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Review Article

Involvement of Retinoic Acid Regulates Wnt Signaling Pathway in Cancer Metastasis

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Abstract

Cancer is a generic term for a large group of diseases that can affect any part of the body. Metastasis is the spread of cancer to other locations in the body. Almost all cancers can metastasize resulting in the major cause of human death. Retinoic acid (RA) is essential for normal regulation of various biological processes including development, differentiation, proliferation, and apoptosis, and also defined as a potent suppressor of the proliferation of cancer cells and has been discovered inhibit various signaling pathways in tumors. Some reports have been found that lack of RA to relate with tumor development and cellular migration Lots of cellular pathways, including Wnt/β-catenin signaling pathway, are related to cancer metastasis. Many reports have suggested that exaggerated Wnt signaling can lead to cancer initiation and progression in a wide range of human tissues. Dysregulated Wnt/β-catenin signaling in cancers appear to more invasive to develop to mesenchymal cells and will undergo metastasis at last. The development of new therapeutic compounds targeting the Wnt/β-catenin signaling pathway promises new hope to eliminate cancers, especially metastasis cancers by natural and synthetic RA. In this review, we provide a highlighting various RA in regulates the Wnt/β-catenin signaling pathway. The mechanism of its anti-tumor effect can be considered as a therapeutic option.

ABBREVIATIONS

RA: Retinoic acid ; NCDs: Non-Communicable Diseases; EMT: Epithelial to Mesenchymal Transition; GSK-3β: Glycogen Synthase Kinase-3β; CK-1: Casein Kinase-1; APC: Adenomatous Polyposis Coli; MMP-7: Matrix Metalloproteinase-7; HCC: Hepatocellular Carcinoma Cells; ATRA: All-Trans-Retinoic Acid; 9-cis-RA: 9-Cis Retinoic acid; 13-cis-RA: 13-Cis-Retinoic Acid; RARs: Retinoic Acid Receptors; RXRs: Retinoid X Receptors; HNSC CSCs: Head and Neck Cancer Stem Cells; PCP: Planar Cell Polarity; TCF: T Cell Factor; EC: Embryonal Carcinoma; NT2: NTERA-2 Clone D; MED: Mammalian Mediator

INTRODUCTION

Cancer is a generic term to describe a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining characteristics of cancer is the rapid creation of malignant cells that grow beyond their usual boundaries then invade adjoining parts of the body and spread to other organs, which is referred to as metastasizing. Metastases are the major cause of death result from cancer. According to the World Health Organization, cancers, cardiovascular diseases, respiratory diseases and diabetes are responsible for 80% of all deaths from non-communicable diseases (NCDs) worldwide. There were an estimated 14.1 million cancer cases around the world in 2012, of these 7.4 million cases were in men and 6.7 million in women, and this number is expected to increase to 24 million by 2035 [1]. Metastasis is a complex process while the original is called the primary tumor. Almost all cancers can metastasize [2]. In some cases, metastatic cancer treatments may help prolong life. Several cellular pathways, including Wnt/β-catenin signaling pathway, are related to cancer metastasis. There are three Wnt/β-catenin signaling pathways, such as canonical Wnt/β-catenin signaling pathway, the non canonical planar cell polarity (PCP) pathway, and the Wnt/$Ca2^{+}$ pathway [3]. A critical and most studied Wnt pathway is canonical Wnt signaling and is the primary subject of this review. Many reports have suggested that over expressed of Wnt/β-catenin signaling can lead to cancer initiation and progression in a wide range of human tissues [4-9]. Dysregulated Wnt/β-catenin signaling in cancers appear to more motility and invasive to induction of epithelial to mesenchymal transition (EMT) and will undergo metastasis at last [10,11]. The central hallmarks of EMT include the downregulation of cell–cell adhesion protein E-cadherin which represents the epithelial

