
EXTRA VIEWS

Targeting prion protein interactions in cancer

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ABSTRACT. In recent years, prion protein (PrP^C) has been considered as a promising target molecule for cancer therapies, due its direct or indirect participation in tumor growth, metastasis, and resistance to cell death induced by chemotherapy. PrP^C functions as a scaffold protein, forming multiprotein complexes on the plasma membrane, which elicits distinct signaling pathways involved in diverse biological phenomena and could be modulated depending on the cell type, complex composition, and organization. In addition, PrP^C and its partners participate in self-renewal of embryonic, tissue-specific stem cells and cancer stem cells, which are suggested to be responsible for the origin, maintenance, relapse, and dissemination of tumors. Interference with protein–protein interaction has been recognized as an important therapeutic strategy in cancer; indeed, the possible interference in PrP^C engagement with specific partners is a novel strategy. Recently, our group successfully used that approach to interfere with the interaction between PrP^C and HSP-90/70 organizing protein (HOP, also known as stress-inducible protein 1 - STI1) to control the growth of human glioblastoma in animal models. Thus, PrP^C-organized multicomplexes have emerged as feasible candidates for anti-tumor therapy, warranting further exploration.

KEYWORDS. prion protein, ligand, cancer, therapy, peptide, cell signaling, cancer stem cell

ABBREVIATIONS. HSP, heat shock proteins; GBM, glioblastoma multiforme; BBB, blood brain barrier; CSC, cancer stem cell

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INTRODUCTION

Prion protein (PrP^C) has been studied thoroughly for decades, due its involvement in transmissible spongiform encephalopathies and conversion to infectious proteinaceous agents called prions.¹ Despite intense discussion of the function of the normal protein, convincing data from different groups indicate that PrP^C has important roles in the nervous and immune systems, regulating cellular processes such as cell death and survival, proliferation, and differentiation.^{2,3} PrP^C is a glycosylphosphatidylinositol-anchored protein, and many of its described functions depend on specific interactions with partners on the plasma membrane (receptors or extracellular molecules), such as laminin, vitronectin, NCAM, caveolin, and HSP-90/70 heat shock organizing protein, also known as stress-inducible protein 1 (HOP/STI1)⁴ (a list of these ligands can be found at <http://www.signaling-gateway.org/molecule/query?afcsid=A003935>), which can modulate cellular signaling cascades. Due to these properties, we have proposed that PrP^C plays a scaffolding role on the cell surface, recruiting diverse partners to organize signaling platforms.⁵ In this review we will discuss how these PrP^C-organized complexes can be involved with the tumoral processes and the strategy to target the engagement of PrP^C to specific ligands for therapeutic interventions.

PrP^C IN TUMOR BIOLOGY: PROCESSES AND MECHANISMS

The functions of PrP^C in tumor cells have been addressed, and evidence suggests that this protein is an important player in tumor biology. Several studies have demonstrated the importance of PrP^C in proliferation, apoptosis, invasion, metastasis, and drug resistance in different cancer types.⁶ In undifferentiated gastric tumors, a worse response to chemotherapy and lower patient survival rate are associated with higher PrP^C expression levels.⁷ Positive correlations between PrP^C expression and invasion, lymph node metastasis, and survival have also been confirmed in patients with gastric tumors, indicating that PrP^C is an independent

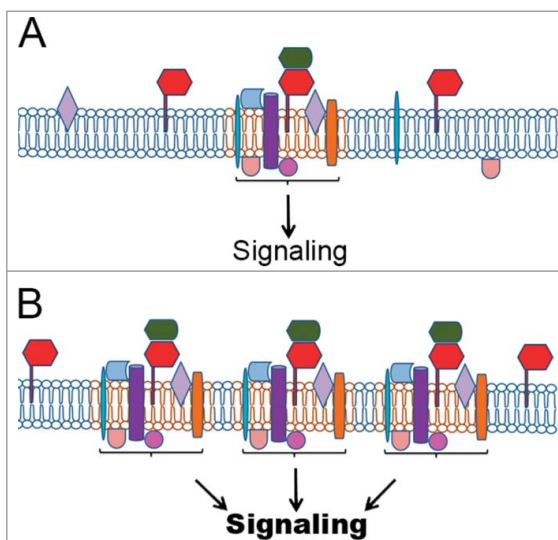
prognostic factor in these tumors.⁸ Proteomic evaluation of colorectal cancer cell lines identified PrP^C as a putative biomarker for adenoma–carcinoma progression, discriminating low-risk adenomas and normal colon from high-risk adenomas and colorectal cancer.⁹ Accordingly, a previous study showed that PrP^C expression could be used as a prognostic factor in patients with colorectal cancer.¹⁰ In breast cancer cell lines, resistance to TNF-induced cell death is associated with greater PrP^C expression.¹¹ Furthermore, lower sensitivity to neoadjuvant therapy has been observed in ER-negative breast tumors expressing higher (*vs.* lower) levels of PrP^C.¹²

