When some human plasma cell lines are cultured with concanavalin A, the original light chain is replaced with another light chain which results from secondary VJ recombination (light chain shifting). We examined various intracellular factors involved in the induction of light chain shifting. Light chain shifting can be induced upon treatment with agents with phosphatase inhibitory activity such as caffeine and okadaic acid. Although the plasma cells used express both RAG-1 and RAG-2, the expression level of these proteins was not affected by caffeine or okadaic acid. Transcription of the germ line locus, which correlates to the locus activation for rearrangement, is also not influenced by phosphatase inhibition. However, the amount of signal broken-ended DNA intermediates generated during V(D)J rearrangement was shown to increase upon caffeine or okadaic acid treatment. The inhibitory activity of caffeine on phosphatase was the same as okadaic acid. However, caffeine exhibited much higher activity for VJ coding joint formation than okadaic acid. Therefore, although phosphatase inhibition might act, in part, on a mechanism by which V(D)J recombination activity is regulated within the human plasma cells, other factor(s) are probably also involved in the process.

Immunoglobulin genes are assembled during B cell development through a series of site-specific recombination events collectively termed V(D)J recombination (1). The V(D)J recombination reaction is initiated by the recombination activating gene products RAG-1 and RAG-2 and is completed by a set of proteins employed in most cell types for DNA double-stranded break repair such as the Ku-80 antigen, a large catalytic subunit of DNA-dependent protein kinase and XRCC4 (2–6). Although many of the VJ recombination reactions at the light chain loci occur in pre-B cells, recent findings suggest that light chain gene rearrangements often continue in immature-B cells and germinal center B cells (7–11). We have also shown that secondary VJ recombination can occur in some human plasma cell lines when stimulated with concanavalin A (ConA)1 (12, 13).

We call this process light chain shifting (14).

Several factors have been shown to be involved in Ig gene rearrangement in terms of timing and placement (1). V(D)J recombination activity is determined by the regulated expression of RAG-1 and RAG-2 (3). These genes are expressed only when B cells rearrange the Ig heavy and light chain loci. The RAG gene products are necessary for Ig recombination, and coexpression of these two genes in nonlymphoid cells is sufficient to confer the ability to recombine artificial plasmid substrates (15). Secondary VJ rearrangements in immature B cells and our plasma B cells are closely correlated with coexpression of the two RAG genes (10, 14). However, there must be additional levels of regulation to determine which loci are targeted for recombination in developing lymphocytes, because endogenous Ig genes are only targeted for complete rearrangement in B lineage cells, and endogenous T cell receptor genes are only completely rearranged in T lineage cells. Plus we have also found that enhancement of RAG expression is not sufficient to induce secondary VJ rearrangement in light chain shifting-inducible human plasma cells (13, 14). Therefore, expression of RAG-1 and RAG-2 is likely to be only part of the mechanism by which V(D)J recombination is activated in lymphoid cells. In lymphoid cells, specific developmental signals result in changes in the chromatin that allows the recombinase access to particular gene segments (16, 17). Results showing that activation of a locus for rearrangement correlates with the transcription of that particular germ line locus support the accessibility hypothesis (18–20).

In this report, we investigated various intracellular factors that may induce light chain shifting in human plasma cells. We found that the RAG gene products and the transcription of the germ line locus is not sufficient to carry out secondary VJ recombination in human plasma cells. However, phosphatase inhibition by caffeine or okadaic acid was found to be necessary to induce secondary VJ recombination. The phosphatase inhibition induced the formation of signal broken-ended DNA intermediates in the cells, which is an initial step in the V(D)J recombination process.

**MATERIALS AND METHODS**

*Reagents—*Caffeine, dibutyryl cAMP (DbcAMP), forskolin, ionomycin, H-89, H-7, phorbol myristate acetate (PMA), were obtained from Sigma. Okadaic acid and sodium orthovanadate (vanadate) were purchased from Wako (Osaka, Japan).

**Cells and Cell Stimulation—**Fusing a B lymphocyte with the IgM secreting human plasma line NAT-30 (21, 22) generated the human hybridoma cell line HB4C5, which secretes a monoclonal antibody specific to the human histone H2B. For cell stimulation, cells (1 × 10⁶ cells/ml) were cultured in the presence of caffeine (2 mM), DbcAMP (50 ng/ml), forskolin (100 μM), ionomycin (250 ng/ml), H-89 (20 μM), H-7 (100 μM), PMA (50 ng/ml), okadaic acid (1, 10, or 100 nM), or vanadate (100 μM).

