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Tyrosine Phosphorylation of c-Maf Enhances the Expression of IL-4 Gene

Chen-Yen Lai,* Shin-Ying Lin,* Chia-Kai Wu,* Li-Tzu Yeh,† Huey-Kang Sytwu,‡ and Shi-Chuen Miaw*

Maf proteins are involved in a variety of biological processes, such as oncogenesis, lens development, and differentiation. In immune system, c-Maf transactivates IL-4 promoter, and ectopic expression of c-Maf skews primary T cell response toward the Th2 pathway. Numerous transcription factors are subjected to posttranslational modification. In this study, to our knowledge, we show for the first time that c-Maf is subject to tyrosine phosphorylation in Th cells and that the level of its tyrosine phosphorylation positively correlates with IL-4 expression by peripheral Th cells, but is negatively associated with the severity of disease in NOD mice. c-Maf undergoes tyrosine phosphorylation at Tyr21, Tyr92, and Tyr131 residues in Th2 cells. Furthermore, tyrosine phosphorylation at these three residues is critical for the recruitment of c-Maf to IL-4 promoter and IL-4 production in Th2 cells. Taken together, this study sheds new light on the role of posttranslational modification of c-Maf in IL-4 production and Th cell-mediated autoimmune diseases. The Journal of Immunology, 2012, 189: 1545–1550.

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-aMaf is a prototype of the large Maf family of transcription factors (1). It is induced in differentiating Th2 cells and is a potent transcription factor of the IL-4 gene. Deficiency of c-Maf leads to a profound defect in IL-4 production and Th2 differentiation. Overexpression of c-Maf has protected animals from developing diabetes in some animal models of human type I diabetes. This protection is presumably mediated by the Th2 promotion effect. c-Maf also has a critical role in the differentiation of other Th cell subsets. It is highly expressed in Th17 and T follicular helper cells. It regulates the expansion and maintenance of Th17 and T follicular helper cells via inducing IL-21 (2). It is also induced by IL-27 and acts synergistically with aryl hydrocarbon receptor to promote the development of Th1 cells (3). However, how the activity of c-Maf is regulated is poorly understood.

Numerous transcription factors are subjected to posttranslational modification, such as phosphorylation, SUMOylation, ubiquitination, methylation, and acetylation. We and others have shown that SUMOylation of c-Maf attenuates its IL-4 transcriptional activity (4, 5). The transforming activity of MafA, a member of the large Maf family, is dependent on its serine/threonine phosphorylation status (6). Whether the tyrosine residue of Maf proteins is phosphorylated and its functional significance have never been studied.

In this study, we show that tyrosine residues in c-Maf of primary Th2 cells are phosphorylated. We further identify Tyr21, Tyr92, and Tyr131 as the dominant sites of phosphorylation. Phosphorylation at these three residues is critical for the recruitment of c-Maf to IL-4 promoter and the expression of IL-4. In addition, the level of tyrosine phosphorylation of c-Maf in Th cells reversely correlates with the disease severity in NOD mice. Our data indicate that posttranslational modification of c-Maf by tyrosine phosphorylation is critical for its function and that attenuated tyrosine phosphorylation may contribute to the pathogenesis of autoimmune diabetes.

Materials and Methods

Mice and cells

Six- to 8-wk-old female BALB/c mice from the Laboratory Animal Center of National Taiwan University College of Medicine were used as the source of CD4+ T cells and naive CD4+ T cells, whereas the NOD mice, 28-wk-old age-matched female NOD mice with or without glycosuria, were sourced from the National Defense Medical Center. The animal experiments were approved by the Animal Use Committee of National Taiwan University College of Medicine. Human embryonic kidney fibroblast cell line, HEK293T, and EL4 thymoma cells were cultured in complete DMEM (containing 10% FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin). D10.G4 Th2 clone cells were maintained in complete growth RPMI 1640 medium and 10% supernatant from rat splenocytes that had been stimulated using Con A. The Th2 clones were stimulated every 2–3 wk with 2500 rad-irradiated C3H splenocytes and 100 μg/ml conalbumin (Sigma-Aldrich). DO11.10 T cell hybridoma were obtained from M.-Z. Lai (Academia Sinica, Taipei, Taiwan) and grown in complete RPMI 1640 medium.