Despite this evidence of PrP^C involvement in tumor biology, the mechanisms associated with these functions remain largely unexplored. In some cases, mechanistic approaches have shown that PrP^C inhibits Bax-induced apoptosis through Bax conformational change prevention, impairing mitochondrial translocation and cytochrome c release in breast cancer cells.¹³ In cell lines derived from colon tumors, PrP^C has been shown to regulate glucose transporter 1 expression through the activation of Fyn-HIF-2 α , increasing glucose uptake, glycolysis, and cell survival/proliferation.¹⁴ PrP^C activation of Fyn in breast cancer cells is also involved in epithelial–mesenchymal transition and results in a more aggressive phenotype.¹⁵ PrP^C silencing in glioma cell lines causes increased autophagy due to induction of LC3-II, an increase in Beclin 1, and simultaneous decreases in p62, Bcl-2, and the phosphorylation of 4E-BP1, a target of mTOR autophagy signaling.¹⁶ Interestingly, mTOR, a master player in cell signaling with pivotal role in tumorigenesis, is also involved in PrP^C-dependent neuronal differentiation and neuroprotection through activation of PI3K/Akt pathways.¹⁷

PrP^C ENGAGEMENT TO ITS LIGANDS: A RELIABLE TARGET FOR THERAPEUTIC INTERVENTION

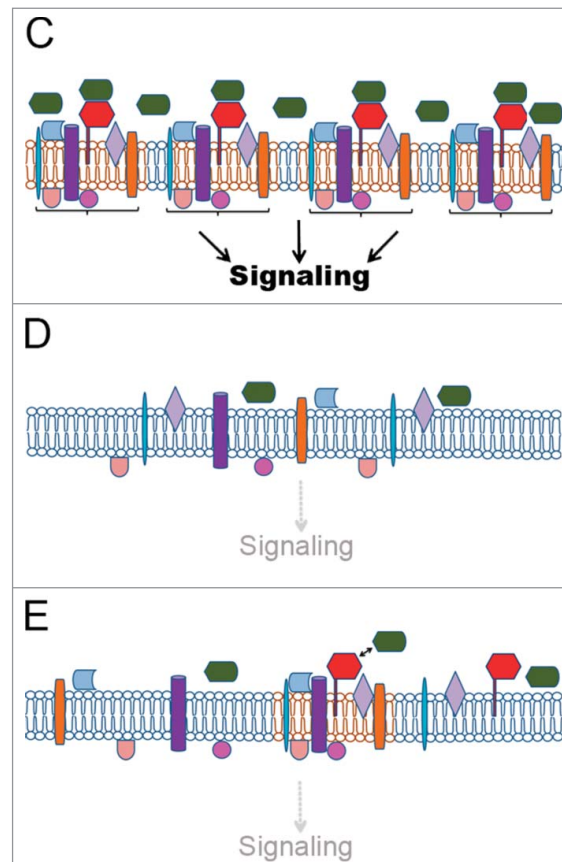
The phenotypes and mechanisms described for PrP^C in tumoral biology are in agreement

