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The multiple functions of the co-chaperone stress inducible protein 1

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ABSTRACT

Stress inducible protein 1 (STI1) is a co-chaperone acting with Hsp70 and Hsp90 for the correct client proteins' folding and therefore for the maintenance of cellular homeostasis. Besides being expressed in the cytosol, STI1 can also be found both in the cell membrane and the extracellular medium playing several relevant roles in the central nervous system (CNS) and tumor microenvironment. During CNS development, in association with cellular prion protein (PrP^c), STI1 regulates crucial events such as neuroprotection, neuritogenesis, astrocyte differentiation and survival. In cancer, STI1 is involved with tumor growth and invasion, is undoubtedly a pro-tumor factor, being considered as a biomarker and possibly therapeutic target for several malignancies. In this review, we discuss current knowledge and new findings on STI1 function as well as its role in tissue homeostasis, CNS and tumor progression.

1. Introduction

The stress inducible protein 1 (STI1; HOP/STI1) or stress inducible phosphoprotein 1 (STIP1), also known as HSP70/HSP90 organizing protein (HOP), is a co-chaperone acting with Hsp70 and Hsp90 chaperones for the correct client proteins' folding, being essential for the maintenance of cellular homeostasis. STI1 interacts with other proteins due to its structure composed of three tetratricopeptide repeat TPR domains (TPR1, TPR2A and TPR2B) and two domains with aspartate

and proline residues (DP1 and DP2). The TRP domains are the ones which allow STI1 interactions with HSP70/HSP90 complex members involved with regulation of RNA splicing, transcription, protein folding and cell signaling mechanisms (reviewed by [1,2]).

STI1 is expressed in the cytosol, Golgi, cell membrane or nuclei of cells in most of the tissues [3–6]. Furthermore, many cells can also secrete STI1. Glial cells, for example, can secrete STI1 as a neurotrophic ligand, triggering prion protein (PrP^c) signaling in neurons [7]. In addition, STI1/HSP70/HSP90 complex is associated not only with

Abbreviations: ALK2, activin A receptor-type II-like kinase 2; $\alpha 7$ nAChR, $\alpha 7$ nicotinic acetylcholine receptor; RCC, cell carcinoma; PrP^c, cellular prion protein; CNS, central nervous system; CCC, Cholangiocarcinoma; ER, endoplasmic reticulum; EMT, epithelial-to-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; ER, estrogen receptor; ECM, extracellular matrix; EVs, extracellular vesicles; GBM, glioblastoma; GNPs, gold nanoparticles; GRK2, G-protein-receptor kinase 2; HCC, hepatocellular carcinoma; HOP, HSP70/HSP90 organizing protein; LSD1, lysine-specific demethylase 1; MAPKs, Erk1/2, mitogen-activated protein kinase; MVBs, multivesicular bodies; PTC, papillary thyroid carcinoma; PAMP, pathogen-associated molecular patterns; PM, plasma membrane; PLA, Proximity ligation assay; STAT3, signal transducer and activator of transcription 3; SREs, skeletal-related events; A β Os, soluble amyloid- β oligomers; STI1, HOP/STI1, Stress inducible protein 1; TNM, tumor-node-metastasis; mGluR1/5, Type I metabotropic glutamate receptors; TKR, tyrosine kinase receptor.

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cellular stress [3] but also with tissue homeostasis by playing a role in protein clearance, as amyloid-like proteins in neurodegenerative diseases [2].

Besides its involvement in neurodegeneration, several studies have been pointed STI1 as a cancer biomarker, both for diseases' diagnosis and prognosis. High expression of STI1 has been observed in diverse cancer types, such as carcinomas, gastric, oral, colorectal cancer and brain tumors [8–11]. In fact, overexpression of STI1 has been correlated with tumor progression [12–18], which suggests that it could be used as a biomarker for better diagnosis in many diseases. Further, the knock-down of STI1 in different cancer cells interferes with several signaling pathways resulting in a decreased tumor cell proliferation and migration [15,19,20]. Thus, in the context of tumor biology, STI1 rises as an important factor involved with tumorigenesis.

In this review, we focus on STI1 function in tissue homeostasis, neurogenesis and cancer. We will summarize STI1 cellular expression patterns and the ascribed STI1 functions obtained from several different study models, especially those employing genetic manipulation (e.g. knockout mice, interference RNA or overexpression). Some of these STI1 functions have been studied in the context of neurodegeneration, particularly Parkinson's and Alzheimer's diseases, and have been covered by other excellent reviews [1,2]. Here, we will highlight STI1 functions in general cellular processes and physiology, particularly regarding its emerging cytokine-like function in CNS development and cancer.

