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Retinoic Acid Induced Cell Signaling as a Counter Against Disease

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Abstract

Many disease processes result from disruption of physiologic cell signaling pathways. Cancer often develops from the loss of cell cycle regulation, while inflammatory disease results from dysregulated immune activity. Likewise, many microbial infections avoid immune clearance by interfering with cellular antimicrobial pathways. Retinoic Acid (RA) is a dynamic compound, derived from vitamin A, that can regulate various signaling pathways. RA induced cell signaling has proven beneficial against different diseases, such as Acute Promyelocytic Leukemia (APL) and psoriasis. Against APL, RA induces cellular differentiation in cancer cells to restore proper function. In psoriasis, RA downregulates inflammatory pathways, such as NF-κB. RA's anti-inflammatory properties have also been examined in the context of sepsis, where recent animal studies have shown positive benefits. Along with regulating inflammation, RA exhibits indirect antimicrobial properties. Unlike conventional antimicrobials which target pathogens directly, RA functions as a host-directed therapy (HDT), promoting cell antimicrobial defenses. Recent studies examining RA have shown that it can improve macrophage clearance of microbial pathogens and stimulate the antiviral type-I interferon (IFN) response. RA's effectiveness has been demonstrated against clinically relevant pathogens, such as *Mycobacterium tuberculosis*, *Aspergillus fumigatus,* and Measles virus. In this review, the therapeutic potential of RA to treat various diseases by regulating cell signaling pathways will be explored.

Keywords: Retinoic Acid, Anti-inflammatory, Cell Signaling Pathways, Interferon Signaling

Abbreviations: ADH: Alcohol Dehydrogenase; AMP: Antimicrobial Protein; APL: Acute Promyelocytic Leukemia; ATRA: All-trans Retinoic Acid; BC01: β-carotene-15, 15'-dioxygenase; CEACAM1: Carcinoembryonic Antigen-related Cell Adhesion Molecule 1; CRABP: Cellular Retinoic Acid Binding Protein; HDT: Host-directed Therapy; IFIT: Interferon-induced Tetratricopeptide repeat protein; IFIT: Interferon-inducible Transmembrane protein; IFN: Interferon; IL: Interleukin; IRF: Interferon Regulatory Factor; MAPK: Mitogen Activated Protein Kinase; MDA5: Melanoma Differentiation Associated gene 5; MxA: Myxovirus resistance protein 1; NF-κB: Nuclear Factor κ B; PGE-2: Prostaglandin E-2; PML: Promyelocytic Leukemia protein; PRR: Pattern Recognition Receptor; RA: Retinoic Acid; RALDH: Retinal Dehydrogenase; RAR: Retinoic Acid Receptor; RARE: Retinoic Acid Response Element; RBP: Retinol Binding Protein; RIG-I: Retinoic Acid Inducible Gene I; RXR: Retinoid X Receptor; SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TBK-1: TANK-binding Kinase 1; TNF-α: Tumor Necrosis Factor α

Introduction to Retinoic Acid

Vitamins are essential nutrients that are required for biological processes, but are unable to be synthesized by the human body in large amounts [1]. In general, vitamins are classified into two groups based on their chemical properties: water-soluble (e.g., vitamin B1, B2, B3, etc.) and fat-soluble (e.g., vitamin A, C, D, etc.) [1]. Vitamin A is a critical fat-soluble nutrient that plays a key role in signaling pathways involved in fetal development, tissue differentiation, and immune regulation [2-4]. It is also a major component in the visual system, where it interacts with opsin proteins to induce visual activity [5]. Vitamin A's effect on cellular signaling pathways results from its function as a transcription factor for different genes [2-4]. For example, vitamin A regulates fetal development by promoting the expression of homeobox genes, which are responsible for

embryogenesis [4]. Because of its extensive physiological activity, vitamin A deficiency results in widespread symptoms [6]. Common symptoms of vitamin A deficiency include night blindness, mucosal membrane breakdown, and increased risk of infection (i.e., immune dysfunction) [6].

Like other essential nutrients, vitamin A can't be synthesized and must be acquired from the diet [3, 7]. Fortunately, vitamin A is present in multiple dietary sources, such as animal (e.g., meat, milk, dairy products, eggs, etc.) and plant products (e.g., carrots, spinach, tomatoes, oranges, etc.) [7]. Unlike animal products which contain preformed vitamin A (Retinol), plant products produce provitamin A carotenoids, such as β-carotene [7,8]. The human body is able to make use of both Retinol and provitamin A carotenoids by metabolizing them into retinoic acid (RA) for cellular use [8].

