RXR signaling targeted cancer therapy

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Graphical Abstract

RXR Signaling Targeted Cancer Therapy

dabrafenib-trametinib  
onc-mutation -

9-cis-RA  

RXRα  

PLK1  

promote mitosis  

P13K/AKT  

promote survive  

IKK/NF-κB  

promote CAC progression  

Hx531  

M2 macrophage (immunosuppressive) polarization  

K-80003/CF31/NSC-640358/TRC4/a-Mangostin  

Hx531  

XS060  

K-80003  

CF31  

α-Mangostin  

NSC-640358  

TRC4

Public Summary

- Retinoic X receptors (RXRs) are important nuclear receptors mediating genetic transcriptions.
- Review the comprehensive role of RXR between RXR signaling and oncogenesis.
- Summarize the undervalued rexinoid-related cancer therapy.
- Discuss and propose its great potential in future clinics.
RXR signaling targeted cancer therapy

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INTRODUCTION

Cancer remains a great threatening disease to human life despite a number of breakthroughs made against it.1 The successful discovery of all-trans retinoic acid (RA) therapy against acute promyelocytic leukemia (APL) and the transcriptional working mechanism elucidation aroused the interest of scientists in the RA signaling pathway in cancer. Retinoic X receptor (RXR), which can be activated by endogenous 9-cis-RA, is an important family of nuclear receptors (NRs). RXRs not only act as receptors for 9-cis-RA or form homodimers to regulate the transcriptional activity but also function as heterodimer partners with other NRs, such as RAR, PPAR, LXR, FXR, and thyroid hormone receptor (TR), in terms of molecular functions.2-13 RXRs play roles in various biological processes, such as cell differentiation, proliferation, and apoptosis.2-13 Additionally, RXRs are proven to take part in oncogenesis. The following section focuses on RXR functions in cancer cells and the potential mechanisms.

Classic mechanism: RXR and RAR in cancer.

Initially,RAR involvement was proven in the pathogenetic process of APL, where it forms aberrant fusion proteins, especially with promyelocytic leukemia (PML) protein. Under normal circumstances, PML protein, as a transcriptional co-activator of p53, prevents cells from growing uncontrollably and functions as a tumor suppressor, and RARs plays a critical role in white blood cell maturation. The PML–RARα fusion protein is produced by t(15;17)(q22;q11) chromosomal translocation, which destroys the normal function of PML and RAR, thereby inhibiting differentiation and maturation of promyelocyte and accelerates proliferation, resulting in APL.13 Additionally, RAR is closely related to the carcinogenesis of some solid cancer. RARβ2 was revealed to act as a potential tumor suppressor, whose expression is lost or epigenetically suppressed in different cancer types, including lung, breast, and colon cancer.14 The loss of RARβ2 in cancer cells during growth induces...
Furthermore, another study in 2019 revealed that inhibits tumor proliferation, invasion, and angiogenesis, suggesting its and p16, while it is reduced in cancer cells. RXRα overexpression in cancer differentiation and activates several cancer suppressors, such as p53, p21, and p16, while it is reduced in cancer cells. RXRα overexpression in cancer cells inhibits tumor proliferation, invasion, and angiogenesis, suggesting its effect on cancer inhibition. Furthermore, another study in 2019 revealed that significant cancer-promoting activity, thereby accelerating tumor progression. Meanwhile, in Adenoid Cystic Carcinoma (ACC), myoepithelial-like cells, with higher tumorigenicity and stemness, act as progenitors of ductal-like cells, and RAR/RXR signaling pathway accelerates the differentiation process from myoepithelial-like cells to ductal-like ones, which also suggests RAR/RXR inhibition as a therapeutic approach.

Phosphorylated-RXRα (p-RXRα) regulates mitotic progression in cancer cells.

