Overexpression of c-Maf Contributes to T-Cell Lymphoma in Both Mice and Human

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Abstract

c-Maf translocation or overexpression has been observed in human multiple myeloma. Although c-maf might function as an oncogene in multiple myeloma, a role for this gene in other cancers has not been shown. In this study, we have found that mice transgenic for c-Maf whose expression was direct to the T-cell compartment developed T-cell lymphoma. Moreover, we showed that cyclin D2, integrin β7, and ARK5 were up-regulated in c-Maf transgenic lymphoma cells. Furthermore, 60% of human T-cell lymphomas (11 of 18 cases), classified as angioimmunoblastic T-cell lymphoma, were found to express c-Maf. These results suggest that c-Maf might cause a type of T-cell lymphoma in both mice and humans and that ARK5, in addition to cyclin D2 and integrin β7, might be downstream target genes of c-Maf leading to malignant transformation. (Cancer Res 2006; 66(2): 812-9)

Introduction

The maf proto-oncogene was originally identified within the genome of the avian musculoaponeurotic fibrosarcoma virus, AS42 (1). The product of the maf gene and other members of the Maf family share a conserved basic region and amphipathic helix (bZip) motif that mediates dimmer formation and DNA binding to the Maf recognition element (MARE; ref. 2). Large Maf proteins, such as c-Maf, MaB, MaFA/L-Maf/Smaf, and NRL, contain an acidic domain that mediates transcriptional activation and plays a key role in cellular differentiation (1–5).

c-Maf encodes a Th2-specific transcription factor that activates the expression of interleukin (IL)-4 and IL-10 in T cells (6). c-Maf gene and other members of the Maf family have been reported to direct expression of an inserted cDNA in the T-cell compartment using the human CD2 promoter and locus control region. c-maf transgenic mice developed T-cell lymphoma, providing the first direct evidence that c-maf can function as an oncogene in T cells in vivo. In addition, we analyzed c-Maf expression in cases of human T-cell lymphoma, showing c-Maf overexpression in angioimmunoblastic T-cell lymphoma (AITL) at high frequency. These results indicate that c-Maf can cause a type of T-cell lymphoma with characteristics similar to multiple myeloma and suggest that the c-Maf transgenic mouse may be a good model to study how the oncogene c-maf contributes to the pathogenesis of lymphoid malignancies.

Materials and Methods

Mice. A 1.5-kb full-length cDNA encoding the murine c-Maf protein was inserted into a VA CD2 transgene cassette containing the upstream gene regulatory region and locus control region of the human CD2 gene. The VA vector has been reported to direct expression of an inserted cDNA in all T lymphocytes of transgenic mice, with expression being linearly proportional to the transgene copy number (15). This c-Maf construct was injected into BDF1 fertilized eggs to generate transgenic mice. c-Maf transgenic allele was genotyped by PCR using a pair of primers: sense 5′-TGAGTTCGAA-3′ and antisense 5′-TGACAGGAGACAGTCCTGT-3′. Mice were maintained in specific pathogen-free condition in a Laboratory Animal Resource Center. All experiments were done according to the Guide for the Care and Use of Laboratory Animals at the University of Tsukuba.

Southern hybridization analysis. High molecular weight DNA was prepared from the tail of each mouse, and 10 μg of this DNA were digested with NcoI and then subjected to electrophoresis through 0.8% agarose gels. After electrophoresis, the DNA was transferred to a nylon membrane (Zeta-probe; Bio-Rad, Richmond, CA). To generate DNA probes for Southern hybridization, we cloned the open reading frame region of c-Maf.
the *c-maf* gene. Transgene copy number was determined using Image J (NIH, Bethesda, MD). To investigate T-cell receptor (TCR) β-chain gene rearrangement, tail and other DNAs were also examined by Southern hybridization as described previously (16). The TCR probes were gel purified and then labeled for hybridization. Hind III-digested DNAs were hybridized with the Jβ2 fragment.

