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Two neuroendocrine G protein-coupled receptor molecules, somatostatin and melatonin: Physiology of signal transduction and therapeutic perspectives

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Abstract

Recent studies have shown that G protein-coupled receptors (GPCRs), the largest signal-conveying receptor family, are targets for mutations occurring frequently in different cancer types. GPCR alterations associated with cancer development represent significant challenges for the discovery and the advancement of targeted therapeutics. Among the different molecules that can activate GPCRs, we focused on two molecules that exert their biological actions regulating many typical features of tumorigenesis such as cellular proliferation, survival, and invasion: somatostatin and melatonin. The modulation of signaling pathways, that involves these two molecules, opens an interesting scenario for cancer therapy, with the opportunity to act at different molecular levels. Therefore, the aim of this review is the analysis of the biological activity and the therapeutic potential of somatostatin and melatonin, displaying a high affinity for GPCRs, that interfere with cancer development and maintenance.

KEYWORDS

GPCRs, melatonin, somatostatin, targeted therapies, tumors

1 | INTRODUCTION

1.1 | G-protein-coupled receptors as oncotargets

G-protein-coupled receptors (GPCRs) represent one of the largest families of cellular membrane receptors involved in a wide variety of cellular responses through activation of heterotrimeric G-proteins (Pierce et al., 2002).

GPCRs are constituted by a single subunit formed by a polypeptide chain that crosses seven times the plasma membrane (Pierce et al., 2002). The binding site with the agonist is located on the extracellular side of the receptor, whereas the binding site with the G protein is on the receptor intracellular side. The term "G protein" identifies a complex of three proteins, named alpha, beta and gamma. In resting conditions, the alpha subunit binds to a GDP molecule and the beta and gamma subunits are associated with the alpha subunit. When the receptor is stimulated by an agonist, the alpha subunit gets rid of GDP and takes on a molecule of GTP, and the beta and gamma subunits dissociate from the alpha (Weis & Kobilka, 2018).

Ligands for GPCRs are represented by a large-scale of factors, including sensory signal mediators, peptide and nonpeptide neurotransmitters, hormones, growth factors, or lipids.

Interestingly, although the different type of ligands commonly shares GPCRs, usually distinct intracellular signaling systems are activated (Weis & Kobilka, 2018).

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The pharmacological manipulation of GPCRs is a well-consolidated approach for human treatment procedures in the nervous, cardiovascular, metabolic, immune and endocrine systems (Roth & Kroeze, 2015).

Moreover, recent findings have demonstrated that many GPCRs and their ligands are implicated in cancer initiation and progression, including upregulated cell proliferation, metastasis, adhesion and angiogenesis (Wu et al., 2019).

Therefore, GPCRs can be considered attractive targets for novel therapeutic treatments of cancer and targeting GPCR-mediated cell signaling has emerged as an important strategy for cancer drug-discovery research.

GPCRs for neuropeptides (i.e., bombesin and somatostatin) are overexpressed in numerous cancer cells, such as small-cell lung cancer (SCLC) or neuroendocrine tumors (NETs; Moody et al., 2018).

A significant upregulation of GPCR-49, an orphan GPCR, in the colon and ovarian tumors has been reported. In particular, this receptor is overexpressed in 66% of colon tumors compared with normal colon tissues. In addition to colon tumors, GPR49 has been also found to be upregulated in 53% ovarian primary tumor tissues (McClanahan et al., 2006).

Although the GPCRs and G proteins are widely dysregulated in cancer, they have been not yet deeply investigated in oncology. This is reflected by the fact that still few anticancer drugs with GPCRs as directly target have been approved, according to the work of Wu et al. (2019).

In this review, we will focus on the biology and the therapeutic potential of two GPCRs ligands with high affinity, somatostatin and melatonin, which have been proposed to interfere with cancer onset, progression and maintenance (Reiter et al., 2017; Ruscica et al., 2013).

1.2 | Somatostatin

Somatostatin, also known as somatropin release-inhibiting factor (SRIF), is a small neuroendocrine hormone that exists in two main bioactive isoforms: the SRIF-14 and the SRIF-28, with 14 and 28 amino acids, respectively (Patel, 1999). Both isoforms originate from the pre–pro-somatostatin (pre–pro-SRIF), a common pre–pro-peptide precursor consisting of 116 amino acids (Günther et al., 2018). Structurally, SRIF is a cyclic molecule containing a disulfide bond between the cysteine residues in positions 3 and 14 (cys3–cys14).