2. Co-chaperones and STI1 functions

Chaperones are molecular complexes responsible for the acquisition of the correct tertiary structure, activation, regulation and stabilization of specific proteins, therefore called 'clients' [21,22]. They have a fundamental role in most cellular processes, such as cell cycle control, cell survival, hormone signaling, signal transduction and response to cellular stress [23,24]. Hence, chaperones are key structures for maintaining cellular homeostasis. To exert its precise function, they require a machinery of associated molecules that modulate their activity called co-chaperones, forming a dynamic multiprotein complex. These molecules can promote direct and indirect influence on clients folding [25]. They can also act by recruiting specific client proteins, altering their conformational dynamics or acting lately in the last stages of client maturation [26–29]. As chaperones, co-chaperones play a determinant role over several cellular processes and not only regulate chaperones activity but are also regulated by them [30,31].

One of the largest representatives of these proteins is the co-chaperone STI1. This co-chaperone is present in multiple fungal, plants and animal species and families, from yeast to mammals, and is important for supporting the transference of client proteins from chaperone Hsp70 to Hsp90 [32]. Structurally, STI1 is composed of three tetratricopeptide repeat (TPR) domains and two aspartate and proline rich domains (DP domains), which are located on the C-terminal of the TPR1 and TPR2B domains (DP1 and DP2 respectively) [33].

Although some protein remodeling functions of the HSP90 and HSP70 chaperones are independent, others may depend on their interaction with each other and with other chaperones. This interaction in turn is mediated by presence of co-chaperones that have the TRP domain in their structures, such as STI1, which when interacting with Hsp90 mutually modify both of its conformational dynamics [34–36].

TPR domains are directly involved in binding to Hsp70/Hsp90 C-terminal stretches. Regarding Hsp70, it was observed *in vivo* that the STI1 domains most related to its binding are TPR1 and TPR2B, while the TPR2A and TPR2B are mainly related to the co-chaperone interaction with Hsp90. Together, these domains are considered the key structures

which mediate the formation of a ternary Hsp90-STI1-Hsp70. These domains are important for inhibiting Hsp90 ATPase activity in a non-competitive way, preventing the N-terminal dimerization reaction, promoting its interaction with the intermediate domain and hence allowing the complex formation and a client protein transfer [33,37]. Binding with STI1 also stabilizes specific regions in all three domains of the Hsp90 molecule and decreases the dissociation of these dimers (Fig. 1) [36,38].

This relationship, however, proved to be much more complex than used to be believed. It was seen that the affinity between Hsp70/STI1, as well as between Hsp90/STI1 are modulated by multiple factors, such as the presence of Hsp90 itself [39], Cdc37 [40] STI1 phosphorylation and structural rearrangements [41] and other co-chaperones Aha1, Cpr6 and Sba1 that modulate Hsp90 conformation [42,43]. For more details on STI1-Hsp interactions specifically, extensive reviews are available [34–36].

Many groups have tried to elucidate STI1 physiological and developmental role using several different study models. In yeasts, STI1 was found to act as a regulator of post-translational importation of proteins into the mitochondria. Furthermore, its deletion causes an alteration in the morphology of this organelle, and also the instability of several mitochondrial proteins [44,45]. In plants, STI1 seems to have important functions in rice innate immunity, helping in the transportation of pathogen-associated molecular patterns (PAMP) receptors from the endoplasmic reticulum (ER) to the plasma membrane and also in signaling in the defensome (a protein complex that plays a role in PAMP-triggered immunity in rice) at the plasma membrane [46]. Another well-studied function of STI1 was related to the steroid hormones receptors activation cascade, where STI1 facilitates the transference of these receptors to Hsp90 chaperone and stabilizes the complexes of Hsp70/90 and these receptors [47,48]. Furthermore, STI1 activity can be regulated by many signaling mechanisms, such as phosphorylation [49] or even by other proteins, as Cpr6, which is also a TPR containing protein and can revert STI1 effect over Hsp90 [26].

STI1 gene knockout is lethal during mouse embryonic development (between E9.5 and E10.5) due to neural tube defects and limb buds [3], suggesting that this protein is also essential in the development and maintenance of the nervous system.

3. STI1 in central nervous system (CNS)

In 2002, Zanata and co-workers [5] identified STI1 as a previously described PrP^c-binding protein predicted by complementary hydrophathy concept [50]. These *in vitro* studies first demonstrated the presence of STI1 on the cell surface, a distinct cellular compartment from its previously described location, as a cytoplasmic component of the macromolecular Hsp70-Hsp90 chaperone complex. STI1 binding to PrP^c in this context was capable of inducing neuroprotective signals that rescues neurons from apoptosis [5,51]. Also, the demonstration of this molecule as a novel PrP^c ligand opened the doors for further understanding the biological functions of PrP^c and its ligands.

