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REVIEW

Retinoids as an Immunity-modulator in Dermatology Disorders

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Abstract
The skin is the largest epithelial surface protecting the body from invading microbes. Vitamin A plays vital roles in the host defence of the skin, including promoting epithelial cell integrity, proliferation, and differentiation and even mediating immune responses. Furthermore, vitamin A derivatives, retinoid drugs, are widely used to treat skin diseases, such as acne and psoriasis. However, the immunoregulatory mechanisms of retinoids in dermatology have not been systematically described. In this paper, we discuss the immunological functions of retinoids during disease treatment, especially in skin disorders caused by exogenous infections.

Keywords Vitamin A · Retinoids · Immunity · Dermatology diseases · Infectious

Introduction

The skin is the largest epithelial surface protecting the body from invading microbes. In addition to epidermal keratinocytes, the skin hosts many types of immune cells, such as Langerhans cells, T lymphocytes, dendritic cells (DCs), natural killer (NK) cells, B cells, mast cells, and macrophages (Di Meglio et al. 2011). When the immune system is activated, the skin can rapidly produce peptide antibiotics and various cytokines to induce immune defences (Handfield et al. 2018; Matejuk 2018). Further, the skin is more at risk from external microbial infections when the immune system is impaired (Prescott et al. 2017).

Vitamin A is reported to play a vital role in skin tissue epithelial integrity, which promotes keratinocyte mitosis, increases epithelial thickness and maintains glycosaminoglycan synthesis (Czarnewski et al. 2017). As an essential immune system modulator, vitamin A also has an important effect on the development and regulation of immune cells. A deficiency in vitamin A can impair immune responses and aggravate existing inflammatory states in skin. Previous studies showed that a lower vitamin A level is associated with proportionately more NK cells and type 1 cytokine dominance, such as tumor necrosis factor (TNF)-α (Galimberti and Mesinkovska 2016; Jason et al. 2002). It has been reported that vitamin A deficiency decreases the phagocytic activity and bacteria-killing ability of peritoneal macrophages and increases the risk of infection by exogenous microorganisms, such as *Staphylococcus aureus* (Wiedermann et al. 1996). As reported, vitamin A deficiency is associated with various dermatology disorders, such as measles (Melenotte et al. 2012; Moss 2017), phrynoderma (Bleasel et al. 1999), and even spontaneous skin papilloma (Hansen et al. 2003). Accordingly, vitamin A supplementation can ameliorate inflammation, improve disease remission and improve the efficacy of therapy (Moss 2017).

So far, there are more than 4000 natural substances and synthetic derivatives found that are commonly known as retinoids. These compounds share a similar chemical structure with vitamin A. Similar to vitamin A, retinoids have a broad spectrum of functions, including epidermal development, differentiation, proliferation, apoptosis and immune responses (Alizadeh et al. 2014). Since the 1940s, several retinoid drugs have been widely used in dermatology (see Fig. 1). Retinoid administration was

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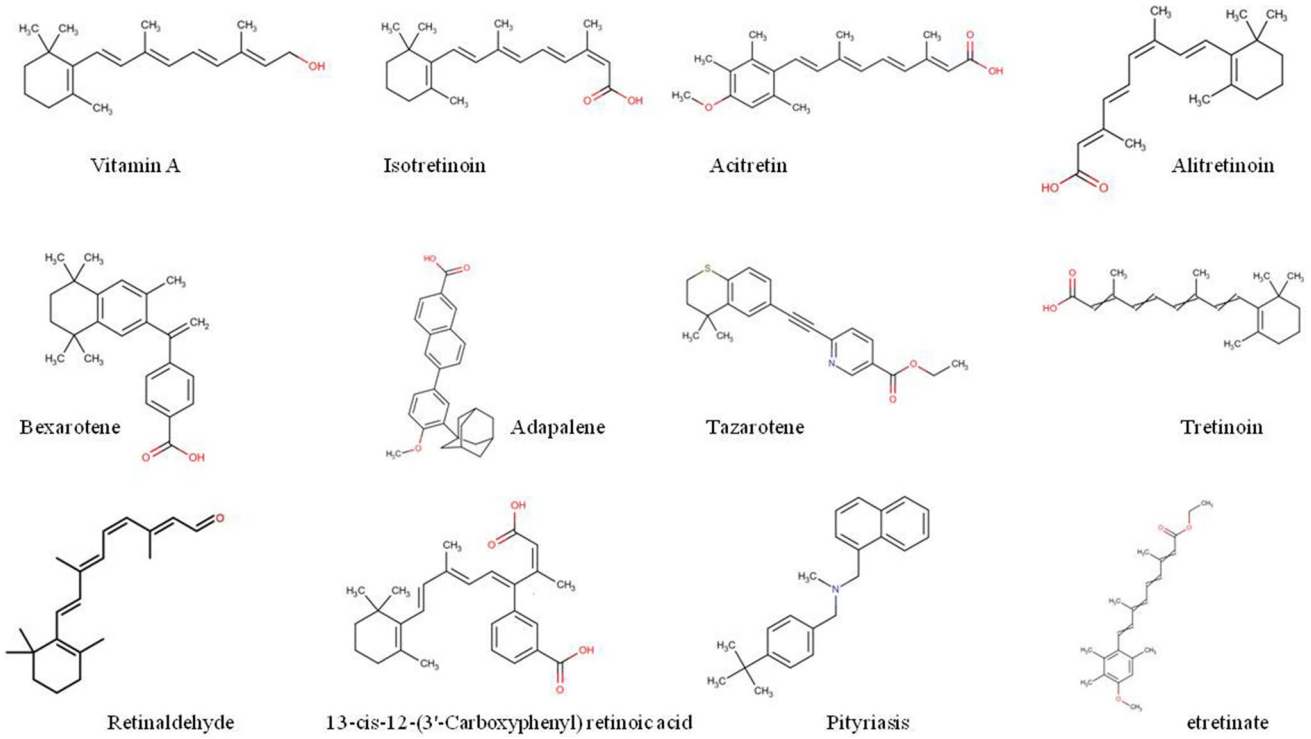

