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Detection of unusually high transcriptomic and proteomic abundance of bromoform-synthesizing halogenase in marine macroalgae *Asparagopsis taxiformis*

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Halogenated molecules produced by marine algae are thought to be defensive secondary metabolites. The extraordinarily high concentration of bromoform in the seaweed *Asparagopsis*—up to 8% dry tissue weight—challenges the exclusivity of this paradigm. In this report, we provide evidence that the *mbb1* gene which encodes the bromoform producing halogenase is among the most highly transcribed genes in *Asparagopsis* tissue, with the resulting Mbb1 protein abundance rivaling that of enzymes involved in photosynthesis and carbon fixation. When the seaweed was stressed with light, transcripts for both *mbb1* and for proteins involved in photosynthesis were significantly downregulated. Conversely, heat stress modestly upregulated some photosynthesis genes but had no impact on *mbb1*. Taken together, these findings allow us to posit that bromoform production is not solely a stress-response or self-defense mechanism for *A. taxiformis*. Instead, we propose that the halogenase Mbb1 likely fulfils a primary metabolic function in this red alga thusly reconceptualizing halogenation biochemistry and pulling it out of the domain of natural product biosynthesis alone.

KEYWORDS

Asparagopsis, bromoform, halogenase, proteomics, transcriptomics, methane

Introduction

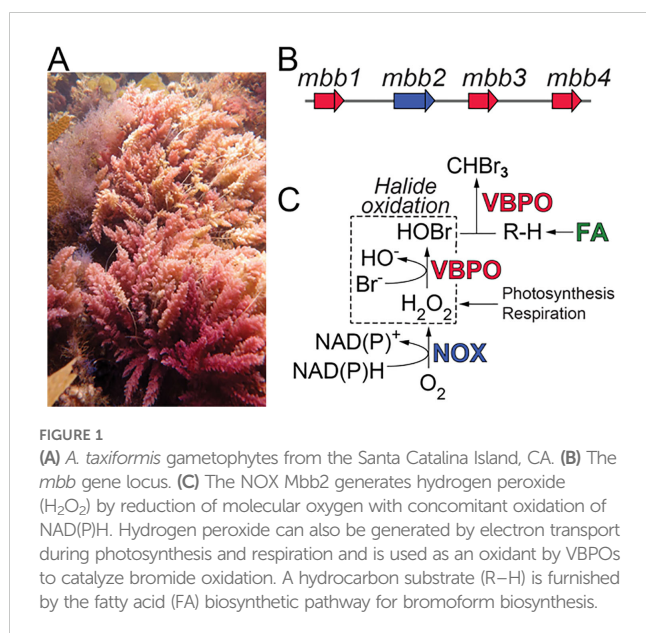
Halogenation of biomolecules is often a bioactivity-defining modification. In addition to numerous fluorinated pharmacophores, aryl chlorination confers antibiotic activity to vancomycin, tyrosine bromination controls *Drosophila* spermatogenesis, and iodination is critical to the activity of the thyroid hormone (Bianco et al., 2002; Pinchman and Boger, 2013a; Pinchman and Boger, 2013b; Gillis et al., 2015; Su et al., 2024). Halogenating enzymes—halogenases—are considered to be highly specialized secondary metabolic enzymes (Agarwal et al., 2017). The discovery, biochemical characterization, and biotechnological application of halogenases has traditionally involved their study in natural product biosynthetic schema (Agarwal et al., 2017).

As the largest reservoirs of halides, the world's oceans shape the global halogen cycle. A large fraction of atmospheric halogen flux is derived from halogenated methanes naturally produced by marine algae (Saiz-Lopez and von Glasow, 2012). Just like anthropogenic chlorofluorocarbons, ocean-derived halomethanes degrade the ozone layer. Among these, up to 30% of ozone depletion is attributed to bromoform (CHBr_3) that is produced by marine biota (Quack et al., 2004; Salawitch, 2006; Navarro et al., 2015). Seaweeds *Asparagopsis taxiformis* and *Asparagopsis armata* are prolific bromoform producers and bromoform has been proposed to protect these seaweeds against biofouling (Figure 1A) (Paul et al., 2006a). Contrary to traditional description of molecules that mediate ecological interactions and are often produced in small quantities, the concentration of bromoform in *Asparagopsis* is exceptionally high with up to 8% *Asparagopsis* tissue dry weight being bromoform (Gribble, 2000). *Asparagopsis* is attracting attention as a cattle feed additive; supplementing cattle feed with *Asparagopsis* reduces emission of the greenhouse gas methane from livestock (Roque et al., 2021; Wasson et al., 2022). *A. taxiformis* is