**Protein Phosphatase Activity Assay—**The protein phosphatase activ-
ity in inhibitor-treated cells was assayed using a serine/threonine protein phosphatase assay kit from Upstate Biotechnology according to the manufacturer's instructions. The cells were incubated with caffeine (2 mM), okadaic acid (1 and 100 nM), or vanadate (100 μM) for 24 h in cell culture dishes. At the end of the incubation period, 1 × 10^6 cells were transferred into Eppendorf tubes, washed with 50 mM Tris/HCl, pH 7.0, and the cells were lysed in 1 ml of extraction buffer (50 mM Tris/HCl, pH 7.0, 0.1% 2-mercaptoethanol, 0.1 mM EDTA, 0.1 mM EGTA, 1 mM phenylmethylsulfonyl fluoride, 0.5% Triton X-100). The lysate was spun down at centrifuged for 5 min at 10,000 × g at 4°C, and then the supernatant was recovered. 20 μl of the supernatant was mixed with 5 μl of 0.1x phosphocellulose substrate (phosphoprotein; K-R-PT-1-B), the mixture was incubated for 60 min at 37°C. 100 μl of Malachite Green solution was added to the mixture to terminate the enzyme reaction, and then the mixture was incubated at room temperature for 15 min to allow color development. Absorbance at 650 nm was measured, and phosphatase activity was calculated by comparing the absorbance to the phosphate standard curve.

**Western Blot Analysis of RAG and λ Light Chain Expression**—Cells were collected, washed once in phosphate-buffered saline, lysed in 60 mM Tris/HCl, pH 7.6, 1% SDS, and boiled for 5 min. Protein concentration was determined using the Bio-Rad protein assay kit, and lysates (600 μg/sample) were electrophoresed on SDS-polyacrylamide gels (10%) and then transferred to a nitrocellulose membrane. The blotted RAG proteins were detected by immunoblotting with human RAG-1 or RAG-2 antibodies (Pharmigen, San Diego, CA). Immunoreactive proteins were detected by incubation with horseradish peroxidase-conjugated goat anti mouse IgG antibody (Sigma) at a 1:2000 dilution for 1 h at room temperature; immobilized horseradish peroxidase was visualized using an enhanced chemiluminescence assay (Amersham Pharmacia Biotech). To detect the human λ light chain, the blotted membrane was incubated in a 1:5000 dilution of horseradish peroxidase-conjugated goat anti-human λ light chain antibody (BIO SOURCE) for 1 h. The membranes were washed in phosphate-buffered saline containing 0.05% Tween 20 and developed with 1.6 mM 4-chloro-1-naphthol, 0.01% H2O2 in phosphate-buffered saline with 20% methanol.

**RT-PCR and Nucleotide Sequence Analysis**—Total RNA, prepared using the TRizol reagent (Life Technologies, Inc.), was reverse transcribed, and the resultant cDNA served as a template for PCR amplification using specific primers. cDNA was synthesized from total RNA using a kit (Amersham Pharmacia Biotech) according to the instructions provided by the manufacturer. To synthesize the cDNA from the Vλ 6 germ line transcript, 20 pmol each of P-Vλ 6P (Vλ 6-CDR1 region-specific) 5'-CTCTGAGCAGTGGGCACAGC-3' and P-GAPDR, 5'-AGCC-3', and P-LLR, 5'-GGAGTT-CCTCCGCC-3' were used for reverse transcription. Glyceraldehyde-3-phosphate dehydrogenase gene (GAPDH) amplification was carried out using a kit (Amersham Pharmacia Biotech) according to the manufacturer's instruction. The cells were incubated with caffeine (2 mM), DbcAMP (50 ng/ml), forskolin (100 μM), ionomycin (250 ng/ml), H-89 (20 μM), H-7 (100 μM), or PMA (50 ng/ml) were analyzed for the secretion of λ light chains by immunoblotting.