Fig. 1 The chemical structure of the retinoids wildly used in the skin disorders

found to result in tumor regression and confined tumors to the primary sites in chickens with Rous sarcoma virus-induced tumors (Frankel et al. 1980). Additionally, retinoids exerted a therapeutic effect on Shope virus papilloma development in the skin of rabbits (Frankel et al. 1980). Most importantly, vitamin A supplementation therapy potentially improves antibody responses to infant measles vaccines and reduces measles-associated infant mortalities (Hoekstra et al. 2006; Moss 2017; Villamor and Fawzi 2005). At present, retinoids are widely used to treat various skin diseases, such as acne, psoriasis, Darier, squamous cell carcinoma, lichen planus, and herpes simplex (see Table 1 and Fig. 1) (Khalil et al. 2017). It has been reported that retinoid drugs influence regulatory T cells, naive T cells, effector T cells, NK cells and innate lymphoid cells (Raverdeau and Mills 2014); however, the detailed mechanisms are not well understood.

In this review, we used the combination keywords "vitamin A", "retinoids", "dermatology", "skin", and "immune" to search on PubMed. After carefully reading the literature, we reviewed the mechanism of retinoids in each type of immune cell and skin disorder. We confirmed that retinoids not only have an anti-proliferative effect on keratinocytes but also play an important role in regulating immune cells and responses. With this review we aim to summarize the main mechanisms of retinoids in the treatment of skin diseases, especially in immune-related pathways.

Retinoids and Their Receptors

The retinoids mainly activate nuclear receptors called retinoic acid receptors (RARs) and retinoid X receptors (RXRs) to exert multiple biological functions. Both of these receptor complexes are divided into three subtypes: α, β, and γ. Moreover, these two types of nuclear receptors can dimerize with the same or different types of receptors; for example, RXRs can bind with the vitamin D receptor (Raverdeau and Mills 2014). In the skin, RARγ and RXRα are present in the epidermis, and RARβ is expressed in the dermis. As reported, RARα is omnipresent and is associated with keratinocyte proliferation, while RARγ is associated with terminal differentiation (Sirisinha 2015). Among the retinoid drugs, all-*trans* retinoic acid (ATRA) binds and activates RARs, and 9-*cis*-retinoic acid activates RXRs. The complexes formed by the retinoids binding to nuclear receptors serve as transcription factors and regulate the expression of several hundreds of genes (Sirisinha 2015; Thacher et al. 2000) (see Fig. 2). Deficiency in RARs/RXRs is associated with abnormal immune responses or disorders. It has been reported that the T helper (Th)1 and Th17 responses are constrained in RARα defective mice (Raverdeau and Mills 2014). The loss of RARγ abolishes retinoid-induced keratinocyte cell cycle arrest and apoptosis, and the loss of RARγ predisposes

Table 1 On and off-label uses of retinoids in dermatology (Khalil et al. 2017)

