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Review

Retinoids and their biological effects against cancer

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ABSTRACT

There are more than 4000 natural and synthetic molecules structurally and/or functionally related to vitamin A. Retinoids are a class of these compounds that are structurally associated to vitamin A. The retinoids have a wide spectrum of functions. Retinoic acid, which is the active metabolite of retinol, regulates a wide range of biological processes including development, differentiation, proliferation and apoptosis. It suppresses carcinogenesis in tumorigenic animal models for the skin, oral, lung, breast, bladder, ovarian and prostate. It is important how major retinoids may act in cancer treatment or prevention. The reports have indicated that lower levels of vitamin A in humans may be associated with relative type 1 cytokine dominance and a higher proportion of NK cells. In addition, very low vitamin A levels would be undesirable explaining the essential role of vitamin A in epithelial and general cell maturation and function. However, the cytokine shifts associated with moderately low levels of vitamin A may be in some ways beneficial in an environment where HIV infection, *M. tuberculosis* infection, or other type 1 infections are highly prevalent and/or when acquired immunity is cooperated. In this review, we intend to describe the biochemical and immunological functions of retinoids against cancer.

Contents

1. Introduction

Vitamins and minerals are nutrients required by the body for normal growth and protection. Examples of these nutrients include vitamins B complex, A, D, K, E, magnesium and calcium [44]. 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 [13].

The body obtains vitamin A from two sources: preformed vitamin A (retinol and retinal in the form of retinyl esters) and provitamin A carotenoids (β-carotene, α-carotene, β-cryptoxanthin; Fig. 1) [18]. Preformed vitamin A is found in butter, eggs, animal products and grains. Provitamin A carotenoids are found in highly pigmented vegetables such as carrots, squash and yams. Once in the body, retinol is ultimately converted into retinoic acid and its isoforms, collectively known as retinoids. Provitamin A carotenoids particularly β-carotene, have also been studied for the prevention of lung cancers. Beta-carotene acts in part through its conversion to vitamin A in the intestine and liver. It has been estimated that up to 88% of β-carotene is converted to retinyl esters in the intestinal wall, while up to 30% enters lymphatic circulation unchanged. Beta-carotene that reaches the liver undergoes further conversion to retinol, however a small percentage enters the blood unchanged [18]. Beta-carotene is one of hundred carotenoid compounds found in richly colored fruits and vegetables. Beta-carotene can be metabolically cleaved into two molecules of vitamin A. Some biological functions of β-carotene include

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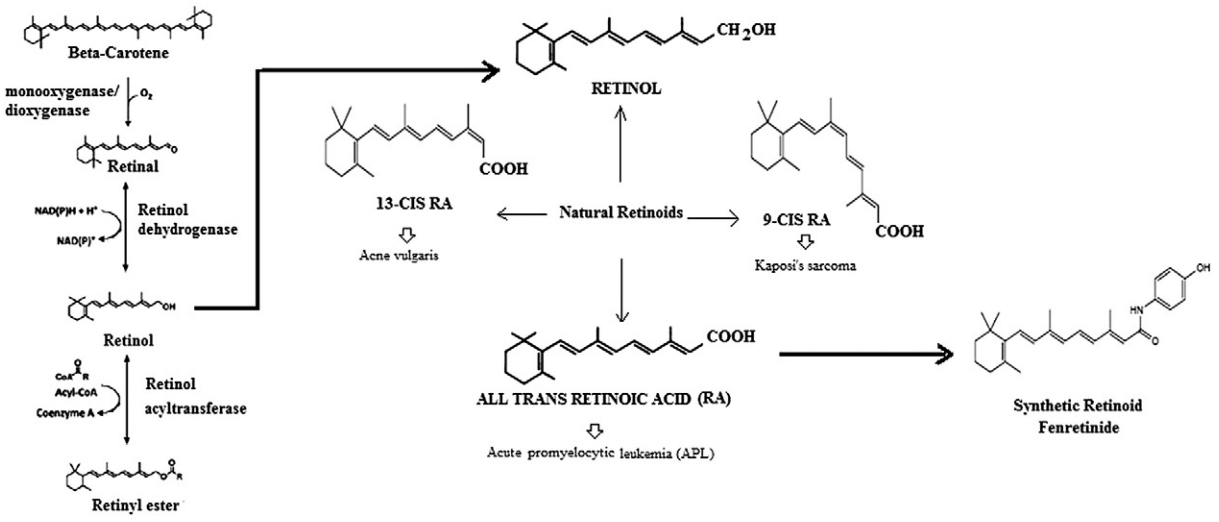

Fig. 1. Generation of retinoids from β-carotene and their use for therapy of different diseases.

anti-oxidant properties, increasing natural killer cell (NK-cell) activity and improved lung function. Beta-carotene is also an approved drug [44]. Retinoids (vitamin A and its natural and synthetic analogs) and carotenoids have been shown to inhibit the growth of certain types of tumor cell lines [5]. Our reports confirm one hypothesis that anti-cancer effect of carotenoids is due to their interaction with DNA and reduction in the H1–DNA complexes [6–8].