STI1 interaction with PrP^c was then demonstrated to be important for a plethora of functions in the developing and adult CNS. In retinal and hippocampal cultured neurons, it was shown that STI1 binding to PrP^c induced neuroprotection through cAMP-dependent protein kinase A (PKA) [5,51] and neuritogenesis *via* mitogen-activated protein kinase (MAPKs, Erk1/2) [52]. Furthermore, the Erk1/2-induced neuritogenesis was dependent of STI1-PrP^c complex internalization *via* clathrin, but not the PKA activation [53]. As PrP^c is not a classical tyrosine kinase receptor (TKR) or G protein-coupled receptor, it activates signaling pathways by acting as a scavenger and forming different multiprotein functional complexes at the cell surface. For neuroprotection and

Fig. 1. Hsp90 / Hsp70 chaperones interaction mediated by co-chaperone STI1. TPR2A and TPR2B domains of STI1 bind to the C-terminal of Hsp90, while the TRP1 domain physically interacts with Hsp70, bringing both together on a ternary Hsp90-STI1-Hsp70 complex and facilitating the transferring process of client proteins. This process is modulated by the presence of other co-chaperones, such as Aha1, Cpr6, Sba1 and Cdc37, which interfere in the structural conformation of Hsp90 and modify its ATPase activity.

neurogenesis, PrP^c forms a complex with $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) and, upon STI1 binding, it triggers an increase in intracellular Ca^{2+} levels [54]. In this context, the induction of neurogenesis is achieved by the orchestration of an even larger PrP^c-based protein complex involving other ligands: laminin- $\gamma 1$ chain and Type I metabotropic glutamate receptors (mGluR1/5) [55]. Neuroprotection, in this case, is also achieved by $\alpha 7$ nAChR-driven activation of autophagic flux that depends on PrP^c expression [56]. Finally, all these neurotrophic and neuroprotective events orchestrated by STI1-PrP^c interaction were dependent on increased protein synthesis mediated by PI3K/AKT/mTOR activation [57] (Fig. 2).

The description of all these neuronal events induced by STI1-PrP^c interaction reveals an essential question regarding the source of STI1 for signaling in PrP^c-expressing neurons. Indeed, cultured glial cells express high levels of STI1, besides PrP^c, in their cell surface and are capable of secreting them in their conditioned media [7].

Astrocytic-derived STI1 was capable to modulate neuronal survival and differentiation [7]. Independently of PrP^c expression, astrocytic STI1 induced neuronal survival. Nevertheless, astrocytic PrP^c expression was crucial for the complete induction of neurogenesis, despite dependent of two other phenomena: (1) astrocytic PrP^c interaction with neuronal N-CAM and (2) neuronal PrP^c interaction with laminin- $\gamma 1$ chain [7,55]. This second phenomenon is disturbed in PrP^c null astrocytes as their extracellular matrix (ECM) is composed of punctual and not fibrillar laminin [7].

During astrocytic development, PrP^c expression is important not only

for the correct deposition of the ECM but also interacting with STI1 to control astrocyte differentiation and survival, via MAPK (Erk1/2) and PKA signaling, respectively [58,59]. In glial cultures, STI1 is still capable of blocking astrocyte proliferation via PKC in a PrP^c-independent manner (Fig. 2) [58,59]. During *in vivo* retina development, STI1 also reduced proliferation without PrP^c interaction [60]. In this sense, this study suggests that STI1 can also signal in the CNS in a PrP^c-independent manner, through a still unknown receptor.

STI1 is largely involved in astrocyte biology. To better understand astrocyte response to cellular stress, Soares and collaborators studied the correlation of STI1 and the DNA damage stress mediated by γ -irradiation. It was shown *in vitro* that after irradiation, STI1 accumulates in the astrocyte nucleus and that STI1 haploinsufficiency reduces cell survival [61]. Another interesting finding is the identification of the protein inhibitor of activated STAT (PIAS1) as a factor specifically involved in STI1 nuclear retention that directly interacts with STI1, which means that it can act as a small ubiquitin-like modifier (SUMO) E3 ligase for STI1 (Fig. 2) [61]. Besides, it was demonstrated by microarray analysis that PIAS1, a nuclear protein that is critical for DNA damage response (DDR) regulation [62], is present in high levels in glioblastoma cells (GBM) in comparison with non-neoplastic tissue, making a correlation with enhanced STI1 in the nucleus of these cells [61,63,64]. These results seem to be important since GBM is very resistant to radiotherapy [62], but further studies are needed to highlight this novel mechanism.

