Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 352 (2007) 42–47
BBRC
www.elsevier.com/locate/ybbrc

All-*trans* retinoic acid negatively regulates cytotoxic activities of nature killer cell line 92

Ang Li [a,*], Meilan He [a], Hui Wang [a], Bin Qiao [b], Ping Chen [a], Hua Gu [a], Mengjie Zhang [a], Shengxiang He [a]

[a] *School of life science, Tongji university, 1239 Siping Road, Shanghai 200092, PR China*
[b] *Department of Public Health and Molecular Biology, Shanghai Municipal Center for Disease Control and Prevention, PR China*

Received 23 October 2006
Available online 2 November 2006

Abstract

NK cells are key components of innate immune systems and their activities are regulated by cytokines and hormones. All-*trans* retinoic acid (ATRA), as a metabolite of vitamin A and an immunomodulatory hormone, plays an important role in regulating immune responses. In the present study, we investigated the effect of ATRA on human NK cell line NK92. We found that ATRA dose-dependently suppressed cytotoxic activities of NK92 cells without affecting their proliferation. To explore the mechanisms underlying the ATRA influence on NK92 cells, we examined the production of cytokines (TNF-α, IFN-γ), gene expression of cytotoxic-associated molecules (perforin, granzyme B, nature killer receptors (NCRs), and NKG2D), and the activation of NF-κB pathways related with immune response. Our results demonstrated that ATRA suppressed NF-κB activity and prevented IκBα degradation in a dose-dependent way, inhibited IFN-γ production and gene expression of granzyme B and NKp46. Our findings suggest that ATRA is a negative regulator of NK92 cell activation and may act as a potential regulator of anti-inflammatory functions in vivo.

Keywords: ATRA; NK92 cells; Nature killer receptors; NF-κB

Vitamin A plays an important role in the regulation of immune function [1,2]. Vitamin A deficiency is associated with decreased resistance to infection and both specific and nonspecific responses are impaired [3]. Vitamin A (retinol) is converted to its active metabolites all-*trans* and -retinoic acid by specific enzymes [4]. Retinoic acid then regulates gene expression by binding to two nuclear receptors, the retinoic acid receptor (RAR-α, -β, and -γ), and the retinoid X receptor (RXR-α, -β, and -γ). Recently, it has been found that the most active vitamin A metabolite, ATRA, has a role as an immunomodulatory hormone in regulating most of lymphocytes' function [5]. The majority of trials have reported that physiological levels of ATRA stimulated the proliferation of normal peripheral blood T cells when the cells were co-stimulated with agents such as PMA (phorbol myristate acetate) or PHA (phytohemagglutinin) [6]. The mechanisms that mediate the enhancement of T cell proliferation by ATRA supplementation are thought to be related to induction of IL-2 production and increased Bcl2a expression [6,7]. Furthermore, ATRA could regulate factors known to be required for Ig class switch recombination and modulated the population dynamics of ligation-stimulated B cells, while promoting the progression of a fraction of B cells into differentiated sIgG-expressing cells [8]. Recent studies showed that ATRA could induce the differentiation of immature DCs into mature DCs, enhance antigen presentation of DCs, and increase the inducible NO synthase activation [9,10]. Although there has been research on relationship between ATRA and immune component cells including T lymphocytes, B lymphocytes, DC, and

* Corresponding author. Fax: +86 21 65986853.
E-mail address: liang3829@sina.com.cn (A. Li).

0006-291X/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2006.10.132

monocytes/macrophage, unfortunately, the effects of ATRA on NK cells have not been completely clear. How vitamin A affects NK cell function still remains controversial. Some studies suggested that vitamin A inhibited the proliferation of NK cells and vitamin A deficiency resulted in enhancement of NK cells' function [11]; in contrast to this opinion, other studies demonstrated that vitamin A deficiency led to decrease in number of NK cells and impairment of NK cells' cytotoxicity [12]. To clarify the effect of ATRA, the active metabolites of vitamin A on NK cells, in the present study, we, for the first time, observed, using human NK cell line NK92 as a model, that human NK92 cells expressed ATRA receptors, ATRA inhibited human NK92 cells' function in vitro, and some molecular mechanisms by which ATRA affects human NK92 cells' function.

