Role of Nuclear Receptors in Esophageal Cancer

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Esophageal cancer (EC), an aggressive and poorly understood disease, is one of the top causes of cancer-related fatalities. GLOBOCAN 2020 reports that there are 544,076 deaths and 604,100 new cases expected worldwide. Even though there are various advancements in treatment procedures, this cancer has been reported as one of the most difficult cancers to cure, and to increase patient survival; treatment targets still need to be established. Nuclear receptors (NRs) are a type of transcription factor, which has a key role in several biological processes such as reproduction, development, cellular differentiation, stress response, immunity, metabolism, lipids, and drugs, and are essential regulators of several diseases, including cancer.

esophageal cancer nuclear receptors agonists antagonists

1. Introduction

Esophageal cancer (EC) is an aggressive and poorly understood disease that remains one of the leading causes of cancer-related deaths around the world [1][2]. This cancer is fundamentally resistant to systemic therapy due to morphological, molecular, and etiological heterogeneity [3]. Even though there are various advancements in treatment procedures, this cancer has been reported as one of the most difficult cancer to cure, and a favorable prognosis is only possible in the pilot stages [4]. EC is one of the most common types of cancer in people; GLOBOCAN 2020 estimated 604,100 new cases and 544,076 fatal cases worldwide [5].

2. Nuclear Receptors in Esophageal Cancer

2.1. Androgen Receptors (ARs)

AR is a ligand-activated TFs in the steroid receptor family [6]. Growth factors, natural hormones, peptides, and synthetic compounds are all examples of ligands that can activate these receptors [6]. The AR is found in skeletal muscle, the prostate, the testes, the uterus, the breast, and other tissues [7]. The AR gene, which is 90 kb in size and situated on the X chromosome, is coded by eight exons [8]. Different domains in the AR include the N-terminal domain (NTD), DNA-binding domain (DBD), and ligand-binding domain (LBD). The least homologous section of the AR is its N-terminal region (amino acids 1–559), with less than 15–20% similarity among the class I members. AF-1, crucial for AR activity, is present in the NTD [9]. AR's AF-1 contains all of AR's phosphorylation sites except for three and is a target for several growth factors that phosphorylate the sites and activate the AR ligand on their own

[10][11]. The DBD helps the AR to bind to the androgen Response Elements (ARE) in the regulatory regions of androgen-responsive genes. The DBD contains two zinc finger motifs necessary for DNA binding and dimerization and is highly conserved among receptors. The DBD and LBD's lysine-rich hinge regions are essential for the nuclear localization of the receptor [12]. The AR's LBD is responsible for ligand binding, is only minimally conserved among receptors, and contains AF-2, which is required for full receptor activation in the presence of ligand [6]. AF-2 refers to residues in the LBD that are implicated in transcription control. In a hormone-dependent way, this region of the AR recruits a set of coregulatory proteins known as p160 coactivators (e.g., steroid receptor coactivator-1 (SRC-1)) [13]. Interestingly, it was reported that AR is implicated in the development and progression of various cancer types, including prostate, breast, ovarian, etc. [14][15][16][17][18]. Therefore, AR's expression and function are often investigated in cell lines and tumor specimens. However, the role of AR expression and function in the development and progression of EC is still poorly understood.

Increasing lines of evidence suggest that AR and AR responsive are highly overexpressed and activated in EC and controls the survival and prognosis of patients. For example, a study in 40 ESCC tumor tissues demonstrated high levels of AR expression in invasive ESCC tissues. In addition, it is also showed that the knockdown of the KYSE450 EC cell line with AR shRNA decreased the expression of AR, cell invasion, pAkt, and matrix metalloproteinase 2 (MMP2) [19]. Another clinical study showed high expression of AR in tissues from tobacco using ESCC patients compared with normal esophageal squamous tissues. Besides, higher expression of AR was also observed in the EC109, EC9706, HKESC-2, and TE-12 EC cell lines. Moreover, the inhibition of AR by shRNA reduced cell viability, cell growth, colony formation, anchorage-independent growth, and the S and G2/M phase. In addition, in mice with various androgen status, the overexpression of AR enhanced tumor growth. Further, AR promotes interleukin 6 (IL6), a common AR target gene in ESCC, transcription by binding directly to the IL6 promoter, and IL6 can then activate AR expression. Furthermore, prominent levels of AR and IL6 expression in human ESCC predict a worse clinical outcome in tobacco users [20]. Another clinical study demonstrated that AR gene expression was substantially higher in normal squamous epithelium than in esophageal adenocarcinomas [21]. According to another study, higher levels of dihydrotestosterone (DHT) inhibited the proliferation and cell division, induced cell cycle arrest and cell senescence and also altered androgen-responsive genes in OE33-AR, JH-AR, and OE19-AR EAC cell lines [22]. In addition, another study showed an increase of FK506-binding protein 5 (FKBP5), which is an androgen-responsive gene in AR-transduced OE33 cells (OE33-AR) [23]. Taken together, these findings demonstrated the significance of AR in the development and spread of EC, and additional research is required to identify the potential use AR as a therapeutic target in EAC and ESCC.