also a traditional Hawaiian food, known as limu kohu or the superior seaweed (Gribble, 2000).

We have recently reported the genetic and enzymatic route for bromoform biosynthesis in *A. taxiformis* (Thapa et al., 2020). The marine bromoform biosynthesis (*mbb*) gene locus in *A. taxiformis* encodes three vanadium-dependent bromoperoxidases (VBPOs; Mbb1, Mbb3, and Mbb4, Figure 1B) in the vicinity of a hydrogen-peroxide producing NAD(P)H-oxidase (NOX; Mbb2). We demonstrated that among the three VBPOs, Mbb1 and Mbb4 furnished bromoform starting from hydrocarbon substrates derived from fatty acid biosynthesis (R-H in Figure 1C) (Thapa et al., 2020). Isofunctional VBPOs in marine cyanobacteria also produce bromoform (Thapa and Agarwal, 2021). The VBPO Mbb3—while oxidizing bromide—did not catalyze bromoform production (Thapa et al., 2020). Akin to other haloperoxidases, Mbb1 and Mbb4 employed hydrogen peroxide (H_2O_2) as an electron sink to catalyze bromide oxidation to hypobromous acid (HOBr, Figure 1C). Hydrogen peroxide, in turn, might be produced by the NOX Mbb2, or derived from electron transport processes in photosynthesis and respiration (Thapa et al., 2020). VBPOs and vanadium-dependent chloroperoxidases (VHPOs), in addition to being involved in natural product biosynthesis schemes, are versatile and broad utility catalysts for C-H activation (Branham et al., 2025; Sharma et al., 2025; Zhao et al., 2025).

While the identity of the primary players in bromoform biosynthesis was thusly established, the rationale for the unusually high bromoform production in *Asparagopsis* remained unknown; the concentration of bromoform in other seaweeds such as *Chondrus crispus* (Irish moss) that also encode isofunctional bromoform producing VBPOs is vastly lower (Thapa et al., 2020). To explore the molecular basis of bromoform abundance in *Asparagopsis*, we undertook a paired multi-omic inquiry into the transcriptomic and proteomic abundance of the *mbb* gene expression and Mbb enzymes, respectively. Here, we describe observations that are suggestive of diverse roles of VBPOs in *Asparagopsis* physiology.



Methods

Detailed materials and methods are available in the [Supplementary Material](#).

Results

Field collected *A. taxiformis* tetrasporophyte samples were cultivated under conditions that allowed for robust growth such that a weekly biomass increase of up to 70% was observed for tissue samples used in this study (Supplementary Figure S1) (Dishon et al., 2023; Hargrave et al., 2024; Resetarits et al., 2024). The proteomic abundance of stress response proteins, such as superoxide dismutase (SOD), heat shock protein 40 (Hsp40), and the molecular chaperone DnaK were much lower than that of primary metabolic proteins such as phycobilisome component CpeB, RuBisCO small subunit RbcS, and ATP synthase alpha subunit AtpA (Supplementary Figure S2) (Kültz,

2005). Taken together, these physiological and molecular data suggest that the algal samples used in this study were experiencing low stress conditions. Sanger sequencing of the mitochondrial *cox2-3* spacer PCR amplicons confirmed that the specimens used in this study belonged to the *A. taxiformis* lineage 2 haplotypes (Nahor et al., 2022).