Materials and methods

Cell culture and reagents. Endotoxin-free recombinant human IL-2 (rhIL-2, 2×10^7 U/mg) was purchased from Peprotech (Rocky Hill, NJ)and all-*trans* RA was purchased from Aldrich–Sigma (Cambridge, MA). The IL-2-dependent NK cell line NK-92, established from a patient with rapidly progressive non-Hodgkin slymphoma [13], was purchased from ATCC and maintained in α-MEM (GIBIO, Grand Island, NY) containing 100 U/mL IL-2 and other necessary components as described [14]. K562, a human chronic myelogenous leukemia cell line, was used as target cells in cytotoxicity assay and cultured in 15% FCS of RPMI 1640 medium (GIBIO, Grand Island, NY).

NK cell proliferation assay. For proliferation assay, NK92 cells were cultured in triplicate at 37 °C in a 5% CO_2 incubator in complete IL-2-containing medium RPMI 1640 in 96-well plates (5×10^4 cells/200 μl/well) in the presence of ATRA at various concentrations. The NK92 cells were examined at 72 h after culture by MTT colorimetric method. Briefly, 5 mg/mL MTT (3-2,5-diphenyltetrazolium bromide; Sigma) was added to all wells and plates were incubated at 37 °C for 4 h, deprived of 100 μl supernatant, and 100 μl of 10% SDS (sodium dodecyl sulfate, Sigma) was added to dissolve formazan. Results were analyzed on a Bio-Rad Microelisa Reader.

^{51}Chromium release cytotoxicity assay. K562, a human chronic myelogenous leukemia cell line, was used as target cells in cytotoxicity assay and cultured in 15% FCS of RPMI 1640 medium. Assay was performed using NK92 cells that had been co-cultured earlier in the presence or absence of ATRA as effector cells. The NK92 cells were admixed with ^{51}Cr-labeled K562 target cells for NK cytotoxicity at an effector (E) to target (T) ratio of 8:1, 4:1, 2:1, and 1:1. After standard 4-h incubation, the supernatant was harvested and analyzed on a gamma counter (model 5500; Beckman Instrument, Irvine, CA). The percentage specific lysis was calculated as follows: $\%\ \text{specific lysis} = \text{cpm}_{\text{exp}} - \text{cpm}_{\text{spontaneous}} / \text{cpm}_{\text{maximum}} - \text{cpm}_{\text{spontaneous}} \times 100\%$.

ELISA for cytokine detection. NK92 cells were washed, resuspended in enriched IL-2-containing medium at the concentration of 1×10^6 cell/mL, and co-cultured in the presence or absence of ATRA for 48 h. Supernatants were collected, filtered, and tested for the presence of TNF-α and IFN-γ by ELISA. The amounts of cytokines were determined using a standard sandwich ELISA technique with corresponding kits from Pharmingen (San Diego, CA).

RT-PCR. The RT-PCR analysis was performed as previously described [15]. Briefly, NK92 cells have been incubated in the presence or absence of ATRA for 48 h. Then the Total RNA was extracted from the NK92 cells with TRIzol reagent (Invitrogen). First-strand cDNA was synthesized from 5 μl of total cellular RNA with a Eppendorff PCR system 5331 cycler (Eppendorf Company, Germany) using the following protocol: 1 cycle at 42 °C for 60 min and 70 °C for 10 min. The cDNA was subjected to 30 cycles of amplification for detecting RARα, RARβ, RARγ, perforin, granzyme B, FasL, NKp46, NKp33, NKp44, and NKG2D mRNA expression using appropriate primers as previously described [15–17]: after denaturation at 94 °C for 5 min, the amplification conditions were as follows: 45 s at 94 °C, annealing at 54 °C for 45 s, and extension at 72 °C for 45 s. The PCR products were resolved on a 1.2% agarose gel. As a control, a 540-bp band corresponding to human β-actin transcript was amplified. Perforin, granzyme B, FasL, NKp46, NKp33, NKp44, and NKG2D mRNA expression was calculated as the ratio of the intensity of the corresponding band to the β-actin band by densitometry, respectively.