The conversion of vitamin A into its active form (i.e., RA) occurs in a stepwise process (**Figure 1**). First, retinol and β-carotene are absorbed by intestinal epithelial cells into circulation [7,9]. In serum, Retinol and β-carotene are transported via retinol binding protein (RBP) and chylomicrons, respectively [3,8]. Circulating retinol and β-carotene are then taken up by liver cells, which contain the highest concentration of vitamin A in the human body [3,7]. Within liver cells, retinol is converted to retinal by alcohol dehydrogenase (ADH) [3,7,10]. β-carotene is also converted to retinal, via the activity of β-carotene-15,15'-dioxygenase (BCO1) [8]. Lastly, retinal gets metabolized into RA by retinal dehydrogenase (RALDH) [3,7,10]. The primary forms of RA include all-trans RA (ATRA), 9-cis RA, and 13-cis RA [3,9]. RA binds to cellular RA binding protein (CRABP) and is transported into the nucleus, where it activates RA specific transcription factors [3,7,10]. Of these three metabolites, ATRA demonstrates the greatest transcriptional activity, capable of binding to RA receptors (RARs) within the nucleus [11,12]. 9-cis RA predominantly binds to retinoid X receptors (RXRs) however, it can also interact with RARs [11,12]. The binding activity of 13-cis RA is unknown [11,12].

Both RAR and RXRs consist of three isoforms: α, β, and γ [12]. RAR is typically bound to RXR as a heterodimer (i.e., RAR/RXR), while RXR is usually present as an inactive tetramer [11-13]. RAR/RXR is bound to RA response elements (RAREs) in the genome [12]. Without RA present, RAR/RXR represses gene expression by recruiting corepressors that promote histone deacetylase complexes [11,12]. With RA present, RAR/RXR induces gene

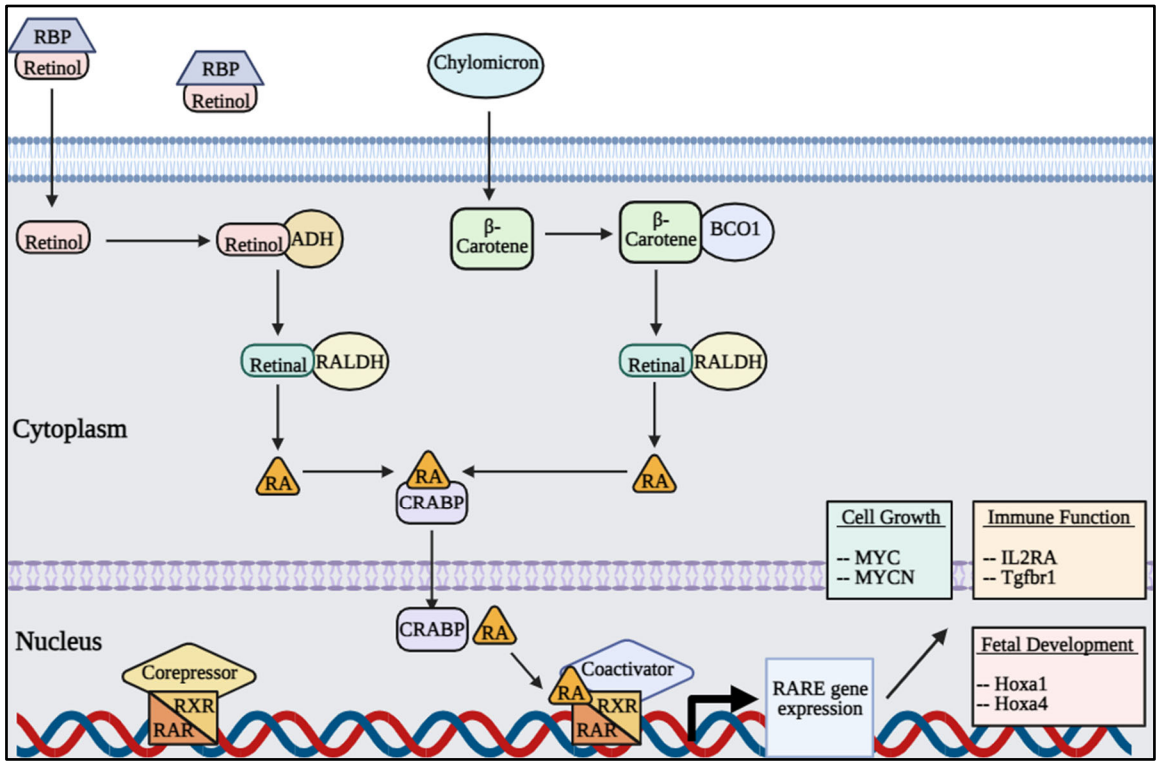

Figure 1. Summary of vitamin A metabolism. Retinol and β-carotene get taken up by the cell and metabolized into RA, the active form of vitamin A. RA is then transported into the nucleus by CRABP, where it activates the nuclear transcription factors RAR and RXR. Activation of RAR and RXR leads to RARE gene expression. Created with BioRender.com.

expression by recruiting coactivators that promote histone acetyl transferase activity [11,12]. RA induced RAR/RXR activation results in the expression of RAREs, which encompass numerous genes involved in different signaling pathways (**Figure 1**) [11,12,14]. For instance, RAREs include genes that regulate fetal development (e.g., *Hoxa1*, *Hoxa4*, etc.), immune function (e.g., *IL2RA*, *Socs3*, *Tgfbr1* etc.), cell growth (e.g., *MYC*, *MYCN*, etc.), and RA activity (e.g., *RARA*, *RARB*, etc.) (**Table 1**) [14, 15]. The transcriptional activity of RXR is less understood than that of RAR/RXR. However, previous studies have shown that RA induces RXR binding to other transcription factors to promote their activity [13,16]. Noticeable transcription factors that are promoted by RXR include thyroid hormone receptor and peroxisome proliferator-activated receptor [13]. Because the effect of RA on RARE expression is more clearly established, the review will focus on the activity of RAR/RXR.

