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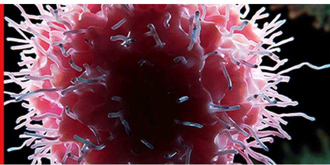
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CUTTING EDGE

Cutting Edge: All-*trans* Retinoic Acid Down-Regulates TLR2 Expression and Function[1]

Philip T. Liu, Stephan R. Krutzik,*† Jenny Kim,† and Robert L. Modlin[2]*†*

***A major consequence of microbial infection is the tissue injury that results from the host inflammatory response. In acne, inflammation is due in part to the ability of* Propionibacterium acnes *to activate TLR2. Because all-*trans *retinoic acid (ATRA) decreases inflammation in acne, we investigated whether it regulates TLR2 expression and function. Treatment of primary human monocytes with ATRA led to the down-regulation of TLR2 as well as it's coreceptor CD14, but not TLR1 or TLR4. The ability of a TLR2/1 ligand to trigger monocyte cytokine release was inhibited by pre- and cotreatment with ATRA; however, TLR4 activation was affected by cotreatment only. ATRA also down-regulated monocyte cytokine induction by* P. acnes. *These data indicate that ATRA exerts an anti-inflammatory effect on monocytes via two pathways, one specifically affecting TLR2/1 and CD14 expression and one independent of TLR expression. Agents that target TLR expression and function represent a novel strategy to treat inflammation in humans. The Journal of Immunology,* 2005, 174: 2467–2470.**

Toll like receptors (TLRs) are components of the innate immune system, providing germline encoded receptors that recognize evolutionarily conserved pathogen associated molecular patterns (1). TLRs are involved in host defense against a variety of pathogens including bacteria, parasites, and fungi (1, 2). Activation of TLRs results in secretion of proinflammatory cytokines and induction of direct antimicrobial mechanisms. However, TLR activation can induce cellular apoptosis and the robust inflammation often leads to concomitant tissue injury (3), for example nerve damage in leprosy (4), myocardial ischemia/reperfusion injury, the manifestations of septic shock, and the pathogenesis of inflammatory acne (2, 5). It is therefore logical to predict that pharmacological agents which down-regulate TLR expression and function may be useful as anti-inflammatory agents in the treatment of disease in humans.

The inflammatory component of acne is mediated in part by the ability of *Propionibacterium acnes* to activate TLR2 on monocytes leading to production of inflammatory cytokines including TNF-α, IL-1β, and IL-8 (2, 6). It is likely that the resulting inflammation contributes to the visibility of lesions and leads to scarring, resulting in emotional stress (7). Therefore, a major goal of therapy in acne is to reduce inflammation. Although retinoids, a class of vitamin A derived compounds that bind various members of the retinoic acid receptor (RAR)[3] family (8, 9), affect keratinocyte maturation, they also have anti-inflammatory activity (10–12). We therefore investigated whether all-*trans* retinoic acid (ATRA) regulates TLR expression and function as a possible mechanism for its anti-inflammatory activity in acne. We focused our studies on TLR2 on human monocytes, given previous findings that TLR2 mediated the monocyte cytokine response to *P. acnes* and that virtually all of the cells TLR2$^+$ cells in acne lesions were CD14$^+$ monocytes (2).

Materials and Methods

Reagents

ATRA (Sigma-Aldrich) was diluted in DMSO to a stock concentration of 10^{-2} M and stored at −80°C. Further dilutions were made in amber tubes (USA Scientific) and aliquoted to prevent repeated freeze thaw cycles. All experiments were conducted with 10^{-7} M of ATRA because it was found to be toxic to monocytes at higher concentrations. The cell viability following ATRA treatment was comparable to the control cells with close to 100% viability by propidium iodide (data not shown). We conducted ATRA treatment experiments for 1–4 days and the earliest observed effect occurred after 1 day, and that cell death became prominent after 2 days. To activate TLR2/1, a synthetic 19-kDa lipopeptide derived from *Mycobacterium tuberculosis* (EMC Microcollections) was used, and to activate TLR4, purified LPS (Sigma-Aldrich) was used and prepared as previously described (13). *P. acnes* sonicate was prepared as previously described (2).

Isolation of monocytes

PBMC were isolated from human whole blood as previously described (13). Monocytes were enriched using Percoll (Amersham Biosciences) and were adhered onto culture dishes for 2 h in RPMI 1640 containing 1% FBS (HyClone). The cells were washed with 1× PBS (Invitrogen Life Technologies) and the adherent cells were cultured as previously described (13).