**Southern blot hybridization.** The PCR products were transferred onto nylon transfer membranes (Hybond-N+, Amersham Pharmacia Biotech), and hybridized with fluorescein-labeled probes. cDNA fragments coding for each λ light chain, which were used for analyzing the variable region sequence, was digested from their respective vectors with restriction enzymes. The resulting fragment, each containing the specific V gene, was labeled using the oligonucleotide labeling kit (Gene Images, Amersham Pharmacia Biotech) for use as probes for the detection of the corresponding Vλ Jλ coding joints. To check for possible Taq polymerase errors, all PCR products were sequenced and compared with previously defined sequences.

**LMPCR Assay for Detecting Signal DNA Broken Ends (SBE)—**The LMPCR assays for detecting signal end breaks, as have been described by Schlissel et al. (24), was performed with minor modifications. The BW linker was made by annealing the oligonucleotides BW-1 (5'-CGTCCTGACGTGGTACCATC-3') and BW-2 (5'-GAATTCATGAC-3'). 2 μg of genomic DNA extracted as described above were ligated with 20 pmol of the BW linker in a reaction volume of 20 μl using 3 units of T4 ligase (Promega). The same reaction mixtures without the BW linker were also prepared as negative controls. After an overnight incubation at 4°C, the ligation reaction was stopped by incubating the samples at 95°C for 10 min. Hot start PCR amplification was performed in a 10-μl reaction volume using 0.5 unit of Taq DNA polymerase (AmpliTaq Gold, Perkin Elmer), 10 pmol each of the sense direction primer BW-1 and the antisense direction primer P-Vλ 6SBER (5'-CTTAGTACGTGAGACATCG-3'), and 1 μl of serially diluted linker-ligated templates. Samples were preincubated at 95°C for 9 min followed by 35 cycles of 96°C for 20 s, 62°C for 10 s, and 72°C for 10 s followed by a final 7-min extension step at 72°C. After amplification, the bands for Vλ 6 SBE were detected by Southern hybridization. Blots were visualized using the fluorescein-labeled locus-specific internal probe P-Vλ 6CA3TR.

**RESULTS**

**Induction of New λ Light Chain Production in the Plasma B Cell Line HB4C5 by Caffeine Stimulation.—**We previously found that ConA simulation can induce light chain replacement in the human plasma cell line HB4C5, which is known to secrete IgM reactive to the human histone H2B (22). This lectin is known to have a multitude of effects in mammalian systems (25, 26). To elucidate which intracellular factors are involved in the light chain shifting, we tested various agents that affect second messenger pathways for their influence on new light chain production in the HB4C5 cells. The HB4C5 cells were cultured in medium containing caffeine, DbcAMP, forskolin, ionomycin, H-89, H-7, or PMA for 2 weeks. Then, the culture supernatants were analyzed for the secretion of λ light chains by immunoblotting (Fig. 1). Among the compounds that increase intracellular cAMP concentration, caffeine, DbcAMP, and forskolin, only caffeine was shown to be able to induce the expression of a new λ light chain. Furthermore, H-89 and H-7 (known to increase free cytosolic calcium concentration), and PMA (known to stimulate protein kinase C) failed to induce the production of a new light chain. These results suggest that induction of the new λ light chain by ConA can be mimicked by treatment with caffeine, whereas several other known factors that affect second messenger pathways cannot.
using an anti human light chain V variable regions of these expressed light chains were analyzed. The level of VJ rearrangements in the new light chain-expressing subclones, FF1, FF2, and FF3. Genomic DNA from HB4C5 cells and the FF1, FF2, and FF3 subclones was subjected to PCR to detect for the presence of a VJ coding joint formation specific for the new light chain using primers corresponding to the V4,6 families. The products were analyzed by Southern blot hybridization. A diagram of the PCR assay is shown in Fig. 4c. PCR product was detected only in the DNA from the new light chain-producing subclones, suggesting that the new VJ rearrangements occurred during the cell stimulation with caffeine (Fig. 4f). In Fig. 1, we tested various agents for their ability to secrete a new light chain and found that only caffeine could stimulate new light chain production. We tested the same agents for their ability to induce secondary VJ recombination by PCR using the V6,6P and J6P primers. Only caffeine activated the secondary VJ recombination (Fig. 4c), which supports the results in Fig. 1. These genetic events in the caffeine-stimulated new light chain-producing cells exactly match the results shown for ConA-stimulated cells, suggesting that caffeine does mimic the effect of ConA stimulation on the light chain shifting.