ATRA Induced Cell Signaling as a Disease Treatment

Therapeutic rationale

Due to its effect on different cellular signaling pathways, ATRA has been extensively studied as a potential therapeutic for diseases resulting from dysregulated signaling pathways. In oncology, ATRA is predominantly used to treat acute promyelocytic leukemia (APL), where it promotes cellular differentiation and induces apoptosis in cancer cells [11,17-19]. During APL, promyelocytes have lost the ability to differentiate into mature granulocytes, so they overcrowd the bone marrow and disrupt other blood cells (e.g., platelets, red blood cells, etc.) [17-19]. Because of its effectiveness in treating APL, ATRA is listed by the World Health Organization as an essential medication for healthcare systems [20]. RA derivatives have also shown positive benefits in the context of melanoma, hepatoma, lung, breast, and prostate cancer [21,22]. In dermatology, ATRA is used to treat severe forms of acne and inflammatory skin conditions, such as psoriasis [11,23]. ATRA can reduce inflammation by upregulating anti-inflammatory signaling in immune cells [3,11,23]. Its anti-inflammatory properties have also been studied in the context of sepsis, where it can downregulate proinflammatory signaling pathways (i.e., NF-κB pathway) [3,24-26].

Although ATRA has predominantly been studied in the context of cancer and inflammatory disease, recent studies have also highlighted its impact on innate immune pathways. Unlike conventional antimicrobials that directly target their associated pathogen, ATRA can enhance immune pathways to improve bacterial and viral clearance [3,27]. This therapeutic strategy, known as host-directed therapy (HDT), has gained interest as an additional treatment option, especially against antibiotic resistant bacteria [28,29]. Resulting in approximately 1.27 million deaths globally in 2019, antibiotic resistance is a significant health problem requiring renewed focus and novel therapeutics [30,31]. Likewise, the emergence of novel viral pathogens necessitates an expansion of antiviral treatments [32].

ATRA induction of differentiation in cancer

Cancer is a multifaceted disease process, encompassing different pathologies that can affect every organ system. Although the causes of cancer are numerous, cancer cells generally exhibit dysregulated cell signaling that results in excessive proliferation, loss of differentiation, and metastasis [33]. Loss of regular signaling pathways often occurs due to mutations in proto-oncogenes or tumor suppressor genes [33-35]. Proto-oncogenes regulate cell growth, so when they become mutated (i.e., oncogenes) they can induce abnormal proliferation [34]. Tumor suppressor genes maintain normal cellular signaling by regulating cell cycle progression and DNA repair pathways [35].

Table 1. Listed RARE Gene Activity.

Gene	Full Name	Function
Hoxa1	Homeobox A1	Regulates cellular differentiation
Hoxa4	Homeobox A4	
IL2RA	Interleukin 2 receptor subunit α	Forms interleukin 2 receptor, a key mediator of inflammation
MYC	MYC proto-oncogene	Regulates cell cycle progression and apoptosis
MYCN	MYCN proto-oncogene	
RARA	Retinoic acid receptor α	Regulates expression of RAREs
RARB	Retinoic acid receptor β	
Socs3	Suppressor of cytokine signaling 3	Promotes anti-inflammatory activity
Tgfbr1	Transforming growth factor β receptor 1	Forms transforming growth factor β receptor, which promotes anti-inflammatory activity

APL is a blood cancer caused by abnormal promyelocytes [36,37]. During erythropoiesis, promyelocytes develop in bone marrow and differentiate into granulocytes (e.g., neutrophils, eosinophils, basophils) [38,39]. In APL, promyelocytes are unable to differentiate, and instead proliferate and crowd out normal developing blood cells (e.g., platelets, red blood cells, etc.) [36,37]. Clinically, this manifests as abnormal white blood cell counts (i.e., promyelocyte proliferation), decreased platelets, and bleeding [36]. Without treatment APL is a fatal disease, with death resulting from hemorrhage due to reduced platelet levels [36]. ATRA treatment has revolutionized APL care, producing response rates of 90% [36,40]. Unfortunately, the high response rate of ATRA monotherapy is tempered by its low remission rate, with 20-30% of patients experiencing APL recurrence [36]. To combat high recurrence rates, current APL treatments utilize combination therapies, relying on ATRA plus other chemotherapy agents (e.g., arsenic trioxide, idarubicin, etc.). Combination therapies drastically improve APL survival by demonstrating complete remission and 5 year survival rates of 91% and 95%, respectively [36].

ATRA treats APL by restoring cell signaling, thus enabling proper gene expression and cellular differentiation. The loss of cellular differentiation in APL is due to a balanced translocation between chromosomes 15 and 17 [36,37]. This results in the formation of a fusion protein involving Promyelocytic Leukemia protein and RARα (PML-RARα) [36,37]. Under physiologic conditions, PML functions as a tumor suppressor protein, regulating cell cycle progression and DNA repair [41,42]. However, when fused to RARα it disrupts normal gene expression by recruiting corepressors, histone modifying proteins, and by blocking RARE [37,43]. ATRA interferes with PML-RARα by directly binding to RARα [43]. After binding ATRA, PML-RARα undergoes conformational changes that prevent it from blocking RAREs or recruiting corepressors and histone modifying proteins [43]. Without interference from PML-RARα, normal cell signaling is restored and the promyelocyte can complete the differentiation process (**Figure 2**).