Quantitative PCR (qPCR)

RNA was isolated from monocytes using TRIzol Reagent (Invitrogen Life Technologies), and cDNA was synthesized using the iSCRIPT cDNA Synthesis Kit (Bio-Rad). The following primers were designed using Primer Express (Applied Biosystems): 36B4, 5′-CCA CGC TGC TGA ACA TGC T-3′, 5′

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[3] Abbreviations used in this paper: RAR, retinoic acid receptor; ATRA, all-*trans* retinoic acid; ΔMFI, mean fluorescence value; qPCR, quantitative PCR; TLR2/1L, TLR2/1 ligand; TLR4L, TLR4 ligand.

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TCG AAC ACC TGC TGG ATG AC-3′; CD14, 5′-CGC TCC GAG ATG CAT GTG-3′, 5′-AGC CCA GCG AAC GAC AGA-3′; and ABCA1, 5′-TGT CCA GTC CAG TAA TGG TTC TGT-3′, 5′-AAG CGA GAT ATG GTC CGG ATT-3′. TLR primer sequences were previously published (14). SYBR Green reactions were conducted with the IQ SYBR Green mix (Bio-Rad). Reactions were run on the MJR Opticon Continuous Fluorescence detector (Bio-Rad) and analyzed with Opticon Monitor Software 1.08 (Bio-Rad). The relative quantities of the gene tested per sample were calculated against 36B4 using the ΔΔC(T) formula as previously described (15).

Flow cytometry

Cells were labeled for surface proteins using mAbs and analyzed by flow cytometry as previously described (13). We used Abs against TLR2 (2392; Genentech), TLR1 (eBioscience), TLR4 (eBioscience), CD14 (Caltag Laboratories), and CD40 (BD Pharmingen). We determined cell viability by propidium iodide labeling (BD Pharmingen).

Cytokine ELISAs

For the pretreatment experiments, monocytes were adhered to 24-well plates and treated with DMSO or ATRA for 24 h, before addition of the TLR2/1 ligand (TLR2/1L), TLR4 ligand (TLR4L), or *P. acnes* sonicate for 16 h, after which the supernatants were harvested. For the cotreatment experiments the incubations were done simultaneously. The supernatants were assayed for cytokines using the sandwich ELISA method with Ab sets for IL-12p40, IL-6, TNF-α (Biosource), and IL-8 (BD Pharmingen).

Results and Discussion

Although TLR activation is essential for host defense against microbial pathogens, the resulting inflammation can contribute to tissue injury. Given the role of TLR2 in mediating inflammation in acne, we hypothesized that one mechanism for the anti-inflammatory activity of ATRA was the regulation of TLR2 expression and function. Primary human monocytes were treated with ATRA (10^{-7} M) for 16 h and mRNA levels for TLR1–10 and CD14 were measured by qPCR. ABCA1 served as a positive control for a retinoid inducible gene (16). In five separate donors tested, mRNA encoding TLR2 and its coreceptor CD14 were consistently down-regulated by ATRA, with a 34% and 65% decrease in mRNA compared with the carrier control, respectively (Fig. 1*a*). The mRNA levels for TLR1, which forms a heterodimer with TLR2 to mediate ligand recognition, was also down-regulated, whereas TLR4 mRNA levels were maintained, and as expected, ATRA induced an 8-fold up-regulation of ABCA1 mRNA (Fig. 1*a* and data not shown).

To determine whether the differences in mRNA levels were reflected in cell surface protein expression, flow cytometry of ATRA-treated monocytes was performed. Treatment of monocytes with ATRA down-regulated the cell surface expression of TLR2 and CD14, whereas TLR4 levels were maintained (Fig. 1*b*). There was no detectable change in the cell surface expression of TLR1 (Fig. 1*b*), even though TLR1 mRNA was consistently down-regulated. The magnitude of the decrease in TLR1 mRNA may not have been sufficient to decrease the level of protein expression, or the expression of TLR1 was already extremely low, such that it may be difficult to detect a change in its expression. ATRA decreased the mean fluorescence intensity of TLR2 expression by 41% and CD14 by 42%. Taken together, these data indicate that ATRA can specifically down-regulate mRNA encoding and cell surface expression of TLR2 and CD14, without affecting expression of TLR1 and TLR4. Currently no RAR binding elements have been reported in the TLR2 upstream region. Our searches within the region have yielded no RAR binding elements as well, thus suggesting that the transcriptional regulation of TLR2 by ATRA is through an indirect method.