Abs and reagents

Anti-c-Maf (M-153) Ab was purchased from Santa Cruz Biotechnology (Santa Cruz, CA). The anti-phosphotyrosine Ab (4G10; Upstate Technology) and protein A agarose beads were purchased from Upstate Technology. Abs to CD3ε (145-2C11), CD28 (37.51), CD62L-FITC conjugated (MEL-14), IL-4 (11B11), and IFN-γ (XMG1.2) were purchased from BioLegend. Biotin-conjugated anti–IL-4 and PE-conjugated anti–CD4 Abs were obtained from eBioscience.

Generation of c-Maf mutants

The tyrosine mutants of HA (hemagglutinin)-tagged c-Maf were generated from pBS-c-Maf by site-directed mutagenesis method (Strategene). The clones were then subcloned into expression vector pcDNA3.1+. Single-residue mutants, Y21F, Y91F, Y92F, Y97F, Y131F, Y181F, Y341F, and Y345F, were generated. All primers used in site-directed mutagenesis PCR are described in Table 1A. The multiple tyrosine mutant of

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Abbreviations used in this article: ChIP, chromatin immunoprecipitation; EGFP, enhanced GFP; HA, hemagglutinin; P+L, PMA and ionomycin; WT, wild-type.

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c-Maf, Y3F (Y21/92/131F), was created by restriction enzyme digestion and three-fragment ligation; and YSF (Y21/92/297/131/181/341/345F) was constructed by the two-step PCR method described previously (7). All the constructs were confirmed by DNA sequencing, and their expression was verified by Western blotting.

Cell transfection

The plasmids were transiently transfected into HEK 293T cells by JetPEI (Polyplus), according to the manufacturer’s instructions. Ten million EL4 thymoma cells were electroporated with plasmids using MicroPorator MP-100 (Digital Bio) as per the manufacturer’s instructions. Briefly, the EL4 thymoma cells were mixed with 15 μg plasmids in resuspension buffer R (Solution kit; Digital Bio). The cells were then pulsed in a golden tip at 1080 V, 50 ms per pulse, by MicroPorator MP-100. The electroporated cells were recovered in complete RPMI 1640 growth medium without antibiotics. Transfection efficiency was examined by measuring the percentage of enhanced GFP (EGFP) that fused to wild-type (WT) and mutated c-Maf constructs by confocal microscopy and by Western blotting at 24 h after transfection.

Immunoprecipitation and Western blotting

For detection of tyrosine-phosphorylated c-Maf, the transfected or primary cells were pretreated with 100 μM pervanadate for 20 min to inhibit endogenous nonspecific phosphatase activity before lysing the cells. Cells were then lysed in radioimmunoprecipitation assay buffer and cell lysates were obtained after centrifuging at 13,000 g for 10 min at 4°C. The appropriate Ab (2 μg, each tube) was added to the lysates for 1–3 h at 4°C. Protein A-agarose was added into the Eppendorf and gently mixed for an additional 2 h. The immunoprecipitation complex with protein A-agarose beads was then washed three times with cold PBS. Following the last washing, the samples were treated with SDS sample buffer for gel electrophoresis, resolved by SDS-PAGE, and analyzed by Western blotting. The product of immunoprecipitation, stimulated primary T cells, or transfected cells were lysed and then subjected to SDS-PAGE and transferred to polyvinylidene difluoride membranes (Millipore). Membranes were blocked and incubated with anti-c-Maf or other indicated Abs. For detection of a phospho-signal, the membranes were incubated in 5% BSA/TBS instead of 5% skim milk in TBS. Then HRP-conjugated goat anti-mouse or goat anti-rabbit L chain Abs (Millipore) were added. The signals were detected by Western Lightning Plus ECL (PerkinElmer).

Luciferase assay

HA-c-Maf (WT or mutant forms), luciferase reporter plasmid (pGL3-IL-4), and Renilla reporter plasmid (pTK-RL) were cotransfected into HEK293T Cells (1 × 105 cells/well). Twenty-four hours after incubation at 37°C, the cells were lysed and analyzed by using Dual-Glo Luciferase Assay System (Promega).