Disease	Microbials related	Retinoids topical	Retinoids systems	Predominant targets
Acne vulgaris	Measles virus	Adapalene Tazarotene Tretinoin	Isotretinoin	RAR/RXR
Rosacea	*Propionibacterium acnes*	Adapalene Tazarotene Tretinoin	Isotretinoin	RAR/RXR
Hidradenitis suppurativa	Streptococcus and Staphylococcus		Acitretin Isotretinoin	RAR/RXR
Psoriasis	Streptococcus and Staphylococcus	Tazarotene	Acitretin	RAR/RXR
Pityriasis rubra pilaris		Tazarotene Tretinoin	Acitretin Isotretinoin	RAR/RXR
Chronic hand eczema			Alitretinoin	RAR/RXR
Lichen planus		Isotretinoin Retinaldehyde Retinoic acid Tazarotene	Acitretin Alitretinoin	RAR/RXR
Ichthyosis		Adapalene Tazarotene Tretinoin	Acitretin Isotretinoin	RAR/RXR
Darier's disease		Tazarotene Adapalene Tretinoin	Acitretin Alitretinoin Isotretinoin	RAR/RXR
Aging/photoaging		Tretinoin Tazarotene		RAR
Actinic keratosis		Adapalene Isotretinoin Tretinoin	Acitretin	RAR/RXR
Squamous cell carcinoma	*Human papilloma* virus	Isotretinoin		RAR/RXR
Basal cell carcinoma		Tazarotene		RAR
Cutaneous T-cell lymphoma	human T-cell lymphotropic virus/ Epstein-Barr virus	Bexarotene	Bexarotene	RXR
Kaposi sarcoma	Human herpesvirus 8	Alitretinoin		RAR/RXR
Muir Torre syndrome			Isotretinoin	RAR/RXR

keratinocytes to squamous cell carcinoma (Chen et al. 2004). As RXRα over-expression or ligand activation increases the host susceptibility to viral infections in vitro and in vivo (Ma et al. 2014), RXRα$^{-/-}$ or antagonist treatment reduces the same viral infections (Ma et al. 2014). Likewise, the retinoid-related receptors (RORs) are members of nuclear receptors (Okamoto et al. 2010). It has been reported that RORγt is required for Th17 differentiation and interleukin (IL)-17 production in adaptive and innate immune cells (Gege et al. 2018; Okamoto et al. 2010). In the IL-23-induced psoriasis-like skin of RORγt-deficient mice, studies showed that inflammation and cytokine expression were decreased, especially IL-17A and IL-22 (Gege et al. 2018; Xue et al. 2016), which may suggest that the development of the IL-17-IL-22 immune axis in psoriasis is dependent on RORγt. Published studies showed that RORα was a potential therapeutic target for atopic dermatitis (Malhotra et al. 2018), and retinoic acid levels and signalling decreased markedly in atopic dermatitis tissue (Mihaly et al. 2011). Interestingly, retinoid supplementation is not an appropriate treatment for atopic dermatitis patients (Feily and Namazi 2010). This may be because both ATRA and ALRT1550 can inhibit RORγt and RORβ transcriptional activity but not that of RORα (Stehlin-Gaon et al. 2003). Therefore, exploring the retinoid drugs that target RORα may contribute to the treatment of atopic dermatitis and other RORα-predominant skin inflammatory disorders.

In addition to RAR/RXR/ROR receptors, retinoids are also the ligands of peroxisome proliferator-activated

