Potent Antitumor Activity of Interleukin-27

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ABSTRACT

Although much promising data that interleukin (IL)-12 could be a powerful therapeutic agent against cancer were reported in animal models, its excessive toxicity has become a problem for its clinical application. IL-27 is a novel IL-12 family member that plays a role in the early regulation of T helper cell 1 initiation, including induction of T-bet and IL-12 receptor β2 expression. In the present study, we have evaluated the antitumor activity of IL-27 against a murine tumor model of colon carcinoma C26. C26 cells, which were transduced with the single-chain IL-27 cDNA and became secreting IL-27 (C26-IL-27), exhibited minimal tumor growth in vivo, and all of the mice inoculated with these cells survived healthfully with complete tumor remission. Inoculation of mice with C26-IL-27 induced enhanced IFN-γ production and cytotoxic T lymphocyte activity against C26 tumor in spleen cells. Recovered mice from the inoculation showed a tumor-specific protective immunity to the following challenge with parental C26 tumor. The antitumor activity of IL-27 was almost diminished in nude mice, and depletion of CD8+ T cells and neutralization of IFN-γ in immunocompetent mice reduced greatly the antitumor activity. Moreover, the antitumor activity was abolished in T-bet-deficient mice, whereas it was observed unexpectedly in mice deficient of signal transducer and activator of transcription (STAT) 4. These results suggest that IL-27 has potent abilities to induce tumor-specific antitumor activity and protective immunity and that the antitumor activity is mediated mainly through CD8+ T cells, IFN-γ, and T-bet but not through STAT4.

INTRODUCTION

Interleukin (IL)-12 is a proinflammatory and immunoregulatory cytokine that plays a central role in the interaction between innate resistance and adaptive immunity by inducing IFN-γ production and generating T helper cell 1 (Th1) responses and cytotoxic T lymphocyte (CTL) (1, 2). In several comparative studies, IL-12 was revealed to be the most effective cytokine that could induce eradication of experimental tumors, prevent development of metastasis, and elicit long-term antitumor immunity (3–6). The great number of promising data obtained from the preclinical models of antitumor immunotherapy has raised much hope that IL-12 could be a powerful therapeutic anticancer agent. In the clinical trials, however, excessive toxicity was observed and has become a problem for clinical application of IL-12 (7, 8). Therefore, local and efficient expression of IL-12 or other cytokine genes in tumors is an alternative immunotherapeutic approach that may avoid systemic toxicity of recombinant cytokines.

A novel member of the IL-12 family was identified recently and termed IL-27 (9). IL-27 is a heterodimeric cytokine that consists of a p40-related protein, EB13, and a newly discovered IL-12 p35-related protein, p28. IL-27 is produced early after activation by antigen-presenting cells, is able to induce proliferation of naive but not memory CD4+ T cells, and synergizes with IL-12 in IFN-γ production of naive CD4+ T cells (9). An orphan receptor designated T cell cytokine receptor (10) or WSX-1 (11) with similarity to the IL-12 receptor β2 (IL-12Rβ2) subunit was shown previously to be important for initiation of Th1 responses. This receptor was identified recently as one of the receptor subunits for IL-27 and is necessary but not sufficient for IL-27 function (9). Interestingly, although activation of T cell cytokine receptor or WSX-1 is required for the initiation of Th1 responses, it is not necessary for the maintenance of Th1 responses (11). Therefore, IL-27 and IL-12 were considered to function sequentially in the initiation and maintenance of Th1 responses, respectively (9, 11). This notion is supported by the fact that T cell cytokine receptor mRNA expression is high in undifferentiated Th cells but low in differentiated Th1 and Th2 cells (10). It has been reported recently that IL-27 induces T-bet and subsequent IL-12/β2 expression, which is a key Th1 commitment step wherein naïve Th precursor cells commence differentiation into Th1 cells by naive CD4+ T cells through signal transducer and activator of transcription (STAT) 1 activation (12).

In the present study, we evaluated the in vivo antitumor activity of the novel IL-12 family member IL-27 against a murine tumor model of colon carcinoma C26. We have found that IL-27 has potent abilities to induce tumor-specific antitumor activity and protective immunity and that the antitumor activity is mediated mainly through CD8+ T cells, IFN-γ, and T-bet but unexpectedly not through STAT4. This is the first report on the antitumor activity of IL-27.