Caffeine-induced Secondary VJ Recombination in Plasma Cells Depends on Phosphatase Inhibitory Activity—Caffeine exerts a multitude of effects in mammalian cells including DNA intercalation and inhibition of protein serine/threonine phosphatase and cAMP phosphodiesterase (29–31). As shown previously, with the exception of caffeine, agents that increase intracellular cAMP could not induce light chain shifting. Interestingly, HB4C5 cells costimulated with caffeine and DbcAMP did not express any new light chains (data not shown). Thus, effects other than the increasing of cAMP are thought to be responsible for the induction of the light chain shifting by caffeine.

To test the possibility that the effect of caffeine on light chain shifting is due to serine/threonine protein phosphatase inhibitory activity, HB4C5 cells were treated with okadaic acid, which is a serine/threonine phosphatase inhibitor (32), or vanadate, which is an inhibitor of dual specificity phosphatase and tyrosine phosphatase (33). Genomic DNA was analyzed for the formation of a VJ coding joint by PCR, as described in the legend to Fig. 4. We focused on the V6,6P-to-J6P coding joint formation because it is the most frequently used V6P segment in light chain shifting. As shown in Fig. 5a, stimulation of HB4C5 cells with okadaic acid at a concentration of 100 nM for 96 h induced the formation of a V6,6P-to-J6P coding joint. Similar induction levels of the VJ recombination were obtained even at lower concentrations (10 and 1 nM). In contrast, a concentration of 100 µM vanadate was less efficient for the induction of VJ recombination. To determine the inhibitory effects of these agents on the serine/threonine protein phosphatase in HB4C5 cells, the phosphatase activity in the cells treated with either the agent or caffeine was measured (Fig. 5b). Caffeine treatment decreased serine/threonine phosphatase activity by 10%. Treatment with okadaic acid or vanadate also caused a 10–20% loss of the phosphatase activity. Therefore, the induction of light chain shifting may be brought about, in part, by the inhibition of serine/threonine protein phosphatase. However, the level of VJ coding joint formation by caffeine was much higher than that by okadaic acid and vanadate. Therefore, other factor(s) may be involved in the process.

RAG Protein Expression and Germ Line λ Gene Transcription Are Not Enhanced by Caffeine or Okadaic Acid—RAG-1 and RAG-2 gene products have been shown to be essential for initiating Ig gene rearrangement, and the levels of the RAG proteins have been known to be affected with cell proliferation (2, 24). Both proteins were expressed in the HB4C5 cells (13). To elucidate the mechanism that couples phosphatase inhibition and light chain shifting, we evaluated the expression of RAG genes in the HB4C5 cells. The level of RAG proteins...
products were detected with the V\(\)... amplified and the new light chain-expressing subclones FF1, FF2, and FF3 were a result of secondary VJ rearrangements. The PCR amplified primers used to detect the VJ coding joint. The directions of primers to J... correspond to the VJ coding joint for V\(\)... homology with the germ line genes.

It has been shown that genes undergoing V(D)J recombination are transcribed coincident with or before their rearrangement (34), and an increase in the production of the germ line transcript is associated with gene rearrangement (35). These observations have led to the hypothesis that stimuli by caffeine or okadaic acid can induce light chain shifting via an enhancement of germ line transcription. Because the V\(6\) locus is frequently used in light chain shifting, we used the unrearranged V\(6\) locus as a model V\(\)... gene segment to test this possibility (14). RT-PCR used to detect and quantify the amount of transcript produced. We found that the HB4C5 cells could transcribe the germ line V\(6\) locus at any of the given time points tested (Fig. 7). The steady-state levels of the transcript did not change upon treatment with caffeine or okadaic acid for 3, 6, 24, and 96 h (Fig. 7, b and c). These results indicate that incubation with the phosphatase inhibitors do not affect the germ line transcription in HB4C5 cells. The failure to observe an increase in germ line gene transcription as well as RAG protein expression, both of which are known to parallel the increase in frequency of V(D)J recombination, leads us to suggest that other factor(s) may be involved when light chain shifting is induced upon stimulation with caffeine or okadaic acid.

