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Retinoid Pathway and Cancer Therapeutics

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Abstract

The retinoids are a class of compounds that are structurally related to vitamin A. Retinoic acid, which is the active metabolite of retinol, regulates a wide range of biological processes including development, differentiation, proliferation, and apoptosis. Retinoids exert their effects through a variety of binding proteins including cellular retinol binding protein (CRBP), retinol-binding proteins (RBP), cellular retinoic acid-binding protein (CRABP), and nuclear receptors i.e. retinoic acid receptor (RAR) and retinoid $\times$ receptor (RXR). Because of the pleiotropic effects of retinoids, understanding the function of these binding proteins and nuclear receptors assists us in developing compounds that have specific effects. This review summarizes our current understanding of how retinoids are processed and act with the emphasis on the application of retinoids in cancer treatment and prevention.

Keywords

Retinoids; Nuclear receptor; RAR; RXR; all-trans retinoic acid; 9-cis retinoic acid; 13-cis retinoic acid

1. History

Vitamin A and its derivatives (retinoids) exert a wide range of effects on embryonic development, cell growth, differentiation, and apoptosis. Vitamin A has been used as a treatment for thousands of years. The Egyptian papyri Kahun 1 (ca. 1825 B.C.) and Ebers (ca. 1500 B.C.) described how the liver was used to cure eye diseases such as night blindness. Greek scholar Hippocrates (460-327 B.C.) described in the second book of "Prognostics" a method for curing night blindness: "raw beef liver, as large as possible, soaked in honey, to be taken once or twice by mouth." Chinese medicine used pigs' liver as a remedy for night blindness, as described by Sun-szu-mo (7th century A.D.) in his "1000 Golden Remedies". Given that the liver is where the body stores excess vitamin A, the liver represents the best source of vitamin A available for treatment in the pre-pharmaceutical world.

One of the first experiments involving vitamin A was performed by F. Magendie (1817) [1], in which he fed dogs a diet of only sugar and water. Three weeks later, the dogs got sick and developed ulcers of the cornea. At the time, Magendie attributed these effects to nitrogen

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deficiency in their diet, but we now understand the sickness could have been due to vitamin A deficiency. The effect of vitamin A on growth was first described in a mouse experiment done by G. Lunin (1881) [2], in which one group of mice was fed pure casein, fat, sucrose, minerals, and water, and another group was fed whole dried milk. The milk-fed group was healthy and grew normally, while the other group was sick and ultimately died. Thus, something in milk was essential for survival. Elmer McCollum at University of Wisconsin-Madison as well as Lafayette Mendel and Thomas Burr Osborne at Yale University independently discovered vitamin A. McCollum began his study in 1907 by feeding cows hay with wheat, oats, or yellow maize.

Wheat-fed cows did not thrive, became blind and gave birth to dead calves prematurely. Oat-fed cows fared somewhat better, but the yellow maize-fed cows were in excellent condition, produced vigorous calves, and had no miscarriages. McCollum postulated that performing the same nutritional study using small animals, such as rodents, which require less food, provide faster reproduction and experimental outcome. Using rats, he found a diet of pure protein, pure milk sugar, minerals, and lard (or olive oil) inhibited growth, while addition of butterfat or an ether extract of egg yolk to the diet restored health. Thinking that he had found a fat-soluble factor that promoted growth in rats, he saponified butterfat, extracted the unsaponifiable mixture into ether, and added the extract to oliveoil and that extract could support growth. This essential component to support growth and development was named “fat-soluble factor A,” and later renamed vitamin A [1].

2. Retinoids

There are over 4,000 natural and synthetic molecules structurally and/or functionally related to vitamin A. Vitamin A cannot be synthesized by any animal species and is only obtained through diet in the form of retinol, retinyl ester, or β -carotene (Figure 1). Ingested vitamin A is stored as retinyl esters in hepatic stellate cells. Retinol is reversibly oxidized by retinol dehydrogenases to yield retinal. Subsequently, retinal may be irreversibly oxidized to all-trans retinoic acid (all-trans RA) by retinal dehydrogenases and further oxidized by cytochrome P450 enzymes (mainly CYP26) in hepatic tissue. Retinol has six biologically active isoforms that include all-trans, 11-cis, 13-cis, 9, 13-di-cis, 9-cis, and 11, 13-di-cis, with all-trans being the predominant physiological form. Endogenous retinoids with biological activity include all-trans RA, 9-cis RA, 11-cis retinaldehyde, 3,4-didehydro RA, and perhaps 14-hydroxy-4, 14-retro retinol, 4-oxo RA, and 4-oxo retinol [3–5]. All-trans RA isomerizes under experimental and physiological conditions. Different isomers activate different receptors and thus lead to different biological effects. RAs designed to be receptor specific can improve efficacy and avoid unwanted side effects. Retinoids that specifically bind to RXR are called rexinoids and have been effective in cancer treatment. Retinoids are comprised of three units: a bulky hydrophobic region, a linker unit, and a polar terminus, which is usually a carboxylic acid. Modification of each unit has generated many more compounds. Please refer to recent reviews [6–8].

3. Retinoid Binding Proteins

There are various types of retinoid-binding proteins, which locate in intracellular and extracellular compartments and associate with isomeric forms of retinoids. Hence, retinoids are either associated with cellular membranes or bound to a specific retinoid binding protein. These binding proteins along with nuclear receptors mediate the action of retinoids. Their interactions are summarized in figure 1. Retinoid-binding proteins solubilize and stabilize retinoids in aqueous spaces. In addition to this general role, specific retinoid-binding proteins have distinct functions in regulating transport and metabolism of specific retinoids. For example, the parent vitamin A molecule, all-trans retinol, circulates in blood bound to

serum retinol binding protein (RBP). Inside the cells, all-trans retinol and its oxidation product, all-trans retinal, are associated with different isoforms of cellular retinol-binding proteins (CRBP), while all-trans RA intracellularly binds to cellular retinoic acid-binding protein isoforms (CRABP).