The observation of a secreted form of STI1 suggests an unconventional secretion mechanism, due to the lack of a consensus secretory

Fig. 2. STI1 role in neurons and astrocytes. STI1 is highly expressed by several cell types in the CNS, such as neurons and astrocytes. In neurons, STI1 binds to PrP^c inducing neuritogenesis through MAPK (Erk1/2) signaling *via* clathrin. Whereas, STI1 induces neuroprotection by the cAMP-dependent protein kinase A. In addition, PrP^c -α7nAChR-STI1 complex triggers an increase in intracellular Ca²⁺ levels and promotes neuritogenesis and neuroprotection. Besides, STI1 can be secreted by astrocytes through extracellular vesicles (EVs) of different sizes (20–50, 100–200 and 300–400 nm) with exosome morphology. During astrocytic development, PrP^c plays an important role not only for the correct deposition of ECMs, but also by interacting with STI1 to induce astrocyte differentiation and survival, *via* MAPK (Erk1/2) and PKA signaling, respectively. STI1 is still capable of blocking astrocyte proliferation *via* PKC in a PrP^c-independent manner. In astrocytes, the protein inhibitor of activated STAT (PIAS1) withholds STI1 in the nucleus by acting as a small ubiquitin-like modifier (SUMO) E3 ligase for STI1, inhibiting the target genes.

signal peptide in its structure. Indeed, it was initially described that STI1 secretion occurs through extracellular vesicles (EVs) of different sizes (20–50, 100–200 and 300–400 nm) with exosomal morphology [65]. These EVs are derived from multivesicular bodies (MVBs) and have STI1 located in their outer leaflet [65]. This unconventional secretion structure was also important for enhancing STI1-PrP^c signaling by the interaction between EVs and other components of the neuronal cellular membrane [65]. Interestingly, another extracellular source of STI1, not associated with EVs, was also observed by Hajj and co-authors; however, the route used by this STI1 to reach the extracellular milieu remains unknown.

STI1, as an extracellular soluble molecule or a plasma membrane (PM)-associated protein, was shown to be important for complex neurobiological processes, as short-term memory formation and long-term memory consolidation [66]. Recently, using a neuronal cell line lacking STI1 and a mouse line with a hypomorphic *Stip1* allele, it was shown that decreased levels of STI1 can disturb the stability of Hsp70/Hsp90 client proteins leading to hippocampal neurodegeneration and volume reduction, both age-dependent, which culminates in spatial memory deficit [67]. STI1 is also important for response to ischemic stroke as STI1 heterozygous mice exhibits decrease survival after 60 min unilateral ischemia (by middle cerebral artery

Table 1

Summary table of STI1 role in cancer.

