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The Cellular Source and Target of IL-21 in K/BxN Autoimmune Arthritis

Katharine E. Block* and Haochu Huang*,‡

IL-21 is a pluripotent cytokine that regulates B cell and plasma cell differentiation and is thought to be an autocrine factor for follicular helper T cell (TFH) and Th17 differentiation. Although IL-21 has been implicated in autoimmune diseases, its relevant cellular source and target cells have not been well characterized. We investigated this issue in the K/BxN mouse model of autoimmune arthritis. Adoptive transfer of KRN-transgenic CD4+ T cells into appropriate hosts drives germinal center (GC) formation and autoantibody production against glucose-6-phosphate isomerase, leading to joint inflammation and destruction. By comparing transfer of T or B cells deficient in IL-21 or IL-21R, we were able to dissect the contribution of each cell type. T cells deficient in IL-21 did not induce GC formation or autoantibody production, but they went through normal TFH differentiation. However, T cells lacking IL-21R induced Ab titers, GC B cell frequency, and arthritis development similar to wild-type T cells, suggesting that IL-21 is not required for TFH differentiation and function. IL-21 acts on B cells, because IL-21R expression on B cells was required to induce disease. In contrast, Th17 cells, a T cell subset that also produces IL-21 and can provide help to B cells, are not required for the GC response and arthritis. These data have implications in developing effective therapies for rheumatoid arthritis and other Ab-mediated autoimmune diseases. The Journal of Immunology, 2013, 191: 2948-2955.

*Committee on Immunology, University of Chicago, Chicago, IL 60637; and ‡Knapp Center for Lupus and Immunology Research, University of Chicago, Chicago, IL 60637

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1

Interleukin-21, a member of the common γ-chain–signaling
family of cytokines, plays an important role in lymphocyte
activation, survival, and differentiation (1). IL-21 production
is restricted to activated T cells, such as follicular helper
T cells (TFH), Th17 cells, and NKT cells. The receptor for IL-21
is widely expressed on a variety of cell types, including B cells,
attracted T cells, NK cells, and dendritic cells. IL-21 promotes
B cell proliferation, Ig class switching and production, and plasma
cell differentiation (2). IL-21 also enhances the proliferation of
T cells stimulated through their TCRs (3) and was shown to
be an autocrine growth factor for TFH and Th17 cell differentia-
tion (4–8).

The TFH subset, a canonical producer of IL-21, is controlled by
the transcription factor Bcl6. Changes in chemokine receptor expression
allow TFH to migrate from the T cell zone into B cell follicles.
Expression of cell surface molecules promote cell–cell contacts with
B cells presenting cognate Ag. It is in these intimate interactions that
IL-21 from TFH is thought to act on B cells to promote germinal
center (GC) and plasma cell differentiation (reviewed in Refs. 9, 10).
In addition to TFH, the Th17 cell subset produces IL-21. Th17 is
a dominant proinflammatory T cell subset, controlled by the tran-
scription factor RORγt, and is involved in a number of autoimmune
diseases (reviewed in Ref. 11). Th17 cells were shown to directly
interact with and help B cells (12) and promote spontaneous GC
formation in autoimmune BXD2 mice (13).

IL-21 is important in a number of animal models of systemic
lupus erythematosus and rheumatoid arthritis (14–18). Accord-
ingly, an association of certain IL-21 and IL-21R alleles with
a risk for systemic lupus erythematosus in humans was reported
(19, 20). In the NOD mouse model, IL-21 is required for the
development of type I diabetes (21, 22). Given the complex bio-
logical functions of IL-21, it is important to understand the rele-
vant cells producing and responding to the cytokine in the context
of B cell–mediated autoimmune

We investigated this question of the relevant targets of IL-21 using
the K/BxN model of rheumatoid arthritis. K/BxN mice develop
arthritis by 4 wk of age (23). The disease is initiated by KRN TCR-
transgenic CD4+ T cells that recognize a peptide from the ubiqui-
tously expressed self-protein glucose-6-phosphate isomerase (GPI)
presented by the NOD-derived MHC class II molecule I-A^d (24).
Activated KRN T cells drive B cells to form GCs and to pro-
duce anti-GPI IgG autoantibodies, which induce joint pathology (25).
K/BxN mice develop spontaneous disease, unlike other models
of arthritis that involve Ag vaccination with adjuvants and can
affect TFH development (26). The advantage of the model for these
studies is that the disease can be induced by transferring naive KRN
T cells into T cell–deficient hosts expressing the MHC class II
molecule I-A^d (25, 27).