Cyclin-dependent kinase 1 is a proto-oncogene, which phosphorylates RXRα at Ser56 and Ser70 during mitosis in cancer cells. The phosphorylation causes a conformational change of RXRα and enables p-RXRα to migrate from condensed chromosomes to the centrosome. Polo-like kinase 1 (PLK1) is a mitogenic kinase that is highly expressed during the G2 to M phases of the cell cycle, which exists in centrosomes, microtubules, the central spindle, the midbody, and kinetochores. It functions in different events of mitosis, such as centrosome separation and bipolar spindle formation. The C-terminal of PLK1 has a polo-box domain (PBD), which interacts with phosphorylated serine and threonine (pSer and pThr). PBD is responsible for regulating PLK1 localization and activation. pSer in p-RXRα binds to PBD, thereby inhibiting the intramolecular interaction between PBD and N-terminal kinase domain in PLK1, enabling Aurora A to activate PLK1. Another earlier study suggested that Cep192-dependent Aurora A-PLK1 activity is essential for the correct separation of centrosome and bipolar spindle. Additionally, p-RXRα may participate in Cep192 recruitment to the centrosome, resulting in enhanced PLK1 activity. The enhanced PLK1 activity leads to centrosome maturation, which promotes mitotic progression in cancer cells (Figure 4A).

Truncated RXRα (tRXRα) promotes survival in cancer cells.

Different kinds of proteolytic cleavage of RXRα protein were found in many tumor cells. One of the tRXRα that lacks 80 amino acids in the N-terminal (RXRα-Δ80, hereinafter referred to as tRXRα) was proven to act as a cancer promoter through non-transcriptional action. Activating RXR with UAB30 decreases CD133 expression, which is a CSC marker, in medulloblastoma, and reduces its ability to form tumorsphere in vitro. Additionally, a recent study reported that MSU-42011, which is a novel rexinoid, inhibits the growth of Kras-driven lung cancer, and the combined use of MSU-42011 and chemotherapy reduces tumor-promoting macrophages involved in neoplastic transformation in early stages.

Conversely, RXRα overexpression promotes phosphorylation of AKT and FAK, thereby leading to metabolism reprogramming, especially glycolysis suppression, which is probably a critical course in cell carcinogenesis, indicating the possibility of inhibiting RXRα to prevent cancer formation. A recent study revealed that RXRα is closely related to early recurrence and poor prognosis in hepatoma carcinoma (HCC), in which the interaction between RXRα and β-catenin in the cytoplasm induces this complex to translocate to the cell nucleus and bind to the promoter region of amphiregulin (AREG), which has been identified as an early DNA-binding domain (DBD)

PDB: 3DZY).

Figure 2. Structure diagram of RXR (A) Schematic illustration of RXR domain structure. (B) Schematic illustration of RXR crystal structure. This diagram was created with PDB coordinates (PDB: 3DZY).

RXR in CSCs.

CSCs are cells that can self-renew, proliferate, and differentiate into cancer cells and are closely related to cancer recurrence, metastasis, and therapy resistance. More CSC biomarkers, related mechanisms, and targeted therapies remain developed to achieve better therapeutic effects due to the importance of CSCs in cancer (Figure3). RXR, as a part of the retinoid signaling pathway and the heterodimer partner of RAR, was proven to activate or repress downstream stemness gene by histone acetylation or deacetylation, thus mediating cancer stemness. Recently, researchers revealed that RXR exhibits more double-sided association with CSCs. A study in 2018 revealed that RXRα is highly expressed during normal cell differentiation and activates several cancer suppressors, such as p53, p21, and p16, while it is reduced in cancer cells. RXRα overexpression in cancer cells inhibits tumor proliferation, invasion, and angiogenesis, suggesting its effect on cancer inhibition. Furthermore, another study in 2019 revealed that
caspase 8 form a death-inducing signaling complex to cut pro-caspase 8 into an active form, caspase 8, which transduces downstream pro-apoptotic signals, leading to cell apoptosis. However, tRXRα, instead of FADD, is recruited to TNFRs in cancer cells. In the presence of TNF-α, tRXRα interacts with p85α, which is a regulatory subunit of phosphatidylinositide 3-kinases (PI3K). The interaction between tRXRα and p85α results in the PI3K/AKT signaling pathway activation; therefore, the TNFα function is transformed from apoptosis to cancer cell survival (Figure 4B).

tRXRα promotes colitis-associated cancer (CAC) tumorigenesis.