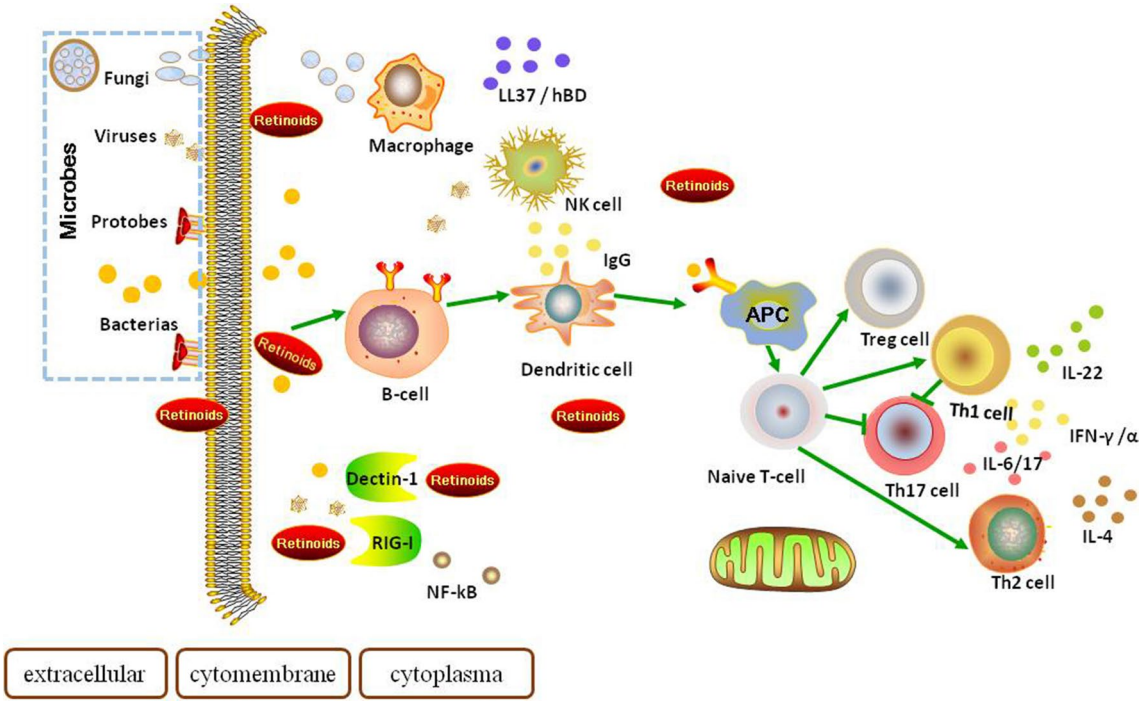

Fig. 2 Retinoidsbind with nuclear receptors and regulate the genes transcription. The retinoids can bind with RARs/RXRs/RORs nuclear receptors and be transported into the cell nucleus by CRAP/CRBP. When binding to DNA, the retinoids induce the transcription factors then regulate the target genes expression

receptors (PPARs), which play an essential role in the regulation of skin barrier permeability, keratinocyte metabolism and immune defences (Berry and Noy 2007). The PPAR subfamily also consists of three isotypes, PPARα, PPARβ/δ and PPARγ, which are all present in keratinocytes. Some skin diseases (e.g., acne and atopic dermatitis) have increased PPAR expression (Kuenzli and Saurat 2003; Ramot et al. 2015). PPARβ/δ is the predominant subtype in human keratinocytes (Kuenzli and Saurat 2003), and the activation of PPARβ/δ causes psoriasis-like skin disease; retinoid drugs are taken as a potent way to cure psoriasis via inhibiting PPARβ/δ receptors (Romanowska et al. 2010). Specific ligands of PPARγ inhibit the production of inflammatory mediators and cytokines and the activities of transcription factors, such as members of the nuclear factor (NF)-κB and AP-1 families (Ramot et al. 2015).

The Link Between Vitamin A Deficiency and Skin Disorders

As mentioned above, vitamin A is essential in maintaining the integrity of the epithelial barrier and has substantial effects on the maturation and functions of different immune cells, including T cells, B cells, neutrophils, macrophages, NK cells, etc. (Czarnewski et al. 2017; Huang et al. 2018; Patel and Vajdy 2015). Vitamin A deficiency is strongly associated with immune dysfunction, which causes several systemic immune skin disorders and infections. On the other hand, common infections increase the risk of vitamin A deficiency by decreasing the intake and absorption of vitamin A and increasing its excretion (Islam et al. 1993; Stephensen 2001). In other words, there is a vicious cycle between vitamin A deficiency and infectious disorders.

Retinoid Drugs as Mediators of Immunity

When microorganisms attack, cytokines, beta-defensin, and antimicrobial peptides (LL-37) in the skin are remarkably induced (Handfield et al. 2018). To control infections, retinoids inhibit the levels of beta-defensin (hBD-1, -2, -3, and -4) and the innate chemical defence system in the human skin (Harder et al. 2004). Moreover, retinoids downregulate the gene expression of cytokines, including *IFN*, *IL12*, and *IL23*, and retinoid deficiency is associated with increased production of the type 1 cytokine interferon (IFN)-γ and decreased IL-5 and IL-10 cytokines (Jason et al. 2002; Patel and Vajdy 2015; Tang et al. 2012). Furthermore, retinoids inhibit the release of pro-inflammatory cytokines, such as TNF, IL-6, monocyte chemotactic protein-1, and vascular endothelial growth factor (Wojtal et al. 2013). Thus, retinoid

drugs may exert vital immunomodulatory roles in different immunoregulatory ways (see the following content and Fig. 3).

Adaptive Immunity

Modulation of Cellular Immunity

Retinoids have important effects on the regulation of T cell (Th17, Th1, and Th2 cells and regulatory T cells) responses and immunity during infections or autoimmune diseases (Patel and Vajdy 2015; Pino-Lagos et al. 2011; Raverdeau and Mills 2014; Tang et al. 2012). It has been reported that the retinoid-RARα pathway is a critical component limiting Th1 cell conversion into Th17 effector cells and preventing pathogenic Th17 responses in vivo (Brown et al. 2015); thus, retinoids are positively associated with the Th1-cell function. In addition, the chemokine IFN-γ is a component of Th1 responses, and IFN-γ concentration in serum is positively associated with vitamin A stores (Ahmad et al. 2009). Moreover, retinoids promote naive T cells to convert into $Foxp3^+$ regulatory T cells and inhibit the differentiation of naive T cells into Th17 cells (Raverdeau and Mills 2014). In summary, retinoids inhibit Th17 cell differentiation and prevent the pathogenic reactions caused by Th17 cells in vivo. Retinoid supplementation could decrease the risks and severity of Th17-related autoimmune diseases, such as psoriasis.

In addition to Th1 and Th17 cells, retinoids also promote Th2 cell differentiation and responses (Jason et al. 2002), and retinoid deficiency diminishes the antibody-mediated responses directed by Th2 cells (Stephensen 2001).