The synthesis and release dynamics of the two SRIF isoforms are cell-type specific, as a consequence of the different mechanisms, employed to process the pre–pro-SRIF. Specifically, SRIF-14 predominates in pancreatic islets, stomach and neural tissues and is virtually the only isoform expressed in the retina, peripheral nerves and enteric neurons. In the brain, SRIF-28 accounts for approximately 20%–30% of total SRIF-like immunoreactivity. In the periphery, SRIF-28 synthesis predominates in intestinal mucosal cells (Patel, 1999).

SRIF exerts its effects by interacting with a family of five GPCRs receptors (SST1–5). Functionally, different activities of this small neuroendocrine hormone can be recognized: In fact, being this hormone also produced by the stomach antral D cells, it inhibits gastrin-producing G cells (therefore inhibiting the production of hydrochloric acid). In the hypothalamic–pituitary axis, SRIF inhibits the secretion of various hormones, such as thyroid-stimulating hormone, adrenocorticotropic hormone (ACTH), growth hormone (GH), and prolactin. At the pancreas level, SRIF inhibits insulin (produced by β-cells) and glucagon (produced by α-cells) release, thus contributing to the regulation of blood glucose. As already mentioned, SRIF acts as an important neurotransmitter and has a stimulating action on cholinergic and β-adrenergic receptors (de Boon et al., 2019; Ortiz et al., 2020; Rossini et al., 2019).

In addition to SRIF-producing neuroendocrine cells, inflammatory, immune response cells and tumor cells may also express SRIF (Günther et al., 2018; X. P. Wang et al., 2005).

1.3 | SRIF receptors, signaling and biological effects

All five SRIF receptors have seven highly conserved α-helical transmembrane domains, with most divergence occurring in the extracellular N-terminus and intracellular carboxyl terminus (C-terminus) domains (Rai et al., 2015).

SRIF 5 receptor subtypes share many structural features and intracellular signaling pathways and have been defined as SST1, SST2, SST3, SST4, and SST5 (Alexander et al., 2017). Each SRIF receptor subtype can be distinguished according to its cellular and subcellular localization, as well as distinct regulation behavior following unique functional and pharmacological properties (Günther et al., 2018).

SST2 and SST5 have been reported to be the most expressed receptors, whereas SST1, SST3 and SST4 expression seems to be more limited. Liver and spleen organs have displayed higher expression of SST3, whereas SST4 has mainly been detected in the lungs, heart and placenta (Patel, 1999). The expression of SST2 and SST3 receptor messenger RNAs has been reported in immune cells, such as activated macrophages, T and B lymphocytes (Dalm et al., 2003; Krantic, 2000; Patel, 1999).

The antiproliferative role achieved upon the activation of all SRIF receptors has been widely recognized, even though the molecular mechanisms underlying these processes are slightly different among the different subtypes (Barbieri et al., 2013). SST1, SST2, SST4, and SST5 have a crucial role in promoting cell cycle arrest. In contrast, SST2 and SST3 activate proapoptotic pathways and anti-angiogenic activity (Florio, 2008a; Moller et al., 2003).

SST1 activation displays antisecretory effects on GH, prolactin, and calcitonin (Weckbecker et al., 2003) and also inhibits the secretion of GH and ACTH, glucagon and insulin (Stengel et al., 2011). SST2 and SST5 have inhibitory effects on GH secretion, on adrenocorticotropin, insulin, glucagon-like peptide-1, interferon-γ and

gastric acid (Strowski et al., 2003; Weckbecker et al., 2003). SST3 interferes with cell proliferation and induces apoptosis in breast cancer cell lines (War et al., 2015, 2011). The role of SST4 remains largely unknown and still needs to be clarified.

The SRIF binding to its specific receptor results in the activation of multiple signaling pathways. Specifically, all five SRIF receptors are able to inhibit the activity of adenylyl cyclase and, simultaneously, activate other effectors, such as mitogen-activated protein kinase (MAPK), to promote signaling transduction (Weckbecker et al., 2003).

SRIF antisecretory activities are reflected to the inhibition of adenylyl cyclase effects and Ca^{2+} intracellular reduction levels through coordinated steps on $K^+$and Ca^{2+} channels, on the contrary, the activation of phosphotyrosine phosphatases (PTPs), density-enhanced phosphatase 1/PTPη, and the activity control of MAPK are mainly responsible for SRIF antiproliferative outputs (Günther et al., 2018).

SRIF receptor subtypes are responsible for both adenylyl cyclase inhibition and PTP activation. At the same time, literature data reported that the stimulated signaling network by RAS has been augmented by SST4, is decreased by SST3 and SST5 and modulated by both SST1 and SST2. Moreover, SST receptor interaction acts on K^+ and voltage-gated Ca^{2+} channels, NA^+/K^+ exchanger and cyclooxygenase-2 (SST2 and SST5) and phospholipase A2 (SST1 and SST2) functionalities (Barbieri et al., 2013; Florio, 2008b). A schematic illustration of the intracellular networks modulated by SRIF receptors is shown in Figure 1.