Type of cancer	Increased STI1 expression	STI1 suggested as a biomarker	STI1 effect/correlation	References
Oral squamous cell carcinoma	✓		- Expression increases during tumor progression.	[12,82]
Esophageal squamous cell carcinoma	✓	✓	- Patients present higher serum levels of autoantibodies against STI1.	[83,84,85]
Papillary thyroid carcinoma	✓	✓	- Related with tumor progression and poor prognosis.	[86,87]
Cholangio carcinoma	✓	✓	- Increased expression in a cohort of 60 patients.	[88]
Hepatocellular carcinoma (HCC)	✓	✓	- Associated with worse overall survival and recurrence-free survival of patients; - Correlated both with HCC staging and patient prognosis; - Levels in patients' serum higher; - Higher expression in human metastatic tissues and serum samples; - - Related to metastasis of residual HCC after radiofrequency ablation; - <i>In vivo</i> : depletion of STI1 strongly decreased tumor growth, and intrahepatic and lung metastasis; - Activates Wnt/ β -catenin pathway, promoting growth and migration of cells.	[8,20,88,89,90]
Gastric cancer	✓	✓	- Associated with tumor progression and poor prognosis; - High levels in patients' serum; - Induces tumor cell proliferation via PLC γ 1-ERK1/2 pathway and apoptosis inhibition by caspase-3, -9 and BCL2 activities; - Increases the migration and invasion of cancer cells, induces epithelial-to-mesenchymal transition and promotes lung metastasis with involvement of Wnt/ β -catenin pathway; - Suggested as a prognostic factor.	[13,91]
Colorectal cancer	✓		- Correlated with advanced tumor-node-metastasis stage, being a marker of worse prognosis; - An independent prognostic factor for overall and disease-free survival.	[9,92]
Ovarian cancer	✓	✓	- Patients present high serum levels of anti-STI1 antibodies; - Correlated with tumor stage and grade, and to a poor overall and progression-free survival of patients; - <i>In vivo</i> : silencing of STI1 in cancer cells resulted in inhibition of tumor growth; - Acts through the ALK2 receptor, activating the Smad-ID3 signaling, resulting in proliferation of tumor cells; - Suggested as a potential prognostic marker.	[14,15,16,93,94,95,101]
Lung adenocarcinoma			- High levels associated with proliferation and migration of tumor cells, and regulation of epithelial-to-mesenchymal transition proteins, both with involvement of the JAK2/STAT3 signaling pathway.	[97]
Melanoma			- Induces proliferation, migration and invasiveness of cancer cells through the JAK2/STAT3 pathway.	[98]
Breast cancer	✓		- High level of STI1 in breast cancer tissues positive for the oncogene HER-2.	[102]
Renal cell carcinoma	✓		- High expression associated with an advanced stage of disease; - - STI1 silencing induces a reduction in proliferation and migration/invasion.	[19]
Glioma	✓		- In glioblastomas (GBM), STI1 and PrP ^c are highly expressed, contributing to tumor aggressiveness and poor outcome of patients; - <i>In vivo</i> : Interference with STI1/PrP ^c binding in tumor site or PrP ^c knockdown in GBM cells reduce tumor growth; - <i>In vivo</i> : overall expression of STI1 increases over time, and infiltrating microglia, macrophages and lymphocytes have their STI1 expression upregulate along with tumor development; - <i>In vivo</i> : Wnt3a-treated GBM cells generate large tumor mass with aggressive features and also present a prominent microglia infiltration; - GBM cells treated with Wnt3a induce microglia to acquire a pro-tumor M2-like phenotype, increasing the expression of STI1, Arginase-1, Interleukin-10 and Wnt3a; - Human GBM cells synthesize and secrete STI1 that, in turn, induces the proliferation of these cells; - Microglia also produce and release STI1 to the extracellular medium, inducing GBM cell proliferation and migration; - - STI1 knockdown in glioma cells presents a reduction in cell proliferation and invasiveness through TRAP1/AKT pathway.	[4,10,17,105,106,107,110]

occlusion) with an increased stroke area, decreased performance in behavioral tests and decreased weight [3].

Finally, STI1 deletion during embryonic development is lethal in mice around E9.5 and E10.5, although evidence show that it also affects survival of the embryos prior to implantation [3]. STI1^{-/-} embryos showed defects in neural tube and limb buds formation, increase in cellular apoptosis and placental disruption [3]. Mechanistically, STI1 knockout did not affect the protein levels of Hsp90, but the levels of G-protein-receptor kinase 2 (GRK2), signal transducer and activator of transcription 3 (STAT3) and p53 were greatly decreased [3].

Newer functions of STI1 in the CNS development and pathogenesis are still being decrypted. Both STI1 and Hsp90 can modulate neuroblast migration in the subventricular zone through an extracellular mechanism [68]. Also, cultured neurons submitted to oxygen-glucose deprivation and treated with STI1 presents significantly less apoptosis not only in a PrP^C-α7nAChR-STI1 complex dependent manner but also upon STI1 binding to activin A receptor-type II-like kinase 2 (ALK2) [69]. When STI1 is transiently silenced in embryonic stem cells, these get to a more differentiated phenotype which causes a reduction in the ability to form embryoid bodies [70,71], linking STI1 with a role in embryonic stem cell biology. In fact, STI1 has also been detected in extracellular vesicles of mouse embryonic stem cells [72]. Besides, studies have shown that STI1-PrP^C signaling is crucial for neurosphere formation, maintenance and proliferation [73]. Hajj and collaborators investigated the expression of STI1, PrP^C, and Vitronectin on PrP^C KO and wild-type mice development. It was observed that the expression of these proteins was spatiotemporal. STI1 expression in the nervous system was evident at E8 and, interestingly, at E10 it was noticed a distribution of STI1, PrP^C and Vitronectin on the notochord and floor plate, indicating a role in axonal growth [74]. Evidence also supports this idea by showing that STI1 interacts with small GTPase Rnd1 to enhance neurite outgrowth in neuronal cell lines [75].

In a context of neurodegeneration, STI1 was proved to prevent neurons from soluble amyloid-β oligomers (AβOs)-induced toxicity [76]. AβOs are known to induce, at least partially, their cytotoxic activity by binding PrP^C residues 95–105 [77–81]; adjacent to the STI1-binding 113–128 residues [5,51]. In this sense, STI1 binding to PrP^C was capable of inhibiting AβOs binding and toxicity [76]. Treatment with STI1 inhibited the classical neurotoxic pathway of AD in a PrP^C-dependent manner, showing once more the potential of manipulating STI1-PrP^C signaling for the treatment of neurological disorders.