Western blot assay. Anti-RARα mAb, anti-RARγ mAb, and anti-IκBα mAb were purchased from Santa Cruz Biotechnology. NK92 cells that had been co-cultured earlier in the presence or absence of ATRA were resuspended in lysis buffer (30 mM Tris, pH 7.5, 150 mM NaCl, 1 mM PMSF, 1 mM Na_3VO_4, 1% Nonidet P-40, and 10% glycerol) and then centrifuged for 10 min at 4 °C. Protein concentration of the supernatant (protein fraction) was calculated using the BCA protein assay. An aliquot of 40 μg total extracts was mixed with protein loading buffer containing 2-ME and boiled for 5 min before loading onto an SDS/10% polyacrylamide gel. After electrophoresis, proteins were transferred onto nitrocellulose membranes and blotted against primary Abs. Membranes were washed with TBS (0.05% (v/v) Tween 20 in PBS (pH 7.4)) and incubated with a 1:2000 dilution of HRP-conjugated secondary Abs for 45 min. Protein bands were visualized by an enhanced chemiluminescence reaction (Amersham Pharmacia Biotech, Piscataway, NJ) as described [18].

Measurement of luciferase activity. The pNF-κB-luciferase (pNF-κB-luc) gene reporter vector and pRL-CMV vector were purchased from Promega. NK92 cells were plated in 12-well plates 1 day before the experiment, and transient co-transfection of pNF-κB-luc and pRL-CMV, which expresses *Renilla* luciferase was used to normalize for transfection efficiency, was conducted using the calcium phosphate method. The next day, the cells were treated with ATRA (0.1–10 μM) for 24 h. Then, the cells were washed twice with PBS and lysed in 300 μl of reporter lysis buffer (Promega). The two luciferase activities were measured using a dual luciferase assay kit according to the manufacturer's instructions (Promega).

Statistical analysis. Statistical analysis was performed with the SPSS10.0 program. A *p*-value of 0.05 was used to determine statistical significance unless otherwise indicated.

Results

ATRA receptors are constitutively expressed in human NK92 cell line

To determine the expression of ATRA receptors (RARα, RARβ, RARγ), the NK92 cell line, which was harvested at the logarithmic phase of growth, was first examined by semiquantitative RT-PCR. The results revealed that RARα and RARγ were constitutively expressed in NK92 cell line, but higher level of RARγ mRNA expression than RARα mRNA was observed. Whereas RARβ could not be detected in NK92 cell line, even if using a highly sensitive nested RT-PCR (Fig. 1A). The results demonstrated that RARγ was constitutively and strongly expressed in NK92 cell line, RARα was expressed at a low level, while RARβ was not expressed in NK92 cell line. The finding was confirmed by detecting the RARα and RARγ protein via Western blot (Fig. 1B). The same results were also obtained in primary human NK cells (data not shown).

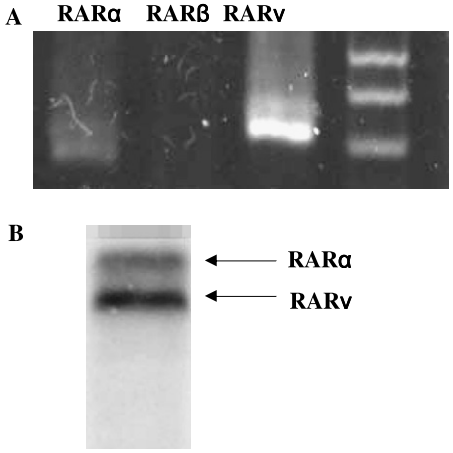

Fig. 1. Expression of ATRA receptors on human NK92 cells. (A) Gene expression of ATRA receptors by RT-PCR analysis. The RT-PCR analysis was performed as described in Materials and methods. RNA was extracted from NK-92 cells. PCR primers for RARα, RARβ, and RARγ were synthesized according to previous report. (B) Western blot assay for detecting RAR protein in NK-92 cells. NK-92 cells were positive at both forms of RARα and RARγ. Experiments were performed at least three times with a representative experiment being shown.

ATRA suppresses cytotoxicity of human NK92 cell line, but has no effect on its proliferation

After confirmation of RARα and RARγ presence in NK92 cells, we then explored the effects of ATRA on NK92 cells. NK92 cells were stimulated with graded doses of ATRA (0.1–10 μM), even at a higher concentration (data not shown), and no effects on cell proliferation were observed (Fig. 2A). To further determine the effect of ATRA on the cytotoxicity of NK92 cells, cytotoxicity assays were performed with the NK92 cells as effector cells and the erythroleukemia cell line K562 as target cells. In contrast to proliferation assay, ATRA exerts potent inhibitory effect on the cytotoxic activity of human NK92 cells in a dose-dependent manner with a maximum inhibitory effect at 10 μM ATRA . E:T ratios from 1:1 to 8:1 were studied. When E:T ratio reached 8:1 at 10 μM ATRA, the lytic activity was decreased by 50% compared with untreated cells (Fig. 2B).