Moreover, tRXRα is expressed in colorectal tissues of patients with ulcerative colitis which is a kind of precancerous disease or precancerous lesion. The expression of TNF receptor-associated factor 6 (TRAF6) is increased in these cells when tRXRα exists in the cytoplasm of lamina propria macrophages. The interaction between TRAF6 and tRXRα activates the IκB kinase/nuclear factor-κB pathway possibly through inducing TRAF6 autoubiquitination, thereby increasing the interleukin-6 (IL-6) secretion. Notably, TRAF6 interacts with tRXRα instead of full-length RXRα, which means this activation pathway specifically occurs in tumors. IL-6, which is a proinflammatory cytokine, stimulates STAT3 expression, which is essential for preventing pre-malignant intestinal epithelial cells (IEC) from apoptosis, thereby promoting the survival and proliferation of pre-malignant IEC and enhancing the migration and invasion of CRC cells, accelerating the transformation from chronic colitis...
Different functions of RXR heterodimers in cancer cells.

PPAR heterodimerizes with RXR to work as a gene transcription regulator. It is aberrantly expressed in several cancer types. Earlier studies revealed that PPAR-γ/RXRα heterodimers bind to peroxisome proliferator-responsive element (PPRE) and regulate target gene expression in breast cancer and colon cancer. C-Jun, which is a transcription factor in AP-1, was identified to be inhibited by the interaction between PPAR-γ/RXR and PPRE. AP-1 is involved in COX-2 upregulation, whose high expression promotes proliferation, angiogenesis, invasiveness, and metastasis, and inhibits apoptosis in breast and colon cancer cells. The inhibition of c-Jun and AP-1 reduces COX-2 and leads to growth inhibition. However, RXRα is phosphorylated in colon cancer cells. p-RXRα loses the function as the heterodimeric partner of PPARγ and the synergistic effects to inhibit growth. Thus, colon cancer cells grow out of control.

Table 1. Key RXR inhibitors launched or are under evaluation.

<table>
<thead>
<tr>
<th>Name</th>
<th>Activity/Target</th>
<th>Indication</th>
<th>Stage</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>HX531</td>
<td>pan-RXR antagonist</td>
<td>reduce drug resistance and delay relapse in melanoma; prevent M2 macrophages polarization</td>
<td>preclinical</td>
<td>57,60</td>
</tr>
<tr>
<td>XS060</td>
<td>p-RXRα and PLK1 interaction inhibitor</td>
<td>suppress the activation of PLK1 in centrosome, and eventually results in mitotic catastrophe in cancer cells</td>
<td>preclinical</td>
<td>37</td>
</tr>
<tr>
<td>K-80003</td>
<td>tRXRα inhibitor</td>
<td>induce apoptosis via inhibiting AKT pathway activation; prevent CAC progression via inhibiting IL-6-STAT3 pathway</td>
<td>approved by FDA to enter clinical trials</td>
<td>11,42,44,45</td>
</tr>
<tr>
<td>CF31</td>
<td>tRXRα inhibitor</td>
<td>induce apoptosis via inhibiting AKT pathway activation</td>
<td>preclinical</td>
<td>63</td>
</tr>
<tr>
<td>NSC-640358</td>
<td>tRXRα inhibitor</td>
<td>induce apoptosis via inhibiting AKT pathway activation</td>
<td>preclinical</td>
<td>66</td>
</tr>
<tr>
<td>TRC4</td>
<td>tRXRα inhibitor</td>
<td>induce apoptosis via inhibiting AKT pathway activation</td>
<td>preclinical</td>
<td>68</td>
</tr>
<tr>
<td>α-Mangostin</td>
<td>tRXRα inhibitor</td>
<td>induce apoptosis via inhibiting AKT pathway activation</td>
<td>preclinical</td>
<td>69</td>
</tr>
<tr>
<td>R-etodolac</td>
<td>RXR/RXR homodimer antagonist but RXR/PPARγ heterodimer agonist</td>
<td>induce apoptosis in prostate cancer</td>
<td>terminated clinical trials</td>
<td>70</td>
</tr>
</tbody>
</table>

