene 1, *TR2* Testosterone receptor 2, and *THRα* Thyroid hormone receptor α

+ denotes promotion of tumor development

-denotes inhibition of tumor development

± denotes that the mechanism of action to promote or inhibit tumor development has been reported in the literature

[#] denotes that the mechanism of action on tumor development has not yet been studied or reported in the literature

cell line MCF-7 and reported that 100 nM fulvestrant downregulates the expression of the nonhomologous repair protein DNA-PKcs and the homologous recombination repair protein RAD51, thus attenuating the repair of radiation-induced DNA damage, inducing the redistribution of cells in the G1 phase, and reducing G2/M arrest to increase cellular radiosensitivity [68]. However, the direct target of fulvestrant is still unclear. Fulvestrant has been shown to induce ERα degradation through the ubiquitin proteasome pathway, and significantly inhibit the expression of the ERα protein in MCF-7 of human breast cancer cells [69].

Piperine is a plant alkaloid from black pepper that can enhance the activity of several anticancer drugs in cancer cells; it has been found to increase the radiation sensitivity of breast cancer cells by increasing ERβ expression and decreasing ERα expression in MCF-7 cells, thereby downregulating the expression of repair proteins in the NHEJ pathway, leading to the accumulation of radiation-induced DNA DSBs and triggering cell death [107].

Another study revealed that ERβ is involved in the resistance of non-small cell lung carcinoma (NSCLC). The expression of cleft lip and palate transmembrane 1-like (CLPTM1L, also known as cisplatin resistance-associated gene 9 (CRR9)) is positively correlated with radioresistance in NSCLC cell lines. Radiation upregulated CLPTM1L expression in a radioresistant cell line (A549) but not in a radiosensitive cell line (H460).

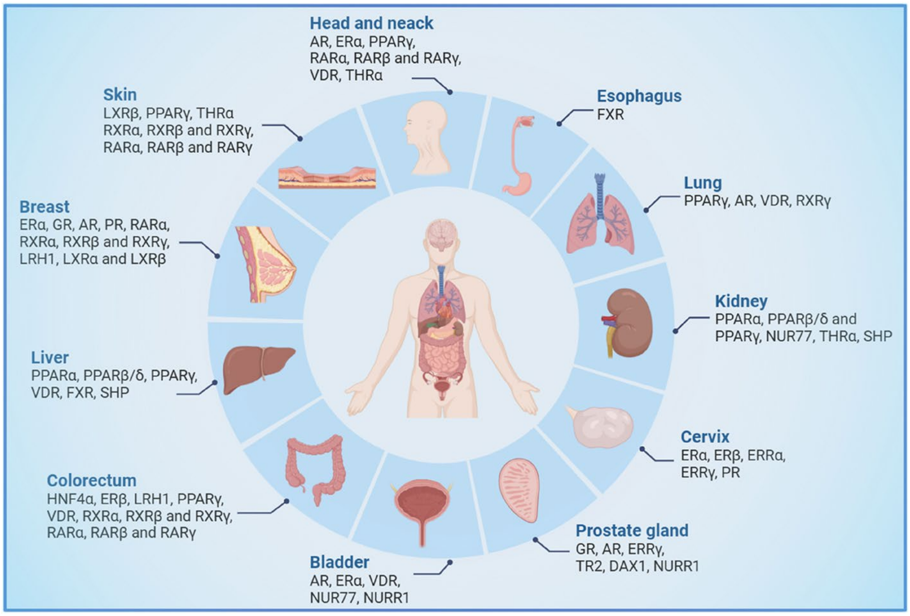

Fig. 3 Names and expression distribution of tumor-associated nuclear receptors [66]. Distribution of nuclear receptor expression in major human organs. ER, estrogen receptor; AR, androgen receptor; PR, progesterone receptor; GR, glucocorticoid receptor; PPAR, peroxisome proliferator-activated receptor; VDR, vitamin D receptor; RXR, retinoic acid X receptor; RAR, retinoic acid receptor; LXR, liver X receptor; FXR, farnesol X receptor; LRH1, hepatic receptor homology 1; SHP, small heterodimeric chaperone receptor; HNF4α, hepatocyte nuclear factor 4α; Nur77, neuron-derived clone 77; NurR1, nuclear receptor-related protein 1; ERR, estrogen-associated receptor; DAX1, dosage-sensitive sex transition syndrome adrenal hypoplasia gene on the X chromosome, gene 1; TR2, testosterone receptor 2; and THRα, thyroid hormone receptor α. (Created with bioRender.com)

CLPTM1L activated ERβ through directly binding, promoting the transcription of its target genes and inducing resistance in NSCLC cells. Thus, silencing ERβ attenuates the radioresistance of NSCLC cells induced by CLPTM1L [108].

Therefore, there are various mechanisms of radiosensitization after ligand binding to ER, including enhancing radiation-induced DNA damage via equol [67, 109]; inhibiting radiation-induced DNA damage repair via guggulsterone [76, 110] and caffeic acid phenethyl ester [72]; inducing cell cycle arrest and apoptosis via genistein [70, 73] and metformin [71]; suppressing tumor immunity [77] and inhibiting cell clony formation.

However, there are also inconsistent evidence of role of ERs in modulating cancer cell radiosensitivity. ERα expression has also been reported to increase radiotherapy sensitivity in specific types of cancer cells. Triple-negative breast cancer (TNBC) cell lines transfected with ERα are less radioresistant than non-transfected cells, resulting in increased DSBs, delayed repair, cell cycle arrest and apoptosis after X-rays irradiation [74]. In contrast to the role of ERβ described earlier, ERβ has been implicated in poor prognosis in some breast cancer-related studies. The researchers found that ERβ mRNA expression was upregulated in 121 invasive breast cancer extracts and tamoxifen-resistant cells [75, 78]. In conclusion, ERs may play distinct roles in different tumors, and the specific mechanisms related to radiosensitivity need to be further explored.

Androgen receptor (AR)

Like ER, AR belongs to the steroid hormone receptor family. The human AR gene is located on the X chromosome and is widely distributed throughout the body, with the highest expression in reproductive organs. The AR ligands testosterone and its reduced metabolite, 5α-dihydrotestosterone (DHT), bind directly to AR and promote its translocation into the nucleus, where it recognizes androgen response elements (AREs) on target genes, whose biological functions include initiating the sexual development and differentiation of the male [111]. In addition, AR plays an important role in the development of various cancers, such as prostate cancer (PCa), AR-positive triple-negative breast cancer and ovarian cancer, in which AR overexpression is usually observed in advanced stages [112].