3.1. RBP

Retinol is secreted from its storage pools and circulates in blood by binding to RBP. The main storage site for vitamin A and the main site of synthesis of RBP is the liver, although other tissues (including adipose tissue, kidney, lung, heart, skeletal muscle, spleen, eye and testis) also express this protein. Secretion of RBP from the liver is regulated by the availability of retinol [9]. Vitamin A deficiency inhibits RBP secretion, leading to protein accumulation in the endoplasmic reticulum of hepatic parenchymal cells. In the presence of retinol, RBP associates with retinol, moves to the Golgi apparatus and is secreted into blood. The mechanism by which retinol initiates RBP secretion from cells is not known. In blood, RBP is bound to the small protein transthyretin, which in addition to associating with RBP functions as a carrier protein for thyroid hormones. Binding of RBP to transthyretin prevents the loss of this smaller protein by filtration in the renal glomeruli. The transthyretin-RBP-retinol complex transports retinol in the circulation and delivers it to target tissues [10].

Important insights into the biological role of RBP have been obtained by studies of mice and humans in which the RBP gene is disrupted. RBP-deficient mice display both reduced blood retinol levels and impaired visual function during the first months of life. When maintained on a vitamin A-sufficient diet, they acquire normal vision by 5 months of age, even though their blood retinol level remains low. A striking phenotype of the RBP-null mice is that they possess larger than normal hepatic vitamin A storage, but are dependent on a continuous dietary intake of vitamin A [11], further proving the importance of RBP as a transporting protein. A study of two human siblings that harbored point mutations in their RBP gene and exhibited undetectable plasma RBP levels revealed that these sisters suffered from night blindness and mild retinal dystrophy but did not exhibit other clinical symptoms of vitamin A deficiency [12]. Taken together, RBP is critical for the mobilization of retinol from hepatic storage pools; however, RBP is not essential for the delivery of retinol to target tissues. Supply of vitamin A to target tissues in the absence of RBP is likely to be accomplished via newly absorbed retinyl esters or β -carotene present in circulating chylomicrons. Increased RBP has been shown to contribute to insulin resistance and type 2 diabetes [11]. All-trans RA has recently been shown to increase insulin sensitivity in diabetic mice while lowering RBP [13]. The effect on binding proteins must be considered when retinoids are used for disease treatment.

3.2. STRA6

The stimulated by retinoic acid gene 6 (STRA6) encodes the cell surface RBP receptor, which binds specifically to RBP and mediates retinol uptake from holo-RBP [14]. STRA6 is a widely expressed transmembrane protein. In mouse mammary epithelial cells, STRA6 expression can be up regulated by Wnt1 and retinoids. In addition, STRA6 mRNA levels are up regulated in mouse mammary gland tumors and human colorectal tumors [15]. Importantly, while the RBP-null mice and humans give rise to relative mild phenotypes, STRA6-null mice develop anophthalmia, congenital heart defects, diaphragmatic hernias, alveolar capillary dysplasia, lung hypoplasia, and mental retardation. These findings suggest that STRA6 may have additional functions that are not related to RBP transport [16].

3.3. CRBP

CRBPs belong to the family of fatty acid binding proteins in which expression of CRBP family members are tissue specific. For example, CRBP-II is expressed only in the

enterocytes of the intestine, while CRBP-I and -III are expressed throughout embryonic and adult tissues [17]. Knockout studies for CRBP isoforms have identified differences in function due to altered tissue localization. CRBP-I knockout mice are healthy. However, they have low levels of hepatic retinyl esters [18], and their hepatic lipid droplets appear to be smaller and less abundant than in wild type littermates. CRBP-II-null mice have impaired retinol uptake, but they develop and reproduce normally under vitamin A-enriched diet, albeit with reduced retinol storage [19]. Reduction of vitamin A in the maternal diet of CRBP-II-null mice during gestation results in neonatal mortality immediately following birth [19]. CRBP-III null mice have impaired vitamin A incorporation into milk, but they are otherwise healthy [20]. CRBP-I and CRBP-III compensate for each other to maintain normal retinoid homeostasis, but the compensation is incomplete during lactation [20]. The binding affinity of CRBP-I towards retinol is about 100-fold higher than that of CRBP-II. They display a similar binding affinity towards retinal and CRBP-II associates with retinol and retinal with similar affinities. CRBPs, and especially CRBP-I with its high affinity for retinol, may sequester retinol from its ability to disrupt cell membranes. Epigenetic silencing of CRBP is a common event in human cancers [21]. Silencing CRBP reduces the availability of retinyl esters in the bloodstream and decreases the body's ability to metabolize retinol [22].

3.4. CRABP

CRABP-I and -II have been identified with a high affinity for all-trans RA. In humans, these isoforms display 74 percent sequence identity and are highly conserved among species; however, these CRABP isoforms display different patterns of expression across cells and developmental stages. In adults, CRABP-I is expressed ubiquitously, while CRABP-II is only expressed in the skin, uterus, ovary, and the choroid plexus. Both CRABPs are widely expressed in the embryo, although they do not usually co-exist in the same cells. The biological functions of CRABPs are not completely understood. In mouse knockout studies, disruption of either CRABP-I or -II only display mild defects in limb development [23], which suggests CRABPs may be involved in generation of appropriate RA concentration gradients in the developing limb bud. Both CRABP isoforms are present in cytosol and nucleus and thus may deliver the ligand directly to the nuclear receptor. The differential role of these two binding proteins remains to be studied (reviewed in [24] and [25]). Increased CRABP-I expression may also contribute to RA resistance of cancer cells [26]. The effect of CRABP on cancer therapy deserves more attention.

4. Retinoic Acid Receptors

The major breakthrough in understanding RA's function occurred upon identifying and cloning the receptors for RA [27,28]. RA regulates gene expression by binding to its nuclear receptors, which in turn activates transcription of their downstream target genes. Thus, retinoids exert their biological functions primarily by regulating gene expression. This was predicted by Sporn and Roberts in 1983, when they wrote: "Ultimately, it would appear that the problem of the molecular mechanism of action of retinoids in control of differentiation and carcinogenesis is converging on one of the central problems of all biology, the control of gene expression." [29]

4.1. RAR and RXR

Two distinct classes of receptors for retinoids have been identified: retinoic acid receptors (RAR) and retinoid X receptors (RXR). Each class of receptor contains three subtypes - α , β , and γ . RARs can be activated by both all-trans and 9-cis-RA, while, RXRs are exclusively activated by 9-cis RA. However, due to the conversion of all-trans to 9-cis RA, high

concentrations (10^{-5} M) of all-trans RA can also activate gene transcription in cells transfected with RXRs [30].