FIGURE 1. PrP^C in signaling platforms and their regulation. (A) PrP^C (red) interaction with a prime soluble ligand (green) modulates a group of multiple partners at the plasma membrane, organizing signaling platforms that regulate specific cellular functions. Other PrP^C partners include integral transmembrane proteins (purple, blue or orange) or peripheral membrane proteins, including cytoplasmic (beige or rose) or proteins attached to outer leaflet of the plasma membrane (light blue or light purple). Importantly, the prime ligand can be a membrane protein in the same domain of PrP^C localization (cis), in the membrane of another cell (trans), or on an extracellular vesicle surface. (B) The upregulation of PrP^C allows the formation of additional tissue-specific complexes with the ability to regulate events associated to tumorigenesis. (C) Higher levels of the prime ligand can also improve the number of PrP^C molecules able to organize signaling platforms, thereby inducing cancer processes. (D) Conversely, PrP^C downregulation or silencing disorganizes these complexes, impairing PrP^C-mediated signaling and, consequently, the tumoral process. (E) The inhibition of PrP^C interaction with the prime ligand impairs the organization of these platforms and serves as a target for cancer therapy, potentially with fewer side effects.



with its roles in multicomplex protein formation and organization of diverse signaling platforms.⁵ PrP^C priming can be induced after ligand

FIGURE 1. (Continued.)



binding, stimulating the acquisition of specific conformations and allowing additional interactions in the complex.⁵ The upregulation of PrP^C or its primary ligands in different tumor types may favor the assembly of tissue-specific complexes with different protein compositions. These complexes could alter the pattern of cellular signaling and, consequently, processes such as proliferation, adhesion, migration, differentiation, and drug resistance. Indeed, we believe that the identification of PrP^C ligands that coordinate these processes will help researchers focus on mechanisms that can be targeted for therapeutic interventions (as illustrated in Fig. 1).

In recent years, several independent studies have characterized novel PrP^C complexes modulating specific tumoral cell behaviors. In breast cancer, PrP^C engagement to multidrug resistance protein (P-gp) and caveolin is associated with drug resistance.¹⁸ In addition, the PrP^C-P-gp complex may include CD44, a membrane

receptor involved in cell adhesion, motility, and metastasis, promoting resistance to neoadjuvant therapy.¹⁹ However, the researchers proposing this association provided no clear explanation of the predominant nuclear localization of PrP^C observed in tumor samples.¹⁹

In pancreatic tumors and melanomas, an unconventional transmembrane form of PrP^C (pro-PrP) can interact with filamin A (a cytoplasmic protein involved in actin organization), perturbing cytoskeleton organization and conferring growth advantage.²⁰ Pro-PrP also confers a worse prognosis for pancreatic ductal adenocarcinomas.²¹ Thus, the identification of compounds that can interfere with this binding would be of great importance.

The PrP^C complex formed with 37-kDa/67 kDa laminin receptor (LRP/LR, also known as MGr1-AG/37LRP) is well understood, and many of its functions in nervous system cells have been examined.²² LRP/LR is involved in various tumorigenic processes, and the upregulation of PrP^C and LRP/LR in gastric tumors predicts poor prognosis.⁸ In this case, therapeutic interventions using antibodies to MGr1-AG/37LRP have been addressed.²³

TARGETING THE PrP^C-HOP/STI1 COMPLEX IN GLIOBLASTOMA: PROOF OF CONCEPT

The interaction of PrP^C with HOP/STI1 is one of the best-characterized PrP^C complexes and it has emerged as one of the most important in tumorigenesis. PrP^C-HOP/STI1 interaction was first glimpsed in 1997, when we characterized a novel PrP^C partner using complementary hydrophathy theory;²⁴ subsequently, we identified this ligand as the co-chaperone HOP/STI1²⁵ and demonstrated the involvement of the complex in neuroprotection, neurogenesis, and astrocyte proliferation, among others.⁴ HOP/STI1 was initially identified as a co-chaperone that cooperates with HSP70 and HSP90 to assist in the folding and stability of client proteins, with a key function in cellular homeostasis.²⁶ Since that time, many functions in addition to its role as a co-chaperone and PrP^C ligand have been attributed to this protein.²⁶