Some studies have shown that there is an interaction between AR and DNA-PKcs. DNA damage induces AR activity, which promotes the activation of genes involved in DNA repair, including DNA-PKcs, thereby promoting

Table 2 Nuclear receptors associated with tumor radiosensitivity

Tumor type	Cell line	Relevant NR	Relevant drug or compound or gene	Enhancement/ Decrease of tumor radiosensitivity	Mechanism(s)	References
Breast	Human breast cancer cells MCF-7	ERα	Fulvestrant	Enhancement	Inhibition of X-ray-induced DNA damage repair and induction of cell cycle G2/M blockade	[67]
	Human breast cancer cells MCF-7	ER	Tamoxifen	Enhancement/ Decrease	Blockade of the effects of ionizing radiation on cell proliferation by estradiol; Reduction of overall estrogen availability	[68, 69]
	Human breast cancer cells MCF-7	ERα	Guggulsterone	Enhancement	Inhibition of cell growth, proliferation and DSB repair	[70, 71]
	Human breast ductal carcinoma cells T47D and human breast cancer cells MDA-MB-231	ER	Equol	Enhancement	Inhibition of cell clone formation ability, induction of apoptosis	[72, 73]
	Human breast cancer cells MCF-7 and MDA-MB-231	ER	Genistein	Enhancement	Induction of cell cycle G2/M blockade and apoptosis	[74, 75]
	Human breast cancer cells MCF-7	ERα&ERβ	Piperine	Enhancement	Inhibition of DSB repair, induction of cell cycle blockade and apoptosis	[76]
	Human breast ductal carcinoma cells T47D and human breast cancer cells MDA-MB-231	ER	Caffeic acid phenethyl ester	Enhancement	Reduction of cell viability and disruption of DNA damage repair	[77]
	Human breast cancer cells MCF-7 and MDA-MB-231	ER	Metfoemin	Enhancement	Inhibition of the mTOR signaling cascade pathway, induction of cell cycle G2/M blockade and apoptosis	[78]
	Human breast cancer cells MDA-MB-453	AR	Seviteronel (INO-464)	Enhancement	Inhibits DNA double-strand break damage repair pathway NHEJ and HR	[79]
	AR-positive triple-negative breast cancer cells	AR	Enzalutamide	Enhancement	Inhibition of DNA double-strand break damage repair pathway NHEJ	[80]
Prostate gland	Human prostate cancer cells LNCaP	AR	Enzalutamide	Enhancement	Inhibits PTEN expression and promotes PDGF D expression	[81]
	Human PCa cells C4-2 and CWR22Rv-1 (22Rv1)	AR or ARV7	Quercetin	Enhancement	Inhibition of circNHS/miR-512-5p/XRCC5 signaling and radiation-induced DDR	[82]
	Human prostate cancer cells C4-2, CWR22Rv-1 (22Rv1)	AR	ASC-J9	Enhancement	Prevention radiation-induced DDR, promotion of endogenous ROS production, and induction of AR-dependent ATR-CHK1 signaling pathway to promote apoptosis	[83]
	Human prostate cancer cells LNCaP	AR	Radicicol	Enhancement	Degradation of AR	[84]
	Human prostate cancer cells DU145 and primary human prostate cancer cells hPCA9	RXRα	9-cis-RA	Enhancement	Unknown	[85]
	Human prostate cancer cells C4-2、PC3、LNCaP	TR4	Metformin	Enhancement	QKI/circZEB1/miR-141-3p/ZEB1 signaling pathway	[86]
Esophagus	Human esophageal cancer cell lines Eca-109 and TE1	PPARα	Fenofibrate	Enhancement	Induction of cell cycle G2/M blockade	[87]

Table 2 (Continued)

Tumor type	Cell line	Relevant NR	Relevant drug or compound or gene	Enhancement/ Decrease of tumor radiosensitivity	Mechanism(s)	References
Pancreas	Human pancreatic cancer cells PANC1, PaTu8988, SW1990 and human in situ pancreatic adenocarcinoma cells BxPC-3	PPARα	Clofibrate	Enhancement	Inhibits NF-κB, Wnt/β-catenin signaling pathway and induces apoptotic effects	[88, 89]
	Human pancreatic cancer cells PANC1, PaTu8988	PPARα	Fenofibrate	Enhancement	Causes aberrant cytokine receptor interactions, retinoic acid-induced gene I-like receptor signaling pathway, transcriptional regulation	[90]
Bladder	Human urothelial cancer cell lines UMUC3, 5637 and 647 V	AR	Flutamide	Enhancement	Delays repair of DNA double-strand breaks	[91]
Lung	Human non-small cell lung cancer cells A549	VDR	1α,25-$(OH)_2D_3$	Enhancement	Activates the NADPH oxidase-ROS-apoptosis axis	[92]
	Human non-small cell lung cancer cells A549 and H1299	PPARγ	Rosiglitazone	Enhancement	Inhibits the expression of phosphorylated AKT and CDKN1B and promotes the expression of apoptotic factor BAX	[93]
	Human non-small cell lung cancer cell A549 and human large cell lung cancer cell H460	PPARγ	Thiazolidinediones, except rosiglitazone	Enhancement	Promotes ROS production, thereby exacerbating ionizing radiation-induced DNA damage and promoting apoptosis	[94]
Cervix	Human ovarian epithelial adenocarcinoma cell line SKOV3	VDR	1α,25-$(OH)_2D_3$	Enhancement	Activates the NADPH oxidase-ROS-apoptosis axis	[92]
	Human cervical epidermoid carcinoma cells ME180	RARβ	13-cis-RA	Enhancement	Promotes up-regulation of Bcl-2 expression	[95, 96]
Head	Human Glioblastoma GB	PPARα	AA452	Enhancement	Inhibits the expression of cyclin D1 and c-myc genes	[97, 98]
Bone marrow	Mouse-derived primary bone marrow-derived macrophages	LXR	GSK1440233/GW233	Enhancement	Increases pro-inflammatory effect of the cells and alterations in the tumor microenvironment, reduces the cellular viability by increasing cellular pyroptosis	[99]

ER Estrogen receptor, *DSB* Double-strand break, *AR* Androgen receptor, *NHEJ* Nonhomologous end joining, *HR* Homologous recombination, *PTEN* Phosphatase and tensin homologous protein detected on human chromosome 10, *PDGF D* Platelet-derived growth factor D, *XRCCs* X-rays repair cross-complementary proteins, *DDR* DNA damage response, *ASC-J9* dimethyl curcumin, *ROS* Reactive oxygen species, *ATR-CHK1* Ataxia telangiectasia mutated and Rad3-related-checkpoint kinase 1, *RXRα* Retinoid X receptor α, *9-cis-RA* 9-cis retinoic acid, *PPAR* Peroxisome proliferator-activated receptor, *QKI* Quaking, *ZEB* Zinc finger E-box binding homeobox 1, *NF-Kb* κ-light-chain enhancement of nuclear factor-activated B-cells, *AKT* Protein kinase B, *CDKN1B* Cell cycle-dependent kinase inhibitor 1B, *BAX* B-cell lymphoma-2 gene-associated X protein, *RARβ* Retinoic acid receptor β, *13-cis-RA* 13-cis-retinoic acid, *Bcl-2* B-cell lymphoma-2, *AA452* N-(methylsulfonyl)amide. cyclin D1, cytokine D1, *LXR* Liver X receptor, *HSD3B1* Hydroxy-δ−5-steroid dehydrogenase, 3 β-and steroidδ-isomerase 1, *CLPTM1L* Cisplatin resistance-associated gene 9, *CRR9* ID3, inhibitor of differentiation 3