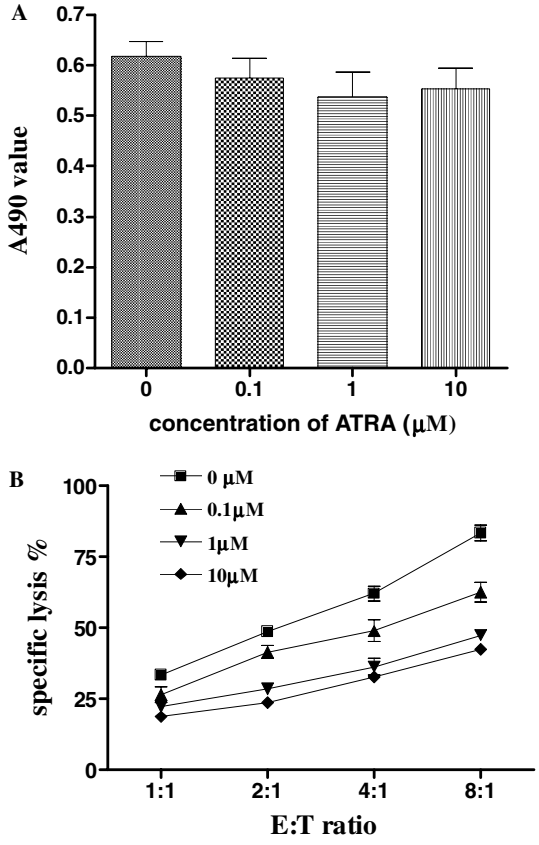

Fig. 2. Effects of ATRA on IL-2-dependent NK92 cell line proliferation and cytotoxicity. (A) NK92 cells were treated by ATRA at various concentrations. Seventy-two hours later, proliferation assay was conducted by MTT colorimetric method. (B) NK92 cells were treated by ATRA as described above for 72 h, then the cytotoxicity assay was performed as described in method. The percentage specific lysis was calculated as follows: % specific lysis $cpm_{exp} - cpm_{spontaneous}/cpm_{maximum} - cpm_{spontaneous} \times 100\%$. All values are represented as means ± SEM of triplicate determinations. ($p < 0.05$, 0.1, 1, 10 μM vs 0 at ratio of 4:1 and 8:1. $p < 0.05$, 1, 10 μM vs 0 at ratio of 2:1.)

ATRA inhibits IFN-γ production and gene expression of NKp46 and granzyme B in NK92 cells

After it was recognized that ATRA is capable of suppressing NK92 cells' activity, we further explored the molecular mechanisms by which the ATRA suppressed cytotoxicity of human NK92 cells. We first tested expression of cytokines related with cytotoxicity of NK cell by ELISA after ATRA treatment. When the NK92 cells were co-cultured with ATRA for 48 h, expression of IFN-γ decreased markedly compared with control group in absence of ATRA (Fig. 3A), whereas the secretion of TNF-α was not affected by ATRA. Because NKG2D, NCRs (NKp30, NKp46, NKp44), FasL, granzyme B, and perforin were shown to involve in NK-mediated cytotoxicity [19], we then detected gene expression of these molecules in NK92 cells by semiquantitative RT-PCR. As shown in Fig. 3B, incubation of NK92 cells with ATRA resulted in a extremely down-regulation of NKp46 and granzyme B and to a lesser extent of NKp30, which may, at least partly, explain why ATRA inhibits cytotoxicity of human NK92 cell line. However, the gene expression of NKG2D, NKp44, perforin, and FasL in NK92 cells was not affected by ATRA.