**Flow cytometry analysis.** Single-cell suspensions were prepared from the thymi and splenic tumors of each mouse, which were then blocked with anti-FcR antibody (2.4G2) for 10 minutes on ice to inhibit the interaction of the staining reagents with the cell surface. Multicolor flow cytometric analysis was done using LSR and CellQuest software (Becton Dickinson, Franklin Lakes, NJ) on viable cells as determined by forward light scatter intensity and propidium iodide exclusion. The following phycoerythrin (PE), FITC, and peridinin chlorophyll protein (PerCP) labeled monoclonal antibodies were used: anti-CD4-PE, anti-CD8-FITC, anti-CD25-PerCP, and anti-CD44-FITC (BD PharMingen, San Diego, CA).

**Histopathologic analysis.** Each mouse was bled while under ether anesthesia. At autopsy, organs were fixed with 10% formalin in 0.01 mol/L phosphate buffer (pH 7.2) and embedded in paraffin. Sections were stained with H&E stain for histopathologic examination by light microscopy. The immunohistochemistry and analysis for CD3, B220, CD4, and CD8 antigens were done using the streptavidin and biotin technique. Anti-CD3 antibody was purchased from Serotec (Oxford, United Kingdom). Anti-B220, CD4, and CD8 antibodies were obtained from BD PharMingen.
Quantitative reverse transcription-PCR assay. Total RNA (1 μg) was reverse transcribed into cDNA with SuperScript II reverse transcriptase (Invitrogen, Carlsbad, CA). TaqMan PCR primers and TaqMan probes were used to quantify c-Maf and ARK5 cDNAs as follows: c-Maf sense 5′-AAGGAG-AATACCGAAGACTGTTGTA-3′, antisense 5′-TGGGATCGCTGGTACACT-CACATG-3′, and probe 5′-CGACAACCTCCTCCTCCGAAATTT-3′ and ARK5 sense 5′-GAGCCACCTCTATGCGGTC-3′, antisense 5′-ATGTCCTCAGTGTTGGCT-CT-3′, and probe 5′-ACCTCTACCTTGGAGAGTACGGCC-3′. Mixture of primers and TaqMan probes for cyclin D2, integrin αv, and β3, and IL-4 were obtained from Assays-on-Demand Gene Expression products (Applied Biosystems, Foster City, CA). Each reaction was done in duplicate. The cDNA quantities were normalized to the amount of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA, which was quantified using Rodent GAPDH Control Reagents (VIC probe, Applied Biosystems). PCR reaction mixtures were prepared according to the manufacturer’s instructions and the amplification was carried out in MicroAmp optical 96-well reaction plates (Applied Biosystems) in the ABI Prism 7700 Sequence Detection System (Applied Biosystems).

Tissue samples of human T-cell lymphoma. Formalin-fixed, paraffin-embedded samples of a series of previously diagnosed T-cell lymphoma tissues, comprising 7 unspecified peripheral T-cell lymphoma (PTL), 7 adult T-cell leukemia (ATL), and 18 ATL cases were obtained from the files of the Department of Pathology of Biological Response of the Nagoya University Graduate School of Medicine (Nagoya, Japan). Multiple myeloma samples of human tissues were used as controls. Immunohistochemical staining was done using the streptavidin and biotin technique. Anti-c-Maf antibody was provided kindly by Dr. Masaharu Sakai (University of Hokkaido, Sapporo, Japan). Lymph node samples from lymphoma patients were obtained under approval of the Ethical Committee of Kumamoto University (Kumamoto, Japan).