phenotype and up regulation of vimentin, which represents the mesenchymal phenotype [12]. β-catenin plays a pivotal role as a transcriptional co-activator in this process. In the absence of Wnt signaling stimulation, cytoplasmic β-catenin is phosphorylated by disruption complex including glycogen synthase kinase-3β(GSK-3β), Axin and the tumour suppressor adenomatous polyposis coli (APC) , which is targeted for ubiquitin-mediated proteasome to degradation [13]. While stimulation by Wnt, β-catenin molecules are freed from the disruption complex and trans located into the nucleus and binds to LEF1/TCF family of transcription factors [14,15]. In turn, transactivate its target oncogenes such as *cyclin D1* and *C-myc* lead to cancer initiation and metastasis (e.g., matrix metalloproteinase-7(MMP-7)) [3,16-19]. Uncontrolled Wnt/β-catenin signaling pathway is often associated with tumorigenesis such as in breast cancer cells [20] and in colon cancer [21] and hepato cellular carcinoma cells (HCC) [22]. It is now believed that vitamin A, through its active derivative, retinoids regulate a variety of important cellular processes during normal development, help maintain homeostasis, and also exert anti-cancer activities in a number of types of cancer cells [23-28]. Vitamin A can transformed into isomers such as all-trans-retinoic acid (ATRA), 9-cis retinoic acid (9-cis-RA) or 13-cis-retinoic acid (13-cis-RA) reversibly, resulting in slightly different receptor binding properties and hence biological activities. Retinoids are essential for the maintenance of epithelial differentiation which can be oxidated to retinoic acid (RA) as an agent in chemoprevention of epithelial carcinogenesis [29]. RA regulates gene transcription through two nuclear receptor super family, retinoic acid receptors (RARs) and retinoid X receptors (RXRs) which with significant anti-cancer effects [29-31]. RARs as well as RXRs has three main subtypes α, β, and γ, and each receptor has an N-terminal A/B region which contains an autonomous transcriptional activation function called AF-1, a central DNA-binding domain (the C region), and a C-terminal E region which containing a ligand binding domain and a ligand-dependent activation function-2 (AF-2). These receptors are ligand-dependent DNA binding transcription factors. Retinoids have been investigated in preclinical models for a long time, by now clinical data have already supported the potential of these compounds in cancer prevention and treatment [32]. Such as retinoic acid is being increasingly included in both therapeutic schemes and chemo preventive for a series of tumour diseases [32-34] and inhibit invasion and metastasis in diverse types of cancer such as in breast cancer cells and HCC [35-38]. Several reports have demonstrated that RA treatment caused a significant decrease in MMPs expression in breast cells and also in colon cancer cells, they suggest that it may contribute to the cell migration and invasion decrease [39-40]. In general, RA is believed to inhibit carcinogenesis by blocking the promotion of initiated or transformed cells by three mechanisms: such as arrest of tumour growth and/or differentiation, induction of apoptosis [41]. RA alone can suppress proliferation of HNSC CSCs and glioma in vitro and in vivo [42-44]. Many reports have been showed that RA and its receptors can inhibit invasion and metastasis by regulating Wnt/β-catenin signaling pathway and blocking the transformation in a fibroblastic phenotype of cancer progression.

Cross talk between RA and Wnt protein in cancer cells

The Wnt signaling pathway has been extensively studied which is related to cancer metastasis. Many reports have suggested that dysregulation of Wnt signaling can lead to cancer initiation and progression in a wide group of human tissues [4,7-9]. Wnt family genes comprise 19 members which are classified as non-canonical Wnts and canonical Wnts. Non-canonical Wnt ligands Wnt4, Wnt5a and Wnt11 activate Wnt/planar cell polarity (PCP) and Wnt/$Ca2^{+}$ pathways whereas canonical Wnt ligands including Wnt1, Wnt2, Wnt3, Wnt8a, Wnt8b, Wnt10a and Wnt10b, activate the β-catenin and translocate it into nucleus to induce its target genes [45]. And various evidences indicating that downstream components of the Wnt signaling pathway are over activated in many metastatic tumors [46]. The potential for Wnt signaling to cooperate with RA signaling pathways was revealed in a recent research demonstrating cross-talk between the two pathways. Researchers have found that non-canonical Wnt signals can repress β-catenin/TCF activity downstream of β-catenin, in parallel, evidence has been shown that RA can represses β-catenin/TCF activity in embryonal carcinoma (EC) NTERA-2 clone D1 (NT2) cells and that this is accompanied by increased expression of non-canonical Wnt protein Wnt-4 and Wnt-11 [47], both of which inhibit endogenous β-catenin/TCF activity. Wnt-1 is the oncogenic driver because this signaling pathway is hyperactivated in a high percentage of human cancer [48]. As in genuine cross-talk, some studies have demonstrated that retinoic acid-responsive gene *stra6* could induced by Wnt-1, and this process is strictly dependent upon retinoic acid receptor activity, while other genes such as tumor necrosis factor family 4-1BB ligan, ephrin B1 , autotaxinand ISLR synergistically induced by ATRA plus Wnt can be activated independently by Wnt signaling [49]. Moreover, up-regulation of *stra6* gene transcription also happened in RA given to transplanted mammary tumors, derived from Wnt1 transgenic animals or colon cancer xenografts (lacking functional APC) [50]. Genomic analysis by Li laboratory found a major shift in expression of Wnt and RXR-α pathway genes (up and down, respectively) coincident with the transition from hepatoblasts to hepatocytes, which categorized HCC cells into two subtypes (high Wnt, low RXR-α and low Wnt, high RXR-α) [51]. These data imply that retinoids may be useful for increasing the efficacy of therapeutic targeted at oncogenic targets of Wnt transformed cells.