1.4 | SRIF and cancer

Multiple signaling pathways are modulated by SRIF in controlling cancer cell proliferation and leading to cytostatic effects mediated by p27 or p21 cell cycle inhibitors, or some tumor suppressors like Zac1 (Theodoropoulou et al., 2006). Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, the antiapoptotic protein Bcl-2 and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factor are inhibited by SST2 subtype, while SST3 is reported to be responsible of apoptosis induction via Bax activation (Ferrante et al., 2006; Guillermet-Guibert et al., 2007; Guillermet et al., 2003).

SRIF is also a powerful neovascularization inhibitor. The formation of a new vessel from pre-existing ones passes through several well-defined stages, characterized by modifications of the endothelium and the extracellular matrix. In particular, it has been reported that activation of SST2 and SST3 displays antiangiogenic properties, with a consequent blockade of viability and migration of endothelial cells and the inhibition of the proangiogenic factors release, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor and basic fibroblast growth factor (Dal et al., 2018; Dasgupta, 2004; Florio et al., 2000; O'Toole & Sharma, 2020). SRIF reduces PDGF levels following inhibition of cell proliferation and motility of endometrial cells (Annunziata et al., 2012).

Tumors that can be targeted by SRIF and its analogs include, besides the pituitary adenomas, NETs of the gastro-entero-

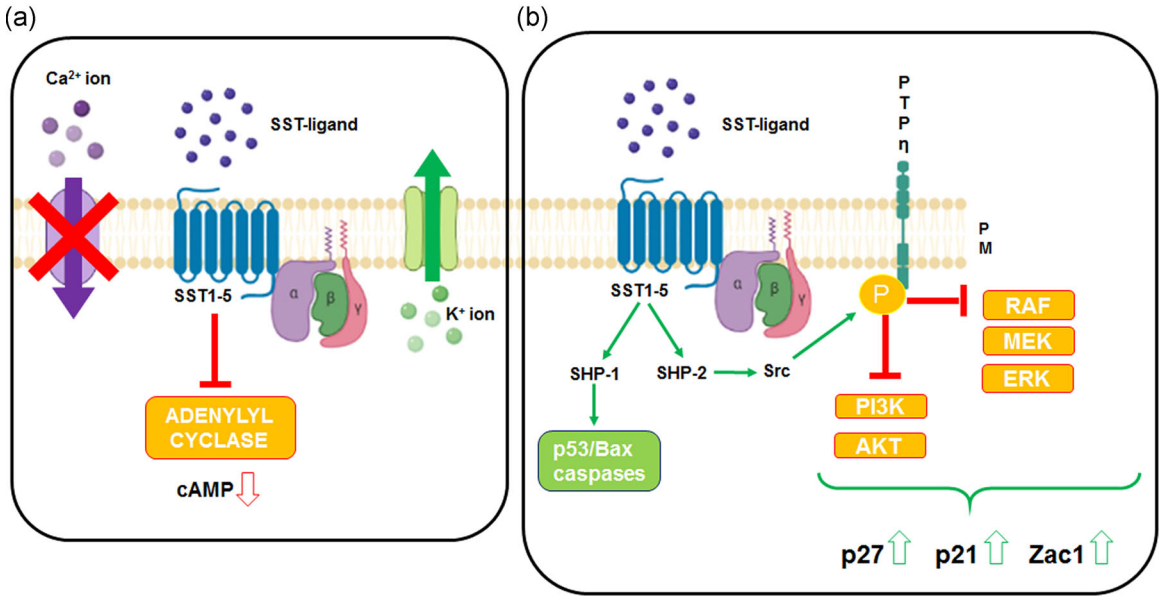

FIGURE 1 Schematic illustration of the intracellular signaling pathways modulated by somatostatin receptors (SST1–5). (a) SRIF-bound SST1–5 receptors induces the inhibition of the activity of adenylyl cyclase and the calcium channels, with a decrease of cyclic AMP (cAMP) levels and the intracellular Ca^{2+} concentration. (b) The SRIF receptor activation involves different cellular phosphorylation patterns. SRIF and analogs activate different PTPs, such as SHP-1, SHP-2, and PTPη. Activated SHP-1 triggers intracellular proapoptotic signals involving the induction of caspase activation and p53/Bax. SHP-2 activates Src that directly interacts with PTPη inducing its phosphorylation and hence activation. PTPη dephosphorylates intracellular effectors involved in the control of cell cycle progression, such as the MAPK/ERK and the PI3K/AKT pathways, upregulating the cyclin kinase inhibitors $p21^{cip1/waf1}$ and $p27^{kip1}$ and the tumor suppressor gene Zac1. As a result, PI3K/AKT and MAPK pathways are inhibited resulting in decreased cell growth and proliferation. PM, plasma membrane