In vitro Th cell differentiation

CD4+ T cells were purified from lymph nodes of 5- to 6-wk-old female BALB/c mice by EasySep CD4 Selection Kit (StemCell Technologies). Naive CD4+ T cells (CD4+CD62Lhigh) were prepared from peripheral lymph nodes and spleens of the indicated mice, stained with CD4-PE and CD62L-FITC Abs, and purified by flow sorter (FACSAria; BD Biosciences). CD4+ T cells were seeded at 1 × 105 cells/ml in complete RPMI 1640 growth medium and stimulated with plate-bound anti-CD3 mAb (1 μg/ml) and soluble anti-CD28 mAb (1 μg/ml), referred to as Th0 condition, along with IL-4 (10 ng/ml) combined with anti–IFN-γ Ab (10 μg/ml) referred to as Th2-skewed condition, or along with IL-12 (5 ng/ml) combined with anti–IL-4 mAb (10 μg/ml) referred to as Th1-skewed condition. Human IL-2 (100 U/ml) was added with fresh medium each other day. Five days after first stimulation, half the cells of each well were harvested for intracellular cytokine staining and quantitative PCR analysis, and cells at 1 × 105 cells/ml were restimulated with plate-bound anti-CD3 mAb (1 μg/ml) for 24 h and subjected to ELISA.

Retrovirus infection

Bead-isolated or sorted naive CD4+ T cells were stimulated with plate-bound anti-CD3 and anti-CD28 Abs without polarization for 48 h. Cells were then infected with GFP-RV WT, Y3F c-Maf, or GFP RV mock. After an additional 72 h of incubation, retrovirally infected cells were sorted for GFP+ population. Cells were sorted on FACS(Aria (BD Biosciences, San Jose, CA) through the service provided by the Cell Sorting Core Facility of the First Core Laboratory, National Taiwan University College of Medicine. The supernatants were collected from sorted cells, and the amount of IL-4 production was analyzed by ELISA (eBioscience).

Chromatin immunoprecipitation assay

Forty hours after retrovirus infection, the infected cells were restimulated with PMA and ionomycin (P + I) for 2 h; the cells were then fixed with 1% paraformaldehyde; chromatin immunoprecipitation (ChIP) assays were performed by using anti–c-Maf Ab or normal rabbit IgG as a negative control, and the immunoprecipitated genomic DNA was analyzed by quantitative PCR. The primers used for IL4 promoter are described in Supplemental Table 1B. The c-Maf or nonspecific bound DNA was quantitated by real-time PCR and represented as percentage of input DNA.

Measurement of IL-4 production in primary T cells

Two hundred thousand sorted GFP+ T cells were cultured with complete RPMI 1640 growth medium and stimulated with plate-bound anti-CD3 mAb for 24 h. The culture supernatants were then collected, and the concentration of IL-4 was measured by ELISA.

Confocal microscopy

COS-1 cells were seeded on glass coverslips and cultured in complete DMEM growth medium. Cells were then transfected with EGF-fused c-Maf or mock constructs. After 24 h, the transfected cells were fixed with 3% paraformaldehyde and washed, and DAPI was used to stain the nucleus. Images were taken by a Nikon A1R confocal microscope with ×60 objective (Plan Apo VC OIL DIC N2) and were analyzed using NIS Elements Viewer software.

**FIGURE 1.** The tyrosine residues of c-Maf can be phosphorylated upon activation. (A) D10.G4.1 cells were stimulated with P + I for the indicated periods of time. Cells were lysed and then immunoprecipitated with anti–c-Maf Ab. The immunoprecipitate was then probed with 4G10 or anti–c-Maf Ab. (B) Purified primary CD4+ T cells were stimulated in vitro under Th2 skewing conditions with 2 μg/ml plate-bound anti-CD3 and anti-CD28 Abs in the presence of 10 ng/ml IL-4 and 10 μg/ml anti–IFN-γ Ab. After 40 h, the skewed cells were lysed, and tyrosine phosphorylation of c-Maf was examined as in (A). The data shown are representative of at least three independent experiments.
Results
Tyrosine residues of c-Maf can be phosphorylated in T cells
Previous studies have shown that the activity of many T cell transcription factors, such as T-bet (8, 9), GATA-3 (10), and Ets-1 (11), can be modulated by phosphorylation. We find in D10.G4.1 cells, a classical Th2 clone, that c-Maf undergoes tyrosine phosphorylation after stimulating with P + I (Fig. 1A). To further examine whether c-Maf can be tyrosine phosphorylated in primary T cells, primary CD4+ T cells were polarized into Th2 condition over 48 h. The lysate of skewed cell was then immunoprecipitated with either anti-c-Maf Ab or a control Ab and immunoblotted with 4G10 Ab. As shown in Fig. 1B, a clear protein band corresponding to the size of c-Maf was detected by the 4G10 Ab, but was absent in the lysates immunoprecipitated by the control Ab. These data demonstrate that c-Maf can be tyrosine phosphorylated in Th2 cells.