Reverse transcription-PCR Southern hybridization. Total RNA was obtained from frozen human lymph nodes from patients diagnosed with T-cell lymphoma. The samples were obtained from the archives of the Department of Internal Medicine II, Kumamoto University School of Medicine. RNA (1 μg) isolated from each sample was reverse transcribed into the corresponding cDNA as described previously. PCR products were then hybridized on Southern blots under stringent hybridization conditions to specific probes. PCR primers and specific probes were as follows: human hypoxanthine phosphoribosyltransferase sense 5′-CTATAGACTATCATGTCCT-3′, antisense 5′-CTGTTCTTCTTATTTTCAAC-3′, and probe 5′-CATT-GAAGCTATCTGGTAAGAATAAGA-3′; human c-Maf sense 5′-CTGCGC-GCTCTCAAGGCTGTC-3′, antisense 5′-TCCGCTGTAGCAGACTCAT-3′, and probe 5′-CTGCGTACATCTGGTCACCAAATCGGA-3′; and human ARK5 sense 5′-GAGTACCTCTATGTTGTC-3′, antisense 5′-ATGTCCTACGTTGGCC-3′, and probe 5′-TCAGAGTTGGCGAACCACGCG-3′. The level of c-Maf mRNA in the thymus of Tg 50 was several-fold greater than that in Tg 17 or 78 or in wild-type thymus, indicating that the level of expression of the transgene mRNA was copy number dependent. Thymi from Tg 312 mice showed relatively high levels of expression of c-Maf (data not shown).

T-cell development was arrested at the double-negative CD4/CD8 stage in c-Maf transgenic mice. To investigate the effect of c-Maf overexpression on T-cell differentiation, we did flow cytometric analysis on thymocytes isolated from transgenic mice carrying high copy number (Tg 50) at 5 weeks of age (Fig. 1E). Levels of mature, single-positive (CD4+ or CD8+) and double-positive (CD4+CD8+) T cells were decreased in c-Maf transgenic mice (Tg 50). On the other hand, double-negative (CD4+CD8-) T cells were increased significantly in these mice. These results suggested that c-Maf overexpression arrested T-cell development at the double-negative (CD4+CD8-) stage. During thymocyte development, immature double-negative (CD4+CD8-) precursor cells pass through four phenotypically distinct stages defined by expression of CD44 and CD25. Double-negative cells subsequently go through DN1 (CD44+CD25+), DN2 (CD44+CD25-), DN3 (CD44+CD25-), and DN4 (CD44+CD25+) stages before giving rise to CD4+CD8+ double-positive T cells (17). We found that numbers of CD44+CD25+, CD44+CD25−, and CD44+CD25+ cells were increased in c-Maf transgenic thymus, whereas CD44+CD25− cells were significantly decreased. These results suggested that T-cell development was arrested at the DN3 stage in these mice. We found that the CD4/CD8 distribution in the lower copy number Tg mice (Tg 17 and 78 lines) was similar to that observed in wild type mice (data not shown).

c-Maf transgenic mice developed lymphoma. Mice from Tg lines 50, 312, and 235 appeared healthy up to 50 weeks of age. However, three lines of transgenic animals subsequently developed lymphoma.
tumors (Fig. 2). The mean age at diagnosis was 72.2 weeks for Tg line 50 and 78.4 weeks for Tg line 312. Mice from Tg lines 17 and 78, which contained low copy numbers of the transgene, developed tumors in very low frequencies. The level of expression of the transgene is determined both by the activity of the locus where integration takes place (18) and by the copy number of the integrated genes (19). The difference in the incidence of lymphoma between Tg 50, 235, and 312 lines may have arisen due to differences in the sites of transgene integration. The tumors were classified as lymphomas due to the enlargement of lymphoid and bronchial tissue. H&E stain, ×50. D, atypical cells were observed in the lung. H&E stain, ×400. E and F, immunohistochemical examination revealed that infiltrated cells were mainly CD3+ cells (E, ×50; F, ×400, CD3 immunohistochemical stain). G to I, CD3+ lymphoma cells also expressed B220 (G, ×400, FITC anti-CD3 antibody; H, ×400, PE anti-B220 antibody; I, ×400, G and H merged, lung). Autonomic proliferation in nude mice of T-cell lymphoma cells from c-Maf transgenic animals. To ascertain whether the infiltrating tumor cells in c-Maf transgenic mice could proliferate autonomously, we isolated mononuclear cells from the spleens of...
three individual mice (two from Tg line 50 and another from Tg line 17) and injected these cells into nude mice via the tail vein (10^6 cells per mouse). These studies showed that the tumor cells were transplantable from nude mouse to nude mouse. Recipient nude mice displayed prominent splenomegaly and enlarged lymph nodes throughout their bodies within 6 weeks of transplantation. The tumor cells were transplantable from nude mouse to nude mouse. A typical example is shown in Fig. 4 A. To assess clonality, we examined the rearrangement of the TCR locus in the c-Maf transgenic lymphoma cells. A Southern blot hybridization analysis was carried out using a murine Jh2 probe (Fig. 4B). We extracted DNA from the tail, spleen, and lymph nodes of the recipient nude mice. Fig. AB (lane 1) contains DNA isolated from control germ line cells. Rearrangement of the TCR locus was found in DNA isolated from spleens of the c-Maf transgenic mice (Fig. AB, lanes 2-4). The same pattern of rearrangement observed in lane 4 was present in DNA samples isolated from the nude mice (lane 5) that received lymphoma cells isolated from the mice whose DNA was probed in lane 4. These results support our contention that clonal lymphoma cells committed to the T lymphoid lineage proliferate in the c-Maf transgenic mice.