2.2. Estrogen Receptors (ERs)

Estrogen receptors (ERs) belong to the NR superfamily, which also comprises receptors that mediate the effects of thyroid hormones, steroid hormones, retinoids, and vitamin D [24]. ERs, similar to other steroid receptors, primarily serve as ligand-inducible TFs that bind chromatin at specific response regions as homodimers [24]. To interact with estrogen response elements (EREs) or other TFs, ERs dimerize and move to the nucleus, where they interact with them. This causes the recruitment of coregulatory proteins (coactivators or corepressors), an increase or decrease in mRNA levels and associated protein synthesis, as well as physiological responses [25][26][27]. The ligand-induced

transcriptional activity of ER is mediated by two distinct activation functions, AF-1 and AF-2 [25][26][27]. ERs, similar to other members of the NR family, have structurally and functionally different domains. The DNA recognition and binding are carried out by the C or DNA-binding domain (DBD), which is the protein's central and most conserved domain, while the COOH-terminal multifunctional D/E/F or ligand-binding domain (LBD) is responsible for ligand binding. The NH2-terminal or A/B domain is the least conserved and has the greatest variation in sequence and length [28][29]. Based on sequence homology with other receptors, the domains in the receptor have been split into six regions, A-F. Exon 1 codes for the N-terminal domain (regions A and B), exons 2 and 3 for the DNA-binding domain (region C), exon 4/hinge region (region D), and exons 5-8 for the hormone binding domain (regions E and F) [30]. ERs are divided into two subtypes: estrogen receptors *α* (ER*α*, also known as ER1 or ESR1) and estrogen receptors *β* (ER*β*, also known as ER2 or ESR2), which are encoded by the estrogen receptor 1 (ESR1) and 2 (ESR2) genes, respectively. They are members who belong to the NR superfamily and carry out a range of biological processes [25][31][32].

In humans, ER*α* and ER*β* play a critical role in the control of various intricate physiological processes. A multitude of disorders is linked to abnormal ER signaling, including cancer, metabolic and cardiovascular disease, neurodegeneration, inflammation, and osteoporosis [33][34][35]. For years, scientists have known that estrogen and its receptors play a critical role in cancer development [36]. Multiple investigations using esophageal tissues and various cell lines have demonstrated higher expression of both ER*α* and ER*β* at variable levels, pointing to the significance of ER in the development of EC. For example, a recent study on EC has proved that apart from typical risk factors, the hormonal environment may play a crucial role in EC development [37]. Studies have demonstrated that positive ER*α* expression in combination with negative ER*β* expression is an unfavorable independent prognostic predictor in ESCC [38][39]. In tumor tissues, the expression of ER*β* is higher in AC and poorly differentiated SCC, and it increases with tumor stage and dedifferentiation. As a result, ER*β* seems to be a sign of poor biological function, dedifferentiation, or a more advanced stage of disease [40]. Further studies on ESCC tissues showed that the levels of ER*α* and ER*β* were inversely connected, and the downregulation of ER*α* and the overexpression of ER*β* could indicate a poor prognosis [41]. Another study has demonstrated that the different isoforms of ER*β* (ER-B1, ER-B2, ER-B3, and ER-B5) were shown to be overexpressed in EA tissues and suggests a possible role of antiestrogens in the treatment of EA [42]. Interestingly, it was noted that in EC cells, estrogen ligands such as 17*β*-estradiol and selective estrogen receptor modulators (SERM) inhibited cell proliferation. The amount of anti-growth effects caused by receptor agonists was proportional to the quantity of ER expression in the cell lines. Therefore, this research revealed that selective ER ligand treatment in EC and BE cells results in decreased cell growth and induced apoptosis [43][44]. In a distinct study, 1, 3, 5-tris (4-hydroxyphenyl)-4-propyl-1H-pyrazole (PPT), an ER*α* agonist, was shown to reduce the number of ECGI10 + ER*α* cells. Moreover, estradiol significantly increased the cell proliferation of ECGI10 + ER*β* cells, and the addition of ICI 182780 dramatically reduced estradiol-mediated cell proliferation. In conclusion, the findings unequivocally show that the presence of ER*β* was strongly correlated with poor prognosis in ESCC, possibly by affecting the proliferation of carcinoma cells [45]. Another study showed that the ER system contributes to the spread of EC, and a highly selective ER*α* antagonist (MPP) and an ER*β*-specific antagonist (PHTPP) elicited a concentration-dependent reduction in proliferation in EC cell lines. In addition, caspase 3/7 activity was significantly elevated in OE33 cell lines treated