RA Regulates Wnt/β-catenin signaling pathway in various cancer cells

The Wnt signaling pathway plays a critical role in gene expression, cell adhesionand is pivotal to every stage of cancer progression, including initiation, development, and metastasis [20,52-56]. A principal executioner of Wnt pathway is β-catenin and suppression of β-catenin may be a good target for inhibition of Wnt pathway. There are three different ways to degrade of cytosolic β-catenin: (1) by the serine/threonine kinase, glycogen synthase kinase (GSK)-3β, which is part of the Wnt signaling pathway, (2) by the p53/Siah-1 pathway, and (3) by a nuclear hormone receptor-mediated degradation pathway [21]. Some reports proved treatment with ATRA can decrease the phosphorylation of GSK-3β which causes the cytosolic β-catenin destruction complex to become stabilized, allowing for the disruption of β-catenin in the cytosol, decrease cellular proliferation, and increase the expression of pro-apoptotic proteins in cancer cells [57]. Thus, RA increase of GSK-3β

function leads to a disruption in the equilibrium of β-catenin concentration in nucleus and decreased Wnt signaling. As is widely known that cross-talk between the PI3K/Akt pathway and the Wnt/β-catenin signaling pathway occurs with GSK-3β (The relationships of RA regulates the function of GSK-3β and PI3K/Akt are shown in (Figure 1)). ATRA has been shown to inhibit PI3K activity and decrease the phosphorylation of GSK-3β which means the cytoplasmic β-catenin can be phosphorylated by disruption complex and weaken Wnt/β-catenin signaling, then decrease cell invasion and metastasis at last [58]. The phosphorylated form of GSK-3β also results in the increased accumulation of snail which is the repressor of E-cadherin, decreasing cell-cell adhesion through E-cadherin [59]. In additionally, retinoids have been shown to alter PTEN activity in many cancers, such as smooth muscle cells, neuroblastoma and glioblastoma cells, promyelocytes, leukemia cells, fibroblasts, and breast, endometrial, and HCC [60-69]. Increases of PTEN and consequent decreases of Akt and eventually decrease β-catenin in the cytosol. As described previous, the second way for RA regulates β-catenin is through the p53/Siah-1 pathway. Mutations of the tumor suppressor gene p53 are the most common mutations found in human cancers [70], this loss of p53 function during a defined step such as K-ras and the Wnt/β-catenin signaling pathway may already be dysregulated. Siah-1 is a p53-inducible protein that binds ubiquitin-conjugating enzymes and degrades both mutant and wild-type β-catenin result in a decrease in TCF/LEF reporter activity and the consequent reduction the levels of β-catenin target genes *cyclin D1* and *c-Myc* [71]. Because Siah-1 expression is regulated by p53, the loss of p53 inhibits Siah-1 expression and activity, preventing the p53/Siah-1 pathway activity to cause β-catenin degradation [72]. A high percentage of evidences have proved that retinoic acid treatment in various different cell types induces p53 mRNA and protein expression, increased p53 expression resulted in increased degradation of β-catenin and a decrease in TCF/LEF activity(The relationship of RA regulates the function of P53 is shown in (Figure1) [73-76]. Another research has demonstrated that the β-catenin/TCF pathway was playing some role in the action of retinoic acid, treatment with retinoic acid, in fact, does stimulate the stabilization of β-catenin levels and retinoic acid prompts an activation of LEF-TCF-sensitive transcription in F9 teratocarcinoma cells. This cross-regulation between retinoid signaling and the Wnt/β-catenin pathways is focused on the formation of primitive endoderm, so the mechanism is different from carcinoma [77]. Thus, the relationship between RA and Wnt pathways is variable, contextual and cell type specific.