pancreatic tract, SCLCs, carcinoids, breast cancers, and malignant lymphoma. SST1 dominates in prostate cancer tissue, whereas SST1–3 subtypes are expressed in breast, thyroid, melanoma, and GI tumor tissue. SST1–3 are also found in hepatocellular carcinoma and in ovarian tissue (both benign and malignant), where the expression of SST5 is also reported (Barbieri et al., 2013; Hasskarl et al., 2011; Soukup et al., 2019). SST receptors are also commonly expressed in tumors displaying both endocrine (pituitary adenoma, neuroendocrine, and gastropancreatic neoplasms, thyroid, adrenal, and small-cell lung carcinomas) and nonendocrine (gliomas, meningiomas, breast, and ovarian, prostate cancers, osteosarcomas) histological characterizations (Lee et al., 2020; Manoochehri et al., 2020; Thodou & Kontogeorgos, 2020).

In a phase 1–2 recruiting clinical trial with 30 subjects affected by differentiated metastatic NETs involving the gastrointestinal tract, lung and pancreas, the pharmacological combination of the mammalian target of rapamycin, inhibitor Everolimus, and a radiolabeled SRIF analogous has been analyzed as first-line therapy. The study is ongoing, with the aim to assess the progression-free survival and overall survival (OS), as well as the treatment safety (see www.clinicaltrial.gov, NCT03629847).

However, SRIF has a short circulating half-life (less than 3 min in human serum), therefore its use in the clinical practice is not simple. This relevant feature leads to the need for continuous parenteral administration and to the postinfusion rebound observed for several target hormones, such as GH and insulin. For these reasons, more potent and long-acting synthetic somatostatin analogs (SSAs) have been developed. To date, two classes of SSAs can be distinguished: the first and the second generation of SSAs (Gatto et al., 2019).

The SSAs first generation is represented by small molecules (octapeptides). These molecules have a large hydrophobic residue, consisting of phenylalanine, leucine, or isoleucine located at position 8, and a small hydroxylated residue or glycine at position 5. The two main clinically approved molecules are octreotide (OCT) and lanreotide (LAN). An example of octapeptide is angiotensin II, which has a crucial role in the rennin–angiotensin system. In particular, angiotensin II type 2 receptor blocks cell proliferation and induces apoptosis. These compounds display enhanced half-life compared to SRIF and several clinical trial data reported their anti-secretory activity in hormone-secreting pituitary adenomas and neuroendocrine neoplasms (NENs). NENs comprises tumors that are heterogeneous from a clinical and biological point of view and originate from neuroendocrine cells located in different body organs (e.g., pancreas, stomach, lung, and colon; Oronsky et al., 2017). Nowadays, OCT and LAN are considered the first-line clinical treatment for acromegaly, a serious systemic condition mainly dependent on somatotroph pituitary adenomas, due to the predominant expression of SST2 on tumor pituitary cells (Giustina et al., 2014).

Pasireotide (PAS), consisting of a stable cyclohexapeptide with a long half-life (about 24 h), is the only SST ligand approved by EMA and FDA for clinical use (Reubi et al., 2002; Smith et al., 2004). PAS is the first approved drug treatment for Cushing's disease, an extremely disabling neuroendocrine condition caused by chronic hypersecretion of the ACTH, which, in over 70% of cases, originates from a pituitary adenoma. This results in a stimulation of the adrenergic glands to produce cortisol excess.

Currently, two PAS formulations are available in the clinics: a short-acting formulation and a long-acting formulation for intramuscular injection (Kjell & Steven, 2016).

In addition to their approved use in modulating antisecretory effects, these SSAs are also being investigated for their antitumor activity in patients with cancers of the thyroid, prostate, breast, ovary and other solid tumors (Gomes-Porras et al., 2020).

A study focused on the effects of SRIF analogs on two different human late-stage prostate cancer cell lines showed that SST1, SST2, and SST5 are differently distributed amongst cell compartments like the nucleus, microsomes, and lysosomes (Ruscica et al., 2014). Some studies have demonstrated that OCT and, to a lesser extent, LAN are associated with positive outcomes in patients with solid tumors in which SST2 and/or SST3 levels predominate, such as prostate and gastric cancers (Hasskarl et al., 2011).