The Amount of Signal Broken Ends Derived from the Initiation of Chain Gene Rearrangement Is Increased by Phosphatase Inhibition—V(D)J recombination is initiated by a precise cleavage at the junction between a coding gene and a flanking recombination signal sequence to generate two broken-ended species, a signal end, and a coding end (cutting phase). The signal ends and coding ends are subsequently joined to generate signal joints and coding joints (joining phase) (36). We investigated whether the two phases are enhanced upon stimulation with the phosphatase inhibitors. SBE are in a blunt-ended conformation until they are joined, and this broken-ended species is joined before the onset of DNA synthesis (24, 37). Thus, in cycling cells, SBE can be a reliable measure of VJ recombinase activity. If the cutting phase of V(D)J recombination is activated by stimulation with caffeine or okadaic acid, the amount of SBE produced might increase (38). Genomic DNA prepared from HB4C5 cells stimulated with one of the phosphatase inhibitors for 24 and 96 h was assayed for SBE using LMPCR (24). DNA were subjected to ligation with a double-stranded linker capable of ligating in only one orientation. Linker-ligated DNA was then used as template for amplification by PCR using a linker-specific primer and a locus-specific probe. This is to test whether the linker is joined to the coding or the signal end of the recombination signal sequence.
specific primer (Fig. 8a). The same experiment using independently prepared genomic DNA samples were performed several times, and a representative result is shown. HB4C5 cells after cultivation with caffeine or okadaic acid for 96 h contain a definitely higher level of V6 SBE compared with unstimulated cells (Fig. 8c), whereas the SBE signal was barely detected in the DNA obtained from the cells treated with these agents for 24 h (Fig. 8b). These results show that at least early steps in the Vμ-Jμ recombination are enhanced in HB4C5 cells treated with agents with phosphatase inhibitory activity.

**DISCUSSION**

We have previously found that the λ light chain replacement from an original to a novel chain can be induced in some human plasma cells by ConA stimulation (12, 13). We call this process light chain shifting. This finding is in contrast to reports stating that continuous novel light chain expression can occur in some sIgM+ B cells in vitro and in vivo but not in Ig-secreting plasma cells (7–11). In the current study, we address the mechanism by which light chain shifting occurs in some human plasma cells. To elucidate the intracellular factors involved in light chain shifting, we tested agents that affect second messenger pathways, which can induce light chain shifting in the human plasma cell line HB4C5. Several agents that stimulate protein kinase C, increase intracellular cAMP and calcium, and inhibit protein kinase A did not mediate the induction of light chain shifting. We found that light chain shifting can be induced by caffeine. However, other agents that also can increase intracellular cAMP concentration, DbcAMP and forskolin, could not induce light chain shifting. Therefore, the induction of light chain shifting is thought to be independent of intracellular cAMP, and other effect(s) of caffeine should be considered to be responsible for the induction of the light chain shifting.

Caffeine has pleiotropic effects in mammalian cells, for example DNA intercalation and inhibiting poly(ADP-ribose) polymerase, cAMP phosphodiesterase, and serine/threonine phosphatases (29–31). To test the possibility that the effect of caffeine on light chain shifting is due to the inhibition of phos-
Fig. 8. LMPCR analysis of signal end double-stranded DNA breaks in V, J, recombinaton. a, diagram of the LMPCR assay used to detect signal end double-stranded DNA breaks on the rearranging loci. A pair of annealed oligonucleotides (thick bar) is ligated to signal end present in DNA prepared from the cells. PCR was performed using appropriate primers (BW1 and BW6 SBER). b and c, genomic DNA, extracted from HB4C5 cells cultured with the stimuli indicated above each lane for 24 h (b) and 96 h (c) were ligated with (linker (+)) or without (linker (-)) the BW linker, and were subjected to PCR to detect SBE. 100 and 10 ng of genomic DNA equivalent samples ligated with the BW linker were prepared and used as templates. PCR products were probed with an internal locus-specific oligonucleotide probe (P-VCA3GTR). Bands for V, SBE were expected to be 497 bp in length, and the positions are indicated by the arrows. GAPDH gene amplification followed by Southern hybridization using the same samples for detection of V, SBE was simultaneously performed as a DNA loading control.