RXRs can form homo- and heterodimers with other receptors. In fact, RXRs are promiscuous receptors forming heterodimers with many different kinds of receptors, which include receptors for fatty acids [peroxisomal proliferator activated receptors (PPAR)], bile acids [farnesoid $\times$ receptor (FXR)], oxysterols [liver $\times$ receptor (LXR)], xenobiotics [pregnane $\times$ receptor (PXR) and constitutive androstane receptor (CAR)], vitamin D [vitamin D receptor (VDR)], and RA (RAR). RXRs can also form homodimers. Hypervitaminosis A leads to bone fracture suggesting that vitamin A and D compete for the same receptor [31]. Within these heterodimers, RXRs can exist as both active and silent partners. When it serves as an active partner, 9-cis RA and the ligand for the heterodimeric partner can activate the heterodimer, and addition both ligands give synergistic induction in gene transcription. For example, RXR is an active partner for PPAR. Similarly, heterodimeric complexes of RXR with LXR or FXR also retain 9-cis RA responsiveness. Thus, RAs can regulate PPAR- and FXR-mediated pathways [32]. Recently, we demonstrated that RAs could also activate PXR-, VDR, and CAR-mediated signaling and thus regulated xenobiotic metabolism and potentially its own oxidation [33–35]. When RXR serves as a silent partner, the heterodimer of RXR and its partner does not respond to RA. Regardless of their active or silent role, RXRs must be present in order to exert biological actions of various nuclear receptors. Using hepatocyte RXR α -deficient mice [36,37], we have demonstrated that RXR α does play vital roles in xenobiotic (alcohol, acetaminophen) and endobiotic (fatty acid, cholesterol, amino acid, and carbohydrate) metabolism [33–40]. Thus, RXR functions as an auxiliary factor and determines the effects of other hormones, making RXR a master regulator. The structure of nuclear receptors is summarized in recent review articles [7,38].

Existing data suggest that the binding protein and receptor work together to exert the specific effect of RAs. For example, RAs can bind to both PPAR β , the receptor for fatty acids, and RAR. Fatty acid-binding protein 5 (FABP5) and CRABP-II are specific binding proteins that channel RAs from the cytosol into the nucleus for binding to either PPAR β or RAR, respectively [39]. The ratio of FABP5/CRABP-II concentrations determines which receptor is activated. By activating PPAR β , RAs induce expression of genes affecting lipid and glucose homeostasis, such as the insulin-signaling gene pyruvate dehydrogenase kinase 1 (PDK1), which enhances insulin action. Hence, RAs stimulate lipolysis and reduce triglyceride content. RA implantation into obese mice causes up regulation of PPAR β as well as an increased expression of PPAR β target genes, including PDK1, which led to weight loss [40].

4.2. Receptor Isoforms

Multiple receptor isoforms for both RAR and RXR have been identified. RAR isoforms are either transcribed from two different promoters or produced by alternative splicing. There are two major isoforms for RAR α ($\alpha 1$ and $\alpha 2$) and RAR γ ($\gamma 1$ and $\gamma 2$) and five major isoforms for RAR β ($\beta 1$ – $\beta 4$ and $\beta 1'$). RAR isoforms can be classified as those which are transcribed from either P1 promoter (class I: RAR $\alpha 1$, $\beta 1$, and $\beta 3$, $\gamma 1$) or P2 promoter (class II: RAR $\alpha 2$, $\beta 2$ and $\beta 4$, $\gamma 2$). All class II isoform promoters have an RA response element and are RA inducible. Two major isoforms for RXR α ($\alpha 1$ and $\alpha 2$), RXR β ($\beta 1$ and $\beta 2$), and RXR γ ($\gamma 1$ and $\gamma 2$) have been identified. These RXR isoforms have different amino-terminal regions [41]. RARs and RXRs are expressed in a tissue-specific manner during development reflecting their pleiotropic roles. The tissue distribution pattern of these receptors is summarized in a review article entitled “Developmental Expression of Retinoic Acid Receptors (RARs)” [42].

Knockout studies have been generated in order to determine the function of RAR and RXR *in vivo*. RAR α -null mutant males are sterile due to degeneration of the seminiferous epithelium, inhibiting spermatogenesis [43]. RAR β -null mice display abnormalities in the vitreous body of the eye and impaired locomotion and motor coordination [44], while ablation of RAR γ causes both skeletal and epithelial defects [45]. The loss of RXR α was found to be lethal during fetal life due to hypoplasia of the myocardium [46]. Moreover, fetuses lacking RXR α have ocular malformation [47]. In addition, it has been shown that RXR α is involved in mediating the teratogenic effect of retinoids [48]. The ablation of RXR β led to approximately 50% lethality of mice in utero. Similar to RAR α -null mice, RXR β -null mice are also sterile; however, this is due to testicular defects and abnormal spermatid maturation [49]. Moreover, RXR β mutation causes abnormal lipid metabolism in Sertoli cells, suggesting functional interactions of RXR β with other nuclear receptors that control lipid metabolism [50]. In contrast, RXR γ -null mice are fertile but have elevated serum levels of both L-thyroxine and thyroid-stimulating hormone (TSH), as well as increased metabolic rates when compared to wild type animals [51]. The function of RARs during embryonic development is summarized in a recent review article [52].

4.3. Non-genomic Actions

Retinoids also exert their effects via transcription independent pathway, which can occur in the presence or absence of nuclear receptor. Retinoids mediated via RARs inhibit AP-1-regulated cell proliferation [53]. RA also inhibits NF κ B activity in mice [54]. Mediated through RAR β , RA changes the intracellular Ca⁺⁺ level and thus controls PI3K activation in neural cell [55–57]. RAR α can interact with mRNA in cytoplasm and control translation [58,59]. Via nuclear receptor independent pathway, RA rapidly activates cAMP response element (CREB) binding protein in human bronchial epithelial cells [60]. These mechanisms add a new dimension to the action of retinoids.