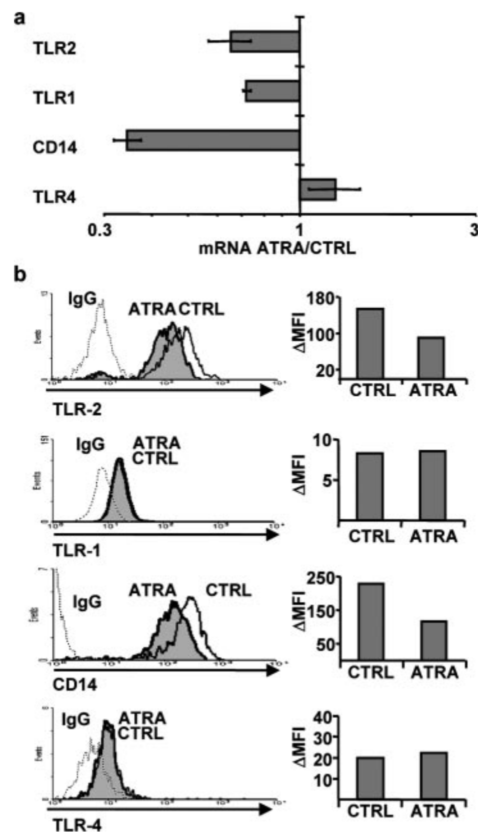

FIGURE 1. TLR2, TLR1, and CD14 down-regulated by ATRA, but not TLR4. Monocytes were stimulated with ATRA and (*a*) qPCR was run on TLR2, TLR1, CD14, and TLR4. Data is represented as fold change compared with carrier control and graphed on a log scale. *b*, Similar down-regulation was seen in TLR2 and CD14, and there was no change in TLR4 and TLR1 protein levels as measured by mean fluorescence value (ΔMFI). ΔMFI values are calculated by subtracting the mean flourescence intensity value of TLR2, TLR1, CD14, and TLR4 peaks by their corresponding isotype control peak. Representative of five donors.

Although the observed down-regulation of TLR2 was partial, we hypothesized that because CD14 is a coreceptor of TLR2, the simultaneous decrease in all proteins would result in a functional reduction of TLR2/1-mediated responses. One of the hallmarks for TLR activation of monocytes is the induction of inflammatory cytokines such as IL-12p40, TNF-α, IL-6, and IL-8 (3, 17). Therefore, we investigated the effect of ATRA on TLR2/1-induced monocyte cytokine release. Monocytes were treated with ATRA for 24 h and then stimulated for 16 h with a TLR2/1L or TLR4L at a range of concentrations and the supernatants assayed for cytokine release. We found that pretreatment of monocytes with ATRA decreased the TLR2/1-induced release of IL-12p40, TNF-α, and IL-6 by 91%, 70%, and 74%, respectively, at the highest concentration of TLR2/1L. Pretreatment with ATRA had little or no effect on TLR4-induced release of any of the cytokines measured (Fig. 2*a*). Similarly, pretreatment with ATRA did not decrease the TLR2/1- nor TLR4-induced IL-8 release and the up-regulation of CD40 expression (Fig. 2*b*), suggesting that not all signaling pathways induced by TLR activation were affected by ATRA pretreatment. Taken together, these data indicate that ATRA can inhibit monocyte cytokine release by down-regulating TLR2 and CD14 expression and function.

We also sought to determine whether ATRA had the ability to directly suppress TLR-mediated inflammatory responses.

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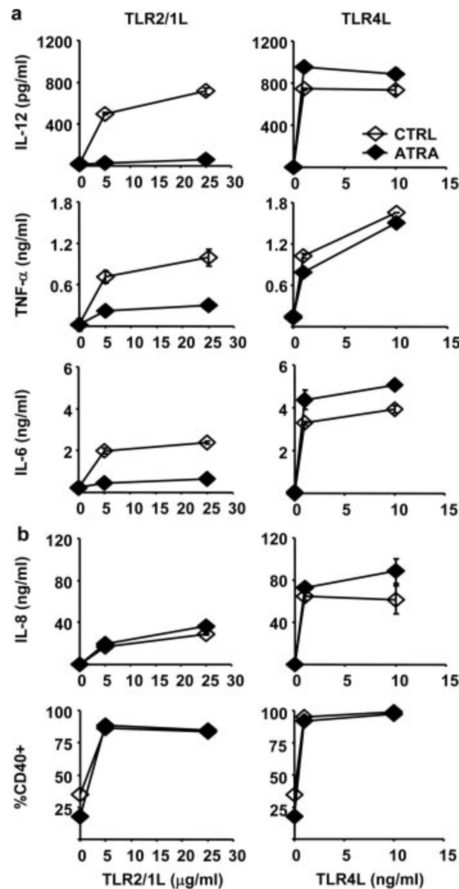