Retinoids are lipophilic isoprenoids composed of a cyclic group and a linear chain with a hydrophilic end group. These compounds include retinol, retinal, retinoic acid, retinyl esters and various derivatives of these structures [Fig. 1]. Retinoids are used as cosmetic agents and effective pharmaceuticals for skin diseases [9,27]. Animals produce retinoids from carotenoids (e.g., β-carotene) obtained from fruits and vegetables, but plants cannot synthesize retinoids [27]. The role of vitamin A and its analogs (retinoids) in the modification of skin tumor promotion as well as in the prevention of epithelial cancers is well documented. Systemic applications of high doses of retinoids have a prophylactic effect on skin tumor promotion and a therapeutic effect on established skin papillomas and carcinomas [48,49].

Both natural and synthetic retinoids have recently been shown to inhibit mammary carcinogenesis in the experimental animal. Although, these studies indicate a new approach to the prevention of breast cancer in human subjects, but, the potential chronic toxicity of the retinoids should be considered in the experimental studies. For instance, retinyl methyl ether is also more effective than retinyl acetate for inhibition of mammary carcinogenesis induced in rats by 7, 12-dimethylbenz-(α) anthracene [39]. Furthermore, among dietary factors, vitamins A, C and E have been hypothesized to reduce the risk of colon cancer because of their anti-carcinogenic properties. In this approach, vitamin A regulates nuclear receptors that suppress tumor formation, induces cell apoptosis and enhances immune function [40]. Retinoic acid (RA) has also been shown to down-regulate markers of proliferation such as hTERT and cyclins D1 and 3, markers of DNA damage such as 8-oxo Guanine and growth factors such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), potentially inhibiting tumor growth, angiogenesis and metastasis. Retinoids are also thought to modulate additional targets such as reactive oxygen species, mitochondrial permeability, lipoxygenase, cyclooxygenase-2 (Cox-2), nuclear factor- B, ubiquitination, tumor necrosis factor-α (TNF-α), c-Myc, Ap-1 and cell surface death receptors [18]. Briefly, there are three generations of retinoids including a) First generation (retinol, retinal, tretinoin/retinoic acid/retin-A, isotretinoin and alitretinoin); b) Second generation (etretinate and its metabolite acitretin); c) Third generation (tazarotene, bexarotene and adapalene) [Table 1]. Up to now, two families of retinoid acid receptors, the RAR isotypes and the three RXR isotypes have been identified [Table 2]. The retinoic acid receptor (RAR) is a type of nuclear receptor which can also act as a transcription factor that is activated by both all-trans retinoic acid and 9-cis retinoic acid [3,20]. There are three RAR, RAR-α, RAR-β and RAR-γ encoded by the *RARA*, *RARB*, and *RARG* genes, respectively. The retinoid X receptor (RXR) is a type of nuclear receptor that is activated by 9-cis retinoic acid. There are three RXR, RXR-α (known as NR2B1, nuclear receptor subfamily 2, group B, member 1), RXR-β (known as NR2B2) and RXR-γ (known as NR2B3) encoded by the *RXRA*, *RXRB*, and *RXRG* genes, respectively [3,20]. RAR heterodimerizes with RXR and in the absence of ligand, the RAR/RXR dimer binds to hormone response elements known as retinoic acid response elements (RAREs) complexed with co-repressor protein. Binding of agonist ligands to RAR results in dissociation of co-repressor and recruitment of co-activator protein that, in turn, promotes transcription of the downstream target gene into mRNA and eventually protein [3,20]. Regarding to different properties of retinoids, we describe their biochemical and immunological effects against cancer in this review.

2. Retinoids and immunity

The essential roles of vitamins in modulating a broad range of immune responses have attracted a great attention including lymphocyte activation and proliferation, T-helper (Th)-cell differentiation, tissue-specific lymphocyte homing, the production of specific antibody isotypes and regulation of the immune response [37]. One of the main processes that affect the adaptive immune response is Th cell differentiation. The balance of Th1 and Th2 cell populations is of great importance for the generation of specific immune responses which is influenced by environmental factors. Th1 cells are responsible for protection against intracellular pathogens while Th2 cells are protective against extracellular parasites. The studies have suggested that vitamin A influences the process of naïve Th cell differentiation into Th1 or Th2 cells. In fact, Th cell differentiation is directly dependent not only on antigen stimulation but also on the cytokine levels, promoting a certain Th cell lineage. Vitamin A deficiently increases constitutive IL-12 and IFN-γ production by macrophages, but decreases IL-4 and IL-5 levels. On the other hand, supplemental treatment with vitamin A decreases IFN-γ but increases IL-5, IL-10 and IL-4 production. Therefore, a vitamin A deficiency biases the immune response in a Th1 direction whereas high level dietary vitamins may bias the response in a Th2 direction. RA is the most potent in restoring impaired antibody responses. Considering these data, RXR signaling plays an important role in Th cell differentiation. The experiments