4. STI1 and Cancer

Besides its role on CNS cells and development, STI1 has been strongly related to several types of cancer, including those of the CNS. Here, we will discuss the role of STI1 in several malignancies. Table 1 summarizes these findings.

Oral cancer studies, especially in oral squamous cell carcinoma, have shown that STI1 expression is higher in neoplastic cells than in healthy cells [82] and also its expression increases during tumor progression [12]. In esophageal squamous cell carcinoma (ESCC) increased levels of STI1 were observed as compared to healthy cells and tissues [83,84]. Recently, it was demonstrated that ESCC patients present higher serum levels of autoantibodies against STI1 compared to healthy patients, making it possible to discriminate with sensitivity and specificity early-stage patients from controls, and, despite their small sample sizing of patients, suggesting that STI1 could be used as a biomarker for ESCC [85].

As observed in ESCC, in papillary thyroid carcinoma (PTC), STI1 expression is also elevated in tumor tissues compared to noncancerous tissues, being related with tumor progression and poor prognosis,

pointing STI1 also as a biomarker for PTC [86,87].

Cholangiocarcinoma (CCC) is a rare malignant tumor originated from the epithelial cells lining the bile ducts. The challenging diagnosis and limited treatment options have revealed the need of new biomarkers to improve diagnosis. Padden and colleagues identified STI1 as a novel diagnostic biomarker for CCC by analyzing the increase in protein expression in a cohort of 60 patients using immunohistochemistry studies complemented with 2D-Dige and mass-spectrometry-based label-free proteomics [88].

Another tumor with high expression of STI1 is hepatocellular carcinoma (HCC), compared to non-tumor tissue, and high STI1 levels were associated with worse overall survival and recurrence-free survival of patients [20,89,90]. Additionally, STI1 levels in serum were also higher in HCC patients. In an HCC mouse model, depletion of STI1 strongly decreased tumor growth, suggesting STI1 could be a promising therapeutic target [20]. Moreover, it was also reported that STI1 was closely related to metastasis of residual HCC after radiofrequency ablation [89]. In another study, using an HCC mouse model, deletion of STI1 in HCC cells reduced intrahepatic and lung metastasis. Remarkably, in human metastatic tissue and serum samples, STI1 had higher expression than in non-metastatic controls [88]. Besides, STI1 activates Wnt/β-catenin pathway, promoting growth and migration of HCC cells [8]. Finally, STI1 was identified as a biomarker considering the Barcelona Clinic Liver Cancer staging; where STI1 levels would correlate both with HCC staging and patient prognosis [90].

In the same way, STI1 was analyzed in gastric cancer exhibiting higher levels than in healthy tissue and being associated with advanced Bormann classification and tumor-node-metastasis (TNM) staging, namely, tumor progression and poor prognosis [13]. Mechanistically, it was demonstrated that tumor cell proliferation and apoptosis inhibition were induced by autocrine STI1 signaling, via PLCγ1-ERK1/2 pathway and caspase-3, -9 and BCL2 activities, respectively. Interestingly, patients with gastric cancer also had higher STI1 serum levels than healthy ones, suggesting STI1 as both a biomarker and a prognostic factor [13]. Furthermore, the same research group showed that STI1 expression increases the migration and invasion of gastric cancer cells, induces epithelial-to-mesenchymal transition (EMT) and promotes lung metastasis. Wnt/β-catenin pathway was demonstrated to be upregulated and responsible for this metastasis process [91].

In colorectal cancer, it was shown that STI1 expression was increased when compared to healthy tissue [9,92]. Moreover, higher STI1 expression was correlated with advanced TNM stage, being a marker of worse prognosis. STI1 expression was also demonstrated to be an independent prognostic factor for overall and disease-free survival, suggesting STI1 as a prognosis biomarker for patients with colorectal cancer [9].

Another cancer intimately associated with STI1 expression is ovarian cancer. It has been reported that ovarian tumors have increased expression of STI1 and that patients present high serum levels of anti-STI1 antibodies and STI1 protein itself compared to healthy controls, suggesting that STI1 could be used as a biomarker for this type of cancer [93–95]. More specifically, it was shown that STI1 is secreted by ovarian cancer cells and acts through the ALK2 receptor, activating the Smad-ID3 signaling, which results in proliferation of tumor cells in an autocrine/paracrine fashion [95]. The increase in STI1 expression in ovarian tumors was correlated with tumor stage and grade, and to a poor overall and progression-free survival of patients, being also suggested as a potential prognostic marker [14,15]. Other mechanisms regulated by STI1 can be associated to the worst prognosis like as the histone lysine-specific demethylase 1 (LSD1) which interacts with other oncogenes, such as p53 and DNMT1, by being phosphorylated by GSK3-β through the STI1-HSP90 complex. It has been shown that gene silencing