The level of tyrosine phosphorylation of c-Maf correlates positively with IL-4 production but negatively with disease activity in NOD mice
The NOD mouse strain is a murine model of human type I diabetes. Approximately 60–80% of female NOD mice spontaneously develop diabetes at 12–14 wk of age (12). It has been shown that NOD mice were unable to mount protective Th2 immune responses...
efficiently. We postulated that the process of tyrosine phosphorylation of c-Maf was impaired in NOD mice, thereby resulting in attenuated IL-4 production and contributing to the development of diabetes. We purified Th cells from NOD mice that had developed glycosuria and age-matched NOD mice that stayed healthy. The Th cells were stimulated in vitro for 40 h under Th2 conditions to induce the expression of c-Maf. We detected no difference in proliferation and induction of GATA3 between Th cells of healthy and glycosuric NOD mice (Supplemental Fig. 1). We detected tyrosine phosphorylation of c-Maf in both populations of Th cells. The degree of phosphorylation was decreased by at least 50% in Th2 cells from mice with glycosuria compared with mice without glycosuria (Fig. 2A, 2B). Such a reduction in tyrosine phosphorylation of c-Maf correlated with impaired IL-4 expression by bulk Th spleen or lymph node cells (Fig. 2C).

One possible explanation for the difference in IL-4 production is that glycosuric mice have fewer already differentiated Th2 cells than mice without glycosuria. To exclude this possibility, we isolated CD4+CD62Lhigh naive T cells from spleen or lymph nodes of these two groups of NOD mice and subjected the cells to in vitro Th2 differentiation. We again detected attenuated IL-4 expression, but not GATA3 expression, in Th2 cells of NOD mice with glycosuria (Fig. 2D, Supplemental Fig. 1). In addition, we obtained the similar results in the secondary stimulation (Fig. 2E).

**Tyr^{21}, Tyr^{92}, and Tyr^{131} are the dominant tyrosine phosphorylation sites of c-Maf**

c-Maf contains eight evolutionarily conserved tyrosine residues (Supplemental Fig. 2A). To identify the dominant tyrosine phosphorylation sites of c-Maf, we generated several c-Maf mutants, in which various combinations of tyrosine residue were changed to phenylalanine by site-directed mutagenesis. These mutants were then expressed in EL4 cells, and their ability to undergo tyrosine phosphorylation was examined by immunoprecipitation. As expected, tyrosine phosphorylation was completely abolished when all eight tyrosine residues were converted to phenylalanine (Y8F) (Fig. 3A). We found that mutation in any one of the tyrosines alone had no impact on tyrosine phosphorylation of c-Maf, suggesting that multiple tyrosine residues were used (data not shown). Conversion of Tyr^{21}, Tyr^{92}, and Tyr^{131} to phenylalanine (Y3F) nearly abolished tyrosine phosphorylation, whereas Y5F compound mutant actually had a slight increase in tyrosine phosphorylation, indicating that the three tyrosine residues were the dominant phosphorylation sites. These three residues probably