In this study, we used this cell-transfer approach of the K/BxN
model to determine the source and action of IL-21 in arthritis. We
showed that T cells deficient in IL-21 did not induce GC formation
or autoantibody production, but they went through normal TFH
differentiation. However, T cells lacking IL-21R induced similar
Ab titer, GC B cell frequency, and arthritis development as wild-
type (WT) T cells, suggesting that IL-21 is not required for TFH
differentiation and function. IL-21 must act on B cells, because
IL-21R expression on B cells was required to induce disease.
Surprisingly, Th17 cells are not required for arthritis development,
stressing the importance of IL-21 production specifically from the
T Fah subset. These results have implications for developing effective therapies for rheumatoid arthritis and other Ab-mediated autoimmune diseases.

**Materials and Methods**

**Mice**

KRN TCR-transgenic mice (23), IL-21R−/− mice (28), and RORγtFPPGPPFPF mice (29) were maintained on C57/BL6 background. IL-21−/− mice (B6:129S5-Il21tm1Slj, obtained from the Mouse Mutant Regional Resource Center, Davis, CA) were maintained on a B6:129S5 mixed background. KRN was crossed to IL-21R−/− or IL-21+/− mice to generate K/IL-21R−/− or K/IL-21+/− mice, respectively. TCR Cα−/− BxN mice used as hosts were F1 of C57/BL6 x B6 and Cα−/− NOD (25). IL-21 knockout mice crossed to B6.H2g7-congenic mice (30) were used as donors for purified B cells. All experiments were approved by the Institutional Animal Care and Use Committee of the University of Chicago.

**Cell-transfer induction of arthritis**

CD4+ cells were isolated from splenocytes using AutoMACS positive selection program. A total of 1 × 10^6 cells in sterile DMEM were injected into the tail vein of C57/BL6 BxN mice. B cells were enriched from splenocytes by depleting T cells with anti-CD90.2 Ab (clone 53-2.1; BioLegend), followed by rabbit complement (Cedarlane).

**Abs and flow cytometry**

Anti-KRN TCRα-specific Ab 3-4G-B7 (J. Perera, B. Stadinski, X. Liu, E. Huseby, and H. Huang, manuscript in preparation) was labeled with Alexa Fluor 647 or biotin. Abs used were against CXC5R5, Bc16, and Fas (BD Biosciences); CD45.1, TCRβ, GL-7, CD19, IL-17A, and B220 (eBioscience); and CD4 and PD-1 (BioLegend). Intracellular staining for Bcl-6 was performed using the Foxp3 intracellular staining kit from eBioscience, according to the manufacturer’s protocol. Intracellular staining for IL-17 was performed using the intracellular staining kit from BD Biosciences. Data analysis was conducted using FlowJo software (Tree Star).

**Immunohistochemistry staining of splenic sections**

Sections of frozen spleen (5 μm) were thawed, rehydrated, and then stained. Peanut agglutinin (PNA; Alexa Fluor 488), anti-mouse IgD (PE), and anti-mouse Vβ6 (Alexa Fluor 647) or anti-KRN TCRα (Alexa Fluor 647) were used. Images were taken on an Axiosvert 200m microscope (Zeiss) and visualized with ImageJ.

**ELISA for anti-GPI total IgG**

Ninety-six–well plates were coated with 5 μg/ml recombinant GPI in PBS overnight at 4°C and blocked with 1% BSA 0.05% Tween-20 in PBS at room temperature. A serial dilution of the samples added to the plate was detected with a biotinylated goat anti-mouse IgG (subclasses 1+2a+2b+3) Fcy– or goat anti-mouse IgM Fcμ, fragment–specific Ab, followed by alkaline phosphatase–conjugated streptavidin (all from Jackson ImmunoResearch). Samples were developed with phosphatase substrate (Sigma) and were read at 405 nm. A four-parameter variable slope was fitted to the data points, and the EC50 (infection point) for a standard sample was calculated from this nonlinear regression. Serum titers were calculated as the serum dilution (x value) that gave the calculated EC50 (y value) based on the fitted nonlinear regression for each sample. Samples where the curve could not be fitted because of low signal (low Ab binding) are indicated as ND (not detectable), and a titer of 1 was assigned for statistical comparisons. All analyses were conducted using Prism 5.0b software (GraphPad).