MATERIALS AND METHODS

Cell Culture and Mice. Colon carcinoma C26 and fibrosarcoma MethA cell lines were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum. Spleen cells and primary and naïve CD4+ T cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum and 50 μM 2-mercaptoethanol. Female BALB/c mice and BALB/c-nu/nu mice were purchased from Japan SLC (Hamamatsu, Japan). T-bet-deficient mice (13) and STAT4-deficient mice (14) of BALB/c background were purchased from The Jackson Laboratory (Bar Harbor, ME). All of the mice were maintained under specific pathogen-free conditions and used in accordance with our institutional guidelines.

Preparation of C26 Transfectants. Mouse IL-12 p40 and p35 and IL-27 EB13 and p28 cDNA were isolated by reverse transcription-PCR using total RNA prepared from conA-activated spleen cells. For preparation of single-chain (sc) IL-12 and IL-27 expression vectors, fragments encoding the mature part of p40 or EB13, followed by the (Gly4 Ser)3 linker and then by the mature coding sequence of p35 or p28, respectively, were generated by using standard PCR methods and cloned into p3xFLAG-CMV-9 (Sigma Chemical Co., St. Louis, MO) vector, which has preprotypsin signal peptide and 3xFLAG epitope-tag sequences at N-terminal (15). C26 cells then were transfected with these expression vectors or the empty vector using Fugene 6 (Roche Molecular Biochemicals, Indianapolis, IN) and selected with geneticin (G418).

Immunoprecipitation and Western Blot Analysis. Each transfectant (1 × 10⁶ cells/ml) was cultured for 48 h, and the culture supernatant was used for analysis of secreted IL-27 and IL-12 proteins. The supernatant was incubated with anti-FLAG (M2; Sigma Chemical Co.) conjugated to protein G-Sepharose (Amersham Pharmacia Biotech, Little Chalfont, United Kingdom) for 2 h at 4°C. After washing the beads, the complexes were separated on an SDS-PAGE under reducing conditions and transferred to polyvinylidene
diffuoride membrane (Milipore, Bedford, MA). The membrane then was blocked, probed with anti-FLAG and antimouse IgG conjugated to horseradish peroxidase, and visualized with the enhanced chemiluminescence detection system (Amersham Pharmacia Biotech) according to the manufacturer’s instructions.

T-Cell Proliferation Assay. Primary T cells were purified by passing BALB/c mouse spleen cells depleted of erythrocytes through nylon wool. The flow-through fraction was incubated with biotin-conjugated anti-CD8α, anti-B220, anti-Mac-1, anti-Ter-119, and anti-DX5, followed by incubation with antibiotin magnetic beads (Miltenyi Biotec, Bergisch Gladbach, Germany) and passed through a magnetic cell sorting column (Miltenyi Biotec), and the negative fraction was collected (CD4+ T cells >95%). CD4+ T cells then were incubated with anti-CD26L magnetic beads (Miltenyi Biotec), and the positive fraction was collected as naive CD4+ T cells (CD62L+ cells >99%). For measurement of proliferation induced by IL-12, primary CD4+ T cells (1 × 10^5 cells/ml) were stimulated with 2 μg/ml plate-coated anti-CD3 (145–2C11; American Type Culture Collection, Manassas, VA) for 4 days, and after washing, they were cultured additionally overnight. These activated CD4+ T cells (4 × 10^5 cells/200 μl) then were stimulated with culture supernatant of each C26 transfectant for 2 days and pulsed with [3H]thymidine for 6 h. For measurement of proliferation induced by IL-27, naive CD4+ T cells (2 × 10^5 cells/200 μl) were stimulated with plate-coated anti-CD3 (2 μg/ml) in the presence of 100 μg/ml anti-IL-2 (S4B6; American Type Culture Collection) and culture supernatant of each C26 transfectant for 4 days and pulsed with [3H]thymidine for 20 h.

IFN-γ Production Assay. The spleen was removed from each mouse, and spleen cells (5 × 10^6 cells/ml) were restimulated in vitro with coculture with C26 parental tumor cells (5 × 10^5 cells/ml) irradiated with 150 Gy for 2 days. These culture supernatants were collected and assayed for INF-γ production by ELISA as described previously (16).