Replicate cDNA libraries were prepared and RNA-Seq was used to query global gene expression profiles (Supplementary Table S1; Supplementary Figure S3). A high degree of transcript overlap was observed among three biological replicates (Supplementary Figure S4). The bimodal distribution of transcript abundances, denoted as mean values for transcripts per million (TPM), was consistent across all three biological replicates (Figure 2A). Expectedly for a phototrophic organism, some of the highest abundance transcripts belonged to components of the photosynthetic complexes (Supplementary Data Sheet 1). The bromoform producing VBPO encoding gene *mbb1* was among the most abundant transcripts based on the average TPM values in the *A. taxiformis* transcriptomes (ranked 75, Supplementary Data Sheet 1). Other genes in the *mbb* locus, *mbb2-4*, were found at much lower abundance levels (*mbb2* ranked 20,361; *mbb3* ranked 4,002; *mbb4* ranked 1,679). These RNA-Seq-derived observations agreed with quantitative reverse transcription PCR (qRT-PCR) data wherein the abundance of the *mbb1* transcript, relative to the housekeeping actin gene, were much higher than that of *mbb2-4* (Figure 2B; Supplementary Table S2).

Does the mRNA abundance of the *mbb1* transcript translate to the abundance of the Mbb1 VBPO protein in *A. taxiformis* tissue? To investigate this question, proteomic analyses were conducted using the same *A. taxiformis* tissue samples that were used to generate the transcriptomic profiles (Supplementary Data Sheet 2). High confidence datasets were generated wherein two or more unique peptides were mapped to each protein sequence (Supplementary

Data Sheet 3). Among these, 80.3% peptides were common across all three biological replicates signifying fidelity of the proteomic inventory (Supplementary Figure S5). A search for posttranslational modifications revealed that 66 proteins were phosphorylated, 110 were methylated, and 250 were acetylated (Supplementary Figure S6). Across the three biological replicates, Mbb1 bore two modifications—Lys530 acetylation and Arg539 methylation (Supplementary Figure S7). Gene ontology (GO) functional enrichment analysis was conducted to classify genes and proteins (Supplementary Data Sheets 4, 5). Similar categories were found to be shared across the transcriptome and proteome datasets, suggesting consistent expression of gene and protein functional groups (Supplementary Figure S8).

Between the three biological replicates, the mean abundance of Mbb1 denoted it to be the eleventh most abundant protein in the entire *A. taxiformis* proteome (Figure 2C). The Mbb1 protein abundance rivals that of the photosynthesis-related RuBisCO small and large subunits (RbcS and RbcL, respectively) and phycobilisome complex members CpeA, CpeB, ApcA, and ApcB—in phototrophs, these are expectedly the most abundant proteins. Mbb4 was detected at far less abundance (rank ~900) while Mbb2 and Mbb3 were not detected, at all.

The high expression of the *mbb1* gene and the extraordinarily high abundance of the Mbb1 protein are not tied to molecular response to stress—the laboratory cultivated algae samples used here do not bear the molecular hallmarks of stress response (*vide supra*). To further investigate whether *mbb1* expression is responsive to stress experienced by the algae, *A. taxiformis* tissues were exposed to light and to heat stress using well established growth protocols (Dishon et al., 2023; Hargrave et al., 2024; Resetarits et al., 2024). Under these stress conditions, differential gene expression was queried by transcriptomic profiling, in addition to measurement of