with MPP and PHTPP, and there was an increase in LDH activity in the presence of MPP-treated OE-33 cell lines [46]. However, a recent study showed that 17β-E2 inhibited the proliferation of human EC109 ESCC cells in a dose-dependent manner, which was inhibited by the ER antagonist ICI 182,780. Additionally, 17β-E2 significantly increased the release of intracellular Ca^{2+} and the entry of extracellular Ca^{2+} into ESCC cells, which was also inhibited by the ER antagonist IC1 82,780. When combined, it is showed that estrogen inhibits the proliferation of human ESCC cells, most likely via the ER-Ca^{2+} signaling pathway and it could a reason for the male predominance of ESCC [47]. In conclusion, it is evident that in a vast majority of cases of EC, ERs are markedly overexpressed and play a critical role in cell survival. Moreover, ES cancer cell invasion, migration, and proliferation have all been demonstrated to be inhibited by ER targeting, which also causes apoptosis. Additionally, the development of particular ER modulators would help in the prevention and treatment of ESCC patients.

2.3. Farnesoid X Receptors (FXRs)

The farnesoid X receptor (FXR) is a ligand-activated TF that belongs to the family of the NR, which is also classified as a nuclear bile acid (BA) receptor [48]. BAs operate as powerful endogenous ligands for FXR activation in the body [48]. FXR is a common receptor present in the intestine and liver that regulates bile acid, glucose, lipid metabolism, and energy balance to aid in maintaining systemic metabolic equilibrium [48][49]. FXR is encoded by the NR1H4 gene and controls the activities of several organs, including the brain, breast, cardiovascular system, gut, kidney, liver, and pancreas. As a result, FXR has become a popular therapeutic target for a wide range of disorders [48][49]. FXR detects physiologic and pathological metabolic changes and alters by regulating the transcription of genes related to cholesterol, fatty acid (FA), glucose, and amino acid balance. FXRα (NR1H4) and FXRβ (NR1H5) are two FXR genes that have been discovered, and the FXRα gene encodes four physiologically active versions (FXRα1, α2, α3, α4) as a result of several promoters and RNA splicing [50][51]. FXRα1/α2 and FXRα3/α4 are expressed at equal levels in the liver, whereas FXRα3/α4 isoforms are mostly expressed in the gut [52]. FXR binds to DNA (i.e., FXR response elements) as a monomer or as a heterodimer with the retinoid X receptor (RXR), another ligand-activated TF [51]. The N-terminal ligand-independent transcriptional activation AF-1 domain, DBD, a hinge region, and the C-terminal LBD comprising a transcriptional AF-2 comprises the structure of FXR, which is the same as the typical NR structure [53]. The hinge region sequence and the length of the AF-1 region differ between the four FXR isoforms. FXR agonists bind to the pocket produced by LBD, promoting its binding to FXR response regions in downstream target genes, which stimulates transcriptional activation [54].

According to recent research, FXR overexpression has been linked to the development and progression of breast, lung, pancreas, and esophageal malignancies. It has also been linked to tissue and cell-specific involvement in a variety of malignancies. It was also noted that FXR is strongly expressed in esophagitis, BE, and EAC [55]. For example, a study has demonstrated that FXR is overexpressed in BE, and guggulsterone, an FXR antagonist, significantly enhances apoptosis in a human BE-derived cell line which implies that FXR may play a role in apoptosis regulation [56]. According to another similar study, the suppression of FXR with FXR shRNA or guggulsterone reduced tumor cell survival and metastasis and induced apoptosis in vitro, as well as decreased EC growth in nude mice xenografts [57]. Another study demonstrated that, FXR was expressed in GERD tissues, and the level of expression has greatly increased in esophagitis [58]. In addition, the same study showed that FXR and

basal TLR2 expression were linked, and TLR2 and FXR were significantly elevated during reflux esophagitis [58]. On the contrary, an in vitro and in vivo investigation has reported that the activation of FXR performs an antitumor role in the ESCC. FXR activation by its ligand GW4064 inhibited the ERK1/2 pathway and cell growth, increased apoptosis, and caused cell cycle arrest in ESCC cells. Further, the FXR ligand GW4064 reduced the growth of ESCC in a mouse xenograft model [59]. Altogether, it was identified that FXR could be a potential target for the management of ESCC.