Expression of c-Maf target genes in T-cell lymphoma. To gain insight into the molecular mechanism of the development of the T-cell lymphoma, we measured the level of the c-Maf and target genes mRNA in c-Maf transgenic mice using a quantitative RT-PCR assay (Fig. 5). As we described previously, c-Maf overexpression has been implicated in the development of multiple myeloma, a mature B-cell lymphoid tumor. However, a relationship between c-Maf overexpression and T-cell lymphomagenesis has yet to be established. Using gene expression profiling, Hurt et al. (13) identified cyclin D2 and integrin β7 as c-Maf target genes in myeloma. c-Maf transactivated the cyclin D2 promoter and enhanced myeloma cell proliferation, whereas dominant-negative c-Maf blocked tumor formation in immunodeficient mice. c-Maf-driven expression of integrin β7 enhanced myeloma adhesion to the bone marrow stroma and increased the production of vascular endothelial growth factor (VEGF), which led to effects on cellular proliferation and adhesion (13). Recently, we observed high expression of ARK5 in human myeloma cells expressing high levels of c-Maf (21). ARK5 is the fifth member of the AMP-activated protein kinase (AMPK) catalytic subunit family, which is also known as the cellular stress response factor (22–24). Furthermore, experiments done in vitro and in nude mice revealed that ARK5-expressing tumor cells were characterized by accelerated invasion and metastasis (25). These facts suggest a relationship between ARK5 and c-Maf in other cancers, such as T-cell lymphoma. c-Maf is also known as a Th2-specific transcription factor, which promotes the differentiation of Th2 cells mainly by an IL-4-dependent mechanism (6). Thus, we next analyzed expression of cyclin D2, integrin β7, ARK5, and IL-4 in c-Maf-induced T-cell lymphoma. The level of c-Maf expression in the thymus and lymphoma-infiltrated spleens of c-Maf transgenic mice was 8- to 10-fold greater than levels in wild-type mice (Fig. 5). We found elevation of the expression of both integrin β7 and cyclin D2 in c-Maf transgenic mice, consistent with what was reported previously in myeloma (13). Importantly, we observed a significant elevation of ARK5 expression, which has been shown to accelerate...
invasion and metastasis in tumor cells. There was no difference in IL-4 expression between wild-type and transgenic mice, which might be due to dysregulation of normal T-cell differentiation in c-Maf transgenic mice.

**Overexpression of c-Maf is also identified in a type of human T-cell lymphoma.** The evaluation of c-Maf transgenic mice has thus shown that overexpression of c-Maf is able to induce T-cell lymphoma in mice. To examine whether c-Maf overexpression might contribute to the development of human lymphomas, we analyzed c-Maf expression in samples of human lymphoma by immunohistochemical and RT-PCR analyses. We tested 7 cases of unspecified PTL, 7 cases of ATL, and 18 cases of AITL using an anti-c-Maf antibody. Immunostaining analysis (Fig. 6A-D) revealed that 60% of AITL (11 of 18 cases) samples were positive for nuclear staining by anti-c-Maf, whereas only 29% of PTL or ATL (2 of 7 cases) expressed c-Maf. We have found variable levels of c-Maf expression levels in AITL (Fig. 6A and B). We also stained multiple myeloma samples as a positive control (Fig. 6C). For a nonlymphoma control, we analyzed reactive lymphoadenopathy samples. We found that not many but some lymph node cells, including lymphocytes and macrophages expressed c-Maf (Fig. 6D).