resistance to DNA damage; DNA-PKcs also enhances AR function, thus forming a positive feedback loop [31]. A study revealed that half of men with advanced prostate cancer inherit an adrenal-permissive HSD3B1 (1245 C) allele. This allele increases the levels of 3β-hydroxysteroid dehydrogenase 1 (3βHSD1), which catalyzes the synthesis of testosterone, or DHT, from adrenal dehydroepiandrosterone (DHEA), thereby facilitating the AR-DNA-PKcs circuit, enhancing the DDR, and attenuating tumor radiosensitivity [113]. Another study revealed that the expression of phospholipase Cε (PLCε), AR and DNA-PKcs is significantly upregulated in prostate cancer, especially in nonmetastatic castration-resistant prostate cancer (CRPC). PLCε deficiency can inhibit the DDR by suppressing the AR-DNA-PKcs circuit and related downstream molecules, and *in vivo* and *in vitro* experiments have demonstrated that PLCε knockdown significantly enhances tumor radiosensitization, decreases tumor cell viability and promotes apoptosis [114]. Therefore, in prostate cancer treatment, ionizing radiation combined with androgen therapy leads to enhanced DNA repair and reduced DNA damage, whereas ionizing radiation combined with anti-androgen therapy has the opposite effects, resulting in radiosensitization [115].

Nonsteroidal AR antagonist drugs include the pioneering flutamide nilutamide and the newer generation drugs bicalutamide, enzalutamide (ENZA), and apalutamide (ERLEADA), all of which have similar mechanisms of action. Apart from the above mechanisms for DDR, these drugs can competitively inhibit the binding of androgens to AR, thereby preventing AR from entering the nucleus and binding to AREs and thus inhibiting the expression of downstream target genes, ultimately inhibiting tumor growth, and prolonging the survival of patients with advanced cancer. Flutamide is oxidatively metabolized *in vivo* to active hydroxyflutamide, which delays the repair of DNA double-strand breaks in irradiated AR-positive bladder cancer cells, and low doses of flutamide have been shown to potentiate the tumor-inhibitory effects of ionizing radiation in a mouse xenograft model [116]. The radiosensitizing effect of enzalutamide, which antagonizes the action of AR on DNA-PKcs has been demonstrated in prostate cancer, triple-negative breast cancer and AR-positive glioblastoma (GBM). Enzalutamide also enhances the effects of radiation through cell cycle blockade, the induction of apoptosis, and the downregulation of the expression of pro-carcinogenic development genes (NKX3-1, ZMIZ1, SPDEF and PDE9 A, among others) [91, 117–120]. Human prostate cancer LNCaP cells treated with enzalutamide before ^{60}Co irradiation exhibit a significant reduction in colony formation; the mechanism of sensitization to radiotherapy may be related to the upregulation of platelet-derived growth factor D (PDGF-D) expression after deleting phosphatase and tensin homolog (PTEN) on human chromosome 10 [121]. Combined radiotherapy with apalutamide or enzalutamide provides better radiosensitization in patients with AR-expressing androgen-dependent prostate cancer and CRPC than does androgen deprivation therapy (ADT), which is commonly used in clinical practice [117, 122]. The combination of the positron-emitting drug ^{18}F-FDG with antiandrogen drugs such as bicalutamide has been shown to have radiosensitizing effects in the treatment of triple-negative breast cancer [123].

Seviteronel (INO-464) is a dual inhibitor of CYP17 (a member of the cytochrome P450 family), which cleaves enzymes and AR. After binding to the AR-binding domain of DNA damage repair genes, seviteronel not only regulates the expression of DNA-PKcs, but also regulates the expression of X-rays repair cross-complementary proteins (XRCCs) 2 and 3 of the Rad51 family of protein genes, thus exacerbating radiation-induced DNA damage through the NHEJ and HR pathways. The results of *in vivo* experiments combining seviteronel and radiotherapy in human breast cancer MDA-MB-453 cell transplantation tumors showed that the two act synergistically to reduce the tumor volume and prolong the doubling time of the tumor volume after radiation [124].

Androgen deprivation therapy is commonly used to treat prostate cancer and may enhance the cytotoxic effects of radiotherapy by inhibiting the AR-supported DDR. Resistance to androgen deprivation therapy may be associated with androgen receptor shear variant (ARV), which can be induced by androgen deprivation therapy or radiotherapy or generated by AR gene rearrangement, resulting in reduced radiosensitivity [81]. AR variant 7 (ARv7) contributes to the resistance to radiotherapy by altering circNHS/miR-512-5p/XRCC5 signaling. *In vivo* and *in vitro* experiments have revealed that quercetin, which targets AR and ARv7, enhances radiosensitivity and thus inhibits prostate cancer progression [125]. Similarly, the folate-targeted nanoparticle delivery of AR shRNA enhances radiosensitivity in AR-dependent and hormone-independent prostate cancer by silencing AR, as demonstrated by both *in vivo* and *in vitro* experiments [80]. Dimethylcurcumin (ASC-J9), the first certified AR degradation enhancer, is a bimethoxy derivative of curcumin that inhibits the growth of a variety of AR-associated tumors, including prostate, bladder, liver, and renal cancers, and has a high safety profile and is easier to deliver than AR-shRNA. In addition to degrading AR, ASC-J9 exacerbates radiation-induced genomic DNA damage by blocking the DDR and enhancing endogenous ROS production [79]. Radicicol, an inhibitor of the heat shock protein 90 (Hsp90) chaperone complex, also increases tumor cell radiosensitivity by degrading AR [126]. The above studies indicate that targeting AR is likely to facilitate the efficacy of radiotherapy.

Vitamin D receptor (VDR)

VDR is predominantly distributed in the nucleus. The radiosensitization ability of various tumors to vitamin D and its metabolites is dependent on VDR [82]. The active metabolite of vitamin D3 (1α,25-$(OH)_2D_3$) is a steroid hormone as a ligand for VDR that plays an important role in the regulation of calcium-phosphorus metabolic homeostasis and bone tissue metabolism. 1α,25-$(OH)_2D_3$ inhibits expression of the *RelB* (a nonclassical dimer of the NF-κB family consisting of the p52/RelB) gene by specifically binding to a VDR response element located in the promoter region of *RelB* [83, 127]. RelB mediates radiation-induced production of manganese superoxide dismutase (MnSOD) in cancer cells. Thus, VDR acts as a cancer cell radiosensitizer through attenuated ROS scavenging pathway. This effect occurs at a radiation dose of 2 Gy, which may be significant for clinical applications [84, 128, 129]. Another study demonstrated that 1α,25$(OH)_2D_3$ is dependent on VDR to activate the NADPH oxidase-ROS-apoptosis axis, which enhances the radiosensitivity of human lung and ovarian cancer cells [130]. However, none of the specific mechanisms by which VDR is associated with radiosensitivity described above have been fully elucidated and need to be further explored.