Cytotoxicity Assay. The spleen was removed from each mouse, and spleen cells (5 × 10^6 cells/ml) were restimulated in vitro with coculture with C26 parental tumor cells (5 × 10^5 cells/ml) irradiated with 150 Gy for 5 days and used as effector cells in a standard 51 Cr release assay. C26 parental tumor cells (1 × 10^6 cells) were labeled by incubating in 100 μCi 51Cr for 1 h at 37°C and washing three times. Labeled target cells (1 × 10^6 cells/200 μl/well) and serial dilutions of effector cells were incubated in RPMI 1640 containing 10% fetal bovine serum in a 96-well U-bottomed plate at 37°C for 4 h. Supernatants then were analyzed in a scintillation counter. The percentage of lysis was determined for each triplicate experiment as (experimental count – spontaneous count) × 100/(maximal count – spontaneous count). Results were expressed as the percentage of specific lysis.

Depletion of CD8α and CD4+ T Cells and Neutralization of IFN-γ with Monoclonal Antibodies. For depletion or neutralization with monoclonal antibodies (mAbs), each mouse was injected i.p. with 0.5 mg rat antimouse CD8 (53-6.7), anti-CD4 (GK1.5), anti-IFN-γ (XMG1.2; all from American Type Culture Collection) mAbs, or normal rat IgG (Sigma Chemical Co.) as control antibody in 200 μl PBS 1 day before tumor inoculation, once daily for the following 3 consecutive days, and then twice a week.

RESULTS

Characterization of C26-IL-27 Transfectant in Vitro. Colon carcinoma C26 tumor cells were transected stably with the expression vector of sCIL-27. sCIL-12 tagged N-terminally with 3xFLAG, or the empty vector (C26-IL-27, C26-IL-12, and C26-vector, respectively). First, the supernatant of each transfectant cultured for 2 days was analyzed for the relative amount of these secreted proteins by immunoprecipitation with anti-FLAG followed by Western blot analysis with anti-FLAG (Fig. 1A). Large amounts of secreted sCIL-27 and sCIL-12 in each culture supernatant were observed but not in the culture supernatant of C26-vector. The proliferative activities to activated primary CD4+ T cells or naive CD4+ T cells then were compared among these C26 transfectants. The proliferation of activated primary CD4+ T cells was induced strongly by the culture supernatant of C26-IL-12 but not of C26-IL-27 or C26-vector (Fig. 1B). In sharp contrast, the proliferation of naive CD4+ T cells was induced greatly by the culture supernatant of C26-IL-27 but induced slightly by that of C26-IL-12 or not by that of C26-vector (Fig. 1C).

Potent Antitumor Activity of IL-27 in Vivo with Enhanced IFN-γ Production and Augmented Tumor-Specific CTL Activity. To examine the antitumor activity of C26-IL-27, each C26 transfectant (2 × 10^6 cells) or a mixture of C26-vector and C26-IL-27 (total 2 × 10^5 cells) were injected s.c. into syngeneic BALB/c mice, and in vivo tumor cell growth and survival rate were compared. As reported previously (6, 17–19), C26-IL-12 and C26-IL-27 efficiently secreted bioactive IL-12 and IL-27 proteins, respectively. Moreover, there was no difference in cell growth in vitro and surface expression of MHC class I among these C26-IL-12, C26-IL-27, and C26-vector transfectants (data not shown).
tumor inoculated into recovered mice from inoculation with C26-IL-27 never became palpable, and all of the these mice survived healthily (Fig. 3A, and data not shown). However, MethA tumor inoculated into these recovered mice or C26 tumor inoculated into nontreated mice grew vigorously (Fig. 3A). Spleen cells of mice then recovered from inoculation with C26-IL-27 or C26-IL-12; nontreated mice were cultured with irradiated parental C26 cells for 2 days, and culture supernatants were analyzed for IFN-γ production by ELSA. Data are shown as the mean, bars, ±SD. Similar results were obtained in three independent experiments. B, enhanced IFN-γ production from spleen cells by IL-27. BALB/c mice (n = 3) were injected s.c. with each C26 transfectant (2 x 10^6 cells), and culture supernatants were analyzed for IFN-γ production (Fig. 3B). As reported previously (4), T-bet and STAT4, which is essential for signaling through IL-12R (14, 20), in the induction of antitumor activity by IL-27 using T-bet-deficient mice (13) and STAT4-deficient mice (14). Tumor growth of C26-vector in T-bet-deficient mice was slightly more vigorous than that in wild-type mice (Fig. 5A). Although C26-IL-27 exhibited a strong antitumor activity in wild-type mice, all of the T-bet-deficient mice inoculated with C26-IL-27 developed rapidly growing tumors (Fig. 5B). In contrast, tumor growth of C26-vector in STAT4-deficient mice was similar to that in wild-type mice (Fig. 5A), whereas unexpectedly C26-IL-27 showed a significant antitumor activity by IL-27. A, induction of tumor-specific protection by interleukin (IL)-27. Recovred mice (n = 5) from inoculation with C26-IL-27 or nontreated mice were challenged by parental C26 or irrelevant syngeneic MethA tumor targets in a standard 51Cr release assay. Data are shown as the mean; bars, ±SD. Similar results were obtained in three independent experiments.