2.4. Peroxisome Proliferator-Activated Receptors (PPARs)

Peroxisome proliferator-activated receptors (PPARs) are fatty acid-activated TFs, which belong to the nuclear hormone receptor superfamily, that control energy metabolism. PPAR*α* (NR1C1), PPAR*γ* (NR2C2), and PPAR*δ* (NR3C3) (also known as PPAR*β*) are the three PPAR subtypes that have been discovered so far [60][61][62][63][64][65]. All PPARs, which have four functional domains termed A/B, C, D, and E/F, share the fundamental structural characteristics of the majority of NRs. The PPAR is phosphorylated by the ligand-independent AF-1 in the N-terminal (A/B) domain [66]. PPARs bind to the peroxisome proliferator response element (PPRE) in the promoter of PPAR target genes, and this interaction is mediated by the two-zinc fingered conserved core DBD, also referred to as the C domain. The cofactor docking site is the D domain, and the E domain is also known as the LBD. The E/F domain's ligand-dependent AF-2 mediates the recruitment of PPAR cofactors involved in the transcription processes [66].

PPAR*α* and PPAR*δ* are also expressed in oxidative tissues and control gene expression involved in oxidative phosphorylation (OXPHOS), substrate delivery, and oxidation. PPAR*α* stimulates energy dissipation and is found mostly in the brown adipose tissue (BAT), gut, heart, kidney, liver, and skeletal muscles [67][68]. PPAR*α* influences esterification, fatty acid transport, and oxidation to mediate its actions. PPAR*β*/*δ* is widely expressed and plays a role in fatty acid oxidation as well as blood glucose control. White adipose tissue (WAT) has the highest levels of PPAR*γ* expression, which is largely engaged in energy storage through promoting adipogenesis and lipid synthesis [66]. The PPAR*γ* is expressed mainly in the gut, immune cells, liver, and skeletal muscles [67][69].

The binding of cognate lipid ligands, heterodimerization with another NR (RXR), the interaction of a few transcriptional coactivators, including PPAR coactivator-1 (PGC-1), as well as binding of the complex to PPAR response elements (PPREs) in the promoter of target genes are necessary for PPARs to function as NRs for transcription [69]. PPARs are triggered by several ligands. Eicosanoids and long-chain fatty acids (FAs) are examples of some common endogenous ligands for PPAR*α* and PPAR*β*/*δ*, PPAR*γ* on the other hand, is activated by arachidonic acid metabolites [70][71]. Pioglitazone, GW1929, and GW2090 are anti-diabetic thiazolidinedione (TZD) substances that specifically activate PPAR*γ*, whereas GW501516 is a highly selective PPAR*β*/*δ* ligand [62][72].

The activation of PPAR by ligands has been linked with several malignancies. In vitro investigations on human cancer cells indicated growth-inhibitory effects such as cell-cycle arrest, differentiation, and death induced by PPAR ligands [73]. For example, a study has demonstrated the expression of PPAR*γ* in T. Tn, and EC-GI-10 ESCC cell