Progesterone receptor (PR)

PR is mainly expressed in and regulates the development, differentiation, and proliferation of cells in female reproductive tissues and the central nervous system, as well as pathological processes in endocrine-based cancers [131]. PR-A and PR-B are two isoforms of PR that are normally expressed at similar levels [132]. An imbalance in the PR-A to PR-B ratio may be associated with breast cancer [92, 133]. The tumor volume of DMBA-induced rat breast cancer decreases for 30 days after 20 Gy radiation, and it increases for 30–60 days, which is the same trend as that for PR in tumors [134]. Regarding PR ligands, progesterone inhibits the death of progesterone receptor-positive breast cancer cell lines (T-47D, ZR-75–1 and H-466B) after γ-irradiation; it may act as a trigger for cancer progression by combating or preventing ionizing radiation-induced G2/M phase arrest, increasing the survival and proliferation of DNA-damaged cells [135]. The above findings suggest that the inhibition of PR may increase the radiosensitivity of breast cancer cells. However, the best time to use PR agonists or inhibitors for better therapeutic outcomes needs to be studied in depth.

Nonsteroid hormone receptors and radiosensitivity

Peroxisome proliferator-activated receptor (PPAR)

In 1990, when screening liver cDNA, Issemann and Green discovered a factor that can be activated by chemicals known to induce peroxisome proliferation in rodents; peroxisome proliferator-activated receptor [136]. Three predominant isoforms of PPAR were subsequently identified in different vertebrates: α, β/δ and γ, with only 60% ~ 80% structural homology [137]. PPAR belongs to the nonsteroid hormone receptor family and plays a key role in the regulation of inflammation, glucose metabolism, lipid metabolism, and amino acid metabolism in the human body [137, 138]. Depending on the distribution of target genes and tissues, the three PPAR isoforms exhibit different pathophysiological and pharmacological functions, among which PPARα and PPARγ are associated with tumor radiosensitivity.

PPARα PPARα is expressed mainly in tissues with high energy requirements, such as the heart, the liver, the kidneys, and brown adipose tissue, where it stimulates the β-oxidation of fatty acids and upregulates the expression of fatty acid transport-related genes. PPARα is closely related to the development of tumors such as pancreatic cancer, renal cancer, hepatocellular carcinoma, and glioblastoma. A study revealed that bromelain enhances the sensitivity of Ehrlich solid tumor (EST)-bearing mice to γ-radiation. Bromelain directly decreases PPARα mRNA levels by γ-radiation and indirectly enhances the activity of PPAR-bound DNA by increasing the levels of unmodified poly (ADP-ribose) polymerase 1 (PARP1) through the binding of PARP1 to PPAR [139].

Fibrates, including fenofibrate (LOFIBRA®, TriCor® or TRIGLIDE® etc.), clofibrate (Atromid-S®), among others, are dual agonists specific for PPARα and PPARγ. They have long been used to treat diabetes and cardiovascular disease, in addition to being first-line agents for lowering serum triglyceride levels [140]. In cancer treatment, fenofibrate has been shown to increase the sensitivity of pancreatic cancer cells to X-rays and to significantly inhibit the migration and invasion of cancer cells, possibly through mechanisms such as the disruption of gene expression (TAOK2, JAK3, SLC39 A7 (ZIP7), and TRPV1), cytokine-cytokine receptor interactions, the activation of the retinoic acid-inducible gene I (RIG-I)-like receptor signaling pathway, and transcriptional dysregulation [141]. Fenofibrates also enhances radiosensitization of human esophageal cancer cells by increasing G2/M phase blockade [142]. Clofibrate may inhibit the binding of NF-κB to gene promoters through the activation of PPARα, and downregulate the expression key components of the Wnt/β-catenin signaling pathway, i.e., PTPRZ1 and Wnt8a, thus inhibiting the Wnt/β-catenin signaling pathway, enhancing the proapoptotic effect of X-rays on human pancreatic cancer cells and in situ pancreatic adenocarcinoma cells, and sensitizing cells to radiation [143, 144]. Moreover, the combination of X-rays and clofibrate caused human pancreatic cancer PANC1 and PaTu8988 cells to stagnate in the G2 phase, which significantly increased the killing effect on tumor cells [144].

The PPARα antagonist N-(methylsulfonyl) amide (AA452) in combination with radiotherapy significantly inhibits cell proliferation and migration and induces cell death in human-derived glioblastoma [90]; the radiosensitization mechanism may be related to decreased expression levels of the intracellular cell cycle protein D1 (cyclin D1), the c-myc gene and the migration-related protein the protein of focal adhesions (p-FAK), among which cyclin D1 is a key component in the regulation of NHEJ, affecting radiation-induced DNA damage repair, in prostate cancer cells [87, 88].

PPARγ PPARγ is ubiquitously expressed in almost all tissues. Activated PPARγ promotes tumor cell apoptosis, inhibits cell proliferation and prevents angiogenesis, thus