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**FIGURE 3.** Tyrosine phosphorylation of c-Maf is required for optimal transactivation of IL-4. (A) EL4 cells were transiently transfected with vectors expressing HA-WT, HA-Y21/92F, HA-Y92/131F, HA-Y21/131F, HA-Y21/92/131F (Y3F), HA-Y91/97/181/341/345F (Y5F), or HA-Y21/91/92/97/131/181/341/345F (Y8F) c-Maf and subsequently stimulated with P + I for 5 h. Cells transfected with empty vector (HA vector) were used as controls. (B) Primary murine CD4+ T cells skewed under Th2 conditions for 48 h were transduced with control virus or virus expressing EGFP-fused WT or Y3F c-Maf. Transduced cells were sorted and restimulated with P + I for 5 h. Tyrosine phosphorylation of the c-Maf proteins in transduced EL4 cells or transduced Th2 cells was examined as in Fig. 1. (C) HEK 293T cells were transfected with pGL3-IL-4-Luc, pRL-TK together with vectors expressing WT c-Maf or Y3F c-Maf. The normalized luciferase activity obtained from cells transfected with empty expression vector was arbitrarily set as 1. (D) Primary naive CD4+ T cells cultured under Th0 condition for 48 h were infected with virus expressing WT or Y3F c-Maf. After an additional 72 h of incubation, retrovirally infected cells were sorted and restimulated with anti-CD3 Ab. The level of IL-4 in the supernatant was analyzed by ELISA. The data shown in (A) and (B) are representative of two independent experiments. (C) and (D) were performed in triplicate, and means ± SD from one of three independent experiments are shown. **p ≤ 0.01, ***p ≤ 0.001.
contribute equally to tyrosine phosphorylation because conversion of any two of the three tyrosines partly rescued tyrosine phosphorylation (Fig. 3A). The Y3F mutant was also relatively resistant to tyrosine phosphorylation in primary Th2 cells (Fig. 3B). Our data collectively demonstrate that Tyr21, Tyr92, and Tyr131 are the dominant tyrosine phosphorylation sites of c-Maf in Th2 cells.

Optimal c-Maf–dependent IL-4 expression requires tyrosine phosphorylation at Tyr21/Tyr92/Tyr131

c-Maf is known to transactivate IL-4 promoter. We found that Y3F c-Maf was less efficient than WT c-Maf in transactivating a luciferase reporter driven by an IL-4 promoter in HEK 293T cells (Fig. 3C, Supplemental Fig. 2B). We then expressed WT or Y3F c-Maf in primary Th cells differentiated under nonpolarized conditions (Th0), in which very little endogenous c-Maf and IL-4 were induced. In agreement with previous reports, forced expression of WT c-Maf resulted in robust production of IL-4. However, this c-Maf–dependent expression of IL-4 was reduced by 50% when Y3F c-Maf was used (Fig. 3D, Supplemental Fig. 2C). Collectively, these data indicate that tyrosine phosphorylation of c-Maf is required for optimal expression of IL-4.

Tyrosine phosphorylation of c-Maf facilitates its binding to IL-4 promoter

Tyrosine phosphorylation of a transcription factor may be required for its appropriate subcellular localization, stabilization, DNA binding, and/or interaction with other nuclear proteins (13). We first examined whether tyrosine phosphorylation affected the subcellular localization of c-Maf. We expressed EGFP-fused WT or Y3F c-Maf in COS cells and detected the localization of c-Maf by confocal microscopy. The confocal-microscopy images revealed that both proteins were localized mainly in the nucleus (Fig. 4A, Supplemental Fig. 2B), suggesting that localization of c-Maf is not affected by its tyrosine phosphorylation status. We next compared the stability of WT and Y3F c-Maf. We expressed HA-fused WT or Y3F c-Maf in cells that were subsequently treated with cyclohexamide. We found that the Y3F c-Maf was not less stable than WT c-Maf (Supplemental Fig. 3).

We then used pull-down assays to determine whether tyrosine phosphorylation of c-Maf affected its binding to IL-4 promoter. Nuclear extracts from WT c-Maf or Y3F c-Maf–overexpressing EL-4 cells were incubated with biotinylated IL-4 promoter probes attached to streptavidin-agarose. The intensity of the c-Maf bound to biotinylated IL-4 promoter was relatively higher compared with Y3F c-Maf (Fig. 4B).

![FIGURE 4. Tyrosine phosphorylation is required for optimal binding of c-Maf to IL-4 promoter.](http://www.jimmunol.org/)