lines and revealed the marked growth inhibitory ability of PPAR*γ*-ligands (Troglitazone, Pioglitazone, and 15d-PGJ2) to prevent the growth of human ESCC. Moreover, this effect was evident by the dose-dependent inhibition of deoxyribonucleic acid synthesis and G1 arrest and an increased level of cyclin-dependent kinase inhibitor p27 (Kip1), p21 (Cip1/Waf1), and p18(Ink4c). In addition, troglitazone treatment increased the expression of interleukin-1 alpha in EC-G1-10 cells [74]. Similarly, another study showed that troglitazone, a PPAR*γ*-ligand, treatment in TE-13 cells inhibited the development of human ESCC through G1 cell cycle arrest by increasing p27 expression and induced apoptosis by increasing the expression of Bid, Bax, PARP, and caspase 3 and reducing the expression of cyclin E, MDM2, p16, cytochrome C, caspase 8, and Bcl-XL [75]. Interestingly, another study using 55 primary ESCC tissue samples has shown that the expression level of PPAR*γ* mRNA was decreased in ESCC compared with normal esophageal mucosa, and this was correlated with poor prognosis [76]. Moreover, PPAR*γ* and SIRT1 were substantially expressed in ESCC tissues, but high PPAR*γ* expression was correlated with tumor grading but not with poor prognosis [77]. It was observed that increased tumor growth and poor prognosis were associated with the high expression of SIRT1, a protein that supports cell survival and angiogenesis in ESCC patients. However, SIRT1 expression was positively linked with EGFR but not with PPAR*γ* or survivin [77]. In another study, it was observed that miR-10b was elevated while the expression of PPAR*γ* was downregulated in EC tissues and ESCC cell lines EC109 and TE10, which established that PPAR*γ* is a legitimate miR-10b target. Additionally, miR-10b suppression improved the chemosensitivity of EC cells to DDP in vitro and in vivo, and the overexpression of miR-10b decreased the PPAR*γ*-mediated DDP sensitivity. The Akt/mTOR/p70S6K signaling pathway was also activated as a result of the overexpression of miR10b, and the deactivation of Akt/mTOR/p70S6K by Akt inhibitor (GSK690693) reduced miR-10b-induced DDP resistance in EC cells. Together, these findings show that PPAR*γ* inhibition by miR-10b increased DDP resistance in EC by increasing Akt/mTOR/P70S6K signaling. Moreover, it was observed that after DDP treatment, the activation of PPAR*γ* significantly aided DDP-induced apoptosis in EC109 and TE10 cells. In addition, elevated PPAR*γ* consistently resulted in a rise in Bax levels and a decrease in Bcl2 levels after DDP treatment [78]. Interestingly, lycopene, a natural compound, was shown to suppress NF-*κ*B and COX-2 expression and enhance the protein expression of PPAR*γ* and cleaved caspase 3, which leads to an increase in apoptotic proteins and a decrease in inflammatory cytokines. These findings showed that an effective amount of lycopene could prevent the development of EC in NMBzA-injected F344 rats through potential anti-inflammatory and pro-apoptotic pathways [79]. Another study showed that Da Ea (ethyl acetate extract of *D. altaica*), which has anti-cancer effects, increased PPAR*γ* expression levels, induced apoptosis and S phase cell cycle arrest, which prevented the proliferation of ECA 109 cells [80]. In addition, an in vitro and in vivo study in EC cells and ESO26 cells injected mice treated with T0070907 has demonstrated the transcriptional feedback loop between the PPAR*γ* and the master regulator transcription factors (MRTF) that are particular to EC and fatty acid production. PPAR*γ* overexpression was caused by MRTFs functioning together to promote PPAR*γ* transcription by directly controlling its promoter and a distal EAC-specific enhancer. Moreover,it also shows a decrease in cell proliferation and induced apoptosis in T0070907 treated OE33 AND ESO26 cell lines. In addition, in vivo study has demonstrated a decrease in the expression of FASN, ACC, ACLY, SCD and tumor growth in ESO26 cells injected mice [81]. Another study showed increased expressions of PPAR*γ,* COX-2, HGF, gastrin, and NF-*κ*B activity in BE tissues. Moreover, the increased NF-*κ*B activity is probably linked to increased IL-8 and COX-2 expression [82]. Similarly, in EC tissues, upregulation of PPAR*γ* was observed, and the treatment of EC cell lines with

PPAR*γ* antagonists (T0070907 and GW9662) decreased EC cell adhesion, expression of p-focal adhesion kinase (p-FAK) and pERK and induced apoptosis [83]. Another study has reported the reduced expression of PPAR*γ* in esophageal tumor lesions and proved that ESCC cell proliferation could be inhibited by efatutazone, a PPAR*γ* agonist, by inactivating the PI3K–Akt and MAPK pathways [84]. Interestingly, an in vitro and in vivo study demonstrated that the activation of PPAR*γ* inhibits cancer cell growth in vitro by inducing apoptosis through increasing caspase 3 activity, but systemic PPAR*γ* activation increased the growth of OE33-derived transplantable adenocarcinomas in vivo due to increased cell proliferation [85]. Collectively, these data suggest that PPARs play a critical role in the emergence of EC and might serve as a novel therapeutic target.

2.5. Retinoic Acid Receptors (RARs)

RARs are TFs that belong to the NR superfamily which can have non-genomic effects by triggering kinase signaling pathways that regulate the transcription of RA target genes [86][87]. RARs have a significant role in a variety of physiological processes, including embryonic development and organ homeostasis. RARs also help to regulate gene networks that control cell growth, differentiation, survival, and cell death at the cellular level [86][87]. RARs are divided into three different subtypes: RAR*α*, RAR*β*, and RAR*γ* and each subtype has different isoforms. RAR*β* is divided into four isoforms (*β*1, *β*2, *β*3, and *β*4), each with differing affinities for retinoids and biological roles [88]. The first nuclear RAR in humans, RAR*α* (NR1B1), has a high affinity for ATRA and has preserved the NR modular organization structure. RAR*β* (NR1B2) and the RAR*γ* (NR1B3) are the second and the third RAR gene respectively [86].