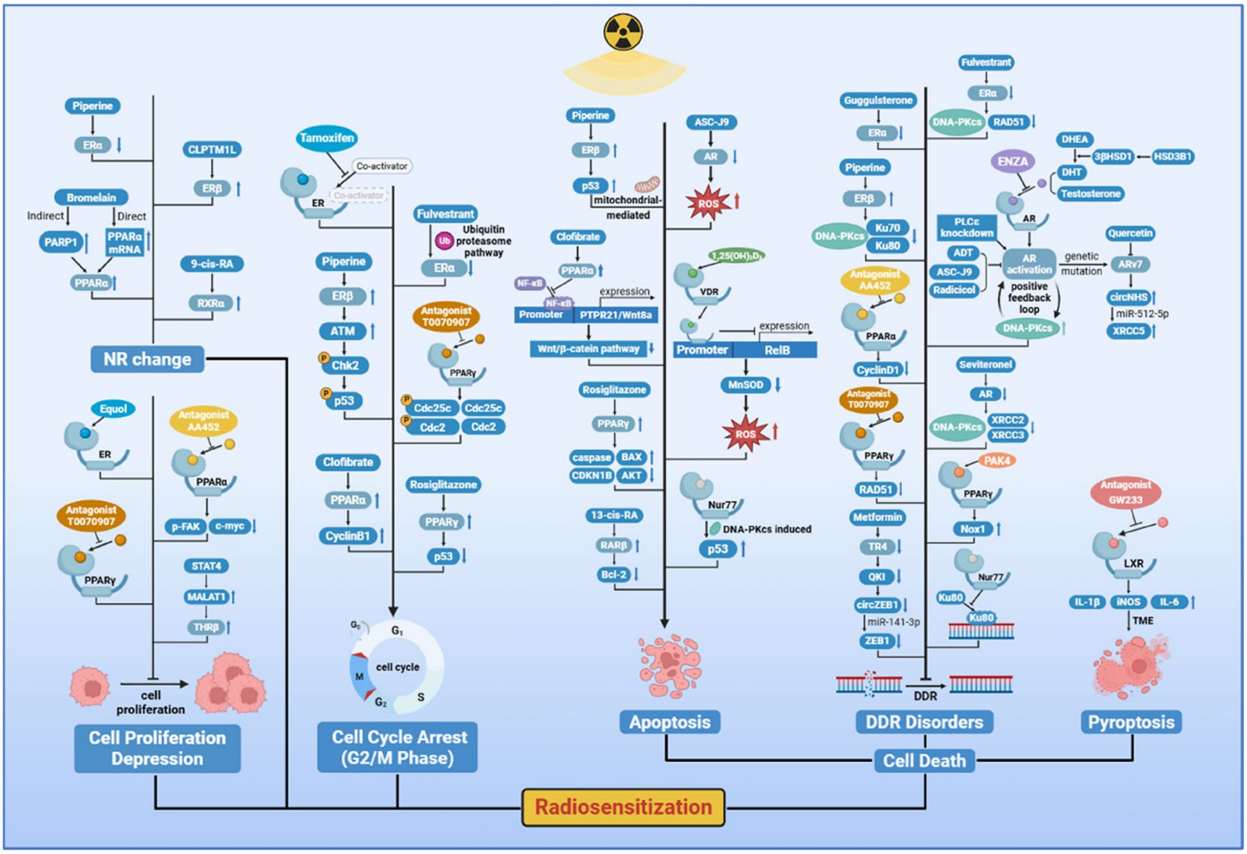

Fig. 4 Mechanisms related to the involvement of nuclear receptors in radiosensitization [67–85, 87–181]. This figure summarizes the molecular mechanisms of radiosensitization involving nuclear receptors in irradiated tumor cells. Radiosensitization is mainly caused by cell proliferation depression, cell cycle arrest (G2/M phase), cell death (DDR disruption, apoptosis, pyroptosis), and NR changes with unidentified molecular mechanisms. ATM, ataxia telangiectasia mutated; BAX, Bcl-2 associated X; Cdc2, cyclin-dependent kinase-1; Chk2, checkpoint kinase 2; DDR, DNA damage response; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; iNOS, inducible nitric oxide synthase; MnSOD, manganese superoxide dismutase; Nox1, NADPH oxidase 1; ZEB1, zinc finger E-box binding homeobox 1. (Created with bioRender.com)

suppressing tumor progression. Synthetic PPAR agonists are mainly substituted thiazolidinediones (TZDs) such as troglitazone, rosiglitazone, pioglitazone, and the CAY family of drugs. These TZDs were initially used orally for the treatment of diabetes, but as studies have expanded in scope, some TZDs have been found to increase tumor radiosensitivity [89]. In human non-small cell lung cancer cells rosiglitazone in combination with γ-irradiation induces apoptosis, with the mechanism involving the downregulation of AKT (protein kinase B,PKB) and cell cycle-dependent protein kinase inhibitor 1B (CDKN1B) expansion and the upregulation of BAX expression [145]. Another study demonstrated that rosiglitazone enhances the radiosensitivity *in vitro* and *in vivo*. Microarray-based experiments suggested the possible differential expression of various genes, including fatty acid binding protein 4 (FABP4) and SLC39 A7 (Zip7) [97]. Rosiglitazone can radiosensitize cells by affecting DNA damage repair, prolonging radiation-induced G2/M-phase blockade, and promoting apoptosis through increased caspase activation. Multiple studies have shown that the effects of rosiglitazone are correlated with p53 levels [98, 145]. Despite not being a PPARγ agonist, p21-activated kinase 4 (PAK4) increases glioblastoma cell radiosensitivity through multiple pathways, including agonizing PPARγ and its target gene *NADPH oxidase 1* (*Nox1*) to regulate DNA damage repair [93, 94]. Nevertheless, this radiosensitizing effect of rosiglitazone may not be related to the expression levels of PPARγ itself [146, 147]. However, several of the studies mentioned above have demonstrated that PPARγ activation is a potential therapeutic strategy to increase tumor radiosensitivity. It is worthwhile to further investigate the clinical utility of rosiglitazone and explore additional agonists that may be of interest.

In addition to PPARγ agonists, PPARγ antagonists also have radiosensitizing effects. T0070907 is a selective

PPARγ antagonist that regulates the interaction between PPARγ and its cofactors by affecting the conformation of helix 12 of the LBD in PPARγ [148]. T0070907 increases tumor radiosensitivity through G2/M blockade and mitotic catastrophe [149]. Studies have revealed that the specific mechanism involves the inhibition of radiation-induced DSB repair via the downregulation of the expression of the key HR protein RAD51 [150]. However, this radiosensitizing effect is not evident in the human cervical cancer HeLa cells, suggesting that the drug may be cell type specific. GW9662, another selective PPARγ antagonist, has a radiosensitizing effect. Docosahexaenoic acid (DHA), which is related to the mechanism of action of GW9662, is radiosensitizing, and low concentrations of DHA have been shown to inhibit γ-irradiation-induced NF-κB activation and sensitize Ramos cells, a highly radiation-resistant and p53-deficient Burkitt lymphoma cell line, to radiation-induced cytotoxicity. The preincubation of Ramos cells with GW9662 has been found to attenuate the PPAR-mediated inhibition of NF-κB by DHA and to reduce the radiosensitizing effect of DHA [151].

Like antagonists, inhibitor of differentiation 3 (ID3) is negatively correlated with PPARγ, and an increase in ID3 inhibits PPARγ expression; the two proteins can form a positive feedback loop in which PPARγ, once inhibited by ID3, further promotes ID3 expression. In turn, an increase in ID3 reduces colorectal cancer radiosensitivity; thus, this loop gradually enhances the malignancy and radioresistance of colorectal cancer cells [152, 153]. Furthermore, the latest research has shown that FLASH radiation reduces PPARγ activity and thus affects lipid metabolism in macrophages, reversing tumor immunosuppression [154]. This suggests that nuclear receptors are associated with the molecular mechanisms of FLASH and are directions worthy of extensive exploration.

In conclusion, owing to differences in tumor types and microenvironments, the expression and activation of PPARs can enhance or inhibit the radiosensitivity of different tumor cells. Therefore, appropriate PPAR agonists or antagonists should be selected according to different types of cells to increase the radiosensitivity of tumor cells. Overall, strategies for radiosensitizing tumor cells to PPARs require further in-depth investigation.