**Statistical analysis**

Normally distributed data were analyzed by the unpaired t test using Prism 5.0b software (GraphPad).

**Results**

**T Fah differentiation in the cell-transfer model of autoimmune arthritis**

To investigate the role of IL-21 in a cell-specific manner, we took advantage of the cell-transfer model of the K/BxN mouse. Naïve CD4+ KRN T cells are isolated from healthy KRN/B6 mice (KRN maintained on C57/B6 background) and transferred into Cα−/− BxN hosts (TCR Cα−/− on B6xNOD F1 background) (25, 27). These hosts lack αβ T cells and express the MHC class II allele I-A^d, which is required for the KRN TCR to recognize a peptide from the self-Ag GPI. Transferred KRN T cells are activated and induce high titers of anti-GPI IgG Abs, resulting in ankle swelling and joint remodeling. To follow autoreactive T Fah differentiation and GC response, T Fah and GC B cells were characterized after T cell transfer. For comparison, naïve KRN/B6 T cells were transferred into Cα−/− B6 hosts. Because Cα−/− B6 mice do not carry the MHC class II allele I-A^d, KRN T cells do not precipitate disease upon transfer. This allowed us to verify that T Fah differentiation is dependent on Ag recognition rather than lymphopenia-induced homeostatic proliferation. PD-1+ CXC5R5 or Bc6+ CXC5R5 T Fah were identified in Cα−/− BxN hosts but not in Cα−/− B6 hosts or KRN/B6 mice (Fig. 1A). In the following experiments, we used CXC5R5 and intracellular Bc6 to mark T Fah, because these markers showed a more distinct pattern. Consistent with the T Fah staining, GC B cells (identified as GL-7+ Fas+) were induced in Cα−/− BxN hosts, whereas Cα−/− B6 hosts had a small GC population, similar to what was observed in naïve KRN/B6 mice (Fig. 1B).

**IL-21 production by T cells is required to induce arthritis**

To determine whether IL-21 production by T cells acts on T cells in an autocrine manner to induce arthritis, we compared naïve CD4+ KRN T cells purified from WT K/B6 mice (denoted as “K”) in the figures) with those purified from KRN mice deficient in IL-21 (referred to as K/IL-21−/−) or IL-21R (referred to as K/IL-21R−/−) after transfer into Cα−/− BxN hosts. In the K/IL-21−/− transfer, KRN T cells could not produce IL-21; in the K/IL-21R−/− transfer, KRN T cells were able to produce IL-21 but unable to receive IL-21R signaling. These two groups allowed us to test whether IL-21 production by autoreactive T cells is required, as
well as whether autoreactive T cells require IL-21 as an autocrine factor for disease. As shown in Fig. 2A, K/IL-21−/− CD4+ T cells transferred into Cx−/− BxN hosts did not induce arthritis. In contrast, K/IL-21R−/− CD4+ T cells induced severe arthritis with the same kinetics as the WT KRN T cells. We determined the anti-GPI IgG titers both early (8 d) and late (29–31 d) in disease. WT KRN T cells and K/IL-21R−/− T cells induced high titers of anti-GPI IgG at both time points. In contrast, both anti-GPI IgM and IgG titers remained low in K/IL-21−/− T cells–transfer model (Fig. 2B). These data demonstrate that IL-21 production by T cells is crucial for IgG Ab response and arthritis but that IL-21R is not required on T cells.

To test the role of IL-21 in extrafollicular response in this model, we determined anti-GPI IgM and IgG at earlier time points after transferring WT KRN or K/IL-21−/− splenocytes. In the WT KRN transfer, anti-GPI IgM titers were elevated by day 4 and continued to increase over time; this occurred before IgG titers increased. In contrast, both anti-GPI IgM and IgG titers remained low in K/IL-21−/− transfers (Fig. 2C). These results suggest that IL-21 is required in even the early extrafollicular response in this model.