Involvement of CD8+ T Cells, IFN-γ, and CD4+ T Cells in the Induction of Antitumor Activity by IL-27. To examine the involvement of particular lymphocytes in the inhibition of tumor growth by IL-27, we next used nude mice, in which T lymphocytes are absent. Tumor growth of C26-IL-27 was almost the same as that of C26-vector in nude mice, and all of the mice inoculated with C26-IL-27 developed vigorously growing tumors (Fig. 4A). No significant difference of survival rates between mice inoculated with C26-IL-27 and C26-vector also was observed (Fig. 4B). We then treated immuno-competent BALB/c mice with neutralizing anti-IFN-γ mAb or depleting anti-CD8 or anti-CD4 mAbs during tumor challenge, and tumor growth was monitored (Fig. 4C). Consistent with the increased production of IFN-γ and enhanced CTL activity by IL-27 as shown in Fig. 2D and E, respectively, treatment of mice with mAb-neutralizing IFN-γ and mAb-depleting CD8+ T cells greatly recovered tumor growth. Similarly, but much less efficiently, recovered tumor growth was observed in mice treated with mAb-depleting CD4+ T cells. These results suggest that IFN-γ production and CD8+ T cells play critical roles in the induction of antitumor activity by IL-27 and that CD4+ T cells also are involved in the induction of antitumor activity.

Critical Role of T-bet, but Not STAT4, in the Induction of Antitumor Activity by IL-27. Because IL-27 induces T-bet and subsequent IL-12Rβ2 expression in naive CD4+ T cells activated by anti-CD3 (12), we examined the role of T-bet and STAT4, which is essential for signaling through IL-12R (14, 20), in the induction of antitumor activity by IL-27 using T-bet-deficient mice (13) and STAT4-deficient mice (14). Tumor growth of C26-vector in T-bet-deficient mice was slightly more vigorous than that in wild-type mice (Fig. 5A). Although C26-IL-27 exhibited a strong antitumor activity in wild-type mice, all of the T-bet-deficient mice inoculated with C26-IL-27 developed rapidly growing tumors (Fig. 5B). In contrast, tumor growth of C26-vector in STAT4-deficient mice was similar to that in wild-type mice (Fig. 5A), whereas unexpectedly C26-IL-27 showed a significant antitumor activity by IL-27. A, induction of tumor-specific protection by interleukin (IL)-27. Recovred mice (n = 5) from inoculation with C26-IL-27 or nontreated mice were challenged by parental C26 or irrelevant syngeneic MethA, and tumor growth was monitored. Data are shown as the mean, bars, ±SD. Similar results were obtained in three independent experiments. B, enhanced IFN-γ production by IL-27. Spleen cells of recovered mice (n = 3) from inoculation with C26-IL-27 or C26-IL-12 were restimulated in vitro with irradiated parental C26 for 2 days, and the culture supernatant was assayed for IFN-γ production. Data are shown as the mean; bars, ±SD. Similar results were obtained in three independent experiments. C, enhanced IFN-γ production by Endogen IL-27. Spleen cells of recovered mice (n = 3) from inoculation with C26-IL-27 or C26-IL-12 were restimulated in vitro with irradiated parental C26 for 5 days, and cytokotoxic T lymphocyte (CTL) activity of resultant effector cells was measured against 51Cr-labeled parental C26 or irrelevant syngeneic MethA tumor targets in a standard 51Cr release assay. Data are shown as the mean; bars, ±SD. Similar results were obtained in three independent experiments.