RAR's modular structure, which includes many domains and functions, allows them to process both ligand binding and transcription [89]. The transactivation domain, AF-1, is found in the amino terminus (A/B region) and forms a recognition surface for co-activators and other TFs [89]. For DNA recognition, the DBD holds two zinc finger motifs, and the LBD of the family members are highly conserved. It has a ligand-induced activation factor called AF-2, which is important in transcriptional coregulator interactions [89]. RARs can bind to specific enhancer regions in DNA, known as retinoic acid response elements (RAREs) in target gene promoters, after dimerization with RXR, resulting in transcriptional activation of target genes in the presence of ligand [86][90].

Retinoids can induce cell differentiation and inhibit proliferation, which is one of the reasons why they are used to treat cancer [91]. Surfeit numbers of clinical evidence have demonstrated that RAR*β*2 expression is usually inversely linked with tumor grade and frequently lost or epigenetically silenced in human malignancies [88][92]. According to a clinical investigation, the state of squamous differentiation and the increase in RAR*β*-expression are early events connected to EC [93]. Several clinical, in vitro, and in vivo studies have reported the leading role of RARs in the development and growth of EC cells. For example, it was found that expression levels of RAR*α* and RAR*β* increased significantly in the higher stages of Barrett's adenocarcinoma while expression of RAR*γ* was significantly reduced. Therefore, RAR*γ* may have a tumor suppressor role in Barrett's carcinogenesis [94]. In EC cases, RAR*β*2 mRNA expressions were markedly decreased, whereas RAR*β*4 mRNA expression was elevated. Additionally, when compared to normal tissues, tumors had higher expressions of cyclin D1 and EGFR, while lower expressions of RAR*β*1, COUP-TFI (COUP transcription factor 1), and COUP-TFII were observed. Therefore, in

tumor samples, decreased RAR*β*2 expression was linked with increased RAR*β*4 expression and the inhibition of COUP-TFI and COUP-TFII [95]. Another study has proven that RAR*α* was overexpressed in human EC tissues, and further, it was demonstrated that RAR*α* knockdown by siRNA inhibited EC cell proliferation by downregulating proliferating cell nuclear antigen (PCNA), Ki67, MMP7, and MMP9 expression and increased the drug sensitivity to 5-fluorouracil and cisplatin [96]. Benzo-[a]pyrene diol epoxide (BPDE) is found to be an active metabolite of tobacco procarcinogens, and a study has proven that by suppressing RAR*β2* transcription, BPDE reduced RAR*β2* mRNA and protein levels. Moreover, retinoic acid was able to partially block BPDE's inhibitory effect on RAR*β*2 expression while increasing the cell cycle G1 phase. Additionally, BPDE-induced COX-2 expression was linked to RAR*β*2 inhibition. The expression of EGFR, ERK1/2 phosphorylation, c-Jun, and COX-2 were decreased after the RAR*β*2-expression vector was transfected into EC cells. Additionally, there was little change in the expression of c-Jun and COX-2 after co-treatment of RAR*β*2 positive cells with BPDE. These studies have proved that BPDE may cause EC via inhibiting RAR*β*2 [97][98][99]. Another study showed that RAR*β2*'s tumor suppressor function may be linked to its ability to decrease COX-2 expression, which plays a role in carcinogenesis and metastasis, and 13 *cis*-RA mediated activation of RAR*β2* suppressed COX-2 expression, implying that COX-2 inhibition is dependent on RAR*β2* expression. BPDE significantly caused time-dependent methylation of the RAR*β*2 gene promoter in esophageal cancer cells, as well as suppression of EGFR, ERK1/2 phosphorylation, c-Jun, and COX-2 expression. RAR*β*2 expression is decreased by BPDE, and the restoration of RAR*β*2 expression lowers COX-2 protein in esophageal cancer cells, implying that RAR*β*2 plays a significant role in preventing esophageal carcinogenesis [100] [101]. It was also observed that RAR*β* expression was gradually lost, starting with the mildly dysplastic stage of esophageal mucosae. Additionally, the expression of RAR*β* was reduced as a result of the differentiation of esophageal squamous. Further, P53 and Ki67 were accumulated in the later precancerous stage of EC. Resesarchers suggests that the expression of RAR*β*, P53, and Ki67 could be used as biomarkers for early EC diagnosis in high-risk populations [102][103][104]. In ESCC, DNA methylation frequently results in the inactivation of the genes RAR*β*, RAR*β*2, CRBP1, and TIG1, which are linked to retinoic acid signaling, and in contrast, another study revealed that RAR*β*2, p16, MGMT, CLDN3, CRBP, and MT1G were increased in ESCC tissues [105][106]. In mice tumors, 4- nitroquinoline 1-oxide (4-NQO), a carcinogen, inhibited RAR*β*2 but increased the expression of p-ERK1/2, c-FOS, and COX-2 proteins, as well as the methylation of the RAR*β*2 gene promoter. Moreover, it was shown that RAR*β*2 expression was decreased and p-ERK1/2, and COX-2 expression were increased by treatment with 4-NQO in human EC cells in vitro. Moreover, upregulated p-ERK1/2 and COX-2 expression were found in EC tissues, and p-ERK1/2 expressions were linked to a more advanced clinical tumor stage [107]. In addition, it was observed that overexpression of RAR*β*2 induced retinoid receptor-induced gene 1 (RRIG1) and inhibited Erk1/2 phosphorylation and COX-2 expression [108]. Another study showed that the knockdown of DNA (cytosine-5)-methyltransferase1 (DNMT1) in KYSE30 and TE-1 EC cells led to promoter demethylation and RAR*β* overexpression. It is showed that smoking status and low RAR*β* expression were associated with DNMT1 overexpression in esophageal SCC patients. Through the activation of DNMT1 in esophageal squamous epithelial cells, NNK, a tobacco-specific carcinogen, might cause RAR*β* promoter hypermethylation, which ultimately increased cell proliferation and inhibited apoptosis [109]. Another study showed that *N*-(4-hydroxyphenyl) retinamide (4HPR) but not RA suppressed the proliferation of the ESCC cell line EC109 in vitro. In addition, RAR*β*2 induction is correlated with growth inhibition in RA-responsive cells, whereas a failure in RAR*β*2 inducibility is correlated with