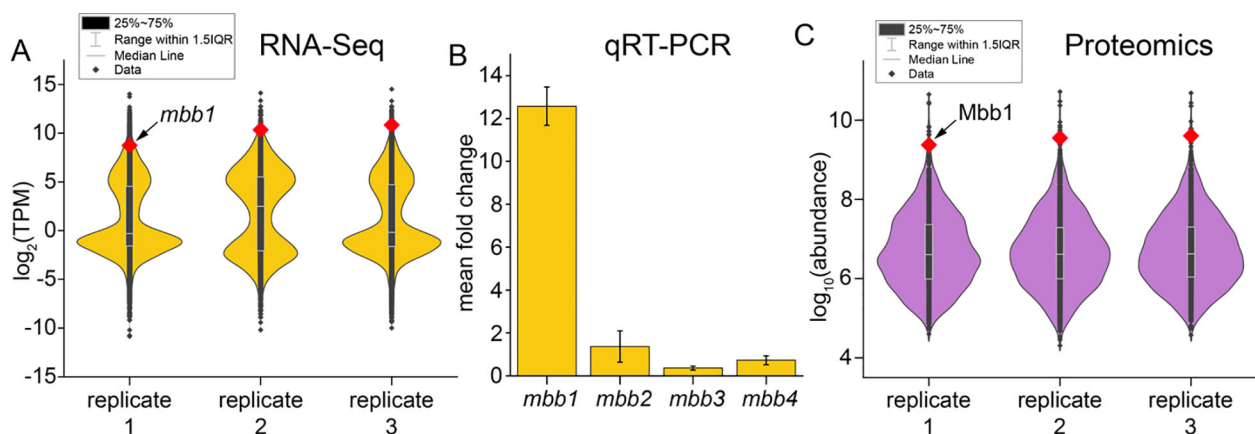


FIGURE 2

(A) Violin plots denoting normalized transcript abundance for the three biological replicates. Each transcript is represented as a data point (black diamond) with the *mbb1* transcript highlighted in red. Median line represents middle value of each dataset when all values are sorted from smallest to largest. The “25–75%” refers to the middle 50% of the dataset, specifically the range between the 25th percentile (lower quartile) and the 75th percentile (upper quartile). Range within 1.5 interquartile range (IQR) refers to the data range between 25th and 75th percentiles. Data points that fall below the lower limit (25th value – 1.5×IQR) or above the upper limit (75th value + 1.5×IQR) are considered outliers. (B) Steady-state mRNA abundance levels for *mbb1-4* genes as determined experimentally using RT-qPCR with the same total RNA sample that was used for RNA-Seq. Mean fold change represents mean ± standard deviation of fold changes for three replicates; fold change calculated relative to housekeeping actin encoding gene. (C) Violin plots depicting normalized protein abundances for the three replicate tissue samples. Abundance of each protein is represented as a data point with the Mbb1 protein abundance highlighted in red. Statistical representation is identical to that in panel (A).

photosynthetic efficiencies and hydrogen peroxide concentrations. Under elevated photosynthetically active radiation (PAR) exposure, photosynthetic efficiency significantly decreased in 10 and 60 min under 700 or 1,000 $\mu\text{mol photons m}^{-2} \text{s}^{-1}$, respectively (Supplementary Figure S9A). Hydrogen peroxide production increased, but the increase was only significant under the 1,000 $\mu\text{mol photons m}^{-2} \text{s}^{-1}$ treatment (Supplementary Figure S9B). Heat stress was assessed by exposing *A. taxiformis* to 21°C (normal) and at elevated temperatures of 26°C and 31°C for 30 min. Photosynthetic efficiency modestly decreased at the highest temperature (Supplementary Figure S9C), but a clear trend of significantly increased hydrogen peroxide concentration was observed at both temperatures (Supplementary Figure S9D).

Unexpected correlations of *mbb1* gene expression alterations were observed with other primary metabolism genes in response to light and heat stress (Figure 3). Under light stress conditions—which was accompanied by decrease in photosynthetic efficiency—we observed a decrease in *mbb1* gene expression together with a general decrease in the expression of other genes annotated to be involved in photosynthesis (Figures 3A, B). In contrast, under heat stress which resulted in minimal changes in photosynthetic efficiency, the *mbb1* gene expression was not significantly altered. Here, photosynthesis gene expression was also not significantly altered or was slightly increased (Figures 3C, D; Supplementary Figure S9C).