FIGURE 2. ATRA pretreatment results in functional decrease of TLR2/1L induced IL-12p40, TNF-α, and IL-6, but not IL-8 or CD40. TLR4L is not affected. Monocytes were treated with ATRA (◆) or carrier control (◇) for 24 h, and stimulated with TLR2/1L and TLR4L for 16 h. Supernatants were assayed for cytokines. *a*, IL-12p40, TNF-α, and IL-6 secretion are reduced by ATRA pretreatment for TLR2/1L but not TLR4L. *b*, IL-8 secretion and CD40 cell surface up-regulation are not effected by ATRA. Representative of five donors.

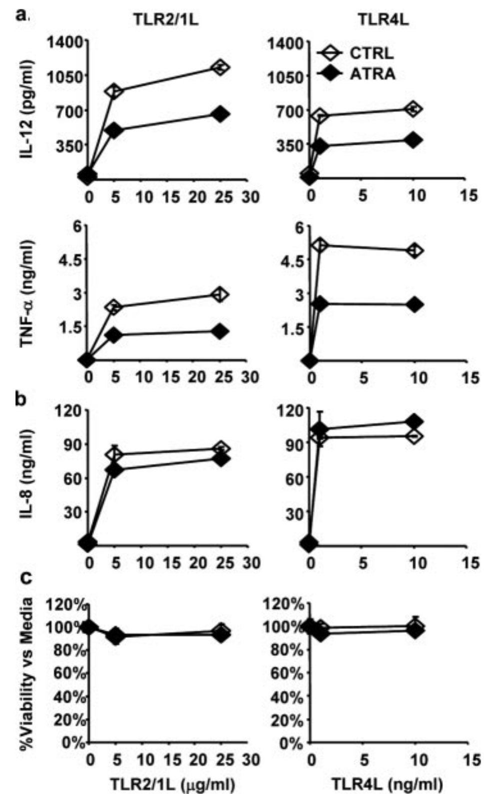

FIGURE 3. ATRA cotreatment results in decrease of TLR2/1L and TLR4L induced IL-12p40, TNF-α, and IL-6, but not IL-8. Monocytes were simultaneously treated with ATRA (◆) or carrier control (◇) and TLR2/1L or TLR4L for 16 h. Supernatants were assayed for cytokines. *a*, IL-12p40 and TNF-α secretion are reduced by ATRA cotreatment for TLR2/1L and TLR4L. *b*, IL-8 secretion is not affected by ATRA. *c*, There is no significant cell toxicity with the treatments compared with medium control as measured by propidium iodide staining. Representative of five donors.

Therefore, we simultaneously treated monocytes with TLR2/1L or TLR4L and either ATRA or carrier control, then assayed the cell supernatants for cytokine levels. Cotreatment with ATRA at the highest concentration of the ligands reduced both TLR2/1L- and TLR4L-induced IL-12p40 release by 42% and 44%, TNF-α by 56% and 49%, and IL-6 by 48% and 37%, respectively (Fig. 3*a* and data not shown). In all cases, ATRA treatment had no significant effect on the release of IL-8 or the up-regulation of CD40 (Fig. 3*b* and data not shown). These findings were in contrast to the pretreatment of monocytes with ATRA, which inhibited TLR2/1- but not TLR4-induced cytokine responses. We investigated cell death during cotreatment of the TLR ligands and ATRA. Using propidium iodide, we labeled for dead cells and found no significant difference, with viability over 95% (Fig. 3*c*). These data suggest that cytotoxicity is not the primary mechanism responsible for the lower cytokine levels. The most likely explanation for the ability of ATRA to directly suppress TLR-mediated inflammatory responses is by affecting TLR signaling or mRNA stability. There is already evidence in the literature that retinoids inhibit TLR4 signaling by physical association of retinoid X receptor with NF-κB, thereby inhibiting IL-12p40 transcription (18), and that activation of NF-κB is a shared signaling pathway by all TLRs (1). Alternatively, retinoids have been reported to decrease mRNA stability (19).