Retinoic acid receptors RAR and RXR regulate β-catenin

Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) are members of the nuclear receptor superfamily. All three RAR subtypes (α, β and γ) can be activated by ATRA or 9-cis RA,

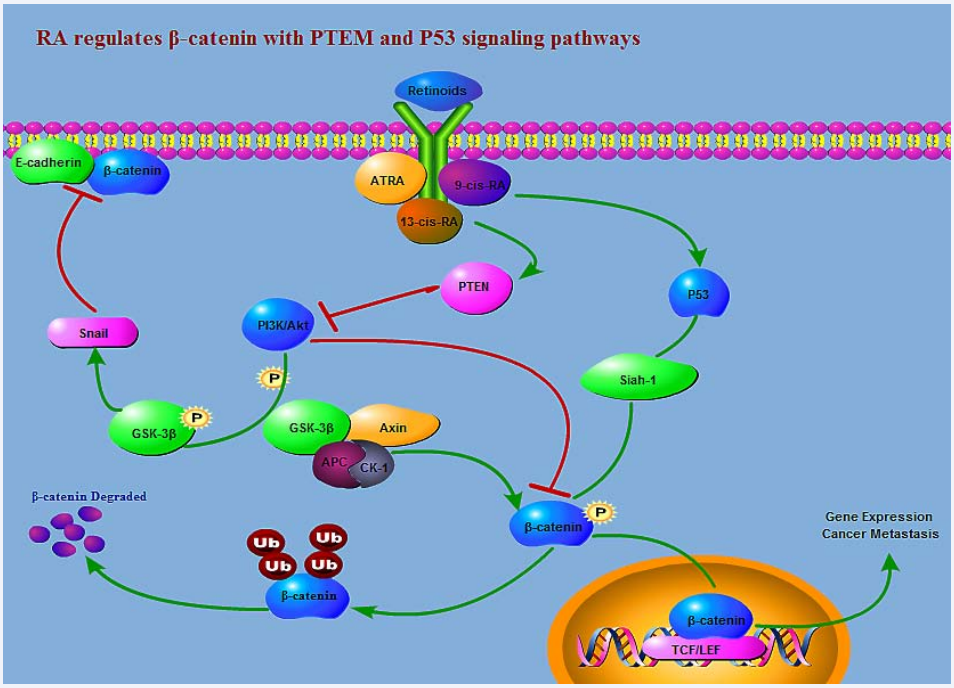

Figure 1 RA regulates β-catenin with PTEM and P53 signaling pathways
1) RA alter PTEN activity , inhibit PI3K/Akt activity and decrease the phosphorylation of GSK-3β which causes the cytosolic β-catenin destruction complex(GSK-3β, APC, CK-1 and AXIN) to become stabilized, allowing for the disruption of β-catenin in the cytosol and inhibit gene expression in nucleus.
2) RA induces p53 expression, and activates the p53/Siah-1 pathway to degrade β-catenin resulted in increased degradation of β-catenin and a decrease in TCF/LEF activity.
3) RA inhibits the phosphorylation of GSK-3β results in the decreased accumulation of snail andincreasing cell-cell adhesion through E-cadherin and β-catenin.

and function as heterodimers with retinoid-X receptors (RXRs) to enhance or drive the expression of target genes [78]. However, the specific receptor which mediates these effects varies with different cell lines. Both RARs and RXRs can bind response elements as RAR-RXR heterodimers or RXR homodimers, even at high protein concentrations [79,80]. More evidences have shown that β-catenin interact directly with RAR or RXR in a retinoid-dependent manner (The mechanisms of RAR and RXR regulate β-catenin is shown in (Figure 2). RAR can compete with TCF for β-catenin binding suggest that direct regulation of β-catenin/TCF signaling is one mechanism whereby RA influences development, cell differentiation and cancer [81].