Modulation of Humoural Immunity

The roles of retinoids in the humoural immune system remain elusive. It has been reported that retinoids play critical roles in memory B cells. Studies have shown that retinoids inhibit $CD27^+$ memory B cell proliferation and IgG secretion when stimulated by anti-RP105; however, retinoids can induce memory B cell proliferation and IgG synthesis when co-stimulated with the Toll-like receptor (TLR)9 ligand CpG (Eriksen et al. 2012), which may occur via activation of the p38-MAPK pathway (Ertesvag et al. 2007). Thus, the impact of retinoids on B cells depends on the intracellular environment and other stimuli and requires further confirmation.

Innate Immunity

The innate immune system is the first line in our defence systems against pathogens, such as viruses, bacteria, fungi and other microbes. In the following sections, the regulatory mechanisms of retinoids on DCs, NK cells and pattern recognition receptors (PRRS) are discussed.

Modulation of DC and NK Cells by Retinoids

As reported, retinoids have a central function in the differentiation and functions of DCs (Manicassamy et al. 2009).

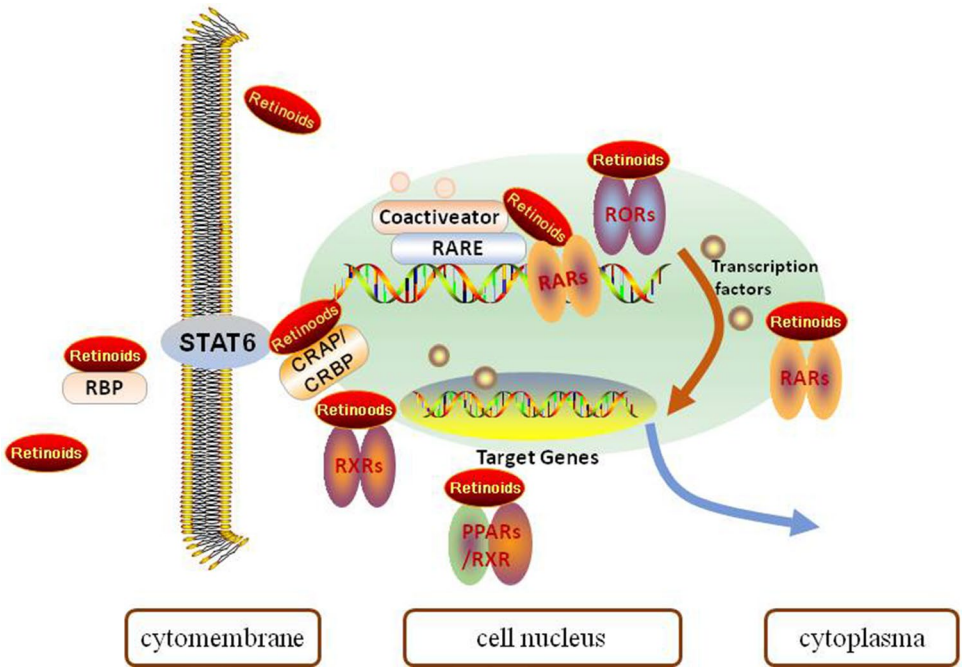

Fig. 3 Retinoids as immune-mediator in the skin. Retinoids have an important effect on the maturation and functions of immune cells, such as T cells, B cells, neutrophils, macrophages, and NK cells, then regulate the cytokines and antimicrobial peptides production and promote or inhibit the immune defenses

Studies demonstrated that ATRA can promote monocyte-derived DCs to become mucosal-type DCs and enhance the migratory properties of DCs, which are crucial for antigen presentation and T cell responses during infections (Jie et al. 2017; Lackey and Hoag 2010). Moreover, retinoids strongly induce IL-22 activity (Martin et al. 2014) and the production of secreted TGF-β and IL-6 through the regulation of immature DCs (Lackey and Hoag 2010). ATRA can also activate skin Langerhans DCs (Meunier et al. 1994). In the presence of the pro-inflammatory cytokines TNF-α and IL-β, ATRA can upregulate the gene expression of MHC class II, *HLA-DR*, *CD11c*, and *CD86* on Langerhans cells (Geissmann et al. 2003; Meunier et al. 1994).

NK cells are vital to innate immunity and immune responses during viral infections of the skin. Vitamin A stores are positively associated with the levels of NK and NK-T cells, which may indicate increased antibacterial and antiviral activities (Ahmad et al. 2009). Studies also indicate that retinoids can trigger NK cells to produce more type 1 cytokines, such as IFN-γ (Chau et al. 2013), which may benefit individuals with infections, especially for type 1 pathogen infections (Alizadeh et al. 2014; Jason et al. 2002).

