

Retinoic Acid and Its Derivatives in Dermatological Disorders

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ABSTRACT

Retinoids are a group of compounds consisting of vitamin A and its active metabolite all-trans-retinoic acid (ATRA). Retinoids can regulate the physiological functions of various organs and tissues and play an important role in normalising immune function, cell growth and differentiation. Vitamin A derivatives have a role in the treatment of tumours and ATRA has a role in the differentiation therapy of acute promyelocytic leukaemia (APL). ATRA and other retinoids also have many applications in dermatological conditions (e.g. skin cancer, psoriasis). ATRA and other retinoids also have many applications in dermatological conditions (e.g. skin cancer, psoriasis, acne and ichthyosis). In addition, the physiological functions of skin cells can also be regulated by modulating retinoic acid receptors and retinoid X (or rexinoid) receptors. The results of numerous genetic modelling experiments have shown that the regulation of retinoic acid receptors (RARs) and retinoid X (or rexinoid) receptors (RXRs) may have great potential for the treatment of serious skin diseases such as skin cancer. Here, we provide a synopsis of the main advances in understanding the role of ATRA and its receptors in dermatology.

KEYWORDS

Retinoids; Retinoic acid receptor; All-trans-retinoic acid; Dermatology

1. INTRODUCTION

Retinoids, first discovered in 1913, are natural forms or metabolic derivatives of vitamin A [1, 2]. Retinol and retinyl ester, which can be obtained from food, are the forms of vitamin A that we commonly know [3]. However, these forms of vitamin A are not biologically active and must be converted by the human body via cytosolic alcohol dehydrogenases (ADHs) and microsomal retinol dehydrogenases (MDHs) to retinaldehyde and then to retinoic acid (RA) [4]. There are several isomers of RA, the most common being all-trans retinoic acid and 9-cis retinoic acid [5]. ATRA is the most abundant physiologically active metabolite of vitamin A [6]. Retinoids are hydrophobic and require binding proteins for transport in the human circulation. Depending on the tissue site, the body has different transport proteins that play binding roles, such as cellular retinol-binding proteins (CRBPs) or cellular retinoic acid-binding proteins (CRABPs), the interstitial retinol-binding protein (RBP 3), and plasma-retinol binding protein (RBP 4) [7]. RA has a half-life of about 1 hour in humans and can be metabolised by cytochrome P450 enzymes (CYP26). RA is not only a metabolite of CYP26s but also an inducer of CYP26s exerting negative feedback regulation. It has been suggested that CYPs or other possible mechanisms leading to ATRA deficiency may be closely related to the development of tumours and dermatological diseases [8].

2. RETINOIC ACID RECEPTORS AND PATHOPHYSIOLOGICAL MECHANISMS

Retinoic acid receptors play an important role as essential developmental regulators in the regulation of several physiological aspects of skin growth and development [9]. In the absence of ligands, retinoid X (or rexinoid) receptors and retinoic acid receptors (RXR-RAR) heterodimers bind to retinoic acid response elements (RAREs) on target genes and can effectively inhibit target gene transcription [10]. Binding of RXR-RAR to the ligand (ATRA) results in a decompression of chromosome helix 12, leading to the replacement of bound co-repressors by co-activators such as DRIP/TRAP/ARC (vitamin D3 receptor-interacting proteins/thyroid hormone proteins/thyroid hormone) [11]. The above alterations induce transcriptional activation of target genes through the process of chromosome de-helicalisation. Three types of translated genes have been identified for RAR (α , β and γ) and RXR. RXR and RAR must bind to form a dimer to regulate the signalling pathway after binding to several other nuclear receptors (e.g. involved in mediating the binding of thyroid hormones and vitamin D3). All three types of RAR genes can be expressed to synthesise two isoforms which, through splicing and differential promoter usage, can perform different biological functions [12]. RARs associated with proteasome-mediated degradation and up-regulation of RAR expression by ATRA may in turn be important in exerting and prolonging ATRA function [13].

CRABP has a high affinity for ATRA and transfers ATRA to the nucleus where it binds to the corresponding receptor [14]. As a result, CRABP II is currently used as a marker of RA activity in skin tissue, and CRABP II expression is significantly reduced in aged mouse or human skin and positively correlates with RA levels [15]. RAR α , RAR γ , and RXR are highly expressed in fibroblasts and keratinocytes, with RAR α being relatively highly expressed in fibroblasts, and RARs can dimerise with RXR to perform physiological functions [15-17]. However, RXR can also form dimers with thyroid hormone receptor, estrogen receptor, constitutive androstane receptor, vitamin D receptor and many other nuclear receptors to perform physiological functions. dimers to perform physiological functions. Therefore, the physiological functions of RA are exerted not only by RAR/RXR action, but also by RXR dimerisation with other receptors [18].