In general, retinoid receptors either inhibit β-catenin-mediated gene transcription, as in the case of RAR, or decrease β-catenin protein levels, as in the case of RXR [82]. When treated with 9-cis-RA, a ligand for both RAR and RXR is recruited to enhance β-catenin protein stability in breast cancers cell SKBR3 which express low endogenous levels of β-catenin [83-85]. But 9-cis–RA treatment do reduce β-catenin/TCF/LEF-mediated gene transcription in the same cell SKBR3 as well as MCF-7, CaCo-2 and HS578t [81]. With a down-regulated RARβ expression, RA resulted ineffective to reduce cellular migration, suggesting that tumour cells could silence RARβ to facilitate the escape of the tumour triggering the metastatic process. RARγ acts as a tumor suppressor or oncogene in different cancers, depending on the cell-specific context [86-90]. RARγ plays as a tumor suppressor of the Hippo-Yap pathway in colorectal tumorigenesis and metastasis, where its expression correlates inversely with tumor size, TNM stage, and distant metastasis [91]. But in cholangiocarcinoma (CCA) and HCC, RARγ is a pivotal oncogene which was frequently over expressed and resulting in poor differentiation, and poor prognosis [89,92]. Researchers have found that RA treatment up regulated RARγ and down regulated phosphorylated β-catenin which escape from the degraded complex, means RARγ up regulating total β-catenin, then increased cyclinD1, P-P glycoprotein, PCNA and MMP9 which plays a critical role in early CCA metastasis [93]. In present studies, the only know molecular mechanism of tumor revealed that RARγ interacted with β-catenin and led to β-catenin nuclear translocation is in CCA, whether RARγ suppresses the level of β-catenin in other cancers is still unknown. These results showed that RARγ upregulated β-catenin in nuclear translocation and subsequently lead to the activation of Wnt/β-catenin pathway. The paradoxical roles of RAR in the regulation of β-catenin might depend on its particular cellular location. As described previous, Wnt-1 promotes the up-regulation of RARγ, which could potentiate the response of the cell to retinoids and increase the expression of retinoic acid-responsive gene *Stra6* in many cancers [50]. These consequences indicate retinoids in various cancer models has been inconsistent, yielding both suppression and enhancement of tumor progression depending on genetic background and tumor type also by different administration protocol [94]. In additionally, Xiao et al found that retinoid X receptor (RXR) can mediated APC-independent pathway in the regulation of β-catenin in APC- and p53-mutated colorectal cancer cells, and results have been found that RXRα and β-catenin have been shown to directly interact in nucleus, which proved retinoids can increase βcatenin degradation by a nuclear hormone receptor-mediated degradation pathway [82,95]. Revealing despite mutations in the p53 and APC proteins that regulate β-catenin protein degradation only by the RXR-mediated pathway remains functional in these human colon cancer cell lines [21]. Further evidence shows that retinol increases migration of β-catenin and RXRα from the nucleus into the cytosol concomitant with the β-catenin-RXRα binding complex, the provement demonstrated that cytosolic RXRα is proteasomally degraded, and more important, the evidence shows that the RXRα and β-catenin binding is required for the proteosome degradation of β-catenin (As is shown in (Figure 2)) [96]. These results are consistent with a transrepression model of β-catenin inhibition, which depends on the high-level expression