The effectiveness of ATRA's antineoplastic properties during APL has led to increased study. Similar to ATRA, RA derivatives are also effective against different blood cancers. For example, Bexarotene is an RA derivative approved by US FDA for the treatment of cutaneous T cell lymphoma [7,22,44]. Positive findings have also been encountered by *in vitro* studies, where RA derivatives were shown to promote cellular differentiation and disrupt proliferation in various cancer cell-lines (e.g., lung, breast, etc.) [7,22,45]. However, these studies have been unable to translate into the clinic, with experiments failing to demonstrate a survival benefit [22,45]. The discrepancy between *in vitro* and clinical studies demonstrates the difficulty of modeling cancer, which can recruit noncancerous cells and adapt to monotherapies. Further study examining ATRA in combination with other therapies (e.g., chemotherapy, immunotherapy, etc.) may better elucidate its effectiveness against cancer.

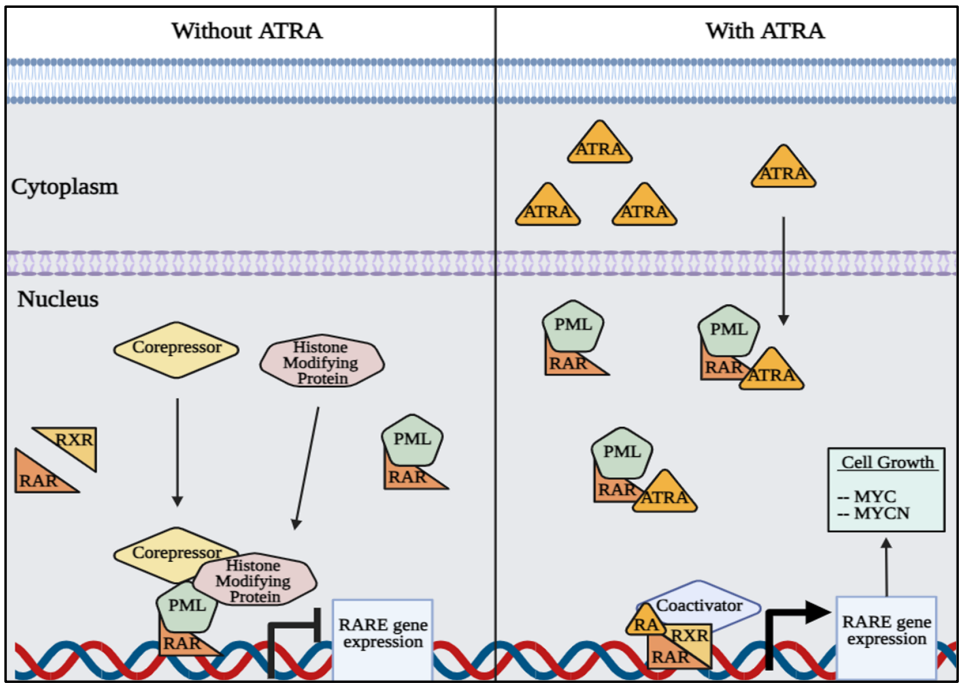

Figure 2. ATRA induced differentiation in APL. ATRA binding to PML-RARα allows for RARE gene expression, preventing cancer induced recruitment of gene silencing proteins (e.g., Corepressors and histone modifying proteins). Created with BioRender.com.

RA has exhibited successful use as a chemo-preventative agent [46]. Unlike chemotherapy agents that directly induce cancer cell death, chemo-preventative agents disrupt carcinogenesis to halt cancer formation [46]. As a chemo-preventative agent, ATRA can reduce cancer progression of oral leukoplakia, which is a potentially malignant disorder [47]. Likewise, 13-cis RA can reduce tumor formation in patients with xeroderma pigmentosum, who exhibit increased rates of non-melanoma skin cancer due to nonfunctional DNA repair proteins [48]. In this context, ATRA's effect is explained by its capacity to upregulate tumor suppressor genes, such as p53, and facilitate activation of apoptotic pathways [49,50]. ATRA's antineoplastic properties have been applied with mixed results, necessitating further research to determine the conditions most susceptible to treatment.

ATRA downregulation of inflammatory disease processes

Inflammatory disease is a complex pathologic process with diverse clinical presentations. Depending on the degree of inflammation, inflammatory disease can affect a single organ system (e.g., psoriasis, atherosclerosis, etc.) or act systemically, such as in sepsis [51]. Regardless of severity, inflammatory processes are mediated by the release of proinflammatory cytokines (e.g., TNFα, IL-6, etc.) [51,52]. These cytokines are produced in response to activation of inflammatory signaling pathways, such as the NF-κB or MAPK pathway [51-54]. During inflammatory disease, these pathways become dysregulated and result in excessive inflammation.