(A) COS-1 cells were transiently transfected with expression plasmids for EGFP-fused WT c-Maf, EGFP-fused Y3F c-Maf proteins, or EGFP. The transfected cells were examined for the distribution of c-Maf (EGFP, green, left panel) and nuclei (DAPI, blue, middle panel) by fluorescence microscopy. The horizontal scale bars, 10 µm. (B) The various c-Maf pull-down assays using biotinylated IL-4 promoter probe were performed. The nuclear extracts from c-Maf–overexpressing EL-4 cells were incubated with biotinylated IL-4 promoter probes attached to streptavidin-agarose. The intensity of the c-Maf bound to biotinylated IL-4 promoter was quantified with ImageJ. The relative c-Maf proteins bound to IL-4 promoter were analyzed and are shown in the bottom panel. (C) Primary murine CD4+ T cells were skewed under Th0 condition. After 40 h, the skewed cells were transduced with WT c-Maf, Y3F c-Maf, or empty virus. The transduced cells were stimulated with P + I for 2 h. The recruitment of c-Maf to IL-4 promoter was examined with ChIP. n.s., Nonsignificant; *p ≤ 0.01.
In addition, we performed ChIP to analyze the binding ability of WT c-Maf or c-Maf mutants to IL-4 promoter. WT c-Maf or Y3F c-Maf was ectopically expressed in nonpolarized Th0 cells by retrovirus transduction. ChIP-quantitative PCR analysis of c-Maf enrichment at IL-4 promoter showed that Y3F c-Maf bound relatively weakly to IL-4 promoter compared with WT c-Maf. By contrast, another c-Maf mutant, Y341F, which was normally susceptible to tyrosine phosphorylation, was recruited to IL-4 promoter as efficient as WT c-Maf (Fig. 4C). Taken together, these results indicate that tyrosine phosphorylation augments recruitment of c-Maf to IL-4 promoter, thereby enhancing the production of IL-4.

Discussion

Although c-Maf has been shown to undergo serine/threonine phosphorylation in human multiple myeloma, the impact of this process on the function of c-Maf remains unclear (6). To our knowledge, our data are the first to show that c-Maf can be tyrosine phosphorylated in Th2 cells and that tyrosine phosphorylation is critical for the binding of c-Maf to IL-4 promoter. We and others have previously demonstrated that c-Maf is also susceptible to SUMOylation at Lys33 and that de-SUMOylation of c-Maf enhances the recruitment of c-Maf to IL-4 promoter and consequently IL-4 expression (4, 5). Therefore, posttranslational modification is an important step in the regulation of c-Maf activity. There is growing evidence indicating functional cross-talk between phosphorylation and SUMOylation. HSF4b, which belongs to the family of heat-shock factors, can undergo both SUMOylation and serine phosphorylation. Both modifications take place within a phosphorylation-dependent SUMOylation motif (KxExxSP), and SUMOylation of HSF4b is serine phosphorylation dependent (14). Stat1, which is activated by phosphorylation on a Tyr701, can be SUMO modified on Lys703. Recent biochemical studies, however, suggest that tyrosine phosphorylation in Tyr701 and SUMOylation in Lys703 are mutually exclusive (15). Thus, cross-talk between phosphorylation and SUMOylation can be either synergistic or counteractive. In both HSF4b and Stat1, the cross-talk probably depends on the close proximity of phosphorylation and SUMOylation residues.

Our data indicate that tyrosine phosphorylation and SUMOylation have opposite effects on DNA binding of c-Maf. Of note, one of the three phosphorylated tyrosine residues in c-Maf (Tyr21) is close to the SUMO-modified residue (Lys33). Given the physical distance between Tyr21/Tyr2/Tyr131 and Lys33, c-Maf is possibly a new model for functional interaction between tyrosine phosphorylation and SUMOylation. However, we observed that the level of tyrosine phosphorylation at SUMO-deficient c-Maf did not change in 293T cells (data not shown). Whether tyrosine phosphorylation of c-Maf affects its SUMOylation in T cells remains to be analyzed.

Previous studies have demonstrated that induction of Th2 response can prevent NOD mice from developing diabetes (16, 17). Our data reveal that diminished tyrosine phosphorylation of c-Maf correlates with poor IL-4 production by Th cells and disease development in NOD mice. Despite the association, we have yet to establish whether the diminished tyrosine phosphorylation of c-Maf is a cause or an epiphenomenon of the impaired Th2 response. It is quite surprising to see that naive CD4+ T cells isolated from glycosuric and healthy NOD mice still display a discrepancy in IL-4 production after in vitro culturing (Fig. 2D). This result implies the presence of a Th cell-intrinsic mechanism regulating the level of IL-4 production and possibly tyrosine phosphorylation of c-Maf. This intrinsic mechanism may influence the development of diabetes in NOD mice. To date, very little is known about the molecular mechanism regulating the tyrosine phosphorylation and dephosphorylation of c-Maf. Identification of tyrosine kinases and phosphatases that use c-Maf as a substrate in Th cells will greatly advance our understanding of the pathogenesis of many Th cell-mediated diseases and may lead to the development of new treatments targeting tyrosine phosphorylation of c-Maf.

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Disclosures

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