Pattern Recognition Receptors

Keratinocytes are critical members of the innate immune system (Suter et al. 2009) that can rapidly detect potential pathogens partly through PRRs and their signalling cascades, e.g., retinoic acid-inducible gene-I (RIG-I) (Hendricks et al. 2012; Kalali et al. 2008). Recognition by RIG-I initiates type I IFNs and pro-inflammatory cytokine production signalling cascades, which may lead to the elimination of pathogens (Prens et al. 2008). As reported, RIG-I is highly expressed in psoriasis skin lesions, and RIG-I$^{-/-}$ mice have a reduced likelihood of promoting imiquimod-induced psoriasis-like lesions under the same microbial environment (Zhu et al. 2017). This conclusion suggests that microbes may contribute to RIG-I-dependent psoriasis. RIG-I expression is also increased in cells infected with measles virus. In vitro studies showed that retinoids inhibit measles virus proliferation by upregulating RIG-I significantly (Soye et al. 2011, 2013). Thus, we suspect that retinoids alleviate the pathogen-induced inflammatory responses well, which may be partly due to the RIG-I pathway.

As a primary fungal PRRs, Dectin-1 can distinguish β-glucan on the surface of fungi and can mediate innate immune responses. After recognizing the fungi, dectin-1 generates inflammation and immune responses in addition to direct phagocytosis and killing of the fungi.

ATRA can significantly suppress the expression of Dectin-1 and Dectin-1-dependent cytokine production (Klassert et al. 2014). In dermatology, many disorders are associated with fungal infections. Therefore, we wondered whether retinoid drugs may be a potent therapy for other fungal-infection-associated skin disorders. On the other hand, the NF-κB pathway is highly activated in autoimmune diseases. Retinoid drugs can significantly reduce the expression of the NF-κB pathway in psoriasis (Zhang et al. 2008). Furthermore, the RIG-I pathway regulates NF-κB production. Therefore, we suspect that retinoids reduce the NF-κB pathway partly by the regulation of RIG-I signalling.

Retinoid Treatment in Skin Disorders

As mentioned above, the skin is a vital immune system in the body, and retinoids play an essential role in regulating the immune responses of skin (Reifen 2002). First, retinoids stimulate the body's humoural immune defences directly (Harder et al. 2004). Second, retinoids increase the production of Langerhans cells, NK cells (Sardana and Sehgal 2003), and the phagocytic activity of macrophages (Sarang et al. 2014). Moreover, retinoids regulate the balance of T cell (Th17, Th1, and Th2 cells and regulatory T cells) responses. However, the critical immune roles of retinoids in each disease are still unclear (Barrat et al. 2016). In this review, we have described the immunological functions of retinoids in skin diseases, especially in infectious skin diseases (Khalil et al. 2017).

Measles

Measles results from measles virus infection and is still responsible for more than 100,000 deaths worldwide every year (Moss 2017). Measles virus suppresses type I IFN signalling, and immune responses are crucial for measles viral infection, viral clearance and even mortality (Druelle et al. 2008). The skin rash is one of the main characteristics of measles. Children with severe measles often develop opportunistic bacterial pneumonia and diarrhoea due to the compromised innate and adaptive immune responses (Bello et al. 2016; Stephensen 2001). Several studies showed that vitamin A deficiency is associated with a higher risk of the measles (Bello et al. 2016; Kantoch et al. 2002; Moss 2017). In the clinic, simultaneous administration of vitamin A and measles vaccine improved the measles vaccine responses remarkably (Villamor and Fawzi 2005) and reduced the mortality by 50–80% in acute measles patients (Villamor and Fawzi 2005), but these results were not due to the effect on virus differentiation, proliferation or apoptosis. It has been reported that retinoids enhance antibody production in response to the measles vaccine and induce T cell proliferation (Villamor and Fawzi 2005). Children with acute measles infection may have enhanced lymphopoiesis, especially naive CD4^{+} cells, after receiving high-dose vitamin A supplementation (Coutsoudis et al. 1992; Gottgens and

Green 1995). In vitro studies showed that vitamin A and retinoids may upregulate innate immune responses, especially through IFN signalling, which was confirmed by Trottier et al. (2009), and retinoid-MeV antiviral responses may be dependent on the RIG-I, IFN, and IRF-1 pathways through RARα activation (Soye et al. 2011, 2013). Further studies are needed to elucidate the mechanisms by which retinoids enhance immune responses to measles.