To confirm c-Maf overexpression in AITL, c-maf gene expression was analyzed by RT-PCR (Fig. 7). RT-PCR analysis showed that c-Maf was overexpressed in AITL but not in other lymphoma cases. Moreover, ARK5 was also expressed at a high level in AITL. In addition, we did RT-PCR on RNA isolated from two additional cases of AITL. The results showed that these two cases also overexpressed both c-Maf and ARK5 (data not shown). We thus confirmed that c-Maf and ARK5 were both overexpressed in 4 of 4 cases of AITL. These results suggest that overexpression of c-Maf and ARK5 may contribute to the development of AITL.

**Figure 6.** Analyses of c-Maf expression in human T-cell lymphoma cases. A, histology of AITL. H&E stain. B, immunostaining analysis of the same case of (A) with anti-c-Maf antibody. C, anti-c-Maf immunostaining of a human multiple myeloma case. D, anti-c-Maf immunostaining of a human reactive lymphadenopathy case.
Discussion

It is important to emphasize that v-maf is a classic oncogene identified in an avian transforming virus (1). Furthermore, Kataoka et al. have shown that overexpression of wild type c-maf is capable of contributing to transformation of fibroblasts (26). Recently, it has been reported that c-maf translocation and/or overexpression are frequently identified in human multiple myeloma (10, 13). However, neither a direct oncogenic function of C-Maf in vivo nor a role for c-Maf in other cancers has yet been reported. In this study, we have shown that C-Maf contributes to T-cell lymphoma in vivo in c-Maf transgenic mouse models.

The c-Maf transgenic mouse model shows several interesting features. First, c-Maf transgenic mice develop T-cell lymphoma or plasmacytoma at older ages. The mean age at diagnosis was ~80 weeks. The advanced age at which the disease appeared in the transgenic mice is reminiscent of the fact that both multiple myeloma and AITL develop predominantly in elderly human patients. These findings suggest a link between the mechanism of c-Maf oncogenesis in humans and our mouse model. Interestingly, lymphoma cells from the c-Maf transgenic mice exhibited a rare CD3/B220 double-positive phenotype, suggesting a potential target population for c-Maf action. RB1N-2 has been shown to induce human T-cell acute leukemia in childhood. Interestingly, overexpression of RBTN-2 in mice under control of the CD2 regulatory elements also leads to the development of T-cell lymphoma. Lymphoma cells isolated from these mice also exhibited a range of phenotypes, the most notable being CD3/B220 double-positive cells (27). Interestingly, a subset of B22O+ thymocytes, which are thought to be T-cell progenitor cells (20), are particularly susceptible to malignant transformation by Philadelphia chromosome–dependent BCR-ABL fusion proteins (28). Thus, CD3/B220 cells might be particularly sensitive to malignant transformation. RB1N-2 transgenic mice develop acute thymic lymphomas (27), whereas c-Maf transgenic mice develop peripheral, long-latency cell tumors probably by transformation of the same CD3/B220+ precursor thymocyte. This is a significant feature of c-maf, because most proto-oncogenes activated in the thymus [rbtn-2 (27), HMGB-1 (29), Rgr (30), etc.] cause T-cell acute lymphoblastic leukemia and not peripheral T-cell cancers. We do not know the reason behind the difference between c-maf and other genes in promoting tumor formation, but one possible explanation is that c-maf is only weakly oncogenic and that overexpression of c-Maf may not be sufficient for full transformation of lymphocytes.

In addition, the number of double-negative T cells was significantly increased in Tg 50 lines, which also developed tumors. However, we found that the CD4/CD8 distribution in the lower copy number Tg lines (Tg 17 and 78), which developed tumors at a very low frequency, was similar to that observed in wild type mice. These results suggest there may be a similar threshold level of c-Maf expression for both arrest of T-cell development and tumor development in c-Maf transgenic mice.