ATRA suppresses activity of NF-κB and prevented degradation of IκBα in NK92 cells

NF-κB signaling pathway plays a vital role in immune response. The production of IFN-γ and granzyme B can be regulated by NF-κB [20,21]. So we investigated whether ATRA exerted inhibitory effect on NK92 cells through

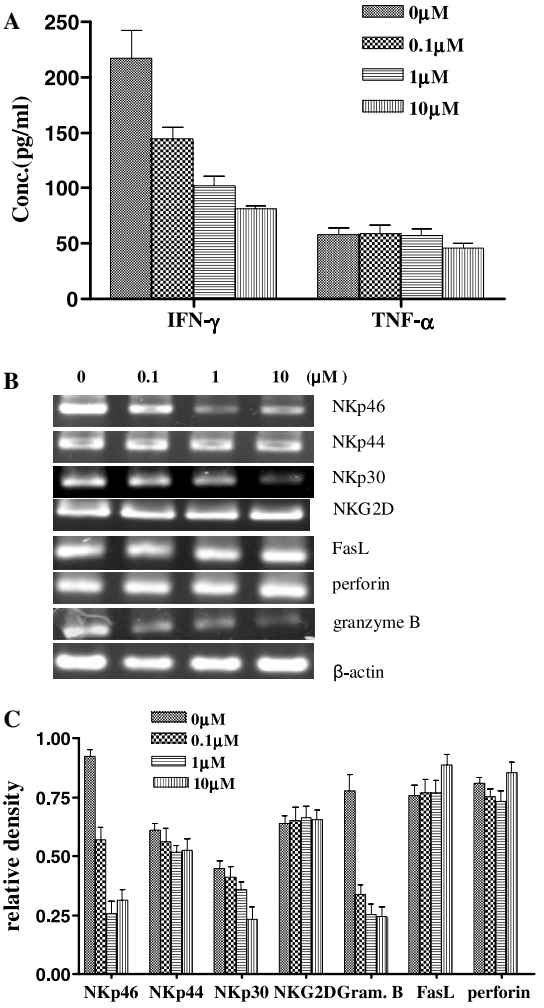

Fig. 3. Cytokine production and granzyme B, perforin, FasL, NKG2D, and NCRs gene expression in NK92 cells after ATRA treatment. (A) NK92 cells were treated by ATRA as described above for 48 h, then TNF-α and IFN-γ production was measured by ELISA. All values are represented as means ± SEM of triplicate determinations (IFN-γ: $p < 0.05$, 0.1, 1, 10 μM vs 0). (B) RT-PCR was performed as described in Fig. 1 to detect gene expression of granzyme B, perforin, FasL, NKG2D, and NCRs in NK92 cells after ATRA treatment. (C) The intensities of the bands were determined with the use of the ratios to β-actin. Experiments were performed at least three times with a representative experiment being shown (NKp46: $p < 0.05$, 0.1 μM vs 0; $p < 0.01$, 1, 10 μM vs 0. NKp30: $p < 0.05$, 10 μM vs 0. granzyme B: $p < 0.01$, 0.1, 1, 10 μM vs 0).

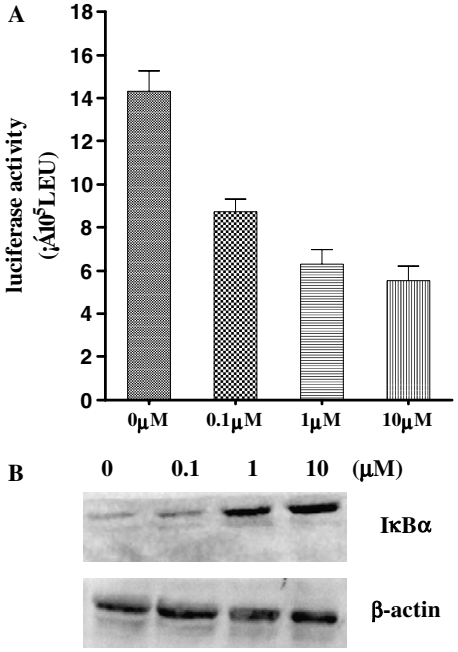

Fig. 4. Effects of ATRA on the NF-κB signaling pathway in NK92 cells. (A) pNF-κB-luc vector was transiently co-transfected with pRL-CMV vector in NK92 cells. After overnight recovery, the transfected cells were treated with ATRA for 24 h, and luciferase activity was measured. All values are represented as means ± SEM of triplicate determinations ($p < 0.05$, 0.1, 1, 10 μM. vs 0). (B) Western blot analysis for IκBα protein from treated or untreated NK92 cells.

suppressing the NF-κB signaling pathway. As shown in Fig. 4A, luciferase activity in NK92 cells transfected with pNF-κB-luc vector was decreased in a dose-dependent manner as the result of ATRA treatment. Translocation of NF-κB to the nucleus is normally regulated by IκBα degradation. We examined whether the inhibition of NF-κB activation by ATRA was due to decreased degradation of IκBα, Western blot for IκBα was done as an index of total inhibitor expression levels. When cells were treated with different concentrations of ATRA for 24 h, significant dose-dependent increase in total IκBα expression levels was observed (Fig. 4B).