5. Retinoids and Cancer

Retinoids are widely used to treat visual and dermatological diseases. Their effect on cancer prevention and treatment has received a lot of attention. This review focuses on the action of retinoids on cancer. Retinoids have been used as potential chemotherapeutic or chemopreventive agents because of their differentiation, anti-proliferative, pro-apoptotic, and anti-oxidant effects. Epidemiological studies show that lower vitamin A intake results in a higher risk of developing cancer, which aligns with observations of vitamin A-deficient animals [61]. Altered expression of RA receptors is also associated with malignant transformation of animal tissues or cultured cells. Furthermore, retinoids suppress carcinogenesis in tumorigenic animal models for skin, oral, lung, breast, bladder, ovarian, and prostate [62–68]. In humans, retinoids reverse premalignant human epithelial lesions, induce the differentiation of myeloid cells, and prevent lung, liver, and breast cancer [69–73].

The following is a summary of how major retinoids may work in cancer treatment or prevention.

5.1. All-trans RA (tretinoin)

All-trans RA is the most abundant natural retinoid and has been widely studied for many years. It is currently in clinical trials for the treatment of lymphoma, leukemia, melanoma, lung cancer, cervical cancer, kidney cancer, neuroblastoma, and glioblastoma. The most effective clinical usage of all-trans RA in human disease was demonstrated in treatment of a rare leukemia, acute promyelocytic leukemia (APL). APL is characterized by selected expansion of immature myeloid precursors or malignant myeloid cells blocked at the

promyelocytic stage of hemopoietic development. APL cells invariably express aberrant fusion proteins involving the DNA and ligand binding domain of RAR α [74,75]. Other fusion partners include the promyelocytic leukemia zinc finger gene, the nucleophosmin gene, the nuclear mitotic apparatus gene, and the Stat5b gene, while the most common fusion partner is promyelocytic leukemia protein (PML). The PML-RAR α chimeric receptor is created by a balanced reciprocal chromosomal translocation, t(15;17)(q22;q11). The expressed PML-RAR α chimeric receptor alters normal function of RARs. PML-RAR α can form a homodimer through the coiled-coil motif of PML, inhibiting RAR α 's ability to bind to RA responsive elements, thereby preventing activation of downstream target genes [76,77]. In addition, RXR is an essential component of the oncogenic PML/RAR α complex suggesting RXR can be a drug target for APL [78,79]. In 1995, the FDA approved all-trans RA for treating APL. The all-trans RA-induced differentiation of APL cells is due to both its ability to promote the degradation of the mutant PML-RAR α and the dissociation of its co-repressors [80]. All-trans RA also causes cell cycle arrest at G1 phase and inhibits cell proliferation [81]. In addition, high concentration of all-trans RA induces post-maturation apoptosis of APL-blasts through the induction of the tumor-selective death ligand tumor necrosis factor-related apoptosis-inducing ligand TRAIL [82].

RA syndrome is a life-threatening complication seen in APL patients treated with all-trans RA. This syndrome is characterized by dyspnea, fever, weight gain, hypotension, and pulmonary infiltrates. It can be effectively treated by giving dexamethasone and holding off all-trans RA treatment in severe cases. An elevated white count is sometimes associated with this syndrome, but is not a prerequisite. The etiology of RA syndrome is not clear; several causes have been speculated including a capillary leak syndrome from cytokine release from the differentiating myeloid cells. Alternatively, all-trans RA may cause the maturing myeloid cells to acquire the ability to infiltrate organs such as the lung [83].

5.2. 9-cis RA (alitretinoin)

9-cis RA differentiates itself from all-trans RA in its ability to activate both RAR and RXR. In addition, 9-cis RA activates PPAR, FXR, PXR, VDR, and CAR via RXR. In preclinical studies, 9-cis RA is effective in the prevention of mammary and prostate cancer [84,85] and it has also been FDA-approved for the topical treatment of cutaneous lesions of Kaposi's sarcoma [86]. In addition, 9-cis RA and all-trans RA can individually induce apoptosis of human liver cancer cells [87]. 9-cis RA not only regulates nuclear genes, but also mitochondria gene transcription [88].

5.3. 13-cis RA (isotretinoin)

13-cis RA is unique that it exhibits immunomodulatory and anti-inflammatory responses. It inhibits ornithine decarboxylase, thereby decreasing polyamine synthesis and keratinization [89]. 13-cis RA noticeably reduces the production of sebum and shrinks the sebaceous glands [90]. It stabilizes keratinization and prevents comedones formation [91,92]. The exact mechanism of action is unknown. This combination of regulating proliferation, differentiation, and inflammation could make 13-cis RA a more effective drug in comparison to other retinoids, which may cause inflammation and irritation [93].

13-cis RA is in clinical trial for different types of cancers, and thyroid cancer received a lot of attention. In follicular thyroid cancer cells, 13-cis RA induces radioiodine avidity of cells formerly unable to accumulate radioiodine [94]. In human thyroid carcinoma cell lines, retinoids induce the expression of type I iodothyronine-5'-deiodinase and sodium/iodide-symporter, which are the thyroid differentiation markers [95]. However, approximately 30% of thyroid tumors dedifferentiate after treatment and thus develop into highly malignant anaplastic thyroid carcinomas [96]. 13-cis RA is also used to treat non-operable thyroid

follicular tumors, which fail to uptake radioiodine. 13-cis RA increases the radioiodide uptake in some patients. The beneficial outcome of this treatment was interpreted as partial re-differentiation of thyroid cancer cells. This effect of 13-cis RA requires the existence of functional RXR [96]. The effect of 13-cis RA on thyroid cancer has been reviewed extensively [97]. Besides thyroid cancer, utilizing 13-cis RA for maintenance therapy has significantly improved the outcome of patients with a high-risk form of neuroblastoma [98]. Along the same line of work, Krüppel zinc-finger protein ZNF423 is critical for RA signaling and is likely a prognostic marker for neuroblastoma [99]. 13-cis RA is also effective in preventing head and neck cancer, which is discussed below.