Acne

Acne vulgaris is one of the most common skin disorders affecting millions of people worldwide. *Propionibacterium acnes* (*P. acnes*) is the key component in the pathogenesis of acne vulgaris and stimulates the production of cytokines and chemokines (Jalian et al. 2008). It has been reported that *P. acnes* is a potent inducer of Th17 cells, stimulates the expression of Th17-related genes, and triggers IL-17 secretion and expression in acne lesions (Agak et al. 2014; Thiboutot et al. 2014). Studies have indicated that vitamin A can inhibit *P. acnes*-induced differentiation and the functions of Th17 cells (Agak et al. 2014). In addition, the retinoid ATRA exerts an anti-inflammatory effect on *P. acnes* by affecting TLR2, leukocyte migration, the AP-1 pathway and CD14 expression in acne (Czernielewski et al. 2001; Dispenza et al. 2012; Liu et al. 2005). On the other hand, retinoids result in decreased production of metalloproteinase and matrix metalloproteinases (MMPs), and the latter has a predominant role in skin inflammation and hyperproliferation (Trottier et al. 2009). It has been reported that ATRA isotretinoin significantly decreases the production of MMP-9, MMP-13, IL-8 and IL-10 in acne lesions (Dreno et al. 2015; Jalian et al. 2008; Papakonstantinou et al. 2005; Trottier et al. 2009). In summary, the retinoid drugs exert immunomodulatory effects in various manners in acne patients.

Kaposi Sarcoma

Human herpes virus 8 (KSHV/HHV-8) is associated with all forms of Kaposi sarcoma (KS) (Boulanger et al. 2004). In the clinic, oral isotretinoin combined with a low dose of α-2 IFN improves the general condition and ameliorates the immunological parameters in KS patients (Somos and Farkas 2000). Retinoid drugs, especially alitretinoin gel, present a superior antitumor effect on the treatment of KS patients (Bodsworth et al. 2001; Gonzalez de Arriba et al. 2007). Retinoids have a pronounced anti-viral effect against the replication of different herpes-viruses, mainly HHV-8 (Caselli et al. 2008). The inhibition prevented endothelial cells from developing spindle tube formation morphology (Caselli et al. 2008). On the other hand, retinoids exert immunological functions through mediating T cell and DC balance and functions in cancers (Alizadeh et al. 2014), e.g., by significantly increasing IL-6 and IL-2 (Gill et al. 1994; Miles et al. 2002).

In addition to HHV-8, combination therapy with IFN and retinoic acid could induce HHV-6B cell death signalling by U95 and U95-interacting protein (Yeo et al. 2008). However, the conclusions are not always consistent. A cross-sectional analysis indicated that vitamin A supplementation was unlikely to decrease herpes simplex virus shedding and infectivity (Baeten et al. 2004). Thus, the benefit of retinoids on human herpes virus needs to be confirmed in a large population by in vivo and in vitro studies.

Epidermodysplasia Verruciformis

Malignant skin changes are widespread, and certain epithelial cancers that are preceded by papillomas might be caused by viruses, including human papillomavirus (HPV)-5, HPV-8 or HPV-14 (Gubinelli et al. 2003). Epidermodysplasia verruciformis (EV) is a rare genodermatosis with immunologic abnormalities that are caused by widespread and persistent infection with HPV (Zampetti et al. 2013). Several treatments for EV have not had consistent benefits. Since the 1980s, retinoids have been used to treat EV and showed a significant improvement (Gubinelli et al. 2003; Lutzner 1984). It was reported that EV patients treated with retinoids resulted in partial recovery of benign lesions, and the effects of virus-specific cytopathogenic, virus particles and viral DNA were no longer detectable (Gross et al. 1983; Lutzner 1984; Lutzner and Blanchet-Bardon 1980; Lutzner et al. 1984). One in vitro study showed that high-dose ATRA inhibited HPV-16 promoter activity via decreased AP-1 binding (Faluhelyi et al. 2004). According to previous reports, retinoids showed no modification of the immune parameters in EV patients (Claudy et al. 1982). Thus, retinoid drugs definitely benefit the clinical status of EV patients, but whether retinoids mediate the immune defence in EV patients remains unclear.

Other Skin Cancers

There is an inverse relationship between vitamin A levels and the incidence of neoplasia. Thus, these studies provided a basis for the use of retinoids in clinical cancer prevention trials. Except for the previously mentioned diseases KS and EV, other skin cancers, such as squamous cell carcinoma, basal cell carcinoma, cutaneous T cell lymphoma and actinic keratosis, can also be treated by retinoid drugs (di Masi et al. 2015; Khalil et al. 2017; Uray et al. 2016). In the 1980s, retinoids were administered to chickens with Rous sarcoma virus-induced tumors and resulted in tumor regression and confinement to the primary site (March and Biely 1972). Subsequently, retinoids exerted a therapeutic effect on Shope virus papilloma development in the skin of rabbits

(Frankel et al. 1980) and on cutaneous verrucous carcinoma (DiGiovanna 2001; Kuan et al. 2007). As reported, the retinoid drugs tretinoin and retinamide were also used to treat skin cancer melanoma in clinical trials (Bushue and Wan 2010). Data from the SKICAP-AK trial indicated that retinol reduced the incidence of first new squamous cell skin cancers in moderate-risk subjects (Moon et al. 1997). Recently, retinoids have been widely used as potential chemotherapeutic or chemo-preventive agents (di Masi et al. 2015). While the anticancer mechanism of retinoids is not well understood.