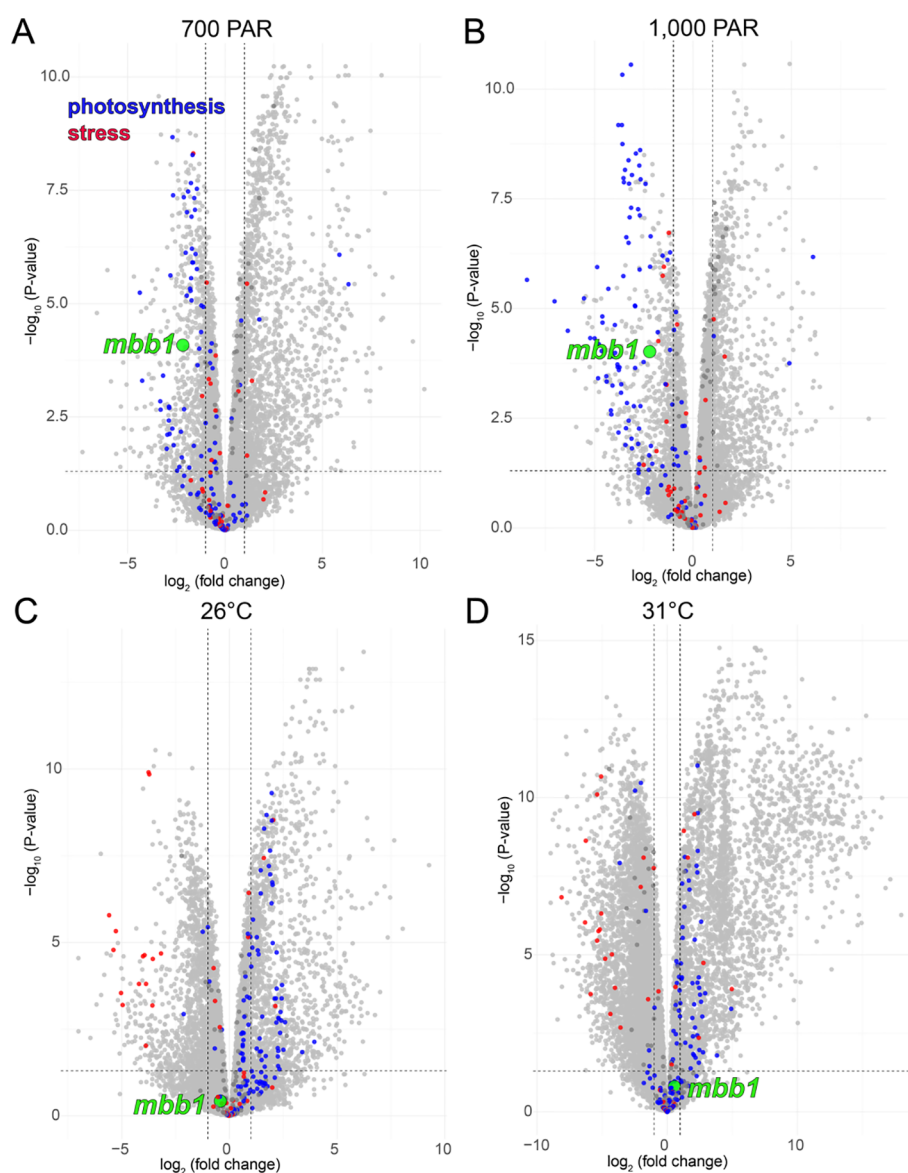


FIGURE 3

Volcano plots demonstrating differential gene expression in *A. taxiformis* under (A) 700 PAR light stress, (B) 1000 PAR light stress, (C) 26°C heat stress, and (D) 31°C heat stress as compared to physiological growth conditions of 25 PAR and 21°C. The node corresponding to *mbb1* is colored green, and nodes corresponding to genes annotated to be involved in photosynthesis and stress response are colored blue and red, respectively.