RA resistance. These results suggest that 4HPR may operate as a growth inhibitor through direct or indirect interactions with RAR*β*2 [110]. Several clinical studies investigated the methylation status and the expression of the RAR*β*2 promoter area and revealed a significant relationship between RAR*β*2 methylation status and tumor grade. Further, only G2 stage (intermediate grade) tumors showed a link between methylation status and lower expression of RAR*β*2, and its restoration was accompanied by growth inhibition after 5-aza-dc treatment [111][112][113]. Therefore, RARs (*α*, *β*, *γ*) can be targeted and used as markers for the prevention and treatment of both EACs and ESCCs.

2.6. Retinoid X Receptors (RXRs)

Retinoid X receptors (RXRs) are heterodimeric partners of other members of the NR superfamily [114]. There are three types of RXRs: RXR*α*, RXR*β,* and RXR*γ*, all of which are nuclear transcriptional transactivator proteins that bind to DNA and are ligand-dependent [115]. The “permissive” subclass of heterodimers, such as PPAR, LXR, and FXR, is transcriptionally activated by RXR ligands (“rexinoids”) either independently or in conjunction with partner ligands in the “non-permissive” subclass, such as RAR, VDR, and TR [114]. The morphogenesis, development, growth, and differentiation of cells are all regulated by RXR, and its expression is found to be altered in several solid tumors [115]. RXR modulators have therapeutic potential for cancer and other disorders involving the acquisition and disposal of nutrients, such as metabolic diseases [116].

A surfeit number of studies have proven that RXR is essential for the development of EC. For example, in a study, it was demonstrated that the mRNA expression of the three different subtypes of RXR is significantly different in EC tissues and RXR mRNA expression levels may be useful biomarkers for BE and related adenocarcinoma since changes in the mRNA expression of all three RXR subtypes (RXR*α*, RXR*β*, and RXR*γ*) are frequently observed in the development and progression of these diseases [115]. According to another study, EC tissues had higher levels of RXR mRNA and protein than normal esophageal tissues. The level of RXR overexpression was linked to tumor differentiation, TNM stage, and lymph node metastasis in EC patients. Further, EC patients with high RXR expression had considerably worse disease-free survival (DFS) and overall survival rates (OS). Moreover, multivariate analysis showed that the expression of RXR may be a predictor of DFS and OS in EC patients [117]. Another study showed that all six retinoid receptor subtypes, including RXR, were active in the tissues of EC patients. RXR*β* was inversely correlated with patient lymph node metastatic status and was linked with a better clinical outcome across these receptor subtypes. According to these findings, retinoid receptors, particularly, RXRs play significant roles in ESCC and are associated with patient prognosis [104]. Furthermore, another study has revealed that both mRNA and protein of PPAR*γ* and RXR*α* were expressed in ESCC cell lines from the KYSE series. Moreover, EC cell growth was decreased by the PPAR*γ* ligand troglitazone (TRO), and RXR*α* ligand 9-cis retinoic acid (9CRA) administration had a synergistic impact. The combined treatment with TRO and 9CRA, which also markedly elevated the sub-G1 phase, showed that ligand administration was predominantly responsible for inducing apoptotic cell death in EC cells. Additionally, TRO + 9CRA treatment significantly inhibited the growth of tumors implanted in nude mice [118].