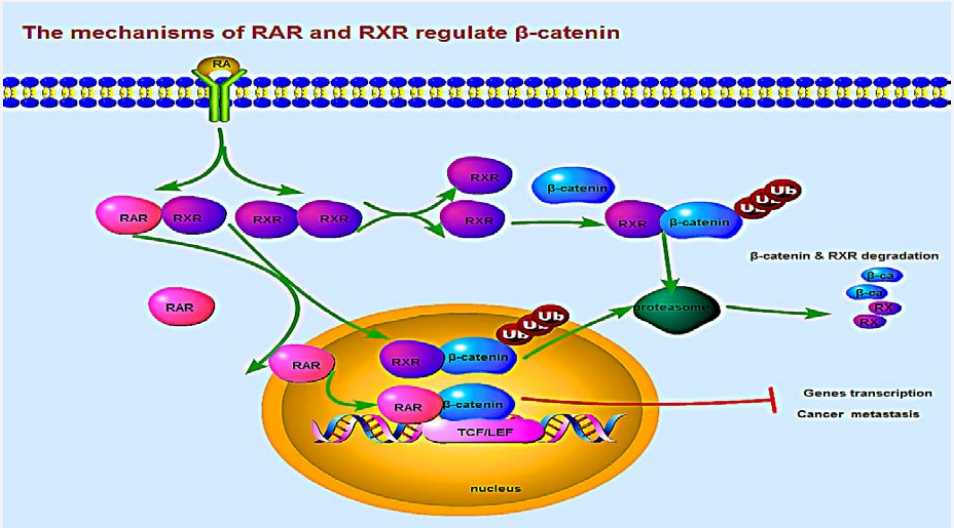

Figure 2 The mechanisms of RAR and RXR regulate β-catenin
1) RAR competes with TCF for β-catenin binding to inhibit β-catenin-mediated gene transcription and cancer metastasis; 2) RXR and β-catenin constitute the β-catenin-RXRα complex, which migrate from the nucleus into the cytosol for proteasoma degraded.

of RXRα. Removal of the AF-1 and DBD region of RXRα eliminated the ability of retinol to decrease β-catenin protein suggest the region mechanism dependent the special region to binding with β-catenin. Thus, these data suggested a distinct mode by which RAR or RXR regulates β-catenin. Whereas RAR operates by decreasing signaling by competition of nuclear cofactors in most cancer cells except RARγ which plays as an oncogene in cholangiocarcinoma, RXR appears to facilitate the degradation of β-catenin by an APC-independent proteasomal degradation pathway. The reasons for differential effects of RA treatment on β-catenin/TCF transcription are unclear, may be the different of basal β-catenin levels, relative levels of cadherins, and ratios of RAR/RXR or RXR/RXR dimers and cell context are involvement. However, the RXR-mediated pathway, which can be regulated by small molecule hormones, has the potential of being a very powerful pharmacological approach to treating Wnt/β-catenin-related cancers. Many results show that β-catenin-associated tumors that concurrently express high levels of RXR have the most responsive to RXR agonist therapy. Furthermore, the use of RXR agonists in conjunction with pharmacological or genetic approaches to elevating RXRα protein levels in target tumors may be effective therapies for cancers [97].