3. NON-GENOMIC EFFECTS OF ATRA

Like other nuclear receptor ligands, ATRA can also play a role in regulating physiological functions through the non-genomic pathway [16]. ATRA and other retinoids can regulate cellular kinases with high cell-specific affinity [6]. For example, PI3K and ERK1/2 can interact with ATRA through the non-genomic pathway to exert physiological functions. The specific mechanism of the non-genomic pathway of ATRA is still unknown, but its physiological and pathological effects on various cell types are worth considering for clinical applications. In addition, ATRA may also play a role in the regulation of gene transcription through a similar mechanism [5]. It has also been shown that ATRA can induce upregulation of G-CSF and GM-CSF receptor expression levels, thereby mediating a number of positive feedback signalling pathways [7]. Therefore, ATRA may exert physiopathological functions through both genomic and non-genomic pathways and its specific mechanism of action remains to be elucidated by further experiments [19].

4. RA AND DERMATOLOGICAL DISORDERS

The successful use of RA in acute promyelocytic leukaemia (APL) has opened a new chapter in its clinical application [20]. In addition, RA has applications in the treatment of skin cancer, ichthyosis, wrinkles and psoriasis [9, 17, 21]. The incidence of multiple-mechanism resistance to ATRA has also led to many limitations in its use in dermatological conditions. The main explanation for this may be related to the action of ATRA and CYPs. Therefore, topical application of ATRA may be more

effective in the treatment of dermatological conditions. Since ATRA exerts its therapeutic effects by regulating keratin expression, and ATRA may induce RA metabolism by the body, which may lead to the adverse effects of hyperkeratosis and keratolysis. Therefore, the therapeutic effect can be further enhanced by inhibiting ATRA 4-hydroxylase enzymes, which can further maintain ATRA levels in the human body. Inhibitors of RA metabolism (e.g. liarozole, azolyl retinoids, benzeneacetic acid derivatives) are currently under investigation [22].

5. RA AND SKIN DIFFERENTIATION

RA plays an important role in the regulation of skin differentiation [8]. In vitro experiments showed that RA is closely involved in promoting the motility of keratinocytes, reducing intercellular adhesion and enhancing their typical cellular morphogenesis. Keratin expression levels were also positively correlated with RA concentrations. When keratinocytes were cultured without RA, the synthesis level of keratin 1 (67 kDa), which reflects the maturation of keratinocytes, was increased, but the synthesis levels of keratin 8/18 (52 kDa) and keratin 19 (40 kDa) were decreased [14]. After administration of RA, the synthetic levels of keratin 7, keratin 13, keratin 15 and keratin 19 expression were increased, whereas the synthetic levels of keratin 1, keratin 5, keratin 6, keratin 10 and keratin 14 expression were decreased. ATRA regulates more than 3,000 genes in keratinocytes and exerts its regulatory effects on keratinocytes as soon as it is administered for 1 hour [15]. Most of the genes affected are involved in DNA synthesis and repair, cell cycle, translation, adhesion, transcription factors, RNA metabolism, apoptosis, receptor expression, protein kinase and membrane expression. RA also regulates its bioavailability by modulating the metabolic synthesis of ATRA. In a rat model, inhibition of RAR-dependent signalling induces immature epidermis formation in basal lamina cells by inhibiting keratinocyte differentiation. In adipose tissue, RA also plays an important role in the induction of preadipocyte differentiation [2-4, 16].

6. RA AND EPIDERMAL BARRIERS

The stratum corneum plays an important role in the formation of the epidermal barrier. The stratum corneum generally consists of 15-20 layers of corneocytes, which are keratinocytes characterised by the absence of cytoplasm and nucleus, intracellular lipid lamellae and corneodesmosomes. The stratum corneum is intimately involved in the body's physical defences, but when the internal or external environment affects its adhesion, differentiation and proliferation, the integrity of the epidermal barrier can be compromised [19].

The body normally protects itself through repair, a complex process known as wound healing; however, age and disease often lead to a significant reduction in wound healing and chronic wounds can develop [5, 16]. Lee et al. found that administration of a synthetic retinoid in a human skin trauma model promoted keratinocyte migration to accelerate trauma repair and promote the formation of the epidermal barrier [20]. The epidermal barrier is characterised by the flattening of the dermal-epidermal junction due to ageing and a reduction in the ability of keratinocytes to proliferate and differentiate [1]. RA or retinol may improve epidermal barrier function by promoting keratinocyte motility and proliferation [9]. Kong et al have also shown that RA or retinol can promote a significant increase in the thickness of the rete ridges by histopathological methods. In addition, some studies have confirmed that RA not only participates in the differentiation process of keratinocytes, but also reduces the synthesis of epidermal lipids by inhibiting the gene for lipid synthesis. In a murine model, Li et al. found that ATRA was able to affect the expression levels of several genes involved in barrier dysfunction, proteases, cornfield envelope and tight junction function. The authors found that ATRA down-regulated the expression of claudin-1, which plays an important role in epidermal barrier function [8].