Another SRIF analogous—Cifetrelin—has demonstrated in vivo antitumor activity in breast adenocarcinoma, cervical cancer, and colorectal cell lines. However, the mechanism of action remains unclear. Cifetrelin is a not cyclic pentapeptide in nature and induces apoptosis in a p53-independent manner and suppresses the NF-κB complex. Moreover, cifetrelin demonstrated a higher antitumor activity than natural SRIF and illustrated its potential as an antitumor therapy element to further studies (Mikhaevich & Krasil'nikov, 2013).

SRIF analogs display high efficacy in the nanomolar range, therefore their selectivity is widely confirmed. However, the development of new analogs that could sustain a strong bioavailability and an adequate persistence in blood would certainly offer an alternative way to parenteral treatments. The clinical evaluation of new analogs will represent a crucial and careful step, as their pharmacological activity has been investigated only in preclinical models.

1.5 | Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous neurohormone produced in mammals to regulate the circadian rhythm (Claustrat et al., 2005). The rhythm is generated by a circadian clock located in the hypothalamus suprachiasmatic nucleus (SCN). This clock is set 24 h a day through the natural light–dark cycle. The light signal through the retina reaches the SCN, which sends a circadian signal to the pineal gland. All this process guides the synthesis of melatonin. Chemically, melatonin is an indolamine, derived from the amino acid tryptophan, and has lipophilic properties due to two functional groups the 5-methoxy group and the *N*-acetyl side chain (Gunata et al., 2020).

Melatonin can be also produced by the gastrointestinal tract, the skin, the bone marrow and the innate immune system, not in response to the light–dark cycle, but according to the requirements of the local tissues (Talib, 2018; Venegas et al., 2012). The extrapineal synthesis of melatonin suggests that signaling pathways responding

to multiple cues (not necessarily restricted to the circadian rhythm of the organism) might be involved in the regulation of indoleamine production (Venegas et al., 2012). Accordingly, melatonin has been described to be involved in the regulation of several cellular processes, which include antioxidant, anti-inflammatory and antiviral properties, genomic instability, regulation of the reproductive cycle and blood pressure and the ability to modulate mitochondrial homeostasis (Akbari et al., 2020; F. Cheng et al., 2020; Gunata et al., 2020; Mayo et al., 2017; Zare Javid et al., 2020).

The melatonin ability to reduce DNA damage surely derives, at least in part, from the direct scavenging actions of the parent molecule as well as its metabolites, following the stimulation of antioxidant enzymes that lead to reactive oxygen species removal, thus avoiding DNA destruction (Fadda et al., 2020). Circulating melatonin hydroxylation takes place in the liver by cytochrome P450 monooxygenases, following melatonin conjugation with sulfate to form 6-sulfatoxymelatonin which is then eliminated from the body with the urine (Claustrat et al., 2005).

1.6 | Melatonin receptors, signaling and biological effects

As for SRIF, also melatonin receptors belong to the G-protein superfamily. In mammals, two subtypes of melatonin receptors, termed MT1 and MT2 respectively, have been described. They can be distinguished on the basis of their specific molecular structure, which leads to different sleep regulation and circadian rhythms, to the development of mood disorders, learning and memory processes, neuroprotection and cancer (Dubocovich & Markowska, 2005).

A third receptor, MT3, has been recently characterized as the enzyme quinone reductase 2 and participate in antioxidant activities by preventing quinone electron transfer reactions (Boutin & Ferry, 2019). This receptor has been reported to synergize with melatonin on cytotoxic and apoptotic processes induced by chemotherapeutics (Pariente et al., 2017).

These melatonin receptors display putative glycosylation sites in their N-terminus and phosphorylation sites for protein kinase C (PKC), casein kinase 1 and 2, and protein kinase A (PKA) which may participate in the regulation of receptor function as demonstrated for other GPCRs (Dubocovich & Markowska, 2005).

Expression of MT1 and MT2 receptors, either alone or together within the same cell, has been reported in various tissues (Samanta, 2020). The MT1 receptors are expressed in the SCN, retina, cerebellum, hippocampus, central dopaminergic pathways (i.e., substantia nigra, ventral tegmental area), as well as in the liver, kidney, gallbladder, skin, ovary, mammary gland, testis, coronary blood vessels, and aorta (Ekmekcioglu et al., 2001; Feinberg et al., 2018; Reyes-Resina et al., 2020; Samanta, 2020; Wen et al., 2020). On the other hand, expression of MT2 receptors is restricted to the brain (El-Khatib et al., 2020; Wongprayoon & Govitrapong, 2020). The MT3 receptor has been found to be expressed in the liver, kidney, brain, heart, lung, intestine, muscle, and brown adipose tissue (Nosjean et al., 2000) and some pharmacological evidence found that it is also expressed in the eye (Pintor et al., 2003).