HOP/STI1 expression is increased in tumor cell lines and tumoral tissues from the breast, colon, pancreas, liver, and ovary; in most of these tumors, greater HOP/STI1 expression is associated with more aggressive disease, poorer survival, and drug therapy resistance. Cytoplasmic HOP/STI1 can modulate migration and invasion due to its interaction with actin and tubulin at the cytoskeleton, as well as modulation of the expression of matrix metalloprotease 2 (see review by Baidur-Hudson et al.²⁶). Extracellular HOP/STI1 was identified in conditioned media from different cell lines, and significantly higher levels of the protein are present in serum from patients with ovarian cancer.²⁶ In this case, the secreted form of HOP/STI1 binds to ALK2 and activates the SMAD signaling pathway, promoting cell proliferation.²⁶ More recently, our group demonstrated that HOP/STI1 is secreted in the membranes of exosome-like extracellular vesicles.²⁷ Together, these data suggest the importance of HOP/STI1 as a prognostic biomarker in some tumors and as a target for therapeutic strategies. Furthermore, because the secreted form of HOP/STI1 may have different ligands at the cell surface, its use as a target for therapy must focus on specific interactions related to tumoral processes.

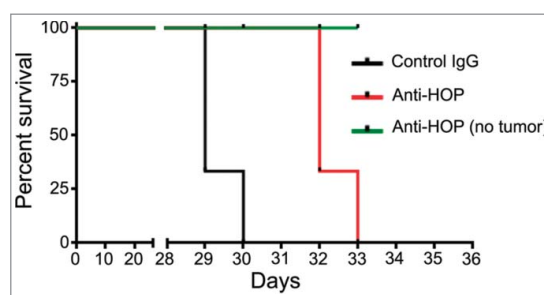
In 2014, our group demonstrated²⁸ that HOP/STI1 and PrP^C are upregulated in human glioblastoma (GBM), which was confirmed by sample analysis from the TCGA consortium. PrP^C and HOP/STI1 expression levels were correlated with higher proliferation rates and poorer clinical outcome. Additionally, data demonstrated that the engagement of HOP/STI1 to PrP^C promoted proliferation and tumor growth in GBM cell lines, and that total or partial PrP^C ablation promoted tumor growth inhibition and improved survival of mice bearing GBM xenografts. To address the importance of PrP^C-HOP/STI1 in GBM biology, we inhibited formation of the complex with a synthetic peptide corresponding to the HOP/STI1 binding site to PrP^C (named HOP/STI1₂₃₀₋₂₄₅). Alone, this peptide had no effect on proliferation; however, it competed with full-length HOP/STI1, displacing it from PrP^C at the cell surface. The HOP/STI1₂₃₀₋₂₄₅ peptide abolished proliferation induced by HOP/STI1-PrP^C in GBM cell

lines. The delivery of HOP/STII_{230–245} into orthotopic xenografts hindered cell proliferation and induced apoptosis, leading to tumor growth inhibition and increased animal survival.²⁸ Remarkably, in addition to its previously demonstrated neuroprotective function and positive effect on memory formation,^{29,30} the HOP/STII_{230–245} peptide was able to prevent cognitive decline caused by tumor growth.²⁸ Indeed, due its antitumoral and neuroprotective functions, the HOP/STII_{230–245} peptide is a promising candidate for testing in brain tumor treatment alone or combined with other conventional therapies.

The use of peptides for the treatment of wide range of diseases has increased recently. Many features favor the use of peptides, rather than small-molecule (<500 Da) or large-molecule (>5000 Da) biological drugs (e.g., monoclonal antibodies or recombinant proteins). High specificity is perhaps the most important feature of peptides, as they can mimic structural domains responsible for protein–protein interactions, competing for their binding and activation. This property reduces the probability of adverse toxic effects, and interference in drug combinations is insignificant.³¹ The disadvantages of peptides as drug candidates are being investigated intensively, and points for both oral bioavailability and half-lives of these molecules in the organism. In the context of brain diseases, the blood–brain barrier (BBB) is an additional drug obstacle. Nevertheless, evidence of partial BBB disruption in GBM indicates that brain tumor cells could be left unprotected, increasing their vulnerability to drugs, including peptides.³¹ Modifications of the chemical structure of peptides,³² in particular the HOP/STII_{230–245} peptide discussed here, such as replacement of L-amino acids by unnatural D-amino acids, cyclization, and peptidomimetics, could be performed to overcome these challenging conditions and increase peptide stability and half-life in the organism; the achievement of such goals would allow systemic administration and improve tumoral diffusion.