**IL-21 is not required for T_{FH} differentiation in vivo**

We next compared the fate of transferred T cells and T_{FH} differentiation in all three transfer settings. Congenic markers on transferred cells (CD45.2+) and Cx−/− BxN host cells (CD45.1+/CD45.2) allowed us to identify the transferred T cells as the CD45.1+ CD4+ population (Fig. 3A). Eight days after cell transfer, just after disease onset, there was a small but significant increase in the percentage and number of K/IL-21−/− T cells compared with WT KRN T cells in the spleen. The percentage and number of K/IL-21R−/− T cells were comparable to WT KRN T cells. At 29–31 d, when disease was fully established in WT KRN and K/IL-21R−/− T cell–transfer mice, there was no significant difference in the percentage and numbers of transferred T cells among the three transfer groups. These data suggest that the survival of transferred CD4+ KRN T cells was not affected by their ability to produce or respond to IL-21.

To determine how T_{FH} differentiation was affected, CXCR5 and intracellular Bcl6 staining were used to identify T_{FH}. WT KRN, K/IL-21R−/−, and K/IL-21−/− T cells differentiated into T_{FH} at similar frequencies in the spleen 8 d after transfer (Fig. 3B). The absolute number of T_{FH} from K/IL-21−/− animals was transiently higher than that from WT donors as a result of the higher total number of CD4+ T cells (Fig. 3A). However, by 29–31 d, K/IL-21−/− T_{FH} percentage and numbers decreased to half of those in WT KRN-transfer mice. This presumably reflects the defects in the maintenance phase of T_{FH} differentiation (31), given that there were no GCs formed in these mice (see later discussion). However, there were comparable numbers of WT and K/IL-21R−/− T_{FH} 8 d after transfer, and a small, but not statistically significant, decrease in T_{FH} numbers in K/IL-21−/− cells compared with WT at days 29–31 (Fig. 3B). These data suggest that IL-21 is not a requisite autocrine factor for KRN T_{FH} differentiation.

**IL-21 is required for GC formation**

Although T_{FH} differentiation was normal in all transfers, anti-GPI IgG Ab production was severely impaired following the transfer of K/IL-21−/− T cells (Fig. 2B). Therefore, we investigated GC formation and T cell migration by immunofluorescence on spleen sections. As shown in Fig. 4A, there were abundant GCs in both KRN WT and K/IL-21−/− T cell–transfer mice. In contrast, GCs in K/IL-21−/− T cell-transfer mice were rarely observed, and the few GCs were amorphous and dimly labeled with PNA. The number of GCs was counted from multiple spleen sections from multiple mice (Fig. 4B). KRN WT and K/IL-21R−/− T cell transfer induced equivalent numbers of GCs/section. GC size was measured; KRN WT mice had slightly larger GCs on average compared with K/IL-21R−/− T cell–transfer mice. We also assessed
Discussion

IL-21 is a pleiotropic cytokine affecting a diverse array of cell types (2). Without conditional deletion of IL-21 or IL-21R, it has been shown to drive the formation of spontaneous GCs in autoimmune responses of the BXD2 mice (13), and they can provide effective help to B cells (12, 32). Therefore, we tested the contribution of Th17 cells in initiating GC responses and arthritis. K/B6 mice were crossed to RORγt(GFP/GFP) mice (33) to generate K/RORγt(GFP/GFP) mice. In these mice, GFP insertion inactivates RORγt expression, and Th17 differentiation is defective. CD4+ T cells were purified from either K/RORγt+/+ or K/RORγt(GFP/GFP) mice and transferred into Cx3(−−) BxN hosts. As shown in Fig. 5A, K/RORγt+/+ and K/RORγt(GFP/GFP) CD4+ T cells induced arthritis with a similar kinetics and severity. There also was no difference in the serum anti-GPI IgG titers (Fig. 5B). The transferred K/RORγt(GFP/GFP) cells were indeed deficient in generating Th17 cells as determined by IL-17 intracellular staining after in vitro stimulation (Fig. 5C). However, there was no difference in the differentiation of Th17 cells (Fig. 5D). These results demonstrate that Th17 cells and their production of IL-21 are not essential for GC responses and arthritis development, supporting the conclusion that T FH are the major source of IL-21 production.