Melatonin binding to its receptors results in the activation of a variety of signaling pathways and this response is both tissue- and cell-type dependent (Chen et al., 2020; Yang et al., 2020).

A well-known signaling network for melatonin receptors is the inhibition of cAMP formation via pertussis toxin-sensitive G proteins, with consequent stimulation of PKC in the SCN. Melatonin-mediated low levels of cAMP have been observed in different mammalian tissues (Hardeland, 2017; Mao et al., 2016) The MT1 melatonin binding can lead to the inhibition of cAMP signal transduction cascade resulting in PKA activity decrease and nuclear factor cAMP-responsive element-binding protein phosphorylation (Chan et al., 2002). Moreover, activation of endogenous MT1 receptors in ovine pars tuberalis cells increases intracellular calcium levels via PTX-insensitive G proteins. On the other hand, it has been documented a calcium influx inhibition PTX-sensitive G protein-dependent in neonatal rat pituitary cells (Slanar et al., 2000).

Similar mechanisms for signaling transduction have been described for MT2 receptors (Oishi et al., 2017) that promote the recruitment and accumulation of second messengers and downstream molecules regulating multiple signaling networks, including phosphoinositide production and the inhibition of both adenylyl cyclase and soluble guanylyl cyclase networks (Dubocovich et al., 2010; von Gall et al., 2002).

In the SCN, melatonin is responsible of PKC activity increment through the activation of MT2 melatonin receptors, and this response is blocked by the selective MT2 receptor antagonist 4-phenyl-2-propionamidotetraline, that is also able to block the phase advances to neuronal firing rate stimulated by the picomolar concentration of melatonin, at distinct times. A schematic illustration of the intracellular signaling pathways modulated by melatonin receptors is shown in Figure 2.

1.7 | Melatonin and cancer

Several studies have reported that melatonin can modulate carcinogenesis for a wide variety of tumors, such as breast, prostate, lung, pancreas, colorectal, skin, and gastrointestinal system cancers (Dana et al., 2020; Ferreira et al., 2020; Moradkhani et al., 2020; Najafi et al., 2020). Melatonin induces antiproliferative effects and apoptosis and this is in part due to antioxidative and free radical scavenging effects (Jardim-Perassi et al., 2014; Sainz et al., 2003). However, the most relevant neurohormone effect has been reported to be more prominent in breast cancer (Hill et al., 2015).

In breast cancer, melatonin inhibits the proliferation of MCF-7 cells, through downregulation of AKT and MAPK networks and matrix metallopeptidase expression inhibition. Moreover, melatonin interacts with estrogen receptor-α (ERα) and exerts inhibitory effects on calmodulin, which phosphorylates ERα, therefore facilitating estrogen binding (Proietti et al., 2013). Melatonin exerts its antitumor activity by reducing proliferation and c-Myc expression of