Another recent study indicated an axis involving cisplatin (CDPP) resistance in non-small cell lung cancer (NSCLC). The axis consists of histone deacetylase (HDAC), RXR, and High Temperature Requirement A Serine Peptidase 1 (HtrA1). The decreased HtrA1 expression was related to CDPP resistance in NSCLC. The HtrA1 upregulation depends on the RXR transcriptional activation, while the RXR activity in this axis depends on RXR/VDR and RXR/RAR heterodimerization. However, the action of RXR to activate HtrA1 is inhibited by HDAC, which is an epigenetic regulatory enzyme. HDAC leads to chromatin compaction and prevents the transcription factor RXR from binding to the specific target region in the HtrA1 promoter, resulting in CDPP resistance in NSCLC (Figure 5B).
Researchers designed a series of XS060 analogs. Among these, B10 was certified as an improved anti-mitotic molecule in cancer cells with stronger cancer cell selectivity.

### K-80003

K-80003 is an RXRα-selective sulindac analog. Sulindac is one of the non-steroidal anti-inflammatory drugs (NSAIDs) that show antineoplastic effects. An earlier study revealed that sulindac binds to RXRα and antagonizes the RXRα transactivation. However, K-80003, which is an analog without COX selectivity, was designed and synthesized because its COX inhibitory effect may result in increased cardiovascular risk. K-80003, compared to sulindac, has more affinity with RXRα and stronger inhibitory effects. The combined use of K-80003 and TNFα induces poly(ADP-ribose)polymerase cleavage and caspase-8 activation and inhibits AKT activation, thereby resulting in cancer cell apoptosis. Additionally, K-80003 inhibits the interaction between tRXRα and TRAF6 and the ubiquitination of TRAF6, thereby slowing down the CAC progression.

### XS060

As previously mentioned, p-RXRα binds to PLK1 and thus promotes mitotic progression in cancer cells. XS060 is an RXRα ligand that was proven to delay the progression and eliminate relapse in melanoma. Moreover, HX531 showed the possibility of therapy targeting the immunosuppressive tumor microenvironment. A recent study used HX531 to pretreat M0 macrophages and then cultured M0 macrophages with IL-4, which leads to M2 polarization, for 24 h. Arginase 1 (Arg1) was used as an M2 marker because it is often overexpressed in M2 macrophages. Researchers revealed that 3% of the M0 macrophages and 30% of the IL-4 polarized M2 macrophages expressed Arg1 in the control groups. However, only 10% of the cells expressed Arg1 in the group pre-treated with HX531, and monocyte chemoattractant protein-1 (MCP-1) secretion, whose reduction prevents the migration and infiltration of immunosuppressive macrophages, was strongly impaired. The possible mechanism is that RXR inhibition reduces the activity of other transcriptional factors, such as PPARs. The expression of MCP-1 in PPARγ-/- macrophages was reduced in earlier research in keeping with the effect of HX531 observed in this study. In conclusion, HX531 strongly prevents M2 macrophage polarization and shows the possibility in cancer immunotherapy (Figure 6).

A recent study revealed the mechanism of how K-80003 acts as an anti-cancer molecule. K-80003 binds to the LBD of RXRα. RXRα-LBD is located in its C-terminal, thus N-terminally-cleaved-RXRα still keeps the RXRα-LBD, suggesting that K-80003 interacts with tRXRα. RXRα-LBD/K-80003 complex was found to be a tetrameric structure with two RXRα-LBD canonical homodimers (labeled A1/B1 and A2/B2) and six molecules of K-80003, in which A1/B2 and A2/B1 create two interfacial cavities and three molecules (K-80003A, K-80003B, and K-80003C) bind in each cavity (Figure 7).