Discussion

Previous studies have demonstrated that vitamin A and its active metabolites, ATRA, could develop Th2 response, accelerate Ig class switch recombination of B cell, and induce the differentiation of immature DCs into mature DCs [6–10]. In the current study, we demonstrated that ATRA could suppress cytotoxicity of NK cell in vitro. We also found that production of IFN-γ decreased in human NK cell line after ATRA treatment, which is consistent with previous report that ATRA diminished Th1 response and inhibited IFN-γ secretion in vivo and in vitro [22,23]. Among cytokines produced by NK cell, IFN-γ is a critical one, which could play vital role in lysing tumor cells and activating other lymphocytes. Our finding showed that ATRA suppressed production of IFN-γ in human NK cell line, which partly explained why NK cells' cytotoxicity decreased after ATRA treatment. In this report, we also provide the first experimental evidence that the gene expression of NKp46,one of NK cytotoxicity receptors (NCRs), and granzyme B is selectively down-regulated by ATRA. The surface densities of NKG2D and NCRs are directly correlated with the magnitude of NK cell cytolytic activity against several target cell types. Granzyme B is an essential molecule involved in secreting cytotoxic granule-mediated cytotoxicity [19]. Our findings imply that down-regulation of NKp46 and granzyme B after ATRA treatment is responsible for the inhibition of NK cell

cytotoxicity. Consistent with previous study indicating that NF-κB activity in vitamin A-deficient mice was increased 1.8-fold in the lymph nodes and 1.4-fold in the thymus in vivo [24], our results also showed that the ATRA could inhibit NF-κB activity and prevented degradation of IκBα in NK cell line in vitro. The NF-κB proteins are a family of transcription factors that regulate expression of genes involved in immune and inflammatory responses including IFN-γ and granzyme B [20,21]. So, this finding indicates that inhibition of NF-κB by ATRA is an important molecular mechanism by which ATRA suppresses NK cells' cytotoxicity. Though unrelated study indicated that perforin gene expression is also regulated by NF-κB signaling in IL-2-stimulated NK cells [25], no any change in gene expression of perforin was observed with the down-regulation of NF-κB activity in ATRA-treated NK cells. Further experiments are required for clarifying the molecular mechanism of downstream pathway of NF-κB after ATRA treatment.

It has been proposed that psoriasis is an immunologically mediated, probably autoimmune, disease in which T-helper type 1 cytokines play an important role [26]. Because ATRA could suppress the Th1 response and skew the immune response to Th2, it has been widely used to treat psoriasis and other immunologically mediated dermatitis. Recently, accumulating evidence has shown that natural killer (NK) and natural killer-T (NK-T) cells are considered key to the pathogenesis of these conditions, which are characterized by reduced numbers of NK cells in peripheral blood and are present in plaques of psoriasis [27–29]. Besides elevated IFN-γ secretion, in psoriatic patients, up-regulation of NCRs on surface of infiltrated NK cells was observed [30]. The data presented here that ATRA suppressed production of IFN-γ and gene expression of NCRs in NK cells may provide another reasonable explanation for ATRA-mediated attenuation of psoriatic syndrome. In view of these findings, it is possible to use ATRA as a novel therapy for NK cell-mediated autoimmnune diseases.

In our study, we also first found that both human NK92 cell line and primary human NK cells express two ATRA receptors, RARα and RARγ, which is a basic indication that ATRA can exert immunoregulatory effect on human NK cells. The retinoic acid isomers bind to nuclear receptors from two distinct classes, the retinoic acid receptors (RAR) and retinoid X receptors (RXR). RAR binds 9-cis retinoic acid and ATRA, whereas RXR binds only 9-cis retinoic acid. RXR forms functional heterodimers with many members of the steroid receptor family including RAR [31]. We speculate ATRA binding to one or more RAR–RXR receptor complexes in NK cells to regulate NK cell function. Further experiments are currently underway to clarify the effect of ATRA on the signal molecules between RAR and nuclear factors.