Considering large-molecule biological drugs, the use of antibodies could be a feasible

FIGURE 2. Disruption of PrP^C-HOP/STII interaction using anti-HOP antibodies in xenografts increases the survival of animals with glioblastoma. Preliminary results indicate that disruption of the PrP^C-HOP/STII complex using a specific antibody increases animal survival. Briefly, nude mice were injected orthotopically with a U87 cell line (5×10^5 cells) and treated with HOP/STII-antibody²⁵ for 28 d (240 ng/day) using osmotic micropumps. The complete methodology is described in Lopes et al.²⁸ Kaplan–Meier survival curve of mice implanted with U87 cells. Log-rank $p = 0.0023$, $n = 3$ mice per group.



approach to target the interaction of extracellular HOP/STII and PrP^C in tumors. In some studies described here, antibodies against PrP^C or HOP/STII successfully inhibited tumor growth *in vivo* in diverse organs other than the brain. A preliminary experiment using a HOP/STII antibody²⁵ has been performed. As indicated in **Figure 2**, intra-tumor delivery of anti-HOP/STII into orthotopic xenografts of GBM cells slightly improved animal survival.

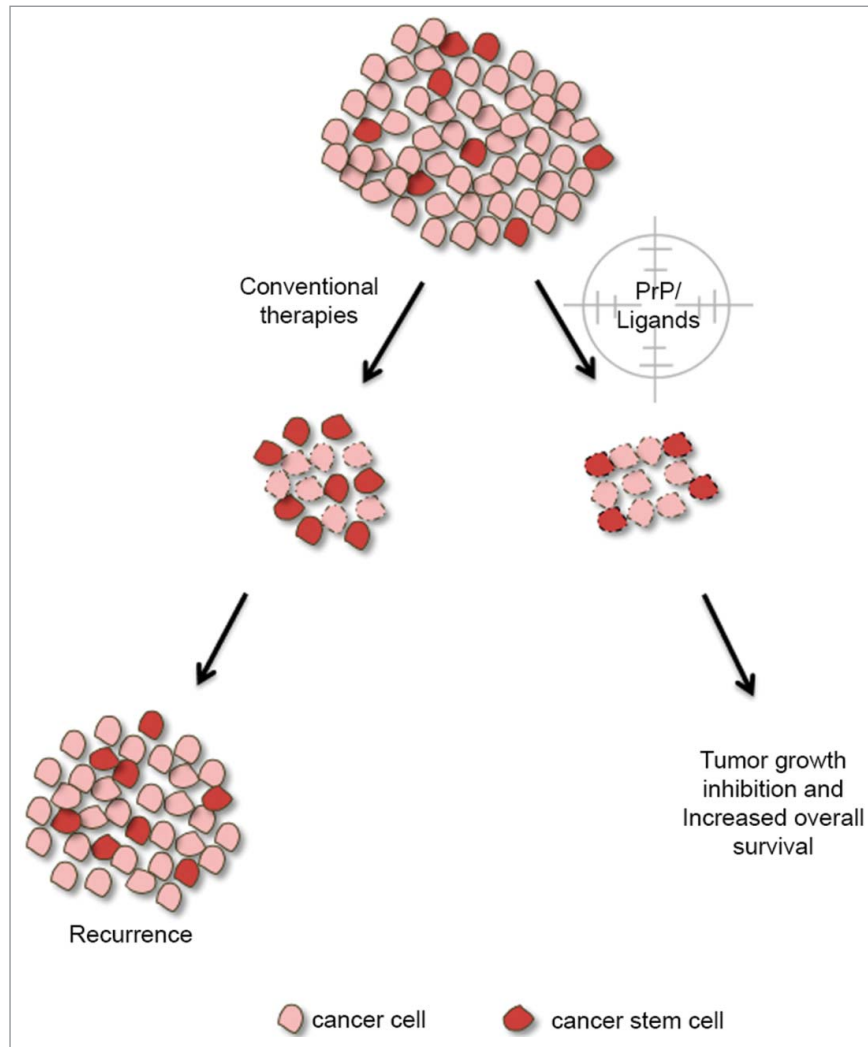
Importantly, however, the blockage of both PrP^C and HOP/STII could be deleterious. Long-term,³³ but not short-term,²⁹ intracranial infusion of antibodies against PrP^C, in particular those directed to the globular domain of PrP^C, can be neurotoxic.³³ The short-term use of polyclonal antibodies against full-length HOP/STII or the HOP/STII_{230–245} peptide has not caused brain toxicity.²⁹ However, we demonstrated that the constitutive deletion of HOP/STII is embryonically lethal, and heterozygous animals expressing half-levels of the protein presented higher sensitivity to brain injury,³⁴ indicating the importance of this protein also in adults. Furthermore, maternally derived