RA increase cell-cell interaction by active E-cadherin

Invasion and metastases are the most life-threatening properties of malignant tumour, considering be later, but critically important carcinogenic steps. The importance of E-cadherin is essential for cell–cell adhesion, which control cell motility, and be considered as an 'invasion suppressor'. E-cadherin works with α- and β-catenin as a functional unit which called the E-cadherin–catenin unit (ECCU), interaction at the cell membrane to maintain the epithelial phenotype [98-102]. Cytosolic β-catenin can be targeted for proteosomal degradation by non-phosphorylated GSK-3β which is complexed with APC, Axin, and CK-1. Nuclear β-catenin induces gene transcription when complexed with TCF/LEF transcription factors. Ultimately, all pathways increase the transcription of genes favoring cellular proliferation and invasion, most via increasing β-catenin-mediated gene transcription. Besides its role in establishing tight cell-cell adhesion and nucleus gene transcription, β-catenin plays a dual role as a tumor suppressor and as an oncogene in human cancers [99,103]. Accumulating researches suggest that the induction of EMT plays a crucial role in cancer cell transformation and progression [100,104]. The central hallmarks of EMT include the down regulation of E-cadherin, and up regulation of vimentin, N-cadherin, snail and twist which represent the mesenchymal phenotype , loss of function or expression of E-cadherin is correlated with the progression of tumors to a more invasive phenotype [12,105]. And the disturbance in protein-protein interaction in the ECCU complex is one of the main events in the early and late steps of cancer development. Over expression of α/β-catenin appears to be important in the invasive phase of early tumor development, which hints loss of ECCU function is important. RA has a profound effect on cell-cell adhesion, invasiveness and cell differentiation in a number of cancer cell lines [106-110]. Result has been shown that RA can elevate the expression of E-cadherin in many different cancer cells and induce aggregation of the E-cadherin/catenin complex while induce cell differentiation and reduce transcription of cyclin D1 by diminishing TCF sites of β-catenin [83,110]. Additionally, Byers et al exposure of breast cancer cells to 9-cis-RA for as little as 4h was sufficient to maintain the adhesive phenotype for at least 4 days, the mechanism involving a 9-cis–RA induced increase in $Ca(2^+)$-dependent adhesion, and β-catenin protein levels were markedly elevated in cancer cells SKBR3 with a poor adhesive phenotype which expresses no E-cadherin and very low levels of β-catenin protein, the involvement mechanism shows that 9-cis-RA treated cells do not change β-catenin mRNA levels but increase β-catenin protein stability and induce it move to cell membrane strength the cell-cell adhesive [83]. Another teams have observed RA treatment can reduces cytoplasmic levels of exogenously expressed β-catenin and increases the expression of a cadherin that mediates strong cell-cell adhesion and translocates β-catenin to the cell membrane in the same breast cancer cell SKBR3, thereby mediating the effects of RA on cell morphology and differentiation and as well as in CaCo2 cells. These results proved RA treatment induce epithelial differentiation characterized by increasing in cadherin expression in regions of cell to cell contact [111]. Remarkably, a recent study performed in HCC concluded that ATRA not only up regulates epithelial marker E-cadherin but also down regulates of mesenchymal markers N-cadherin, vimentin, snail and twist [35]. Indeed the data demonstrated that RA suppressed the proliferation, migration, invasion of and effectively induced its differentiation in vitro through the reversal of EMT. Additionally, ATRA also effectively reversed EMT phenotype with increase in epithelial expression of E-cadherin and cytokeratin 18, as well as reduce expression of vimentin and fibronectin [59]. Recent studies found ATRA could suppress mammalian mediator subunit MED28 and Wnt/β-catenin pathway and up regulate E-cadherin to facilitate the maintenance of epithelial integrity and inhibit cell growth [112-114], for that MED28 can involve in cell growth, migration, and invasion in human breast cancer cells and colorectal cancer cells, and is necessary for the expression of β-catenin target genes and could physically interact with β-catenin and stabilize the trans activation of Wnt target genes. Until now, various experimental data of RA have demonstrated its functions in increasing cell-cell adhesion, and suppressing the proliferation, inhibiting the growth of a variety of neoplastically transformed cells and inducing differentiation [35,110,115,116], suggesting its potential role as a cancer chemotherapeutic agent. Furthermore, because of the potential to maintain EMT, it is regarded as an attractive target for cancer prevention.

DISCUSSION AND CONCLUSION

Conclusion

It is remarkable that RA is effective at the cell proliferation and differentiation as well as the anti-cancer functions during the process of carcinogenesis. Numerous of signaling pathways have involved in the initiation of cancer development and metastasis such as PI3K/AKt, Notch, TGF-β and Wnt/β-catenin pathway [117,118]. As described, RA decreases Wnt/β-catenin pathway and stabilizes cell-cell adhesion in many cancer cell lines. RA activated its receptor RAR and RXR to inhibit β-catenin/TCF transactivation by directly binding to β-catenin or recruiting proteosomal degradation complex to decrease β-catenin levels, and though RARγ acts as a tumor oncogene lead to the activation

of Wnt/β-catenin pathway in CCA [92]. More researches need to demonstrate the relationship between Wnt and RA receptor RARγ to verify its effect on up regulating β-catenin. Taken together with the recent discovery that Wnt-1 and RA signaling cooperate to regulate the expression of the RA responsive gene Stra6 which worked at the cell surface proves the cross talk between these two signals, revealing an appropriate application would be immunotherapy in the progression and metastasis of cancers. Furthermore, because of the potential to maintain cancer cells differentiation and strengthen cell adhesion, which are both linked to tumor progression and metastasis, RA is regarded as an attractive target for cancer prevention and might be useful for the clinical treatment of cancer.

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