Discussion

Taken together, these data allow us to posit that under stressful conditions, differences in *mbb1* gene expression tracks with those of genes encoding proteins that are involved in photosynthesis. High light stress led to a general decrease in photosynthetic gene expression along with a concomitant depression in *mbb1* gene expression (Figures 3A, B). Taken together, 48 photosynthetic genes were downregulated at both 700 and 1000 $\mu\text{mol photons m}^{-2} \text{s}^{-1}$, while only 2 were upregulated in both conditions (Supplementary Data Sheet 6; Supplementary Figure S10). Of these 48 light-responsive downregulated photosynthetic genes, 41 encoded proteins related to those found in the light harvesting complexes (LHCs) (Engelken et al., 2012). In red algae, LHC proteins are generally pigment-binding, intrinsic membrane proteins that are part of the photosystem I light-harvesting antenna (You et al., 2023). The 41 LHC-constituting *A. taxiformis* proteins were aligned with structurally characterized orthologs from Rhodophyta and Cryptophyta photosystems and used to construct a phylogenetic tree (Supplementary Table S3; Supplementary Figure S11) (Pi et al., 2018; You et al., 2023; Si et al., 2024). The *A. taxiformis* proteins were highly sequence diverse, forming clades with different LHC families and reflecting the diverse functions of LHC proteins in light harvesting. While the structures of the orthologs are characterized, their functions are not. LHC proteins are thought to be important in improving photosynthetic efficiency and their sequence variability in different organisms reflects different ecological and physiological requirements (You et al., 2023). Thus, a downregulation of many LHC proteins under light stress is consistent with an overall decrease in photosynthetic efficiency that would help to prevent cellular damage. Simultaneously, expression of *mbb1* was decreased, as described above, which could point towards the involvement of Mbb1 in a primary physiological process related to photosynthesis which would align with its unusually high transcriptomic and proteomic abundance.

Asparagopsis, and other Rhodophytes possess dedicated gland cells—*corps en cerise*—to sequester the highly abundant halogenated metabolites (Paul et al., 2006b; Salgado et al., 2008; Paul and Pohnert, 2011). These physiological adaptations, in addition to the omics-driven observations described in this study allow us to propose that bromide oxidation and bromoform biosynthesis is likely not a specialized secondary metabolite production process alone—akin to how we conceptualize the biosynthesis of other halogenated natural products—but may have primary roles in *Asparagopsis* biology and physiology. Getting firm molecular evidence to support these hypotheses will require the development of forward and reverse genetic tools to manipulate *Asparagopsis* and pairing them with imaging-based techniques to query subcellular localization of bromoform biosynthetic enzymes such as Mbb1. With due acknowledgement that these tools are not yet in hand, findings described herein set the stage to query the broader ecological interconnections between seaweed biology, atmospheric chemistry, and contemporary directions in marine aquaculture.

Natural products and other specialized secondary metabolites produced by seaweeds have important roles in mediating mutualistic and antagonistic interspecies interactions in the marine environment

(Paul VJ. et al., 2006; Rasher et al., 2011; Andras et al., 2012). Bromoform has been postulated to serve a similar role; it was shown to inhibit the growth of epiphytic marine bacteria that may colonize seaweed surfaces (Paul et al., 2006a). Typically, specialized allelopathic molecules have potent bioactivities and are produced in small quantities using tightly regulated molecular processes. Bromoform production in *A. taxiformis* defies this characterization; it is constitutively produced and in remarkably high quantities using a VBPO that accumulates at very high abundance in the macroalgal tissue. The integrative multi-omics data presented herein now allows us to posit that rather than a specialized metabolite, bromoform could be a byproduct of a primary metabolic activity such as reactive oxygen species (ROS) detoxification by the VBPO Mbb1 that consumes hydrogen peroxide as a substrate. Halide oxidation is inextricably tied to ROS chemistry; akin to heme- and vanadium-dependent peroxidases, flavin-dependent halogenases also produce hypohalous acid upon halide oxidation while involving peroxide intermediates (Phintha et al., 2021). It is likely that the bromoform producing *A. taxiformis* VBPOs transcend halogenation biochemistry from secondary metabolite natural product biosynthetic pathways to primary metabolism.

Data availability statement

The transcriptomics data have been deposited to the NCBI with the BioProject accession number PRJNA1108735.

Author contributions

ZL: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Data curation, Software. SI: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. MH: Investigation, Methodology, Writing – review & editing, Resources. RS: Investigation, Writing – review & editing, Data curation, Formal Analysis, Visualization. LZ: Writing – review & editing, Resources. RX: Resources, Writing – review & editing, Formal Analysis. JS: Resources, Writing – review & editing, Conceptualization, Funding acquisition, Supervision. ES: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. VA: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing, Validation.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmars.2025.1664275/full#supplementary-material>

SUPPLEMENTARY DATA SHEET 6

Changes in gene expression upon *Asparagopsis* stress treatments.

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