An inflammatory disease characterized by chronic inflammation in the skin is psoriasis [55]. Psoriasis presents clinically with scaly red plaques that are defined by epidermal proliferation and immune cell infiltration [55-57]. Treatments for psoriasis include anti-inflammatory therapeutics (e.g., infliximab, utekinumab, etc.) and retinoids (e.g., acitretin, tazarotene, etc.) [56,57]. Retinoids improve psoriasis symptoms by reducing epidermal proliferation and downregulating inflammatory cytokines [56,57]. Specifically, retinoid induced activation of RARE leads to decreased IL-6 expression [57].

Another chronic inflammatory condition is atherosclerosis, which is defined by cholesterol buildup that induces inflammation in the vessel wall [58]. This inflammation results in vascular dysfunction that can lead to clot formation, thus disrupting blood flow to downstream organs [58]. Unlike psoriasis, atherosclerosis treatment focuses on limiting cholesterol accumulation and reducing clotting risk. ATRA's efficacy in treating atherosclerosis is currently under investigation [59]. However, its anti-inflammatory effect on mediators of atherosclerosis, such as macrophages and Tregs, highlights a possibility to reduce disease progression [58,59]. RA's anti-inflammatory effect has been extensively studied, with *in vitro* studies illustrating its cell type dependent activity. In macrophages RA decreases TNFα, IL-12, and PGE-2 secretion by interfering with NF-κB activity [25,26,60,61]. This interference has been proposed to occur via direct binding by RXR [26,61] (**Figure 3**). ATRA also stimulates Treg cell expansion, which is a major source of the anti-inflammatory cytokine IL-10 [62].

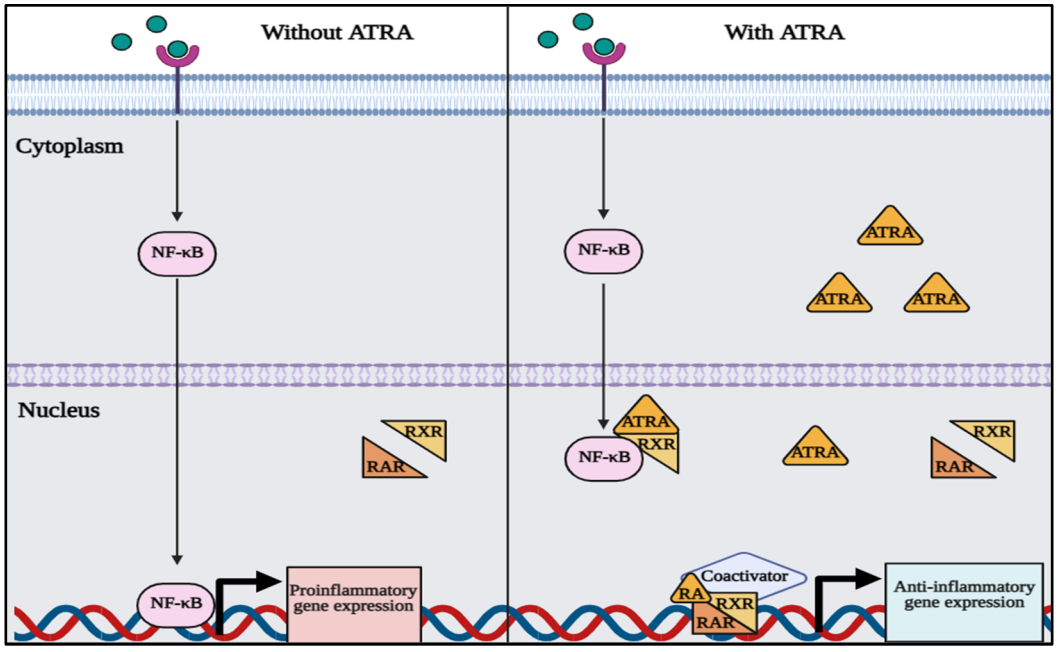

Figure 3. ATRA's anti-inflammatory effect. ATRA reduces inflammation by upregulating anti-inflammatory genes and disrupting NF-κB activity. Created with BioRender.com.

Because of its widespread influence on immune function, RA has been examined as a potential treatment for sepsis [26,63]. Sepsis is a fatal disease characterized as a dysfunctional host response towards an infection with risk of organ failure [63-65]. Regardless of etiology, many of the symptoms associated with sepsis (e.g., fever, excessive clotting, hypotension) result from excessive inflammation [63]. These inflammatory processes are mediated by a dysregulated release of proinflammatory cytokines, such as TNFα, IL-6, and IL-8 [63,66,67]. Current treatments with antimicrobials and corticosteroids (i.e., anti-inflammatory agent) have improved survival rates from sepsis [65,68]. However, mortality rates still range from 15 to 20%, and can increase to between 20 and 50% in cases of septic shock [66,69]. Its severe clinical presentation leads to over 5 million deaths globally [67].

With mortality rates from sepsis still high, ATRA has been examined as a potential treatment option. In lipopolysaccharide induced sepsis animal models, ATRA downregulates NF-κB activation and increases survival rates [24,26]. Similar results were seen in models of polymicrobial sepsis, where ATRA increased survival and was associated with decreased proinflammatory cytokine expression [26]. Clinical studies are needed to confirm RA's potential benefit during sepsis; however, previous work supports a promising outlook for its use.