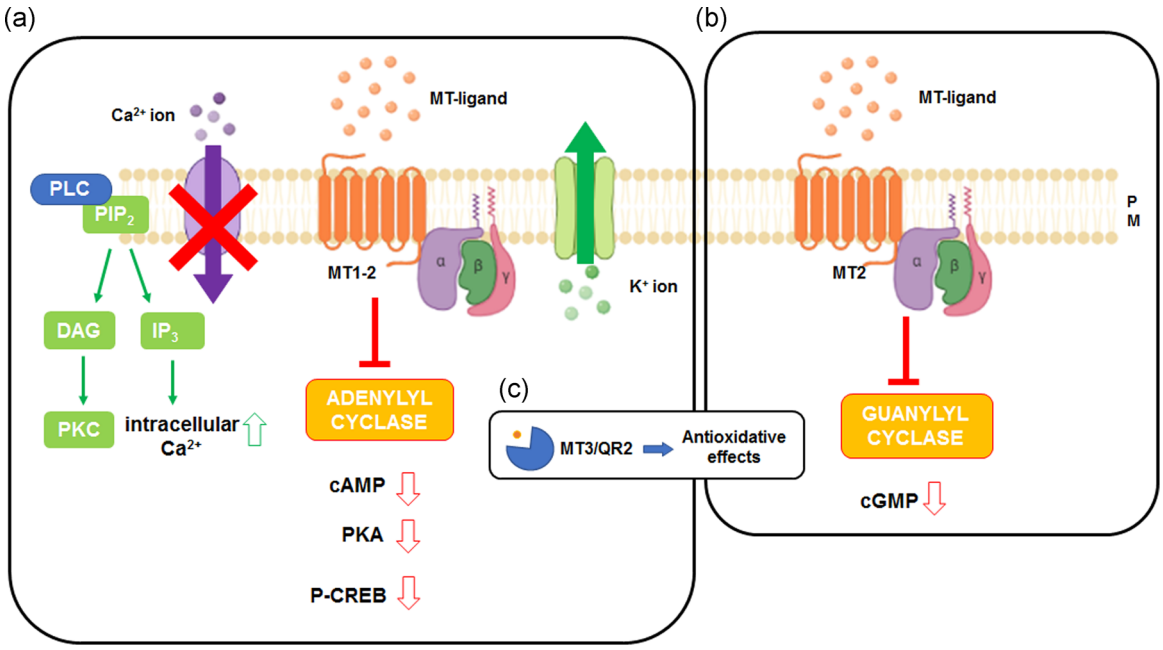

FIGURE 2 Schematic illustration of the intracellular signaling pathways modulated by melatonin receptors (MT1–3). (a) On the left, the common signaling pathways activated by both MT1 and MT2 receptors are shown. The adenyl cyclase inhibition leads to the decrease of cAMP levels and therefore to the decrease of cyclic AMP-dependent protein kinase activity (PKA). As a consequence of the inactivation of PKA, the transcription factor cAMP-responsive element-binding protein is also inhibited. The activation of phospholipase C (PLC) leads to the cleavage of phosphatidylinositol diphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG). These second messengers stimulate increased intracellular Ca^{2+} and PKC, respectively. (b) On the right, the inactivation of guanylyl cyclase, leading the decrease of cGMP concentration via binding to the MT2 receptor is shown. (c) The MT3 is a quinone reductase 2 (QR2), a known detoxifying enzyme that reduces menadione and other quinones. PM, plasma membrane

triple-negative breast cancer cells, and this activity is mediated through the regulation of microRNAs (miRNAs) specific set, following melatonin treatment (Ferreira et al., 2020). Moreover, melatonin can also induce p53 tumor suppressor activity in MCF-7 and in the colorectal carcinoma cell line HCT116 and blocking melatonin activity results in a relevant impairment of p53-mediated prevention of DNA damage (Mediavilla et al., 1999; Santoro et al., 2013).

In two types of breast cancers, specifically the ER+ and the HER2+ tumors, the expression of the MT1-receptor has been shown higher than the triple-negative tumor phenotypes and a substantial MT1 expression level has been reported to be associated with patient's longer OS in the group of ER+ treated with the nonsteroid drug tamoxifen (Jablonska et al., 2013).

Melatonin antiproliferative activity has been also documented in prostate cancer cells (Joo & Yoo, 2009; Jung-Hynes et al., 2011) with the involvement of the MT1-receptor in the oncostatic effect modulation (Tam et al., 2008; Xi et al., 2000). Indeed, in transformed and malignant prostate epithelial cells, melatonin has also been shown to upregulate, in an MT1 receptor-dependent mechanism, $p27^{kip1}$, whose downregulation is involved in the development of this type of cells (Fernandez et al., 1999; Tam et al. 2008, 2007). Additionally, in the same tumor model, melatonin might also dislocate androgen receptors from the nucleus to the cytoplasm (Rimler et al., 2001), further underlining the melatonin anticancer effects. In both androgen-dependent and independent prostate cancer cells, melatonin is able to attenuate the cell cycle progression and cellular differentiation (Sainz et al., 2005), in addition to intervening in the glucose metabolism decrease (Hevia et al., 2017).

In the hepatocarcinoma HepG2 cell line, melatonin administration has been also reported to control carcinogenesis by inducing the upregulation of proapoptotic proteins, transactivation of several transcription factors, and inhibition of signaling networks as extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 (Carbajo-Pescador et al., 2011). Progression of hepatocellular carcinoma has also been described to be regulated by melatonin through the up or downregulation of some miRNAs, such as miRNA Let7i-3p: In this case, melatonin has been shown to inhibit hepatocellular carcinoma progression through this miRNA-mediated RAF1 expression reduction (T. H. Wang et al., 2018).

Different studies have been focused on the molecular mechanism identification regulating the capacity of melatonin to induce apoptosis in tumor cells. Kim and Yoo (2010) have demonstrated that melatonin treatment induced apoptosis in a dose-dependent manner in an in vitro model of human prostate cancer (LnCaP cell line). In this study the treatment of cells with 3 mM melatonin has reduced their viability up to 80% in 48 h, increased levels of BAX, caspase 3, and caspase 9, as well as a potent reduction in BCL-2 (Kim & Yoo, 2010). Authors also have demonstrated that p53 activation by melatonin plays a key role in the initiation of the apoptosis signaling pathway. Moreover, melatonin-induced apoptosis in prostate

cancer cells via activation of the MAPKs pathway (Joo & Yoo, 2009). Additionally, melatonin can promote apoptosis in gastric cancer cell lines via inhibition of NF-κB (W. Li et al., 2015).