K-80003 induces the formation of tRXRα tetramer after binding to tRXRα, thereby concealing the binding sites on tRXRα. The tetramerization of tRXRα blocks the interaction of tRXRα with p85α and TRAF6, thereby inhibiting PI3K/AKT signaling pathway activation. Additionally, they revealed that K-80003 is unable to induce the tetramerization of full-length RXRα because the interaction between RXRα N-terminal and C-terminal prevents it from tetramerization. However, tRXRα is N-terminally-cleaved, thus no N/C interaction in tRXRα. In other words, K-80003 does not affect full-length RXRα in normal cells, but only targets aberrant tRXRα in cancer cells, which possibly is evidence of its safety. Besides, K-80003 promotes tRXRα migration from the cytoplasm, where tRXRα usually functions, to the cell nucleus, and thus reduces its function (Figure 8A).

K-80003 was approved by FDA to undergo clinical trials in patients with advanced CRC in 2016, but details and data remain unavailable.

### CF31, NSC-640358 (N-6), TRC4, and α-Mangostin

These four molecules are put together because they all have similar functions to K-80003, although they are distinct in structure.

CF31 is a xanthone that is extracted from Cratoxylum formosum ssp. pruniflorum. CF31 binds to RXRα-LBD via the nonpolar van der Waals interaction between tRXRα and TRAF6 and the ubiquitination of TRAF6, thereby slowing down the CAC progression.
TR3 activity, which is one of the heterodimeric partners of RXR that induces platinum resistance in ovarian cancer and promotes tumorigenesis in prostate cancer cells. The conformational change of RXRα in RXRα/TR3 heterodimers, induced by N-6, probably blocks the recruitment of TR3 coactivators or affect TR3 activating conformation, thereby inhibiting TR3 transactivation.

TRC4 is a derivative of triptolide. Triptolide was proven to possess a potent antitumor effect in earlier studies, while a cytotoxic effect on normal cells was also detected. Triptolide strongly reduces the expression of tRXRα and full-length RXRα. However, TRC4 inhibits tRXRα expression instead of affecting full-length RXRα, compared to triptolide, so it only has a slight effect on normal cells. α-Mangostin is a member of Mangostin, which is a family of natural compounds separated from the epicarp of the fruit of Garcinia Mangostana Linn. It binds to amino acid residues in RXRα-LBD via hydrogen bond and π-π interaction and induces RXRα and tRXRα degradation (Figure 8C).

Like K-80003, all these four molecules bind to TRXRs and prevent tRXRα interaction with p85α to inhibit TNFα-induced AKT activation and induce caspase-8 activation in cancer cells, thereby contributing to cancer cell apoptosis.

R-etodolac (SDX-101).

SDX-101 is the R-enantiomer of etodolac, which is a kind of NSAID. SDX-101 was previously regarded as the inactive form of etodolac because it has no inhibitory effect on COX. However, it was proven to have an antineoplastic effect afterward.

An earlier study revealed that SDX-101 was certified as an inducer of apoptosis in prostate cancer. Concurrently, researchers found that SDX-101 binds to RXRα, induces the conformational change in RXRα, and most importantly, inhibits the activity of RXRα homodimers. However, they did not think that the antitumor effect of RXRα directly depends on its inhibition of RXRα transactivation, because RXRα agonists also suppress the growth of cancer cells. They proposed that SDX-101 may inhibit cancer growth via activating PPARγ, because RXR homodimer antagonists may activate RXR/PPARγ heterodimers and the activity of PPARγ depends on its heterodimerization with RXR. Another study revealed that the anti-cancer effect of SDX-101 relies on PPARγ activation. As previously mentioned, the interaction between PPARγ/RXR and PPRE may inhibit the growth and induce apoptosis in cancer cells, which contributes to the antitumor effects of SDX-101 in prostate cancer (Figure 8B).

Two clinical trials of SDX-101 were conducted (NCT00151736 and NCT00293111). Both trials were terminated, while no results were posted.

Other modulators.