Fig. 3. STI1 in glioma microenvironment. Glioma cells secrete STI1 to the extracellular medium and can promote M2-like phenotype in microglial cells, inducing the expression of Wnt3a, Arginase-1, IL-10 and also STI1. On the other hand, microglia act in a pro-tumor fashion in gliomas promoting proliferation and migration of these cells by releasing STI1. During the tumor growth, macrophages and lymphocytes infiltrate the tumor and have their STI1 expression upregulated. Moreover, STI1 induces tumoral proliferation and invasion through TRAP1/AKT pathway.

of STI1 in human ovarian cancer cells reduced the interaction of LSD1/HSP90 and LSD1 expression showing an antiproliferative effect [96]. Lastly, *in vivo* experiments showed that silencing STI1 in ovarian cancer cells resulted in inhibition of tumor growth [15], confirming the importance of STI1 in ovarian cancer.

In addition to STI1, STAT3 can also form a complex with Hsp70/Hsp90. Recently, Guo and collaborators demonstrated that in lung adenocarcinoma cells, proliferation and migration of tumor cells is associated with high levels of STI1 through the JAK2/STAT3 signaling pathway and regulation of EMT proteins such as E-cadherin and vimentin [97]. The correlation of STI1 and JAK2/STAT3 pathway was also observed in melanoma cells by being responsible for the proliferation, migration and invasiveness of cancer cells [98]. Besides, the role of STI1 in the regulation of the JAK-STAT pathway using RNA interference in ovarian and endometrial cancer cell lines was explored [98]. Thus, it was demonstrated that silencing STI1 reduced STAT3 phosphorylation and suppressed JAK2 and, consequently, levels of IL-6 were reduced. Cells treated with anti-TPR peptide, which binds to TPR2A domains of STI1, decreased the levels of JAK2 and phospho-STAT3. Histological analysis in patients' biopsies demonstrated that the expression of JAK2 accompanies the presence of STI1. Proximity ligation assay (PLA) corroborated these data in samples from ovarian cancer patients, thus demonstrating that the interactions between STI1, STAT3, JAK2 and

HSP90 occur in the cytoplasm of the cells. *In vivo*, treatment with peptide 520, a peptide fragment in the DP2 domain of STI1, reduced tumor progression in nude mice demonstrating Hsp90/STI1 plays an important role in tumor progression via JAK2 / STAT3 [16]. Although, it has been demonstrated that STI1 binds to MMP-9 promoter by increasing its transcriptional activation independent of JAK2 and NF- κ B in endometrial cancer cells [99]. Since STI1 is involved in invasiveness of ovarian cancer cells by activating the MMP7 levels, the aptamer TOV6 was able to target the STI1 by blocking the cellular invasion in a TOV-21 G ovarian cancer cells [100]. The development of a smart hybrid nanocomposite has contributed to a better diagnosis at different phases of the disease. This type of nanocomposite can select and detect at high sensitivity a target protein-triggered DNA polymerase activation in cells, as S-DNA-functionalized citrate-capped gold nanoparticles (GNPs), for instance. In the serum from ovarian cancer patients, the levels of STI1 were rapidly detected by using S-DNA-GNPs. Besides, STI1 expression was significantly different in the serum samples from an early and advanced stage of ovarian cancer, demonstrating its importance as a useful biomarker for better distinguishing the stages of ovarian cancer in patients [101].

Most breast cancers are estrogen receptor (ER)-positive, and the usual therapy applied to the patients involves anti-hormonal therapy. The oncogene HER-2 is associated with the relapse and shorter overall

survival in patients. Recently, the expression of STI1 protein was investigated in breast cancer specimens and adjacent healthy tissues by immunohistochemistry. A high level of STI1 was observed in breast cancer tissues positive for HER-2 [102]. Furthermore, in another study, it was shown that STI1 expression was reduced after the treatment with resveratrol in a breast cancer cell line MCF-7 [103]. However, the mechanism underlying the STI1 and HER-2 connection is still misunderstood.