ATRA activation of antimicrobial defense

Under typical conditions, the immune system is effective at clearing microbial pathogens. Activation of the innate immune system is facilitated by cellular pattern recognition receptors (PRRs) that recognize invading pathogens and trigger an inflammatory response [63,70]. The release of proinflammatory cytokines leads to leukocyte infiltration, with neutrophils and macrophages responsible for eliminating microbes via phagocytosis [70]. If the invading pathogen was previously encountered, then cells of the adaptive immune response (i.e., T and B cells) also contribute to pathogen clearance [70].

Unfortunately, many pathogens possess tools that allow them to disrupt immune cell signaling processes. A common strategy among different bacteria is to interrupt phagocytosis, either by evading cellular uptake or by inhibiting phagolysosome activity [70-72]. Examples of bacteria that can disrupt phagocytosis include clinically significant pathogens, such as *Mycobacterium tuberculosis, Streptococcus pyogenes,* and *Neisseria gonorrhoeae* [72]. Because phagocytosis is the primary mechanism by which bacteria are eliminated from tissues, therapies that improve cellular phagocytic pathways can improve bacterial clearance [73,74]. *In vitro* studies of rodent derived macrophages have shown that ATRA increases phagocytic activity [27,75,76].

When applied to human HL60 cells (i.e., promyelocyte cell-line), both ATRA and dimethyl sulfoxide induce cellular differentiation into neutrophils [77]. However, only ATRA differentiated neutrophils exhibit increased phagocytic activity against bacteria, such as *N. gonorrhoeae, Escherichia coli*, and *S. pyogenes* [78,79]. Increased phagocytosis was associated with upregulated expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), or CD66a [78]. CEACAM1 is a multifaceted membrane receptor that facilitates extracellular signal transduction to regulate different cellular functions (e.g., motility, proliferation, apoptosis, etc.) [80]. Important for immune function, CEACAM1 promotes monocyte survival and neutrophil function [80,81]. In neutrophils, CEACAM1 acts as a gram-negative bacterial receptor and promotes phagocytosis, especially against *N. gonorrhoeae* [80,82-84].

Along with facilitating leukocyte activity, ATRA can enhance antimicrobial defense in skin tissue. As the body's primary defense against infection, skin tissue protects against pathogen invasion by acting as a barrier and by producing antimicrobial proteins (AMPs) [85]. One notable AMP is cathelicidin, which is a bactericidal compound that disrupts bacterial membranes and facilitates leukocyte recruitment [85-87]. Cathelicidin is encoded by the human *CAMP* gene (i.e., *CRAMP* gene in mice) and is secreted by keratinocytes, sebocytes, adipocytes, neutrophils, mast cells, and dendritic cells [86]. In mouse *Staphylococcus aureus* infection models, cathelicidin secretion by dermal adipocytes was shown to be crucial for limiting bacterial invasion [85,86,88]. When administered ATRA, preadipocytes exhibited increased cathelicidin secretion that reduced *S. aureus* growth [89].

ATRA's antibacterial properties against *M. tuberculosis* (i.e., causative agent of tuberculosis) have been extensively studied and include different mechanisms of action [27,28]. HDTs against *M. tuberculosis* are especially important because of its increasing rate of antibiotic resistance [30,90]. Unlike other bacterial infections, Tuberculosis requires a monthslong multi-drug regimen (e.g., rifampicin, isoniazid, pyrazinamide, and ethambutol) for successful treatment [90]. With growing resistance to front-line antibiotics, ATRA's antimicrobial effect against *M. tuberculosis* has received the most attention. In macrophages, ATRA improves *M. tuberculosis* clearance by promoting autophagy of engulfed bacteria [27,91,92]. Improved autophagy is crucial for *M. tuberculosis* clearance since it can survive inside macrophages by disrupting phagolysosome formation [72]. ATRA's effect on macrophage autophagy stems from its activation of TANK-binding kinase 1 (TBK1), which localizes engulfed *M. tuberculosis* with autophagosomes [92,93]. Although TBK1 regulates the antiviral response, *M. tuberculosis* infection stimulates intracellular DNA PRRs that initiate an inflammatory immune response [93,94] (**Figure 4**). In monocytes, ATRA induces clearance by downregulating total cholesterol and increasing lysosomal acidification, which occurs in response to upregulation of *NPC2* gene expression [95].