JQ1, which is a BET bromodomain inhibitor, was certified to inhibit LXR/RXR lipid metabolic pathway activation when used with gemcitabine in pancreatic cancer. LXR/RXR heterodimers increase lipogenesis, while the exact LXR functions in tumor progression remain unknown although several studies are conducted on this issue. Some studies consider LXR to have an antitumor effect, as activated LXR blocks proliferation and inhibits tumor growth in CRC. Additionally, LXR agonist reduces the proliferation via AKT/p53 signaling pathway in breast cancer and inhibits tumorigenesis and metastasis in melanoma. However, some other studies regard LXR as a promotor in tumor progression, for example, it induces resistance to side-chain hydroxycholesterols in triple-negative breast cancer. Hence, whether the synergy of JQ1 and gemcitabine depends on LXR/RXR inhibition needs further study.

CONCLUSION AND PERSPECTIVE

Targeted therapy rapidly develops accompanied by more recognition of cancer driver genes, including their mutations and genetic changes. In recent years, more attention has been paid to RA signaling pathways since their unique regulation positions in tumorigenesis. However, more drug discovery efforts are focused on RAR agonists so far. The only launched RXR modulator for cancer therapy is bexarotene. However, RXR-modulating drugs begin to attract more interest from oncologists because of their potential in interfering with cancer cell proliferation, differentiation, apoptosis, etc., according to the important and comprehensive regulation effects of RXR in tumorigenesis.

tRXRα is undoubtedly a significant finding in tumor progression. It is an aberrantly-expressed protein in cancerous cells. Its main mechanism of action is to inhibit apoptosis in cancer cells by activating PI3K/AKT signaling pathway. Additionally, tRXRα was proven to promote the transformation from chronic colitis to CAC via promoting IL-6-STAT3 signaling pathway. More functions of tRXRα in tumorigenesis remain to be further revealed.

Several molecules were discovered to target and inhibit tRXRα, such as K-80003, CF31, N-6, TRC4, and α-Mangostin, with remarkable antitumor effects. Among these modulators, K-80003 is the most potential one because it entered clinical trials in 2016; however, more details and data are unavailable at this stage.

p-RXRα is another potential target in cancer therapy. An earlier study revealed that acyclic retinoid prevents HCC carcinogenesis by inhibiting phosphorylating RXRα by the Ras/MEK signaling pathway. Additionally, a recent study revealed the importance of p-RXRα in promoting the mitotic progression of cancer cells, and designed XS060, thereby inhibiting the interaction between p-RXRα and PLK1 and suppressing the PLK1 activation in the centrosome to act as a new anti-mitotic molecule with few cytotoxic to normal cells.

Moreover, RXR heterodimers with other NRs play distinct roles in tumor progression. For example, PPAR-γ/RXRα heterodimer inhibits growth in colon cancer cells, thus some molecules which antagonize RXRα homodimers while agonizing RXR heterodimers, such as SDX-101, exert antineoplastic effects. Conversely, TR3, which is another heterodimer partner of RXR, induces platinum resistance in ovarian cancer and promotes tumorigenesis in prostate cancer cells. However, there is no typical hydrophobic pocket for accommodating ligands in TR3-LBD, thus directly inhibiting TR3 activity by binding to it is difficult. N-6, which is a tRXRα inhibitor, indirectly inhibits TR3 transactivation.
Other RXR inhibitors in cancer therapies

A

binding site

K-80003

tRXRα activity

B

SDX-101

growth inhibition of cancer cells

C

induce apoptosis

CF31/NSC-640358/TRC4/α-Mangostin

promote apoptosis of cancer cells
slow down the progression of CAC

Figure 8. Other RXR inhibitors in cancer therapies (A) K-80003 inhibits tRXRα activity by inducing tetramerization of tRXRα, thus promoting apoptosis in cancer cells and slowing down the progression of colitis-associated cancer (CAC). (B) CF31/NSC-640358/TRC4/α-Mangostin induces apoptosis of cancer cells by inhibiting RXRα. (C) SDX-101 exerts an antitumor effect by inhibiting RXR homodimers and activating RXR/PPAR-γ heterodimers.

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AUTHOR CONTRIBUTIONS

X.C. and X.L. conceived the concept and scope of the review. W.Z., S.L., R.C., J.N., and S.L. performed the literature review, organized and prepared the manuscript. W.Z., X.C. and X.L. revised the manuscript. All authors approved the submission of this manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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