Because *P. acnes* has been shown to induce inflammatory cytokines through activation of TLR2 but not TLR1 (2), we tested whether ATRA could reduce *P. acnes*-induced monocyte cytokine release. Monocytes were pretreated with ATRA, then activated with *P. acnes* sonicate or cotreated with ATRA and *P. acnes* simultaneously. ATRA pretreatment reduced *P. acnes*-induced release of both IL-12p40 and TNF-α by 53% and 67% respectively at the highest *P. acnes* concentration tested (Fig. 4*a*). ATRA cotreatment resulted in a reduction of IL-12p40 and TNF-α levels by 37% and 31%, respectively (Fig. 4*b*). The levels of IL-6, IL-8, and CD40 were not affected with either pre- or cotreatment with ATRA (Fig. 4 and data not shown). These data demonstrate that ATRA is able to reduce *P. acnes*-induced inflammatory cytokine release, and therefore it is tempting to speculate that the ability of ATRA to modulate TLR2 expression and function accounts for the anti-inflammatory activity of retinoids during acne therapy. Commonly prescribed products containing ATRA as the active ingredient contain an equivalent concentration ranging from 6.67×10^{-3} M to 1.33×10^{-3} M, yet the concentrations of the retinoid that penetrate the epidermis are not known. The elucidation of the *P. acnes* ligand that activates monocytes via TLR2 should provide insight into the mechanism by which retinoids exert an anti-inflammatory effect in acne.

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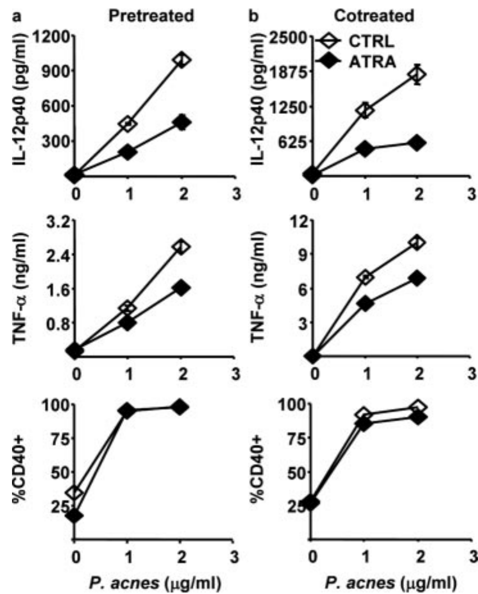

FIGURE 4. ATRA pretreatment and cotreatment result in decrease of *P. acnes* induced cytokine responses. Monocytes were (*a*) pretreated with ATRA (◆) or carrier control (◇) for 24 h and stimulated with TLR2/1L and TLR4L for 16 h. Supernatants were collected and assayed for cytokines. IL-12p40 and TNF-α are reduced with ATRA pretreatment. However, CD40 up-regulation showed no change. Monocytes were also (*b*) simultaneously treated with carrier control or ATRA and *P. acnes* for 16 h. IL-12p40 and TNF-α were reduced in the presence of ATRA, but CD40 up-regulation was not affected. Representative of five donors.

Our data provide evidence that one possible mechanism for the anti-inflammatory effect of ATRA is its ability to regulate TLR2 expression and activation. Other mechanisms may contribute to the anti-inflammatory effect of ATRA, yet in the absence of an animal model, it is difficult to determine which pathway is dominant. Nevertheless, the finding that a pharmacologic agent can inhibit TLR expression and function is novel and provides a rationale for developing other TLR antagonists as therapeutic agents. Clearly, it will be of interest to determine whether other anti-inflammatory agents exert their effect on TLR activation. Already, certain lipid A analogues have been reported to antagonize TLR2 and TLR4 activation through interaction with shared receptor components, resulting in loss of TNF-α secretion but not NO production in both transfected cell lines as well as primary human alveolar macrophages (20, 21). The data suggested that the most likely mechanism for the inhibition was through blocking the physical interactions of the ligand with the receptor components, distinct from the mechanism(s) by which ATRA inhibits TLR2-mediated responses. Therefore, the ability of ATRA to inhibit TLR expression and activation provides a novel therapeutic approach to managing diseases in which TLR-induced inflammation contributes to tissue injury.

Disclosures

R. L. Modlin is a member of the Johnson & Johnson Skin Care Scientific Advisory Board.

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