**Fig. 2.** Potent antitumor activity of interleukin (IL)-27 in vivo with enhanced IFN-γ production and augmented tumor-specific cytotoxic T lymphocyte (CTL) activity. A, inhibition of in vivo tumor growth by C26-IL-27. BALB/c mice (n = 3) were injected s.c. with each C26 transfectant (2 x 10^6 cells) or a mixture of C26-vector and C26-IL-27 (ratios of C26-vector, C26-IL-27 = 99:1 and 90:10; total 2 x 10^6 cells), and tumor volume was monitored and compared after 2 weeks. Tumor volume was calculated using the following volume equation: 0.5(ab^2), where a is the long diameter, and b is the short diameter. Data are shown as the mean; bars, ±SD. Similar results were obtained in two independent experiments. B, minimal tumor growth of C26-IL-27 in vivo. BALB/c mice (n = 5) were injected s.c. with each C26 transfectant (2 x 10^6 cells), and tumor growth was monitored. Data are shown as the mean; bars, ±SD. Similar results were obtained in four independent experiments. C, prolonged survival time of mice inoculated with C26-IL-27. BALB/c mice (n = 7–8) were injected s.c. with each C26 transfectant (2 x 10^6 cells), and survival rate was monitored. Similar results were obtained in two independent experiments. D, enhanced IFN-γ production from spleen cells by IL-27. BALB/c mice (n = 3) were injected s.c. with each C26 transfectant (2 x 10^6 cells), and 2 weeks later spleen cells obtained from each mouse were cultured with irradiated parental C26 cells for 2 days, and the culture supernatant was analyzed for IFN-γ production by ELSA. Data are shown as the mean, bars, ±SD. Similar results were obtained in four independent experiments. E, augmented tumor-specific CTL activity of spleen cells by IL-27. Two weeks after the inoculation, spleen cells obtained from each mouse (n = 3) were restimulated with irradiated parental C26 for 5 days, and CTL activity of resultant effector cells was measured against 51Cr-labeled parental C26 or irrelevant syngeneic MethA tumor targets in a standard 51Cr release assay. Data are shown as the mean; bars, ±SD. Similar results were obtained in four independent experiments.

**Fig. 3.** Induction of tumor-specific protective immunity by interleukin (IL)-27. A, induction of tumor-specific protection by IL-27. Recovered mice (n = 5) from inoculation with C26-IL-27 or nontreated mice were challenged by parental C26 or irrelevant syngeneic MethA, and tumor growth was monitored. Data are shown as the mean, bars, ±SD. Similar results were obtained in three independent experiments. B, enhanced IFN-γ production by IL-27. Spleen cells of recovered mice (n = 3) from inoculation with C26-IL-27 or C26-IL-12 were restimulated in vitro with irradiated parental C26 for 2 days, and the culture supernatant was assayed for IFN-γ production. Data are shown as the mean; bars, ±SD. Similar results were obtained in three independent experiments. C, enhanced IFN-γ production by IL-27. Spleen cells of recovered mice (n = 3) were restimulated in vitro with irradiated parental C26 for 5 days, and cytokotoxic T lymphocyte (CTL) activity of resultant effector cells was measured against 51Cr-labeled parental C26 or irrelevant syngeneic MethA tumor targets in a standard 51Cr release assay. Data are shown as the mean; bars, ±SD. Similar results were obtained in three independent experiments.

**Fig. 4.** Involvement of CD8+ T cells, IFN-γ, and CD4+ T cells in the induction of antitumor activity by interleukin (IL)-27. BALB/c nude mice (n = 5) were injected s.c. with each C26 transfectant (2 x 10^6 cells), and tumor growth (A) and survival rate (B) were monitored. Data are shown as the mean ± SD. Similar results were obtained in two independent experiments. C, BALB/c mice (n = 5) were injected s.c. with each C26 transfectant (2 x 10^6 cells), and tumor growth (A) and survival rate (B) were monitored. Data are shown as the mean ± SD. Similar results were obtained in three independent experiments.
strong antitumor activity even in STAT4-deficient mice (Fig. 5B). As expected, STAT4-deficient mice inoculated with C26-IL-12 developed vigorously growing tumors, although C26-IL-12 showed a strong antitumor activity in wild-type mice (data not shown). These results suggest that T-bet is important for the induction of antitumor activity by IL-27, but STAT4 is not essential for it.