It was shown previously that Th17 cell development is correlated with disease induction in K/BxN mice (34). We investigated whether there were differences in Th17 cell development and distribution in K/BxN mice versus the transfer model. Cells isolated from the spleen, draining lymph nodes (pooled popliteal and inguinal lymph nodes), and mesenteric lymph nodes stimulated in vitro revealed a similar profile of IL-17A production from K/BxN mice and Cx3(−−) BxN hosts after KRN T cell transfer (Fig. 5E). IL-17A production was detected from KRN T cells identified with the anti-KRN Vα4-specific Ab 3-4G-B7. However, non-KRN T cells were the major IL-17A producers in both K/BxN mice and host mice that received KRN/B6 cell transfer.

**B cells require IL-21R signaling to initiate GCs**

Because IL-21 production by T cells is necessary for GC formation, it suggests that the target of IL-21 is the B cell. To directly test the importance of IL-21R expression on B cells, we performed a B and T cell cotransfer experiment. B cells purified from IL-21R−/− or IL-21R−/- mice expressing I-A<sup>g7/b</sup> MHC class II alleles were transferred along with naive K/B6 CD4+ cells into Rag1<sup>−/−</sup> B6xNOD F1 hosts. Most mice that received IL-21R−/- B cells developed arthritis, whereas mice that received IL-21R<sup>−/−</sup> B cells never showed signs of arthritis (Fig. 6A). The disease states were reflected in the dramatic difference in anti-GPI IgG titers between these two groups of mice (Fig. 6B). There was a moderate decrease in T FH in hosts receiving IL-21R−/- B cells compared with those receiving IL-21R<sup>−/−</sup> B cells (Fig. 6C). This result is consistent with what was observed in the K/RORγt<sup>−/-</sup> T cell transfer: T FH numbers decreased after 29–30 d, likely due to a lack of interaction with GC B cells to promote T FH maintenance. There was a more dramatic decrease in GC B cells in hosts receiving IL-21R<sup>−/-</sup> B cells compared with those receiving IL-21R<sup>−/−</sup> B cells (Fig. 6D). Immunohistological analysis of GCs on spleen section confirmed the results obtained by flow cytometry, although there were few B cell follicles and smaller GCs in general compared with T cell transfer into Cx3(−−) BxN hosts (data not shown). This is not surprising considering that Rag1<sup>−/−</sup> mice have defective follicular structures and a much smaller population of transferred B cells. These data support the conclusion that IL-21R signaling in B cells is essential for GC formation, Ab production, and arthritis development, and GC B cells are required for T FH maintenance.
difficult to evaluate the specific roles of IL-21 in autoimmunity. We used a cell-transfer system based on the K/BxN mouse model of autoimmune arthritis to address these roles in TFH differentiation and B cell activation. Our results demonstrate that IL-21 production by T cells is important in disease induction. However, IL-21 is not required for TFH differentiation, maintenance, or function. There was no defect in T cell survival when KRN T cells were deficient in either IL-21 or IL-21R; in fact, survival was increased 1 wk after transfer in IL-21−/− T cells (Fig. 3A). A similar increase was observed in IL-21−/− mice after immunization with NP-KLH (35), although the mechanism for enhanced survival is unclear. Both IL-21−/− and IL-21R−/− KRN T cells proliferated, differentiated into TFH, and were able to migrate into the B cell follicles in an Ag-specific manner, because this process did not take place when KRN T cells were transferred into Cα−/−B6 hosts that do not express the self-peptide–MHC complex.

In an earlier study using IL-21R−/− K/BxN mice, it was shown that there were fewer CD4+ T cells in the spleen and joint-draining lymph nodes compared with normal K/BxN mice (36). IL-21R−/− K/BxN mice did not develop arthritis, and it was attributed to a requirement of IL-21 by KRN T cells for homeostatic proliferation. The different conclusions from our study and the earlier
study highlight the complex biological function of IL-21 and the problem of understanding the direct versus indirect mechanisms in total knockout animals.