Because c-Maf is a transcription factor, it is of interest to identify downstream target genes of its action that might contribute to malignant transformation of T cells. We used RT-PCR analysis to show that cyclin D2, integrin β7, and ARK5 were up-regulated in c-Maf transgenic thymocytes and T lymphoma cells. The transcriptional activation of cyclin D2 by c-Maf provides a potential mechanism for the promotion of cell cycle progression in myeloma cells (13). It is not surprising that c-Maf induces cyclin D2 expression in T-cell lymphoma, because this effect has been already shown in multiple myeloma cells. We also observed overexpression of integrin β7 in T-cell lymphoma. c-Maf-driven expression of integrin β7 enhances myeloma adhesion to the bone marrow stroma and increases the production of VEGF, which enhances cellular proliferation and adhesion (13). Although the interaction of the bone marrow stroma with multiple myeloma cells is an important component of the pathophysiology of this malignancy (31, 32), there have been few reports describing the involvement of adhesion molecules, such as integrin β7, in the development of T-cell lymphoma. A more detailed analysis of the role of integrin β7 in T-cell function is necessary to understand the contribution of this molecule to T-cell malignancy. Interestingly, we found that ARK5 mRNA is up-regulated in c-Maf transgenic thymocytes and lymphoma. ARK5 is also known as the cellular stress response factor (22–24). Previously, it has been shown that overexpression of ARK5 mRNA is associated with tumor progression in colon cancer and that metastatic foci of colon cancer in the liver show markedly increased expression of ARK5 mRNA (33). Furthermore, studies in vitro and in nude mice have revealed accelerated invasion and metastasis in ARK5-expressing tumor cells (25). ARK5 is transcriptionally regulated by members of the large Maf family through the MARE sequence in its promoter (21). Therefore, ARK5 gene transcription is tightly regulated by c-Maf and overexpression of ARK5 might be one of the causes of malignant transformation in c-Maf transgenic mice. c-Maf is a Th2-specific transcription factor that activates the IL-4 promoter (6). However, we did not observe an increase in IL-4 expression in our c-Maf transgenic mice. Flow cytometric analysis of thymocytes and lymphoma cells revealed an increase in levels of immature CD4+CD8+ T cells in the c-Maf transgenic mice. This result suggests that c-Maf alone is insufficient to transactivate the endogenous IL-4 promoter in this immature T cell in vivo.

Our results in mice suggested that c-Maf overexpression might contribute to the development of some cases of human lymphoma. On examination of human lymphoma cases, we found one type of T-cell lymphoma, classified as AITL, frequently expressed high levels of c-Maf. AITL is an uncommon T-cell lymphoma characterized by clear cell accumulation and vascular proliferation. AITL show the most prominent vascular component among lymphomas and their prognosis is difficult to predict. VEGF gene was overexpressed in both AITL lymphoma and endothelial cells.

![Figure 7. RT-PCR analysis of human lymphomas. c-Maf and ARK5 were overexpressed in AITL patients (lanes 2 and 5). Lane 1, extranodal natural killer/T-cell lymphoma, nasal type; lane 2, AITL; lane 3, anaplastic large T-cell lymphoma; lane 4, PTL; lane 5, AITL.](cancerres.aacrjournals.org)
The vascular component, a critical pathologic characteristic inAITL, also contributes to lymphoma progression (34). Mentioned above, c-maf-driven expression of integrin β7 enhanced myeloma adhesion to bone marrow stroma and increased production of VEGF (13). c-Maf might contribute to hypervascularity and prognosis inAITL. The results presented in this article suggest that overexpression of c-Maf might contribute to the development of this lymphoma. Although we have yet to examine the translocation of the c-maf gene to the TCR locus inAITL cells, such a translocation may yet be identified in these cells as has been already shown in some cases of multiple myeloma. In this study, we have shown that c-Maf transgenic mice develop T-cell lymphoma. Further studies will be needed to define the role of c-Maf in the development of both human and mouse lymphomas. Clarification of the mechanism by which c-Maf contributes to oncogenesis may ultimately facilitate the discovery of more specific therapies to prevent the progression of the diseases.

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