Retinoid X receptor (RXR) and retinoic acid receptor (RAR)

Both RXR and RAR mediate diverse effects of retinoic acid at the molecular level. RXR was the first nuclear receptor to be identified as an endogenous ligand that can form homodimers by itself or heterodimers with other nuclear receptors to participate in various developmental and metabolic signaling pathways. RXR and RAR exist as three main receptor isoforms, α, β and γ. RXRα and RARβ are the two receptor isoforms associated with tumor radiosensitivity [155].

RXRα is one of the three receptor isoforms of RXR; it participates in various pathophysiological processes in the body in the form of homodimers or heterodimers, and plays important roles in the growth and development of hepatocytes, skin, prostate, and adipose tissue. RXRα knockdown is embryonic lethal, and N-terminal-truncated RXRα (tRXRα) overexpression may promote tumor growth by interacting with the PI3 K and NF-κB signaling pathways [156]. RXRα has been found to play a key role in mediating retinoic acid(RA)-induced tumor cell growth inhibition in ovarian cancer cells, and the LBD fragment of RXRα has been shown to have a synergistic radiosensitizing effect with RA [157, 158]. 9-cis-RA was the first discovered natural ligand for RXRα. When cultured with 9-cis-RA, the killing effect of radiation on human prostate cancer DU145 and hPCA9 cells significantly increases, possibly related to the interaction between miR-191 and RXRα; however, the specific mechanism still needs to be explored [159].

RARβ is associated with the retinoic acid-induced differentiation of tumor cells, and its binding to all-trans retinoic acid RA inhibits tumor cell growth [157, 160]. The expression of RARβ has been found to be decreased or absent in various malignant tumors such as non-small cell lung cancer, breast cancer and prostate cancer, an effect that may be related to the aberrant methylation of the gene promoter [85, 161, 162].

Retinoic acid, 13-cis-retinoic acid (13-cis-RA) and interferon-alpha2a (IFNα) have been shown to induce radiosensitization in some cancer cell lines, and this selectivity may be related to the differential expression of RARβ. Studies have shown that RARβ is highly expressed in the radioresistant head and neck cancer squamous cell line UMSCC-11B and human cervical cancer cell line ME-180 and mediates the effects of the above radiosensitizers; the mechanism of action may be related to the upregulation of the expression of the Bcl-2 gene [163, 164].

Liver X receptor (LXR)

LXR was originally isolated from a human liver cDNA library around 1995 and received its name because its mRNA expression was highest in the liver [165]. LXR consists of two isoforms, α and β, which share 77% homology [95]. LXRα is highly expressed in tissues related to lipid metabolism, and LXRβ is expressed at low levels in a wide range of tissues. LXR was initially recognized as an orphan nuclear receptor but was later identified as an oxysterol-activated transcription factor involved in the regulation of cholesterol, inflammatory responses, and a variety of biological processes in macrophages [96, 166].

The expression of the intracellular M1-type macrophage markers interleukin 1β (IL-1β), inducible nitric oxide synthase (iNOS), and interleukin 6 (IL-6) increased after the combination of the LXR antagonist GSK1440233 A (GW233) and γ-rays in murine-derived primary bone marrow-derived macrophages. This suggests an increased pro-inflammatory effect of the cells and alterations in the TME, which reduces cell viability by increasing cellular pyroptosis [167]. In addition, ingenuity pathway analysis (IPA) showed that the activation of the LXR/RXR pathway is associated with the development of a variety of tumors and that the expression of its target gene, fatty acid synthase (FASN), was highly upregulated in a radiation-resistant cell line, rSCC-61, suggesting that this pathway may be associated with radiation response [168].

Thyroid hormone receptor (THR)

In 1986, THR was first isolated and described by Weinberger and Sap [99, 169]; it exists in all vertebrates and has two isotypes, α and β. In general, THR binds to thyroid hormones to regulate physiological processes such as cell growth, differentiation, and metabolism [170]. Subsequent, studies have shown that THR mutations, expression downregulation, expression loss and abnormal localization occur in a variety of tumor tissues [171]. In research, wild-type THRβ overexpression in MCF-7 and ARO cells, i.e., a human breast cancer cell line and anaplastic thyroid carcinoma cell line with low THR expression, was shown to improves the radiation sensitivity of cells by inhibiting cell proliferation and promoting cellular senescence [172]. Recent studies have revealed that the transcription factor signal transducer and activator of transcription 4 (STAT4) inhibits miR-21-5p and increases THRβ levels through the transcriptional activation of MALAT1 (metastasis associated lung adenocarcinoma transcript 1), thereby increasing breast cancer cell radiosensitivity [173].

Orphan nuclear receptors and radiosensitivity

Neuron-derived clone 77 (Nur77)

Nur77 (also named as NR4 A1, TR3, NGFI-B, TIS1 and NAK-1) is nuclear receptor subfamily 4 group A member 1; it plays a critical role in glucose homeostasis, apoptosis, cancer, atherosclerosis, endothelial dysfunction and inflammation [174]. A previous study demonstrated two mechanisms by which Nur77 affects sensitivity to radiation therapy in hepatoma cells: Nur77 inhibits the binding of Ku80 and DNA ends to inhibit DNA damage repair, and Nur77 enhances apoptosis by acting as a phosphorylation substrate for DNA-PK to promote DNA-PK-induced p53 activity [175]. Although it does not yet have a definitive ligand [176], Nur77 can still serve as a potential target for tumor radiotherapy [177]. Thus, we suspect that upregulated Nur77 expression could be beneficial for the treatment of radioresistant tumors.

Testicular nuclear receptor 4 (TR4)

TR4, also called NR2 C2, was first cloned from human and rat hypothalamus, prostate, and testis cDNA libraries in 1994, and is relatively highly expressed in the above sites, where it regulates a variety of physiological processes and plays a key role in the development of prostate cancer [178–180]. Subsequent studies revealed that TR4 expression increases in response to radiation in prostate cancer cells and tissues. The radioresistance of prostate cancer cells is compromised after the inhibition of TR4, which is associated with DDR regulated by RNA binding protein quaking (QKI)/circZEB1/miR-141-3p/ZEB1 signaling pathway [181].

Nuclear receptor subfamily 1 group D member 2 (REV-ERBβ)

REV-ERBβ, also called NR1D2, is a variant of NR1D1 (also named REV-ERBα) and one of the components of the heme-binding biological clock. This receptor has also been implicated in physiological and pathological processes such as cell motility, circadian rhythms, and tumorigenesis and progression [86, 185, 186]. In melanoma, LINC01224 promotes tumorigenesis and confers radioresistance by upregulating the miR-193a-5p/REV-ERBβ axis. The overexpression of REV-ERBβ reverses the enhanced radiosensitization of melanoma cells caused by knockdown of lncRNA LINC01224. Further investigation of the molecular mechanism revealed that LINC01224 acts as a ceRNA and competitively binds to miR-193-5p, which targets REV-ERBβ, thereby positively regulating REV-ERBβ [187]. Thus, inhibiting the expression of REV-ERBβ may be an effective strategy to sensitize tumor cells to radiotherapy.