5.4. Synthetic Retinoids

N-(4-hydroxyphenyl) retinamide (Fenretinide or 4HPR) was first synthesized in the late 1960s by R. W. Pharmaceuticals. Since then, the biological properties of fenretinide have been of great interest. Currently, fenretinide is one of the most promising clinically tested retinoids. The modification of the carboxyl end of all-trans RA with an N-4-hydroxyphenyl group resulted in increased efficacy as a chemoprevention agent as well as reduced toxicity when compared with other retinoids [100]. Animal models have demonstrated that treatment with fenretinide prevents chemically induced cancers of the breast, prostate, bladder, and skin [101–104]. Furthermore, the combination of tamoxifen with fenretinide produces efficacy greater than either chemical alone [105].

Natural retinoids like all-trans RA induce differentiation and/or cytostasis in target cells [106–108], while fenretinide has distinct biologic effects including the induction of apoptosis by generating reactive oxygen species (ROS) and lipid second messengers [104]. The apoptotic effect of fenretinide has been documented in a variety of cancer cells including transformed T cells, B cells and breast epithelial cells, as well as bladder, breast, cervical, colon, embryonal, esophageal, head and neck, lung, ovarian, pancreatic, prostate, and skin carcinomas [100]. Furthermore, fenretinide does not induce point mutations or chromosomal aberrations, and is therefore not genotoxic [109]. These qualities suggest that fenretinide could be used for a long-term chemopreventive modality. In animal models, fenretinide has demonstrated chemopreventive efficacy against carcinogenesis of the breast [110], prostate, pancreas, and skin [104,111,112]. Moreover, in a clinical setting, fenretinide slowed the progression of prostate cancer in men diagnosed with an early stage of the disease [113]. Fenretinide protected against the development of ovarian cancer and a second breast malignancy in premenopausal women who had been treated to prevent the progression of early-stage breast cancer [114]. It also prevented relapse and the formation of secondary primary lesions in patients following the surgical removal of oral leukoplakia [115]. Recent studies also illustrated the anti-angiogenic [116] and anti-fibrotic [117] effect of fenretinide. Furthermore, long-term fenretinide treatment prevents high-fat diet-induced obesity, insulin resistance, and hepatic steatosis [118].

The mechanisms associated with fenretinide-induced apoptosis have been explored, but are not well-understood [100]. The components that lead to ROS generation and cause cell death are largely unknown. Depending on cell types and models used, the effect of fenretinide has been shown to be RAR β -dependent or -independent [119]. Our data showed that fenretinide-induced apoptosis of human liver cancer cells was RAR β -dependent [120]. Furthermore, induction and cytoplasmic localization of Nur77 dictates the sensitivity of liver cancer cell to fenretinide-induced apoptosis [121]. It seems that fenretinide enriches the cytoplasmic Nur77 to target mitochondria and induce cell death. The relationship between RAR β and Nur77 in mediating fenretinide-induced apoptosis remains to be determined.

A retinoid-related molecule 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalenecarboxylic acid (AHPN) (also called CD437) and its analog (E)-4-[3-(1-adamantyl)-4-

hydroxyphenyl]-3-chlorocinnamic acid (3-Cl-AHPC) also have Nur77-dependent apoptotic effects [122–124]. AHPN is structurally distinct from fenretinide. AHPN-induced apoptosis activates JNK [125–127], which is required for maximal apoptosis induction and precedes mitochondrial depolarization. Induction of apoptosis of breast and prostate cancer cells by AHPN is also associated with its inhibition of Akt activity [128]. Thus, induction of JNK and inhibition of Akt phosphorylation of Nur77 contribute to Nur77 nuclear export mediated by AHPN [129].

While many synthesized RAs are promising for cancer treatment, only a few are FDA-approved or currently undergoing clinical trials for cancer therapy. A number of retinoids, which have been FDA-approved for dermatological purposes, have potential for cancer treatment. Bexarotene (Targretin) is a synthetic retinoid approved by the FDA to treat skin problems caused by cutaneous T-cell lymphoma that are unresponsive to other treatments [130]. Other synthetic retinoids, such as TAC-101 (Taiho Pharmaceutical, Tokyo, Japan) has shown efficacy in inhibiting tumor growth in the liver and markedly increases survival in both the primary HCC and metastatic colon cancer models [131]. TAC-101 is currently in phase II trial for hepatocellular carcinoma and has shown good preliminary success [132]. Another, Tazarotene (AVAGE™) (Allergan, Irvine, CA) is in phase I trials for the treatment of lymphoma [133]. Please see table 1 for a brief characterization of some of retinoids that are in use or in clinical trials.

Retinoids are frequently tested in head/neck, skin, lung, and breast cancer. The followings summarize those findings.

5.5. Retinoids in Head/Neck and Skin Cancers

While RAs are considered effective for treating cancer, they are also used in cancer prevention of head/neck and skin cancers. Leukoplakia, actinic keratosis, and cervical dysplasia are the three precancerous lesions that can be effectively treated by the classical retinoids, such as 13-cis RA [134,135]. In cancer prevention, classical retinoids delay the development of skin cancer in individuals with xeroderma pigmentosum, an inherited predisposition to UV-induced cancer [6]. RAR β plays a critical role in mediating the growth-inhibitory effect of retinoids in various types of cancer cells, which include breast cancer [136,137], lung cancer [138], ovarian cancer [139], prostate cancer [140], neuroblastoma [141], renal cell carcinoma [142], pancreatic cancer [143], liver cancer [144], and head and neck cancer [145]. In oral cancer, after 3 months of high-dose 13-cis RA treatment, a significant induction of RAR β was noted and its expression level correlated with the intracellular RA levels [146]. Among the RAR β isoforms, RAR β 2 is the most abundant and inducible form and has tumor suppressor activity. In contrast to β 2, RAR β 4 has oncogenic activity [147]. Thus, β 2 and β 4 have antagonistic effect in carcinogenesis. Benzo(a)pyrene diol epoxide, a carcinogen presented in tobacco, suppresses RAR β 2 expression. Moreover, up regulation of RAR β is associated with a positive clinical response to retinoids in patients with premalignant oral lesions [148,149]. The expression of RAR β can be transcriptionally regulated by RAR β itself and epigenetically regulated by DNA methylation and histone acetylation [150,151].