Phosphatase activity, HB4C5 cells were treated with okadaic acid, which is a serine/threonine phosphatase inhibitor (32), or vanadate, which is an inhibitor of dual specificity phosphatase and tyrosine phosphatase (33). Okadaic acid was able to induce secondary VJ rearrangement in the HB4C5 cells upon stimulation with a 1 nM dose, which is equivalent to IC50 for type 2A and 4 serine/threonine phosphatase and much lower than type 1 and type 2B (39). Conversely, vanadate was less efficient for the induction of the VJ recombinaton. These results suggest that at least the inhibition of type 2A and/or type 4 serine/threonine protein phosphatase may play a role in the induction of light chain shifting. More study is necessary to elucidate how this inhibition affects light chain shifting in HB4C5 cells. The role of phosphorylation in the control of recombinaton has only been shown for the expression of RAG proteins, which are critical for initiating the V(D)J recombinaton (2). RAG-2 protein is marked for degradation upon phosphorylation by p34cdc2 kinase (40). It has been shown that p34cdc2 kinase can be activated by caffeine (41, 42), suggesting that caffeine may act as an agent in the degradation pathway of RAG-2 protein. In fact, the expression of RAG proteins was not enhanced in the HB4C5 cells when stimulated with caffeine or okadaic acid. We have previously shown that the enhancement of RAG gene expression did not induce the light chain shifting (13). Taken together, these results suggest that the induction of light chain shifting in plasma cells by caffeine is not due to an enhancement of the RAG gene expression.

V(D)J recombinaton of the Ig genes is initiated by the RAG-1 and RAG-2 proteins, which recognize the recombinaton signal sequences that flank each V, D, and J segment, to introduce double-stranded DNA breaks between the gene segments and the recombinaton signal sequence, resulting in signal broken ends and coding broken ends (cutting phase). The joining of recombinaton signal sequence and coding ends relies on generally expressed cellular factors involved in DNA double-stranded break repair (43). RAG gene expression and germ line transcription are thought to be sufficient enough for activating the cutting phase. Even though HB4C5 cells do produce the germ line transcript, the expression level of V, germ line transcript in HB4C5 cells did not change when stimulated with caffeine or okadaic acid. This suggests that the occurrence of secondary VJ, rearrangement in this plasma cell line is not a result of up-regulation of the V, germ line transcription. Although the level of RAG proteins and V, germ line transcript produced was not affected by the addition of caffeine or okadaic acid, the amount of signal broken end at the V, locus as a result of the action of a V(D)J recombinase clearly increased. This result suggests that the cutting phase in the recombinaton process can be activated by caffeine or okadaic acid, and the inability to rearrange the V, J, region in HB4C5 cells in absence of these agents may be due to the lack of formation of the V, SBE.

These results demonstrate that factor(s) other than the RAG proteins and the up-regulation of germ line transcription may be involved in the induction of secondary V, J, rearrangement by caffeine or okadaic acid. The recruitment process for the recombinase complex to the rearranging locus remains obscure (17). At least, the increase of V, SBE in HB4C5 cells cultured with caffeine or okadaic acid may reflect a recruitment of a recombinase complex to the V, locus. All known stimuli such as cAMP-raising agents, interleukin-4, and/or lipopolysaccharide, which trigger V(D)J rearrangement in pre-B and mature B cells, induce either RAG gene expression or germ line transcription (9–11, 44, 45). Thus, caffeine may play a unique role in determining other aspects of the initiation mechanism for secondary V, J, rearrangement in human plasma cells.

We observed that SBE is generated at elevated amounts after a 96-h stimulation time period with caffeine but was barely detected after 24 h. This time lag suggests that stimulation for over 24 h is needed before change of the chromatin structure at the light chain locus and/or V(D)J recombinase activation in HB4C5 cells can occur. This supports the hypothesis that activation of the recruitment process, which brings the recombinase complex to the V, locus, is regulated by as yet unknown additional factor(s) that may be up-regulated or activated by the phosphatase inhibitory effect of caffeine or okadaic acid. Determining such factor(s) will be informative in elucidating the regulation mechanism for the light chain shifting in human plasma cells.

The observation that the amount of SBE induced by caffeine is almost equal to that induced by okadaic acid is not consistent with the observation that V, J, coding joint formation induced by caffeine is at a much higher level than that by okadaic acid. This result suggests that the difference in VJ coding joint
formation between caffeine and okadaic acid may be correlated with the difference in the activity for joining coding ends and may be mediated by an effect other than phosphatase inhibitory activity of caffeine.

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