One of the most common cancers in adults, the renal cell carcinoma (RCC), causes several skeletal-related events (SREs), as bone metastasis, which occurs aggressively, even before diagnosis. The elevated levels of STI1 mRNA and, consequently, the high expression of STI1 protein in RCC tumor cells is associated with an advanced stage of disease according to proteome analysis and TCGA renal dataset [19]. Moreover, STI1 has been associated with the signaling of tumor-niche interactions. A study showed that the cell proliferation and migration/invasion in a human renal cancer OS-RC-2-BM5 cells were reduced by STI1 shRNA, while in cells treated with human recombinant protein hrSTI1 and inhibitor of ALK2 (LDN193189), the SMAD1/5 activation was suppressed, demonstrating the autocrine STI1-ALK2-SMAD1/5 during bone metastasis of RCC [19]. The hrSTI1 treatment induced the expression of PrP^C in the mouse monocyte-macrophage RAW264.7 cells and, in another way, the treated cells with anti-PrP^C antibody reduced the osteoclast differentiation through ERK1/2 and CTSK [19].

As described above, during brain development STI1 interact with PrP^C and promote neurogenesis, differentiation and neuroprotection [7, 104]. In tumors from the CNS, these proteins are highly expressed, especially in glioblastoma (GBM), contributing to tumor aggressiveness and poor outcome of patients [105,106]. *In vivo* study showed that the injection of the human homologue peptide of STI1 (HOP-230-245), which interferes with STI1/PrP^C binding in tumor site, was able to reduce the tumor growth by inducing the apoptosis of tumor cells. Further, PrP^C knockdown in GBM cells reduces tumor growth and consequently increases the survival of mice [105]. Also, recent evidence shows that STI1 knockdown in glioma cells presents a reduction in cell proliferation and invasiveness through TRAP1/AKT pathway [107]. Indeed, there are a significant number of papers on STI1 and glioma. Our group, specifically, has given much attention to this topic. In 2007, Erlich and colleagues showed *in vitro* that human GBM cells are able to synthesize and secrete STI1, and that STI1 induces the proliferation of these cells [10]. Following, we demonstrated for the first time that microglia, the resident immune cells in the CNS and owning an intimate crosstalk with malignant gliomas [108,109], also produce and release STI1 to the extracellular medium; more than that, microglial STI1 was efficient in inducing GBM cells proliferation and migration (Fig. 3) [4]. Moreover, using an *in vivo* glioma model, we observed that the overall expression of STI1 increased over time; and that infiltrating microglia, macrophages and lymphocytes had their STI1 expression upregulated along with tumor development, unprecedentedly correlating the STI1 expression with glioma progression [17]. In fact, analyzing human samples, it was verified that STI1 expression was higher in GBM than in lower astrocytoma grades (I-III) or healthy tissue [105]. Currently, STI1 has been recognized as a factor released by glioma-associated microglia that promotes tumor progression [18]. On the context of this glioma-microglia crosstalk, we also showed that GBM cells treated with recombinant Wnt3a, a factor presents in this neoplastic microenvironment, induce microglia to acquire a pro-tumor M2-like phenotype, increasing the expression of STI1, Arginase-1, Interleukin-10 and also Wnt3a (Fig. 3). In line with these *in vitro* data, Wnt3a-treated GBM cells implanted intracranially in mice generate larger tumor mass with more aggressive features, compared to control, and also present a more prominent microglia infiltration [110], exacerbating the role of STI1 on

this glioma-microglia interaction.

5. Concluding remarks

In this review, we highlight the importance of STI1 in health and disease. Briefly, STI1 is a co-chaperone acting with Hsp70 and Hsp90 for the correct client proteins' folding and therefore for the maintenance of cellular homeostasis. Nevertheless, STI1 can be found in the extracellular medium, presenting several crucial roles in the CNS and cancer microenvironment. In association with PrP^C, STI1 induces neuroprotection, neuritogenesis, astrocyte differentiation and survival, for instance. In cancer, STI1 is undoubtedly a pro-tumor factor, being considered as a biomarker and possibly therapeutic target for several malignancies, specifically to glioma. Altogether, STI1 protein stands out as a hot topic for future basic, translational and clinical researches.

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CRediT authorship contribution statement

Anna Carolina Carvalho da Fonseca: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Diana Matias:** Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Luiz Henrique Medeiros Geraldo:** Writing - review & editing. **Felipe Saceanu Leser:** Writing - review & editing. **Iohana Pagnoncelli:** Writing - review & editing. **Celina Garcia:** Writing - review & editing. **Rackele Ferreira do Amaral:** Writing - review & editing. **Barbara Gomes da Rosa:** Writing - review & editing. **Izabella Grimaldi:** Writing - review & editing. **Eduardo Sabino de Camargo Magalhães:** Writing - review & editing. **Valentín Cópola-Segovia:** Writing - review & editing. **Evellyn Mayla de Azevedo:** Writing - review & editing. **Silvio Marques Zanata:** Conceptualization, Writing - review & editing, Supervision. **Flavia Regina Souza Lima:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

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