In skin cancer, RAR α and γ mRNA levels are decreased in benign skin tumors in mice [152] and the mRNA level is essentially absent in human undifferentiated squamous cell carcinomas [153]. Priming human skin with RA prevents AP-1-induced matrix-degrading metalloproteinase genes caused by UV irradiation [154,155]. Irradiation human skin using UV rapidly reduces RAR α and γ and loses RA-responsive gene expression in human skin [156]. Essentially, UV irradiation causes a functional vitamin A deficiency in skin, which begins at UV doses that do not cause detectable sunburn. In animal models, RA dramatically delays and reduces chemical-induced squamous carcinoma [157,158]. The anti-tumor effect

could be due to the anti-AP1 activity of the RA [159,160]. In humans, retinoids reverse photodamage to skin [161].

5.6. Retinoids and Lung Cancer

Beta-carotene and retinoids were the most promising agents against common cancers when the National Cancer Institute mounted a substantial program of population-based trials in the early 1980s [162]. However, major lung cancer chemoprevention trials demonstrated these agents had no beneficial effects in preventing cancer. Furthermore, these trials showed significant increases in lung cancer incidence, cardiovascular disease, and total mortality. Several intervention trials have been completed; most of them included supplementation with β -carotene with or without other nutrients. The α -Tocopherol, β -Carotene Cancer Prevention Study (ATBC) was a randomized double-blind placebo-controlled primary-prevention trial to test whether daily supplementation with α -tocopherol (50 mg/day), β -carotene (20 mg/day), or both, would reduce the incidence of lung cancer in 29,133 male smokers [163]. The β -Carotene and Retinol Efficacy Trial (CARET) enrolled 18,314 men and women at high risk for lung cancer. This trial evaluated combined supplementation with β -carotene (30 mg/day) and retinyl palmitate (25,000 IU/day) for an average of 4 years [164]. The Physicians' Health Study (PHS) was a randomized double blind placebo-controlled trial of β -carotene (50 mg on alternate days) supplementation for 12 years among 22,071 male physicians who were 40–84 years of age [165]. These studies concluded that retinoids reduce tumor occurrence and mortality in non-smokers, were beneficial for former smokers, but increased the risk of lung cancer in smokers. A later EUROSCAN study also showed a higher incidence of lung cancer among smoking participants who received β -carotene [166]. The highest serum concentrations of β -carotene during supplementation were observed in ATBC and CARET (medium 3.0 and 2.1 mg/l, respectively), whereas notably lower concentrations were found in the PHS (mean 1.2 mg/l). Thus, high serum concentrations of β -carotene might be detrimental to lung cancer patients who are current smokers. The mechanism that explains the higher incidence of lung cancers observed in smokers who received β -carotene is not clear. Our recent data indicate that retinoids via PXR, CAR, and VDR regulate the expression of cytochrome P450 gene expression and thus xenobiotic metabolism [33–35]. Thus, it is possible that retinoids may facilitate the bio-activation of the carcinogens in cigarettes and enhance lung carcinogenesis.

Deletion of chromosome 3p14-p25 is frequently found in non-small cell lung carcinoma (NSCLC) [167]. The RAR β 2 gene is mapped at 3p24, and its expression is frequently suppressed in lung cancer cell lines [168,169]. Reduced expression of RAR β 2 mRNA is also found in bronchial biopsy specimens from heavy smokers [170], head and neck [171], and breast [172] as well as liver cancer cell lines [144]. Epigenetic modification of the RAR β gene causes reduced RAR β 2 expression, which may lead to carcinogenesis. Although the aberrant expression of RAR β is associated with lung cancer, the majority of human and experimental NSCLC are resistant to all-trans RA, bexarotene, and CD437 [173,174]. Reduced expression of RAR β 1' may account for the resistance of lung cancer cells to RA [175]. In addition, the expression of RAR β is positively associated with the expression of COUP-TF and the growth inhibition by RA in lung cancer cell lines [176]. COUP-TF is required for RA to induce RAR β expression, growth inhibition, and apoptosis in cancer cells. In addition, COUP-TF induces transcriptional activity of the RAR β promoter in a RA- and RAR α -dependent manner through its binding to a DR-8 element in the RAR β promoter. Thus, COUP-TF is an accessory factor for RAR α to recruit its coactivator and induces RAR β promoter activity [177].

5.7. Retinoids and Breast Cancer

Almost every major retinoid is currently in clinical trials by itself or in combination with interferons and estrogen antagonists to treat or prevent the progression of breast cancer [70,178,179]. Retinoids are able to inhibit mammary gland cancer in animal models and human breast cancer. They are effective inhibitors of breast cancer cells at the early stages of tumor progression, but their effectiveness diminishes as the tumors become more aggressive. RARs are differentially expressed in lactating and post-lactating glands. Rat post-lactating mammary glands express all RAR and RXR subtypes, whereas non-lactating mammary tissues only express RAR α and RXR α subtypes [180]. Retinoid receptors are also differentially expressed in normal and malignant epithelial cells and are implicated in carcinogenesis [179]. However, hormone-dependent and -independent breast cancer cells have the similar expression pattern of RAR α , RAR γ , RXR α , and RXR β [181]. Growth inhibition of breast cancer cells by RA has been associated with induction of the expression of RAR β . Conversely, RAR β gene expression is up regulated in normal mammary epithelial cells upon RA treatment. Deficiency of the RAR β expression and deficient responsiveness of retinoids via RAR β may account for decreased treatment efficacy in patients with advanced breast tumors [182].