Warts

HPV infects the squamous epithelia of the skin and may result in warts with abnormal epithelial cell differentiation and immune response (Frazer 2009). After treatment with etretinate, 16 of 20 wart patients showed complete regression without relapse, and the other four subjects achieved partial regression (Gelmetti et al. 1987). Capella et al. reported that in generalized verrucosis patients, oral and topical retinoid drugs yielded good effectiveness (Capella 2012; Gaston and Garry 2012; Sri et al. 2012). Retinoid drugs may disrupt the interplay of HPV replication and epithelial cell differentiation during wart treatment by regulating immune responses. It is speculated that retinoid treatment can increase or prolong the expression of T or B cell antigen production to clear the HPV (Gaston and Garry 2012). While the link between HPV infection and immune responses remains unknown, the anti-papillomavirus mechanism of retinoids needs further research.

Psoriasis

Psoriasis is a chronic inflammatory skin condition characterized by high keratinocyte proliferation, poor differentiation and abundant infiltration of immune cells, especially Th1, Th17 cells and DCs. There are many reasons for psoriasis, such as *Streptococcus* and *Staphylococcus aureus* exogenous infections (Ferran et al. 2013; Hsu et al. 2016; Tomi et al. 2005). These infections trigger keratinocytes to produce pro-inflammatory mediators, such as LL37 and self-DNA. Then, the DNA-LL37 complexes stimulate inflammatory myeloid DCs to release IL-23 and IL-12 cytokines, which can activate IL-17-producing T cells, Th1 cells, and Th22 cells to produce abundant psoriatic cytokines, such as IL-17, IFN-γ, TNF, and IL-22. These cytokines mediate effects on keratinocytes to amplify psoriatic inflammation (Boehncke and Schon 2015; Lowes et al. 2014). Thus, immune responses play a vital role in the pathogenesis of psoriasis.

The retinoid drug acitretin is the first-line drug to treat moderate to severe plaque psoriasis and pustular psoriasis, and tazarotene is used as a topical treatment. As reported, approximately 54% of psoriasis patients responded well, and 36% of patients achieved complete clearing with acitretin monotherapy (Buccheri et al. 1997; Jeong et al. 2014).

In addition to regulating keratinocyte growth, differentiation, and proliferation (Islam et al. 1993), retinoids can inhibit psoriasis immunopathogenesis by interfering with the signalling of specific pro-inflammatory pathways, receptors, cytokines and antigens. Niu et al. found that acitretin decreased the number of T, Th1, Th17 and circulating T follicular helper cells and decreased the expression of IFN-γ and IL-17 in serum and lesions but had no significant influence on Th2 cells (Niu et al. 2012; Raverdeau and Mills 2014; Wang et al. 2016). The retinoid drug acitretin also markedly reduced innate and acquired immune cell responses, particularly production of IL-12 and IL-23 (Tang et al. 2012), and regulated the highly expressed antimicrobial peptide LL-37 and RIG-I in psoriasis (Balato et al. 2013; Handfield et al. 2018; Zhu et al. 2017). Moreover, previous studies indicated that retinoids can suppress the inflammatory factors in the IL-1 family, including IL-1Rα, IL-36Rα, IL-36α/β/γ, etc. (Balato et al. 2013). Thus, the anti-psoriasis effects of retinoids may be due to the mechanisms of immune regulation, which requires further confirmation.

Future Works

In summary, vitamin A plays a vital role in skin tissue integrity and immune responses, and a number of retinoid drugs are widely used in dermatology and yield good responses. Through this review, we showed that retinoid drugs have an important influence on immune cells, such as regulatory T cells, naive T cells, effector T cells, NK cells and innate lymphoid cells, and exert multiple regulatory immune functions in immune-related skin disorders. Of particular note is that excessive use of retinoic acid drugs contributes to so-called retinoid dermatitis. The skin irritation and sensitization reactions, such as dermatitis and even teratogenicity during early pregnancy, are always accompanied by retinoid therapy, which may limit its clinical usage. However, the detailed immune responses of the side effects remain unclear. Therefore, the risk–benefit ratio of retinoid drugs in the clinic must be carefully assessed.

In this review, we summarized the previously published information on vitamin A/retinoid treatment, especially in immune-related skin diseases. Reviewing the previous studies may help us to determine the definite immunoregulatory roles of retinoids in dermatology disorders, and we hope to explore more new indications for retinoid drugs.

Conclusion

Vitamin A plays a vital role in the host defence of the skin, and vitamin A derivative retinoids are widely used to treat dermatology diseases, especially in skin disorders caused by exogenous infections. In addition to epithelium integrity, retinoids also regulate immune responses via various immune pathways, including innate and acquired immune responses, immune cells and cytokines.

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Author Contributions WC and LW outlined the structure and wrote this paper. SZ helped with the disease section and Table 1 of the manuscript. WZ provided valuable guidance. XC revised the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to declare.

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