2.7. Vitamin D Receptor (VDR)

The vitamin D receptor (VDR) belongs to the NR superfamily and is involved in vitamin D's biological activities [119]. The VDR ligand regulates the expression of many genes involved in calcium/phosphate balance, cellular proliferation and differentiation, and immunological response [119]. VDR is abundantly expressed in cardiomyocytes, vascular endothelial cells, and vascular smooth muscle cells [120]. One of three retinoid X receptors (RXR*α*, RXR*β*, and RXR*γ*) forms dimers with VDR. The VDR homodimer or VDR-RXR heterodimer attaches to vitamin D response elements (VDREs), which are enhancer elements [121]. In combination with the RXR, ligand binding induces VDR nuclear localization and promotes VDR–DNA complexation. Particular VDREs have been discovered in the promoter sequences of genes that are activated or repressed by VDR. Interactions with coregulators are required for VDR-mediated gene regulation (coactivator and corepressor) [122]. The natural ligand of the VDR is 1,25-dihydroxy vitamin D ($1,25(OH)_2D_3$), a hormonal metabolite of vitamin D. VDR enters the nucleus after binding to $1,25(OH)_2D_3$ and forms a heterodimer with retinoid X receptor (RXR), which regulates gene transcription by interacting with response elements in target gene promoters [123].

An N-terminal domain, a conserved DNA-binding domain, a flexible hinge region, and a conserved ligand-binding domain make up VDR's structure [123][124]. The LBD has 12 helices and takes the form of a small, 3D structure when bound to a ligand. Deep inside the receptor, the ligand-binding pocket enables highly selective interactions with natural ligands such as $1,25(OH)_2D_3$ [122].

In a study, it was demonstrated that through a bile acid ligand, VDR plays a role in the early development of EC. Interestingly, it has been shown that in both EAC and columnar cell metaplasia (CCM), VDR expression was considerably higher in male patients than in females. Moreover, VDR amplification was linked to a worse prognosis but not VDR protein expression [125]. However, another study has shown that both JNK1 and VDR were decreased in ESCC epithelial cells in comparison to the normal esophagus. JNK1 and VDR stromal expression also reduced the motility, migration, and proliferation of ESCC cells by blocking signaling pathways involved in proliferation and metastasis. Therefore, stromal JNK1 and VDR function as tumor suppressors in ESCC, and the degree of their stromal expression may affect the prognosis of ESCC [126]. Moreover, it was observed that EAC exhibits VDR expression, and as the tumor dedifferentiates, the expression level of VDR also decreases [127][128]. In contrast, another clinical study has demonstrated that the mRNA expression of VDR was higher in BE tissues compared to the normal squamous epithelium tissues [129]. In addition, it was shown that variable polymorphisms in genes involved in vitamin D metabolism are connected to the probability of reflux-BE-EAC development. In addition, low expression of VDR and CYP27B1 and high expression of CYP24A1 were observed in EAC tumor tissues compared to normal esophageal tissues [130]. Another study showed that claudin-2 was found to be strongly expressed in EAC and ESCC tissues, and its expression was linked to the expression of the bile acid receptors VDR and TGR5 [131]. These studies showed that dysregulation of VDR plays a critical role in the development of EC.

2.8. Other Nuclear Receptors

Several other NRs have also been thoroughly investigated and examined for their crucial function in esophageal carcinogenesis. One such receptor is the pregnane X receptor (PXR, NR1I2), also known as PAR (the receptor

activated by pregnane) and SXR (steroid and xenobiotic receptor), which is the NR super family's archetypal member [132]. Both endobiotics and xenobiotics can activate PXR. PXR's biological function as a major xenobiotic receptor is primarily mediated by its ligand-dependent binding to regulatory gene sequences [133]. The 50 kDa PXR protein is composed of the DBD, the relatively short hinge region, and LBD with AF-1 and AF-2 regions [134]. PXR signaling has also been linked to cancer-related processes such as cell survival, proliferation, angiogenesis, and oxidative stress [135]. It was noted that PXR is associated with the development of EC. For example, a study has reported that PXR is highly overexpressed in BE and EAC patients and revealed their nuclear localization in adenocarcinoma tissues. Furthermore, PXR translocates to the nuclei of adenocarcinoma cells after being stimulated with lithocholic acid. This result, together with the discovery of a link between a PXR polymorphism and BE, suggests that PXR may have a role in esophageal illness prognosis and treatment [136]. Hence, insights into NRs and how they interact with TFs can lead to the discovery of novel drug targets that can be used to treat esophageal carcinogenesis.

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