9-cis RA and LGD1069 (Targretin, Bexarotene), a synthetic RXR-selective agonist, are superior to all-trans RA as a chemopreventive compound in the 1-methyl-1-nitrosourea (MNU)-induced rat mammary gland carcinoma model [183,184]. Targretin is well tolerated during chronic therapy with no classic signs of retinoid-associated toxicities. In animal mammary gland carcinoma models, other promising retinoids are retinyl acetate or fenretinide. The potency of retinoids to inhibit proliferation of breast cancer cells was demonstrated when retinoids were administered either alone or in combination with antiestrogens [70]. Tamoxifen and fenretinide combination therapy is an active treatment regimen in metastatic breast cancer patients, but not in estrogen receptor negative metastatic breast cancer or in patients whose disease had progressed after tamoxifen treatment [185]. Retinoids do not require estrogen receptors for their actions; they may affect neoplastic transformation in estrogen-negative cells, in contrast to tamoxifen, whose primary mechanism of action is through estrogen receptors [186,187]. In spite of this, retinoids and rexinoids seem to be more active in estrogen-positive than in estrogen-negative precancerous tissue [188]. Furthermore, retinoids can promote apoptosis of breast cancer cells and that effect is RAR β dependent. Recent study showed that the estrogen-responsive B box protein (EBBP) restores retinoid sensitivity in retinoid-resistant cancer cells via effects on histone acetylation [189]. Despite a number of important findings achieved recently by many laboratories, the precise mechanism(s) by which natural or synthetic retinoids inhibit the growth of breast cancer cell has not been completely elucidated. Great interest has been recently focused on rexinoids in combination with selective estrogen receptor modulators, which dramatically inhibit breast cancer cell growth and induce apoptosis even with intermittent administration [179].

6. Conclusions

Retinoids have a wide spectrum of functions. They are essential for normal development, but can cause congenital abnormality. They are critical for growth, but also have apoptotic effect. They have anti-proliferative and differentiation effects thus are used for cancer prevention and treatment, but they potentially can also increase the risk of cancer. Our recent publication indicating hepatocyte RXR α dictates hepatocyte proliferation during liver regeneration clearly indicates that activation of RXR α may have beneficial (tissue repair and regeneration) as well as detrimental (hepatomegaly) effect [190]. Because of wide usage of retinoids, their effects in cell proliferation cannot be ignored [191]. Since retinoids can activate multiple nuclear receptor mediated pathways, it is crucial to identify the specificity

of retinoid in activation of each nuclear receptor-mediated pathways. Recent progress in high-throughput chromatin immunoprecipitation sequencing (ChIP-seq) can help us to identify ligand/nuclear receptor-dependent signaling *in vivo*, which in turn assist us to design or utilize nuclear receptor specific ligand in order to avoid unwanted effects. In addition to gene transcription, the non-genomic signaling of retinoids deserves more attention [192]. By using ChIP-seq data with microarray or proteomic data, we should be able to identify genomic vs. non-genomic signaling. Knowledge earned using this type of approach can pave the way for the synthesis of new pharmacological agents with extended therapeutic repertoire, reduced toxicity, and improved therapeutic index.

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Figure 1. Retinoid Pathway

Retinoids absorbed from food are converted to retinol and bound to CRBP in the intestine. Then, retinol is converted to retinyl esters and enters into blood circulation. The liver up takes retinyl esters, which are converted to retinol-RBP complex in the hepatocyte. In the serum, the retinol-RBP complex is bound to transthyretin (TTR) in a 1:1 ratio to prevent elimination by the kidney and to ensure retinol is delivered to the target cell. The uptake of retinol by the target cell is mediated by a trans-membrane protein named “stimulated by retinoic acid 6” (STRA6), which is a RBP receptor. In the target cell, retinol either binds to CRBP or is oxidized to retinaldehyde by retinol dehydrogenase (RDH) in a reversible reaction. Then, retinaldehyde can be oxidized by retinaldehyde dehydrogenase (RALDH) to RA. In the target cell, RA either binds to CRABP or enters the nucleus and binds to nuclear receptors to regulate gene transcription. Alternatively, RA can mediate via nongenomic mechanism and regulate cellular function. Hepatocytes not only process retinoids, but also are the target cells. In addition, hepatocytes located next to the storage site (stellate cell). Thus, retinoid-mediated signaling must have a profound effect in regulating hepatocyte function and phenotype [36,190,191]

Table 1

Retinoids: action, targets, and usage

Drug	Target	Effect	Current Clinical Trials	Reference
<p>All-trans RA (Tretinoin)</p>	RAR	<ul style="list-style-type: none"> Natural ligand of RAR Through RAR, all-trans RA exerts a variety of effects from transcriptional control of growth and differentiation genes to AP-1 inhibition 	<ul style="list-style-type: none"> Launched: Acne, APL, Warts, and Psoriasis Phase I: Asthma Phase II: Rosacea, Amyotrophic Lateral Sclerosis, Neuroblastoma, Head and Neck Cancer, Photodamage, Lymphoma, Melanoma, Lung Cancer, Kidney Cancer, Emphysema, and Glioblastoma Phase III: Skin Aging and Lung Cancer 	[8,192]
<p>9-cis RA (Alitretinoin)</p>	RAR and RXR	<ul style="list-style-type: none"> Activate RXR and thus activate the heterodimer of RXR and PPAR, VDR, LXR, FXR and PXR This expands its effects to lipid metabolism, drug interactions, etc. 	<ul style="list-style-type: none"> Launched: Acne, APL, Psoriasis, and Kaposi's Sarcoma Phase I: Breast Cancer, Low HDL Cholesterol, and Asthma Phase III: Eczema and Hand Dermatitis 	[8,192]
<p>13-cis RA (Isotretinoin)</p>	RAR	<ul style="list-style-type: none"> Reduces the production of sebum and shrinks the sebaceous glands Stabilizes keratinization and prevents comedones formation. Decrease cyclin B1 and Bcl-2 expression 	<ul style="list-style-type: none"> Launched: Acne Phase II: Photodamage, Cervical Cancer, Lung Cancer, Prostate Cancer, Lymphoma, Glioblastoma, Neuroblastoma, Skin Cancer, Penile Cancer, and Emphysema Phase III: Brain and Central Nervous 	[193]

Drug	Target	Effect	Current Clinical Trials	Reference
<p>Ethyl 6-[2-(4,4-dimethyl-2,3-dihydrothiochromen-6-yl)ethynyl]pyridine-3-carboxylate (Tazarotene)</p>	RAR β and RAR γ	<ul style="list-style-type: none"> Chemoprevention of basal cell carcinoma in the Ptc^{-/-} mouse model Clinical study revealed efficacy in human basal cell carcinoma treatment Down regulates Gli1 and up regulates CRABP2 	<ul style="list-style-type: none"> Launched: Acne, Psoriasis, and Photodamage Phase II: Lymphoma 	[133]
<p>MDI 301</p>	Not Identified	<ul style="list-style-type: none"> Anti-neoplastic in breast, prostate cancer cell lines, neuroblastoma, and leukaemia cell lines Has topical efficacy and lack of skin irritation 	<ul style="list-style-type: none"> Preclinical: Acne, Cancer, Photodamage and Psoriasis 	[194]
<p>R667</p>	RAR γ	<ul style="list-style-type: none"> Regenerates lung tissues and restores lung function in animal models 	<ul style="list-style-type: none"> Phase II: Emphysema 	[195]