DISCUSSION

In the present study, we found that C26 cells transduced with the scIL-27 cDNA (Fig. 1) showed a strong inhibition of tumor growth in vivo and consequently a prolonged survival by its ability to enhance the initiation of Th1 responses and augment the antitumor cellular immunity (Fig. 2). Mice that recovered from the inoculation with C26-IL-27 acquired a tumor-specific protective immunity (Fig. 3). This potent antitumor activity was mediated mainly through CD8+ T cells and IFN-γ, and CD4+ T cells also were involved in the induction of antitumor activity (Fig. 4). Furthermore, T-bet was revealed to be important for the induction of antitumor activity, but STAT4 was not essential for it (Fig. 5). This seems unexpected because IL-27 induces T-bet and subsequent IL-12β2 expression and therefore enhances synergistically IFN-γ production with IL-12 in naive CD4+ T cells (12). To exert the antitumor activity in vivo, IL-27 may use different pathways or act directly on CD8+ T cells through T-bet but not in collaboration with IL-12. Additional studies are necessary to elucidate the molecular mechanism underlying the antitumor activity induced by IL-27.

Effective eradication of established tumors and generation of a long-lasting systemic immune response with a simple gene delivery system are important goals for cancer gene immunotherapy. Cytokine genes are the most widely and extensively studied immunostimulatory agents in cancer gene therapy (21). For clinical application, local and systemic administration of IL-12 protein has been studied in various murine models (21–24) and in Phase I/II human trials (25, 26). However, IL-12 therapy has been limited by systemic toxicities such as hepatomegaly, splenomegaly, leukopenia, myelodepression, lung edema, and gastrointestinal toxicity (7, 8, 27, 28). Therefore, local and efficient expression of IL-12 or other cytokine genes in tumors is an alternative immunotherapeutic approach that may avoid systemic toxicity of recombinant cytokines. A recently identified novel member of the IL-12 family, IL-27, which plays a role in the early regulation of Th1 initiation but not in the effector Th1 responses, could be an attractive candidate as an agent applicable to the cancer gene therapy (9–12). IL-27 has been demonstrated recently to induce T-bet and subsequent IL-12Rβ2 expression, which is a key Th1 commitment step wherein naive Th precursor cells commence differentiation into Th1 cells, by naive CD4+ T cells through STAT1 activation (12). In addition, we have found recently that STAT1 signaling plays an indispensable role in IL-27-induced T-bet and IL-12Rβ2 expression but not proliferation of naive CD4+ T cells.6 Mice deficient of EB13, one of the IL-27 subunits, have been demonstrated recently to be resistant to Th2-mediated colitis model with a sustained decrease in IL-4 production but susceptible to Th1-mediated colitis model with only transient decrease in IFN-γ production (29). These data suggest presumably that an EB13-dependent factor different from IL-27 is involved in IL-4-mediated Th2 responses. Furthermore, we have found recently that IL-27 has an adjuvant effect on the induction of hepatitis C virus-specific Th2 responses (9–12). This is in contrast to IL-12, which is involved in the induction and maintenance phases of effector Th1 responses, presumably resulting in the excessive toxicity in vivo (7, 8, 27, 28). Therefore, it may be possible to expect the lower toxicity in the treatment with IL-27. During the IL-27 treatment in the present study, we have not observed any apparent adverse effects such as splenomegaly and liver injury with elevated serum glutamic-oxaloacetic transaminase and alanine aminotransferase activities and intensive mononuclear cell infiltration into the liver, which are seen with IL-12 treatment (8, 27, 28). Additional studies with systemic administration of IL-27 and detailed analyses of other organs are necessary to determine the absence or presence of adverse effects with the IL-27 treatment.

Thus, IL-27 may be a novel attractive candidate as an agent applicable to the cancer immunotherapy with a potent antitumor activity and also a potentially lower toxicity.

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