HOP/STI1 autoantibodies were detected in mothers of children with autism, suggesting that neurodevelopment is impaired by these autoantibodies.³⁵ Indeed, interference with PrP^C-HOP/STI1 interaction in tumors, particularly those in the central nervous system (CNS), using peptides that compete for their engagement should lead to better results than the use of antibodies against these molecules.

TARGETING CANCER STEM CELLS BY BLOCKING PrP^C INTERACTIONS

One of the most-studied recent themes in oncology is related to features that govern tumor origin, and cancer stem cells (CSCs) have emerged as a pivotal component able to initiate and maintain tumors.³⁶ CSCs have been functionally defined as a small

FIGURE 3. Targeting of PrP^C and its partners in CSCs for cancer therapy. Conventional therapy targets tumor cells by destroying them or decreasing their proliferation. Tumor growth is governed by multiple cellular mechanisms in which PrP^C plays a role. The progression of tumor development is related to the presence of cancer stem cells that have a pivotal role in cell resistance, culminating in tumor recurrence. Indeed, PrP^C and its ligands in cancer stem cells could also be targeted, suggesting a promising approach for novel cancer therapies. Cells with dotted lines represent cells undergoing cell death.



subpopulation of cells capable of self-renewal, differentiate into all cell types in a determined tumor, and tumor propagation when xenotransplanted into immunodeficient mice.³⁶ An important characteristic of CSCs is their resistance to conventional therapies, which has been implicated in cancer recurrence and has made these cells a key target for therapy.³⁶ Although the origin of CSCs remains unidentified, these cells share key properties with normal tissue-resident stem cells and are thought to arise through malignant transformation events in normal stem cells.³⁶ Considering the emerging functions of PrP^C in stemness, fundamental issues that must be addressed include its interaction with a prime ligand, the role of the complex in CSCs, and its possible use as a therapeutic target in cancer (**Fig. 3**).^{37,38} PrP^C engages CD44, a stem cell marker, and their expression is correlated with resistance to chemotherapy in breast cancer cell lines.¹⁹ Moreover, the CD44⁺ PrP^C⁺ subpopulation of colorectal tumor cells has CSCs properties, including tumorigenesis and metastasis capacities,³⁹ indicating that PrP^C contributes to tumor maintenance by modulating CSCs behaviors. The contribution of the PrP^C-HOP/STI1 complex to CSCs self-renewal remains to be explored. Nevertheless, the HOP/STI1-PrP^C complex is known to play an important role in self-renewal and proliferation of neural stem cells.⁴⁰

Recently, Tomasetti and Vogelstein⁴¹ reported a positive correlation between cancer risk and the number of mitotic divisions of stem cells in different tissues, strengthening the importance of the participation of tissue-resident stem cells in tissue homeostasis or as a substrate that gives rise to tumors. In this scenario, tumors in which PrP^C or HOP/STI1 has been described to play a significant role, such as colorectal, pancreatic, and hepatocellular tumors (discussed above), are related to tissues with more total stem cell divisions during their lifespan. These authors⁴¹ documented a much smaller number of CSCs divisions in GBMs than in the tumors discussed herein; however, PrP^C expression is known to be more abundant in cells from brain tissue than in those from

other tissues, which may contribute to the importance of PrP^C-HOP/STI1 in brain stem cells.²

In conclusion, the mechanisms related to the roles of PrP^C in cancer biology need to be better explored. Its predicted role as a scaffold protein participating in the organization of membrane platforms indicates that specific partners within tumor cells, extracellular matrix, and soluble factors secreted from tumor cells or the tumor microenvironment must be considered as good candidates for therapeutic interventions. Strikingly, our work exploring the engagement of PrP^C with the secreted form of HOP/STI1 allows the development of strategies to target this complex specifically and control tumor growth. The success of this approach for other tumors and PrP^C ligands should be evaluated to direct new discoveries in cancer biology.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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