In conclusion, we, for the first time, identified ATRA receptors on human NK92 cell line, found that ATRA suppresses NK92 cells' cytotoxicity in a dose-dependent manner, and elucidated that the underlying mechanisms of ATRA function are at least partly through inhibition of NF-κB pathway and down-regulating expression of IFN-γ, a key cytokine related with NK function, granzyme B, a fast death-inducing effector molecule, and NKp46, one of NK cytotoxicity receptors. This conclusion will be helpful to explain the relationship between ATRA and NK cells.

Acknowledgment

This work was supported by the Tongji University Medical Grant (2000219014).

References

[1] H.K. Blomhoff, E.B. Smeland, Role of retinoids in normal hematopoiesis and in the immune system, in: R. Blomhoff (Ed.), Vitamin A in Health and Disease, Marcel Dekker, New York, 1998, p. 451.
[2] R.D. Semba, The role of vitamin A and related retinoids in immune function, Nutr. Rev. 56 (1998) 38–48.
[3] A.C. Ross, Vitamin A status: relationship to immunity and antibody response, Proc. Soc. Exp. Biol. Med. 200 (1992) 303–320.
[4] G. Duester, Families of retinoid dehydrogenases regulating vitamin A function: production of visual pigment and retinoic acid, Eur. J. Biochem. 267 (2000) 4315–4324.
[5] J. Bastien, C. Rochette-Egly, Nuclear retinoid receptors and the transcription of retinoid-target genes, Gene 328 (2004) 1–16.
[6] N. Engedal, A. Ertesvag, H.K. Blomhoff, Survival of activated human T lymphocytes is promoted by retinoic acid via induction of IL-2, Int. Immuno. 16 (2004) 443–453.
[7] R. Rasooly, G.U. Schuster, J.P. Gregg, J. Xiao, R.A.S. Chandraratna, C.B. Stephensen, Retinoid X receptor agonists increase Bcl2a1 expression and decrease apoptosis of naive T lymphocytes, J. Immunol. 175 (2005) 7916–7929.
[8] Q. Chen, A.C. Ross, Vitamin A and immune function: Retinoic acid modulates population dynamics in antigen receptor and CD38-stimulated splenic B cells, Proc. Natl. Acad. Sci. USA 102 (2005) 14142–14149.
[9] S. Kusmartsev, F. Cheng, B. Yu, Y. Nefedova, E. Sotomayor, R. Lush, D. Gabrilovich, all-trans-retinoic acid eliminates immature myeloid cells from tumor-bearing mice and improves the effect of vaccination, Cancer Res. 63 (2003) 4441–4449.
[10] C.S. Devaux, Y. Devaux, V.L. Cannard, S. Grosjean, C.R. Egly, F. Zannad, C. Meistelman, P. Mertes, D. Longrois, Enhancement of the inducible NO synthase activation by retinoic acid is mimicked by RAR-a agonist in vivo, Am. J. Physiol. Endocrinol. Metab. 283 (2002) E525–E535.
[11] J. Jason, L.K. Archibald, O.C. Nwanyanwu, A.L. Sowell, I. Buchanan, J. Larned, M. Bell, P.N. Kazembe, H. Dobbie, W.R. Jarvis, Vitamin A levels and immunity in humans, Clin. Diagn. Lab. Immun. 9 (2002) 616–621.
[12] H.D. Dawson, N. Li, K.L. DeCicco, J.A. Nibert, A.C. Ross, chronic marginal vitamin A status reduces natural killer cell number and function in aging lewis rats, J. Nutr. 129 (1999) 1510–1517.
[13] J.H. Gong, G. Maki, H.G. Klingemann, Characterization of a human cell line (NK-92) with phenotypical and functional characteristics of activated natural killer cells, Leukemia 8 (1994) 652–658.
[14] S. Nagashima, R. Mailliard, Y. Kashii, T.E. Reichert, R.B. Herberman, P. Robbins, T.L. Whiteside, Stable transduction of the interleukin-2 gene into human natural killer cell lines and their phenotypic and functional characterization in vitro and in vivo, Blood 91 (1998) 3850–3861.
[15] L. Szabova, D. Macejova, M. Dvorcakova, S. Mostbock, S. Blazickova, S. Zorad, S. Walrand, N. Cardinault, M-P. Vasson, E.