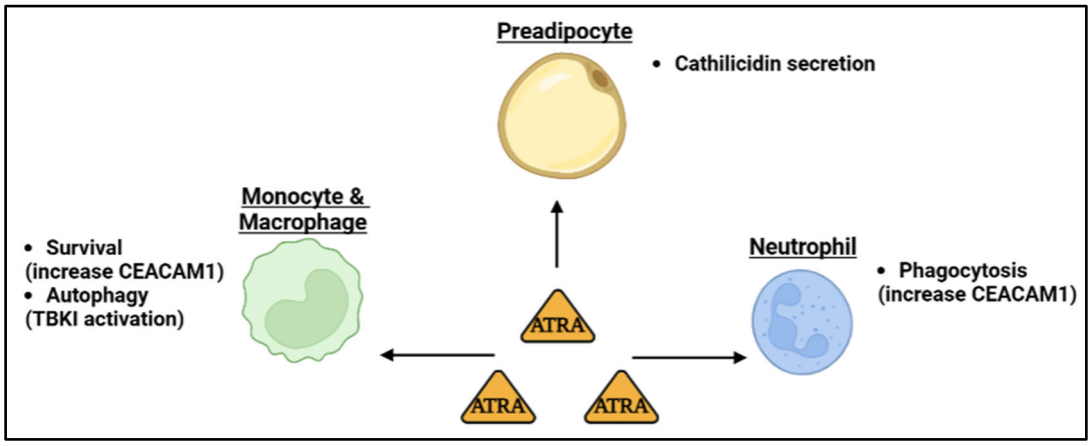

Figure 4. ATRA's antibacterial properties. ATRA upregulates cellular antibacterial pathways through various mechanisms: improving phagocytosis, facilitating autophagy, and promoting Cathilicidin secretion. Created with BioRender.com.

The efficacy of ATRA as an HDT for tuberculosis is currently under investigation. *In vivo* studies of tuberculosis in rats have shown that ATRA treatment reduces disease severity and decreases *M. tuberculosis* growth [96]. Clinical studies examining vitamin A supplementation in tuberculosis patients have shown no benefit during early disease course [97]. However, treatments using active metabolites of vitamin A, such as ATRA, have not yet been tested during tuberculosis infection.

ATRA upregulation of antiviral response

The type-I Interferon (IFN) response is the innate immune system's primary antiviral defense. Recognition of viral antigens by intracellular PRRs leads to IFN regulatory factor 3 (IRF3) activation [94,98]. IRF3 then induces IFNβ secretion, which stimulates antiviral gene expression in an autocrine and paracrine manner [94,98]. IFNβ promotes downstream activation of IRF9, which induces expression of over 300 antiviral proteins, such as IFN-induced tetratricopeptide repeat protein (IFIT), Myxovirus resistance protein 1 (MxA), and IFN-inducible transmembrane protein (IFITM) [94,99-101]. These proteins provide a potent antiviral defense, capable of interfering with each stage of the viral replication cycle (i.e., entry, translation, replication, and egress) [100,101].

Like other pathogens, viruses have developed effective strategies for disrupting immune signaling pathways. A prevalent technique during viral infection is to interrupt activation of the type-I IFN response [102]. Viral proteins can shield the viral genome from PRR detection or inhibit downstream signaling proteins. For instance, measles virus delays the type-I IFN response by inactivating intracellular PRRs, such as RA inducible gene I (*RIG-I*) and Melanoma differentiation associated gene 5 (*MDA5*) [102,103]. Other clinically important viruses, such as SARS coronavirus 2 (SARS-CoV-2) and influenza A virus, disrupt downstream signaling by inhibiting IRF3 activation or IFNβ receptor activity [102,104-106].

Whereas clinicians have a large array of antibiotics to treat bacterial infections, their repertoire of antivirals is much smaller in comparison. To complement the antiviral treatment regimen, different HDTs that can promote the type-I IFN response have been investigated [28]. Chief amongst them is ATRA, which can induce protection against different viral pathogens *in vitro* (e.g., measles, mumps, hepatitis C virus, etc.) [3,107-109]. Although not clinically used as an antiviral therapeutic, vitamin A does improve survival rates in pediatric patients (<2yr old) diagnosed with measles [110].

ATRA's antiviral effect stems from its capacity to upregulate upstream mediators of the type-I IFN response. ATRA treatment increases expression of RIG-I, IFNβ, IFNβ receptor, IRF1, and antiviral proteins [107-109] (**Figure 5**). As a PRR against viral RNA, increased RIG-I expression can improve detection against RNA viruses, such as measles or SARS-CoV-2 [107,111,112]. IRF1 is not classically associated with the antiviral response; however, it can facilitate activation of IRF3 [113,114]. As the main driver of IFNβ secretion, IRF3 activation is crucial for propagating the type-I IFN response. Recent studies have also shown that ATRA exhibits direct antiviral activity, capable of inhibiting reverse transcriptase and 3C-like protease in human immunodeficiency virus and SARS-CoV-2, respectively [115,116]. Further research of ATRA's antiviral properties is required to validate its efficacy in *in vivo* systems. Likewise, studies illustrating ATRA's limited effectiveness against H9N2 influenza virus highlight the need to determine which specific viral pathogens are susceptible to ATRA treatment [117].