We found no difference in the GC B cell response between KRN WT and K/IL-21R−/− T cell–transfer mice by Ab titers or GC B cell formation by flow cytometry or histology, demonstrating that there is no functional defect in \( T_{FH} \) in the absence of IL-21 signaling. These results contrast with a study of lupus-like disease induced in a chronic graft-versus-host model, which found that GC B cells were less frequent and GCs were smaller when IL-21R−/− T cells were transferred (17). The differential dependence on IL-21 signaling may be related to the difference in frequency or affinity of alloreactive T cells, because it was shown that naïve Ag-specific Th cells with TCRs of higher affinity preferentially differentiate into the CXCR5+ “resident” \( T_{FH} \) compartment (37).

Studies on the role of IL-21 in \( T_{FH} \) differentiation and GC formation led to different conclusions in mice immunized with protein Ags. GC formation was relatively unaffected in IL-21−/− or IL-21R−/− mice in some studies (35, 38, 39), whereas a more profound effect on \( T_{FH} \) and GCs was found in other studies (5, 8). It was suggested that the different results obtained in these studies might be explained by the different types of Ag or adjuvant, the avidity of TCR involved for peptide–MHC, or the timing of analysis (35, 39). Our conclusion that IL-21 is not required for \( T_{FH} \) differentiation, but rather acts on GC B cells, is consistent with studies in mixed bone marrow chimeras (35, 39, 40). GC formation appears to be highly dependent on IL-21 in the K/BxN and other models of spontaneous autoimmune diseases (14, 41), although IL-21 does not play any role in the Roquin model of lupus (42). Therapeutic intervention of the IL-21–signaling pathway has been explored in animal models (15, 16, 43). However, the efficacy was found to be variable and partial. For example, repeated treatment of BXSB-Yaa mice with a soluble IL-21–Fc fusion protein had minimal effect on lupus symptoms and survival, even though IL-21R−/− BXSB-Yaa mice have no sign of disease (14). This variation could be attributed to the partial effectiveness of IL-21–Fc in blocking IL-21 signaling. The evidence that \( T_{FH} \) development is not dependent on IL-21 in autoimmunity raises the possibility that an efficient inhibition of ongoing GC B cell response may be difficult to achieve in practice with partial effectiveness of IL-21 blockade. It is tempting to speculate that IL-21 blockade is more effective in cases in which \( T_{FH} \) is more dependent on the cytokine. IL-21 blockade together with a therapy targeting T cells might be most beneficial for treating certain Ab-mediated autoimmune diseases.
Arthritis development in K/BxN mice is dependent on gut microbiota, particularly the colonization of segmented filamentous bacteria. Because the KRN-transfer model involves different strains of mice as the source of donor cells and hosts, the potential difference in their gut microbiota might be a confounding factor in the interpretation of our experiments. However, we think this is not likely to be the case. In our experiments, we always used littermates for our cell-transfer hosts, dividing the hosts housed in the same cage for different KRN-genotype transfers. We used donors of different genotypes housed in the same cage when possible. Furthermore, the gut microbiota of K/L-21−/− and K/L-21R−/− donor mice should be very similar because they are defective in the same pathway.

Th17 cells are now recognized to interact with Ag-specific B cells as potential B cell helpers (12, 13). Therefore, it was important to investigate whether IL-21 required for disease induction was produced by TFH or from Th17 cells that enter the B cell follicle to initiate GC. By eliminating the Th17 subset through RORγT−/− or RORγT−/− T cells did not dramatically alter disease kinetics or severity, suggesting that IL-21 is derived from TBF1 but not Th17 cells.

At first glance, the result that Th17 cells are not essential for disease induction seems unexpected, because Th17 cells were suggested to play an important role in this disease model. Th17 cell induction correlated with disease onset, and neutralizing Ab against IL-17A prevented disease in K/BxN mice (34). IL-17R−/− B cells were defective in differentiating into GC B cells, suggesting that they are the targets of IL-17. However, other lymphocyte and innate-like cell populations, including γδ T cells and some recently characterized innate lymphoid cells, are major producers of IL-17 (44, 45). The intriguing possibility that IL-17 induced constitutively by innate lymphoid cells plays an important role in this disease model.

Acknowledgments

We thank Dr. Michael Grusby for IL-21R−/− mice; Drs. Diane Mathis and Christophe Benoist for KRN-transgenic mice, B6.H2K−/− congenic mice, Co−/− B6 mice, and Co−/− NOD mice; and Xiao Liu and Crystal Rayon for help with mice.

Disclosures

The authors have no financial conflicts of interest.

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