Nuclear receptors and the protection of normal tissues from radiation

In addition to their radiosensitizing role in various cancer cells, several nuclear receptors, including PPAR, VDR, LXR, Nur77, Nurr1 and steroid receptor co-activators, have been reported to confer radioprotection in normal tissues.

PPAR

PPARα

Whole brain irradiation (WBI)-induced microglial activation can lead to cognitive impairment. *In vitro* and *in vivo* experiments have shown that fenofibrate significantly inhibits the radiation-induced proinflammatory response of microglia through the activation of the PPARα receptor, thus preventing whole-body radiation-induced brain damage, and that this effect may be mediated through the negative regulation of the NF-κB and activating protein-1 (AP-1) pathways [188, 189]. In addition, FABP4 overexpression reduces radiation-induced ROS, and the proximal promoter of FABP4 contains three binding sites for PPARα; thus, fenofibrate can stimulate the transcription of FAPB4 in cells by increasing the expression of PPARα, thereby attenuating the oxidative damage caused by radiation to the skin [190]. Finally, *in vitro* experiments and animal models have demonstrated that PPARα activation by fenofibrate ameliorates radiation-induced skin damage, which can be exacerbated by PPARα deficiency [191].

PPARγ

In mice irradiated with 6 Gy γ-irradiation and co-administered 1,25-dihydroxy vitamin D3 (1,25-$(OH)_2D_3$) before and after irradiation, radiation-induced myeloid adipogenesis was significantly inhibited by downregulating the expression of PPARγ compared to irradiation alone, thereby protecting the bone marrow [192].

VDR

On the dorsal skin of rats irradiated with 20 Gy γ-rays and pretreated with vitamin D3, the number of hair follicles inside and outside the irradiated area was not significantly different, whereas the difference in the untreated group was significant. Moreover, the skin of the mice pretreated with vitamin D3 showed stronger immunoreactivity to VDR, indicating that vitamin D3 acts through VDR to reduce hair follicle radiotoxicity [193]. Additionally, VDR has been shown to be associated with radiation-induced bowel injury. VDR activation alleviates radiation-induced damage to intestinal epithelial tissue and promotes cell proliferation through regulation of the expression of apoptotic proteins. A screening of differential genes regulated by VDR indicated that it may act by targeting the hypoxia-inducible factor (HIF)/pyruvate dehydrogenase kinase 1 (PDK1) pathway [194].

LXR

In culturing immortalized murine bone marrow-derived macrophages cultured with the LXR synthetic agonist GW3965, there was a 20% increase in the survival of wild-type cells compared with LXR gene double-subtype knockout cells after irradiation, suggesting that high LXR expression alleviates radiation-induced damage to macrophages [166].

Nur77

Nur77 may also be protective against radiation in normal tissues. Single-cell RNA sequencing of skin samples from radiation-damaged mice and patients suffered from ionizing radiation, revealed that the orphan nuclear receptor Nur77 is highly expressed in fibroblasts and mediates radiosensitization through apoptosis. Nur77 knockout mice present more severe damage after irradiation than do wild-type mice, suggesting that Nur77 plays a role in the protection of normal tissues [195].

Nurr1

The downregulation of the expression of Nurr1 (also known as NR4 A2), a member of the nuclear receptor 4 A subfamily, promotes the migratory inhibition of mast cells after exposure to low doses of ionizing radiation (less than 0.5 Gy). This finding implies that Nurr1 plays a pivotal role in mitigating the damage caused by ionizing radiation through immune modulation mechanisms [196].

Steroid receptor coactivator

As mentioned previously, steroid receptors trigger the transcription of their target genes by enlisting coactivators to commence the process. Although some coactivators such as CLPTM1L and Hsp90, whose role in relation to cellular radiosensitization has been mentioned previously, increase tumor cell radiosensitivity [108, 126], another series of studies revealed that steroid receptor coactivators may affect normal tissue radiotoxicity. Steroid receptor coactivator-3 (SRC-3, also called NCOA3, ACTR, p/CIP, RAC3 or TRAM-1) is a member of the SRC family and plays a role in processes such as growth and development, carcinogenesis and immunity [197, 198]. *SRC-3* knockout mice with 4.5 Gy total body irradiation of γ-rays results in a significant increase in apoptosis in bone marrow mononuclear cells, compared with wild-type mice, suggesting that SRC-3 may be a potential target for the radioprotection of hematopoietic cells [199–202]. Another study revealed that radiation increases the mRNA and protein levels of nuclear receptor coactivator 4 (NCOA4), and that the knockdown of NCOA4 in human intestinal epithelial (HIEC) cells significantly inhibits ferritin reduction, decreases the intracellular free iron level, and attenuates radiation-induced iron death [203]. We believe that further studies on the response of nuclear receptors to radiation in normal tissues have implications for radiation protection and radiotherapy dose adjustment, among other applications.

Perspective and conclusions

Drug-related advances

Translating theoretical research into effective treatments for patients is an issue that must be addressed. Therefore, research related to drugs that target nuclear receptors, including the development of better drug delivery methods and more effective drugs, is needed. Although nuclear receptors can increase radiosensitivity in many tumors, nuclear receptors are not tumor-specific and exist in many normal tissues. Therefore, if nuclear receptor agonists or inhibitors are to be used as radiosensitizing drugs, their targeting should be enhanced, and drug delivery efficiency should be increased. Such approaches could include the use of tumor biomarkers, the coupling of specific antibodies to drugs to better target tumors, and the application of nanotechnology delivery systems to minimize off-target effects and increase bioavailability. The integration of nanoscale delivery systems with self-assembly technologies has enabled efficient and targeted drug delivery, but there are still dilemmas such as systemic toxicity and susceptibility to *in vivo* recognition and clearance [204]. Most of the current drugs that target nuclear receptors are classical ligand-binding pocket agonists and antagonists, whereas newer drugs such as PROteolysis TArgeting Chimera (PROTAC), degrade the proteasome of ubiquitinated nuclear receptors by simultaneously binding E3 ubiquitin ligases and nuclear receptors. These drugs have the advantages of being less susceptible to competing endogenous ligands, being able to overcome feedback upregulation of drug target expression, and being able to target orphan receptors with unspecified ligands [205].

More exploration of nuclear receptor functions

Some nuclear receptors have other functions, such as regulating inflammation and mitochondria-associated apoptosis. For example, Nur77 binds directly to the protein p65, preventing it from binding to the κB element, while the phosphorylation of p38a can antagonize this effect; thus Nur77 regulates the inflammatory response through a balance of the actions of these two molecules [206]. In addition, recent studies have revealed that Nur77 can enter the mitochondria of tumor cells and that ligand binding activates the Nur77/Bcl-2 pathway, inducing the translocation of Nur77 from the nucleus to the mitochondria and leading to mitochondria-associated apoptosis [207]. Therefore, further exploration of the function of nuclear receptors is needed, and analyzing the structure of nuclear receptors in complex with other families of proteins may provide new perspectives for drug design targeting nuclear receptors.