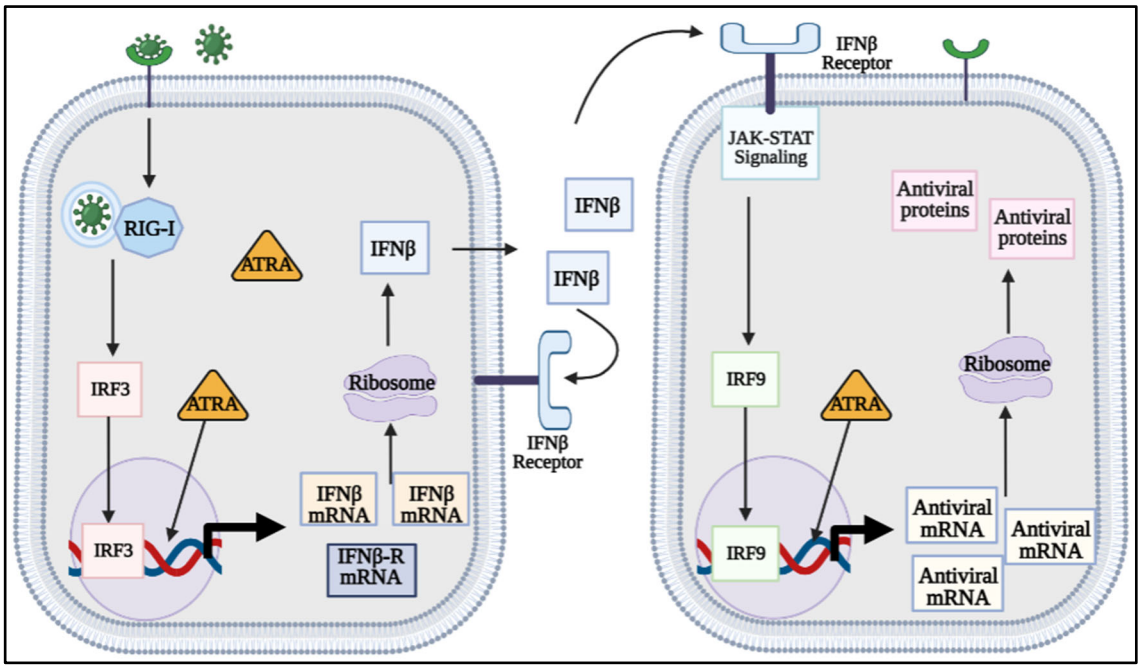

Figure 5. ATRA's antiviral effect. ATRA confers protection against viral infections by upregulating the type-I IFN response. Specifically, ATRA increases IFNβ, IFNβ receptor, and antiviral protein expression. Created with BioRender.com.

Challenges of ATRA as a disease treatment

Unlike other novel therapeutics, RA and its derivatives have a long history of clinical use against various diseases (e.g., acne vulgaris, psoriasis, APL, etc.) [118]. RA's effectiveness stems from its capacity to correct dysregulated cellular signaling pathways. However, its activity in multiple signaling pathways carries a significant risk of side effects, especially in pregnant women [1,119,120]. Common side effects of RA treatment include skin irritation and dryness [119,120]. The skin manifestations are due to RA's effect on cellular differentiation, with RA inducing early maturation of skin cells [119,120]. Acute liver injury is an uncommon side effect of RA treatment, which usually presents with a transient elevation in liver enzymes [1].

The most significant side effect of RA treatment is fetal malformation during pregnancy [1,119,120]. RA's characterization as a teratogen stem from its regulatory role during fetal development [1,4]. The addition of RA treatment during pregnancy alters normal fetal limb development and results in numerous malformations. Because it's a teratogen, RA is never given during pregnancy. In women who require long term treatment with RA, such as in psoriasis, contraceptives are prescribed to reduce the risk of pregnancy. Also, topical RA therapeutics may be used because they act locally and are less likely to be absorbed systemically [120].

Conclusions

RA is a dynamic compound that is capable of inducing various cell signaling pathways. In APL, ATRA functions as an effective anti-cancer therapy by inducing cellular differentiation [36,40]. This process reduces cancer cell proliferation and promotes normal maturation. Its capacity to induce physiologic differentiation has been studied in different cancer cell-lines, with clinical benefits being seen against cutaneous T cell Lymphoma [44]. RA also exhibits an anti-inflammatory effect, which is used to treat psoriasis [56]. The ability of RA to downregulate inflammatory pathways, such as NF-κB, has highlighted its potential as a possible sepsis treatment [63]. Although clinical studies are needed to validate RA's efficacy as a sepsis treatment, recent animal studies have illustrated its ability to improve sepsis survival rates [26].

The growing risk of antibiotic resistant disease and novel viral infection necessitates new therapeutic approaches. With decreasing numbers of approved antimicrobial treatments, HDTs have gained increasing importance as an alternative avenue for pharmaceutical research. Chief among them is ATRA, which can induce host antimicrobial pathways. Against bacterial pathogens, ATRA promotes phagocytosis, autophagy, cell survival, and AMP secretion (i.e., cathelicidin) [75,89,92]. *In vitro* studies with ATRA demonstrate that it improves clearance of clinically important pathogens, such

as *N. gonorrhoeae, S. aureus*, and *M. tuberculosis* [78,89,91]. This effect is also seen against fungal pathogens, with ATRA stimulated macrophages exhibiting increased phagocytosis against *Aspergillus fumigatus* and *Pneumocystis* [121-123]. Against viral pathogens, ATRA upregulates the host type-I IFN response to promote viral clearance (e.g., measles, mumps, and hepatitis C virus) [107-109]. Taken together, RA's capacity to alter cell signaling in different diseases has shown positive benefits that may be applicable to other pathologies.

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