Rock, J. Brtko, Expression of nuclear retinoic acid receptor in peripheral blood mononuclear cells (PBMC) of healthy subjects, Life Sci. 72 (2003) 831–836.
[16] E. Mavoungou, M.K. Bouyou-Akotet, P.G. Kremsner, Effects of prolactin and cortisol on natural killer (NK) cell surface expression and function of human natural cytotoxicity receptors (NKp46, NKp44 and NKp30), Clin. Exp. Immunol. 139 (2004) 287–296.
[17] B. Meresse, Z. Chen, C. Ciszewski, M. Tretiakova, G. Bhagat, T.N. Krausz, D.H. Raulet, L.L. Lanier, V. Groh, T. Spies, E.C. Ebert, P.H. Green, B. Jabri, Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease, Immunity 21 (2004) 357–366.
[18] R. Faggioni, K.R. Feingold, C. Grunfeld, Leptin regulation of the immune response and the immunodeficiency of malnutrition, FASEB J. 15 (2001) 2565–2571.
[19] J.S. Orange, Z.K. Ballas, Natural killer cells in human health and disease, Clin. Immunol. 118 (2006) 1–10.
[20] A. Sica, L. Dorman, V. Viggiano, M. Cippitelli, P. Ghosh, N. Rice, H.A. Young, Interaction of NF-κB and NFAT with the interferon-γ promoter, J. Biol. Chem. 272 (1997) 30412–30420.
[21] C. Huang, E. Bi, Y. Hu, W. Deng, Z. Tian, C. Dong, Y. Hu, B. Sun, A novel NF-κB binding site controls human granzyme B gene transcription, J. Immunol. 176 (2006) 4173–4181.
[22] S. Frankenburg, X. Wang, Y . Milner, Vitamin A inhibits cytokines produced by type 1 lymphocytes in vitro, Cell. Immunol. 185 (1998) 75–81.
[23] S. Yu, M. Xia, W. Xu, Y. Chu, Y. Wang, S. Xiong, All-trans retinoic acid biases immune response induced by DNA vaccine in a Th2 direction, Vaccine 23 (2005) 5160–5167.
[24] L.M.I. Austenaa, H. Carlsen, A. Ertesvag, G. Alexander, H.K. Blomhoff, R. Blomhoff, Vitamin A status significantly alters nuclear factor-κB activity assessed by in vivo imaging, FASEB J. 18 (2004) 1255–1257.
[25] J. Zhou, J. Zhang, M.G. Lichtenheld, G.G. Meadows, A role for NF-κB activation in perforin expression of NK cells upon IL-2 receptor signaling, J. Immunol. 169 (2002) 1319–1325.
[26] R . Perez-Lorenzo, L.A. Nunez-Oreza, P.M. Garma-Quen, E . Lopez-Pacheco, G . Bricaire-Bricaire, Peripheral blood mononuclear cells proliferation and Th1/Th2 cytokine production in response to streptococcal M protein in psoriatic patients, Int. J. Dermatol. 45 (2006) 547–553.
[27] A.L. Cameron, B. Kirby, C.E. Griffiths, Circulating natural killer cells in psoriasis, Br. J. Dermatol. 149 (2003) 160–164.
[28] C. Ottaviani, F. Nasorri, C. Bedini, O. de Pita, G. Girolomoni, A. Cavani, CD56brightCD16(-) NK cells accumulate in psoriatic skin in response to CXCL10 and CCL5 and exacerbate skin inflammation, Eur. J. Immunol. 36 (2006) 118–128.
[29] A.L. Cameron, B. Kirby, W. Fei, C.E. Griffiths, Natural killer and natural killer-T cells in psoriasis, Arch. Dermatol. Res. 294 (2002) 363–369.
[30] A . Gilhar, Y. Ullmann, H. Kerner, B. Assy, R. Shalaginov, S . Serafimovich, R.S. Kalish, Psoriasis is mediated by a cutaneous defect triggered by activated immunocytes: induction of psoriasis by cells with natural killer receptors, J. Invest. Dermatol. 119 (2002) 384–391.
[31] F.J. Piedrafita, M. Phahl, Nuclear retinoid receptors and mechanisms of action, in: H. Nau, W.S. Blaner (Eds.), Handbook of Experimental Pharmacology: Retinoids, Spring-Verlag, New York, 1999, pp. 153–184.