Drug	Target	Effect	Current Clinical Trials	Reference
<p>4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzoic acid (Bexarotene)</p>	RXR	<ul style="list-style-type: none"> G1 and/or G2/M arrest and down regulation of cyclin D Induces apoptosis and differentiation with activation of caspase-3 and cleavage of PARP, and inhibition of surviving Prevents and overcomes multidrug resistance by modulating MDR1 expression Inhibits angiogenesis and metastasis by reduction in MMPs, VEGF, and EGF as well as increase in TIMPs secretion 	<ul style="list-style-type: none"> Launched: Cutaneous T-cell lymphoma Phase 0: Thyroid Cancer Phase II: Lung Cancer, Leukemia, Psoriasis, Cushing's Disease, and Breast Cancer Phase III: Schizophrenia 	[130]
<p>8-(3',4'-dihydro-1'-(2'H)-naphthalen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoic acid (9-cis UAB30)</p>	RXR	<ul style="list-style-type: none"> Down regulates DNA methyltransferases Anti-telomerase activity 	<ul style="list-style-type: none"> Preclinical: Cancer 	[196,197]
<p>N-(4-Hydroxyphenyl)retinamide (Femretinide/4HPR)</p>	RAR	<ul style="list-style-type: none"> ROS generation RARβ activation Nur77 nuclear export 	<ul style="list-style-type: none"> Phase I: Neoblastoma, Phase II: Brain and Central Nervous System Tumors, 	[100,120,121]

Drug	Target	Effect	Current Clinical Trials	Reference
		<ul style="list-style-type: none"> • Ceramide and Ca^{++} mobility • Caspase cleavage 	<p>Lymphoma, Prostate Cancer, Head and Neck Cancer, Melanoma, Ovarian Cancer, Kidney Cancer, Lung Cancer, Geographic Atrophy, and Insulin Resistance</p> <ul style="list-style-type: none"> • Phase III: Breast Cancer, Bladder Cancer, Cervical Cancer, and Ewing's Sarcoma 	
<p>6-[3-(1-adamanty)-4-methoxyphenyl]naphthalene-2-carboxylic acid (Adapalene)</p>	RAR	<ul style="list-style-type: none"> • More chemically stable and lipophilic than all-trans RA • Modulates cellular keratinization • Inhibits lipooxygenase activity and oxidative metabolism of arachidonic acid to exert anti-inflammatory effect 	<ul style="list-style-type: none"> • Launched: Acne • Phase III: Skin Aging • No development reported: Multiple Sclerosis 	[198]
<p>Anhydroretinol</p>	Not Identified	<ul style="list-style-type: none"> • Metabolite of vitamin A • Induces human B lymphoblastoid S/2 cell death by increasing intracellular oxidative stress in a time- and dose-dependent manner 	No known trial currently underway	[199]

Drug	Target	Effect	Current Clinical Trials	Reference
6-[3-(1-adamanty)-4-hydroxyphenyl]-2-naphthalenecarboxylic acid (AHPN/CD437)	RAR γ	<ul style="list-style-type: none"> Induces apoptosis in various cancer cell lines Causes ER stress Nur77 nuclear export SHP mitochondrial association. Shows apoptogenic activity in retinoid resistant cells and in RARγ-negative cells 	No known trial currently underway	[200,201]
3-[4-[3-(2-adamanty)-4-hydroxyphenyl]phenyl]prop-2-enoic acid (AHPN/ST1926)	Not Identified	<ul style="list-style-type: none"> Similar to AHPN Causes genomic instability leading to apoptosis 	<ul style="list-style-type: none"> Phase I: Ovarian cancer 	[202]
3-[4-[3-(1-adamanty)-4-hydroxyphenyl]-3-chlorophenyl]prop-2-enoic acid (3-Cl-AHPN)	Small Heterodimer Partner (SHP)	<ul style="list-style-type: none"> Enhanced interaction between SHP and a multiprotein repressor complex containing the repressor mSin3A, the NR corepressor NCoR, histone deacetylase 4, and heat shock protein 90 Attenuation of proto-oncogene c-Myc mRNA and protein expression NF-κB activation and increase c-Fos/c-Jun expression 	No known trial currently underway	[203]

Drug	Target	Effect	Current Clinical Trials	Reference
<p>MX781 (CD 2674)</p>	RAR and RXR antagonist	<ul style="list-style-type: none"> Induction of apoptosis by caspase 2 Inhibits IκBβ 	No known trial currently underway	[204]
<p>3,7,11,15-tetramethylhexadeca-2,4,6,10,14-pentaenoic acid (Acyclic retinoid/NIK333/polyprenoic acid)</p>	RXR and RAR	<ul style="list-style-type: none"> Induces growth inhibition by suppressing the VEGF-MAPK and Ras-MAPK pathways. 	<ul style="list-style-type: none"> Phase II: Hepatocellular Carcinoma 	[205,206]
<p>(4-nitrophenyl)amino][2,2,4,4-tetramethylthiochroman-6-yl]amino]methanethione (SHetA2)</p>	Not Identified	<ul style="list-style-type: none"> Sensitizes ovarian cancer cells to TNFα induction of the extrinsic apoptosis pathway Exhibits receptor independent mitochondria mediated apoptosis 	No known trial currently underway	[207]
<p>4-[3,5-bis(trimethylsilyl) benzamido] benzoic acid (TAC 101)</p>	RARα	<ul style="list-style-type: none"> AP-1 inhibition Inhibits tumor growth in the liver, exhibits low toxicity, and markedly increases survival in both the primary HCC and metastatic colon cancer models 	<ul style="list-style-type: none"> Phase II: Hepatocellular Carcinoma 	[132]

Note: This table represents the most studied retinoids over the past few years. Retinoids that have not been published on in the last five years were not included.