Functional compartmentalization is an important factor in the regulation of multiple responses in cells. In recent years, nuclear receptors and other factors containing intrinsically disordered regions (IDRs) composed of low-complexity amino acid sequences (proline, lysine, arginine, etc.) can be compartmentalized without membranes through weak protein–protein interactions, a process known as liquid–liquid phase separation (LLPS) [208]. Several nuclear receptors, such as AR, GR, and RXRγ, interact with mediator through LLPS and participate in transcriptional regulation and gene expression [209–213]. For example, the phase separation of AR affects the development of prostate cancer. The phase separation of Nur77 is involved in mitochondrial autophagy, indicating that the phase separation of nuclear receptors is closely related to their functions [214–216]. On this basis, whether the phase separation ability of nuclear receptors can be targeted to promote or disrupt their functions to treat diseases is a new research direction with potential significance.

Conclusions

Radiotherapy plays an extremely important role in the treatment of tumors. To effectively control tumors, reduce the toxic side effects on normal tissues, and improve the long-term quality of life of patients, exploring safe and effective radiation sensitization strategies is highly valuable. Nuclear receptors targeting combined with ionizing radiation can increase the radiosensitivity of tumor cells through various mechanisms, such as cell cycle blockade, the enhancement of the apoptosis-inducing effect of radiation on tumor cells, the inhibition of the radiation-induced DNA damage response, and improvements in the TME, which can promote the killing of tumor cells by ionizing radiation. Some nuclear receptors are involved in damage to normal tissues after exposure to ionizing or ultraviolet radiation; therefore, the activation or inhibition of the action of nuclear receptors may protect normal tissues.

To date, a number of nuclear receptor-based drugs (including ER, AR, LXR, RXR, PPAR and GR) have entered different stages of clinical trials for cancer patients, as summarized by Yang, Z., et al. [217]. These drugs include selective ER modulator bazedoxifene for patients with ductal carcinoma (NCT02694809), selective AR degrader ARV-110 against metastatic castration-resistant prostate cancer (CRPC) (NCT03888612), LXR agonist RGX-104 treating patients with advanced solid malignancies and lymphoma (NCT02922764), RXR agonist bexarotene treating patients with relapsed or refractory cutaneous T cell lymphoma (NCT01134341), PPAR agonist pioglitazone against pancreas cancer (NCT01838317) and GR antagonist relacorilant in combination with nab-paclitaxel in patients with solid tumors (NCT02762981) [217].

In addition, clinical studies of these drugs in combination with radiotherapy for patients have been reported, such as tamoxifen in combination with radiotherapy to reduce local recurrence after breast-conserving surgery, dexamethasone and whole-brain radiotherapy (WBRT) to treat brain metastases from NSCLC, and enzalutamide in combination with radiotherapy to treat intermediate- to high-risk prostate cancer [218–221]. Novel nuclear receptor agonists and inhibitors are expected to be used in the future to sensitize clinical tumors to radiotherapy. There is still a lack of research on and understanding of the role of nuclear receptors in tumor radiosensitivity, and it is believed that with an increase in research, the role of nuclear receptors in tumor radiosensitization will be better understood, providing new targets and strategies for cancer treatment.

Abbreviations

3βHSD1	3β-Hydroxysteroid dehydrogenase 1
AR	Androgen receptor
ASC-J9	Dimethylcurcumin
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3-related
BAX	Bcl-2 associated X
Bcl-2	B-cell lymphoma-2
Cdc2	Cyclin-dependent kinase-1
Cdc25c	Cell division cyclin 25 homolog C
CDKN1B	Cycle-dependent protein kinase inhibitor 1B
CHK1	Checkpoint kinase 1
CHK2	Checkpoint kinase 2
CLPTM1L	Cleft lip and palate transmembrane 1-like
CRPC	Castration-resistant prostate cancer
CTD	Carboxy-terminal structural domain
DAX1	Dosage-sensitive sex transition syndrome adrenal hypoplasia gene on the X chromosome, gene 1
DBD	DNA-binding structural domain
DDR	DNA damage response
DHA	Docosahexaenoic acid
DHEA	Dehydroepiandrosterone
DHT	5α-Dihydrotestosterone
DNA-PKcs	DNA-dependent protein kinase catalytic subunit
DSBs	Double-strand breaks
E2	Estradiol
ER	Estrogen receptor
ERR	Estrogen-associated receptor
FABP4	Fatty acid binding protein 4
FAK	Focal adhesions kinase
FXR	Farnesol X receptor
GR	Glucocorticoid receptor
HNF4α	Hepatocyte nuclear factor 4α
HR	Homologous recombination
HREs	Hormone response elements
HSD3B1	Hydroxy-δ-5-steroid dehydrogenase, 3 β- and steroid δ-isomerase 1
HSPs	Heat shock proteins
ID3	Inhibitor of differentiation 3
IL-1β	Interleukin 1β
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
LBD	C-terminal ligand-binding domain
LRH1	Hepatic receptor homology 1
LXR	Liver X receptor
MALAT1	Metastasis associated lung adenocarcinoma transcript 1
MnSOD	Manganese superoxide dismutase
MR	Mineralocorticoid receptor
NF-κB	Nuclear factor kappa B
NHEJ	Non-homologous end joining
Nox1	NADPH oxidase 1
NR	Nuclear receptor
NSCLC	Non-small cell lung carcinoma
NTD	Amino-terminal domain
NUR77	Neuron-derived clone 77
NURR1	Nuclear receptor-associated protein 1
PAK4	P21-activated kinase 4
PCa	Prostate cancer
PDGF D	Platelet-derived growth factor D
PLCε	Phospholipase Cε
PPAR	Peroxisome proliferator-activated receptor
PR	Progesterone receptor
QKI	Quaking
RA	Retinoic acid
RAD51	RAD51 recombinase
RAR	Retinoic acid receptor
REB	Relative biological effect
REV-ERBα	Nuclear receptor subfamily 1 group D member 1
REV-ERBβ	Nuclear receptor subfamily 1 group D member 2
RIREs	Radiation-induced rescue effects
RXR	Retinoic acid X receptor
SERM	Selective estrogen receptor modulator
SHP	Small heterodimeric chaperone receptor
SRC-3	Steroid receptor coactivator-3
SSBs	Single-strand breaks
STAT4	Signal transducer and activator of transcription 4
THR	Thyroid hormone receptor
TME	Tumor microenvironment
TR2	Testosterone receptor 2
TR4	Testicular nuclear receptor 4
TZDs	Thiazolidinediones
VDR	Vitamin D receptor
XRCCs	X-rays repair cross-complementary proteins
ZEB1	Zinc finger E-box binding homeobox 1

Authors' contributions

S.Z. conceptualized and revised the manuscript. Y.G. participated and edited manuscript. X.M. and X.L. drafted the manuscript. All authors reviewed the manuscript and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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