7. ATRA AND DERMATOLOGICAL DISORDERS

Cohen et al. found that ATRA was effective in the treatment of multiple miliary osteoma cutis, and the authors suggest that the specific therapeutic mechanism may be related to the promotion of normal fibroblast differentiation, independent of ATRA-dependent transepidermal elimination [5]. Kong et al. found that ATRA was effective in increasing collagen type 1 (COL1A1) and collagen type 3 (COL3A1) gene expression levels, which increased skin thickness and may be effective in reducing the wrinkles associated with ageing. There is also a large body of evidence supporting the use of retinoids in the treatment of HPV [2, 5, 21]. Topical application of 0.05% ATRA cream (tretinoin) was effective in removing HPV warts (85% vs 32%). Oral treatment with ATRA (1 mg/kg) for 3 months was also shown to be effective. Retinoids can promote epidermal turnover and inhibit the replicative ability of HPV-infected keratinocytes [6]. ATRA was also found to be effective in inhibiting fibroblasts and other skin cells from UV-induced oxidative damage, and Cheng et al. found that ATRA was effective in protecting against oxidative stress damage. The possible mechanism is that ATRA exerts its therapeutic effect by activating Nrf2.

The role of ATRA in relation to RXR-RAR receptor binding was also investigated in a mouse model of photoaging [3]. It was found that ATRA inhibits UV-induced collagen fibre destruction and promotes collagen synthesis in photodamaged skin by binding to the RXR-RAR receptor. ATRA and RAR agonists activate type I procollagen protein expression and inhibit matrix metalloproteinase (MMP) activity. ATRA also leaves collagen synthesis unaffected by antagonising UV-induced activation of AP-1. Currently, most pharmaceutical forms of ATRA are cream-based. Studies have shown that 0.05% and 5% tretinoin creams are effective in ameliorating epidermal damage caused by photoaging and in controlling the clinical manifestations of stable actinic keratosis. ATRA has also been shown to be effective in improving epidermal morphology and ultrastructure in rats, thus playing an important role in maintaining the skin barrier [20].

Retinoids are now widely used in the treatment of psoriasis. Psoriasis is a chronic inflammatory skin disease with a life cycle of 4 days compared to the normal skin life cycle of 26 days [15]. The therapeutic mechanism of RA is still unclear. One study found that more than 100 abnormal genes are expressed in psoriasis lesions, and RA can regulate and 'normalise' 75% of these genes, thereby exerting a therapeutic effect.

Retinoic acid derivatives have also been shown to be effective in the treatment of basal cell carcinoma (BCC) [6]. Tazarotene has been shown to be effective in the treatment of BBCs, as evidenced by its ability to induce an increase in apoptosis and a decrease in proliferation of basaliomatous cells. Another retinoid drug - fenretinide (4-HPR) - is thought to be effective in inhibiting tumour cells in skin tissue.

Researchers have found that increased levels of ROS in melanoma cells may be involved in the phenomenon of drug resistance to retinoic acid derivatives. Orlandi found that under basaloid tumour in vitro conditions, tezarotene could concentrationally promote RAR β expression and induce apoptotic phenomena without affecting the level of expression of RAR α and RAR γ . The lack of RAR β expression in skin tumour cells is also one of the main reasons for their resistance to retinoic acid derivatives. In addition, upregulation of RAR α and downregulation of RAR γ have been found in melanoma cells [5, 21]. 13-Cis-retinoic acid (CRA) and histone deacetylase (HDA) inhibitors can increase the expression level of RAR β and have been shown to be effective in treating RA-resistant melanoma cell lines when combined with RA. Zhao et al. found that RAR γ -dependent induction of carbohydrate sulfotransferase 10 (CHST10) could effectively inhibit melanoma aggressiveness. In vitro assays showed that low concentrations of ATRA could effectively inhibit the viability of melanoma cells and reduce the activity of mitochondrial enzymes. At high concentrations of ATRA, primary and metastatic melanoma cells showed significant apoptosis, and the above activities induced by ATRA may be closely related to the death receptor pathway or the mitochondrial pathway [6, 10, 20].

8. LIMITATIONS OF USE

Adverse effects of systemic use of retinoids include drying of the skin and mucous membranes, teratogenicity, abnormalities in bone and muscle development, and effects on liver function and blood lipid levels. It is generally accepted that contraception is required for 3 months after discontinuation of isotretinoin and at least 2 years for acitretin. Topical use is mainly manifested by skin irritation, i.e. 'retinoic acid dermatitis', including skin erythema, scaling, stinging, burning and other symptoms, which is mainly mediated by RAR- γ .

9. CONCLUSION

Retinoids are widely used in dermatology, but their specific mechanism of action in the treatment of dermatological diseases needs to be further clarified. Adverse effects associated with their long-term use also require attention. In recent years, new types of retinoids have emerged, such as trimethoprim, mentioned above, as well as Palovarotene, Tamibarotene, etc., which have better receptor selectivity and may have fewer adverse effects, but their efficacy still needs to be further confirmed.

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