The proapoptotic effects of melatonin have been evaluated in human breast cancer and melanoma cell lines (Gatti et al., 2017). In a study, four melatonin analogs at different concentrations have been administered and it has been shown that low concentrations of melatonin have a significant proapoptotic effect in breast cancer cells, such as UCM 1037 and MDA-MB-231. Alonso-González et al. (2018) have reported that the expression of the proapoptotic BAD and BAX genes, induced by melatonin, leads to the inhibition of the antiapoptotic gene BCL-2 expression caused by docetaxel, a chemotherapy drug with antimitotic action. This study further highlights the role of melatonin as an adjuvant in cancer chemotherapy, which may have implications for new clinical trials using melatonin in combination with standard chemotherapies (Alonso-Gonzalez et al., 2018). At the same time, melatonin synergistically enhanced vemurafenib-mediated inhibitions of cell viability, migration, and invasion of melanoma cells, and promoted apoptosis, with cell cycle arresting (Hao et al., 2019). Activation of apoptosis induced by melatonin has been reported also in other cancer types such as in human neuroblastoma, hepatocarcinoma, and ovarian cancer (S. Lin et al., 2017; Suwanjang et al., 2013; Zare et al., 2019).

However, Cucina et al. (2009) have observed that apoptosis induction in MCF-7 cells following melatonin treatment occurs through a biphasic mode. The research group have demonstrated indeed that apoptosis can be triggered by different pathways and at different time points, upon melatonin treatment. Results have shown that early peak of apoptosis can be observed at 24 h after treatment through a caspases-dependent process, while a caspase-independent late peak is observed at 96 h after treatment (Cucina et al., 2009; Santoro et al., 2012).

Finally, melatonin has been shown to have additional properties in tumor growth, like, suppressing the expression of angiogenic markers (Goradel et al., 2017; Xu et al., 2020). Literature data have reported the role of millimolar concentrations of melatonin in reducing the expression levels of an important growth factor involved in tumor angiogenesis, such as the VEGF. The reduction has mainly been observed during hypoxia conditions in breast cancer, in hepatocarcinoma HepG2 and ovarian cells (J. Cheng et al., 2019; Colombo et al., 2016; Zonta et al., 2017).

1.8 | The role of melatonin in potentiating the therapeutic outcome in oncological treatments

In addition to radiotherapy, melatonin showed some evidence for potentiating the therapeutic outcome and alleviation from the chemotherapy side effects (Sanchez-Barcelo et al., 2012). Moreover, melatonin may induce a lower frequency percentage of chemotherapy-induced asthenia, stomatitis, cardiotoxicity, and neurotoxicity (Y. Li et al., 2017).

Experimental studies suggest that melatonin, via different mechanisms, reduces the incidence of breast development in rodents exposed to toxic and tumor-inducing chemicals, therefore giving rise to antitumoral behavior. Indeed, it has been shown that melatonin, given to female rats for 15 days before the use of carcinogens partially prevented the onset of breast adenocarcinomas (Lenoir et al., 2005).

In reference to the administration of taxanes, a class of chemotherapeutic agents, nanomolar concentrations of melatonin potentiates the anticarcinogenic effects of paclitaxel in an endometrial cancer cell line (Ishikawa) expressing MT1 receptors (Watanabe et al., 2008).

A pilot clinical trial recruiting 22 breast cancer patients to assess melatonin neuroprotective effects during a chemotherapy cycle based on taxanes has been carried out. These patients received either paclitaxel (750 mg/m^2 iv, weekly, for 2–3 doses) or docetaxel (75 mg/m^2 iv, every 2–3 weeks, for 6 doses). The result was that patients receiving melatonin during taxane chemotherapy developed a lower incidence of neuropathy onset, suggesting a relevant role of melatonin in the treatment and prevention of neuropathies, therefore a neuroprotective role (Nahleh et al., 2010).

In a recruiting clinical study (see www.clinicaltrial.gov, NCT02506777) the activity of melatonin and metformin in locally advanced breast cancer has been investigated, with a coadministration of chemotherapy made of fluorouracil, doxorubicin and cyclophosphamide. First data have reported that both melatonin and metformin reduce chemotherapy side-effects, increasing objective response during treatment. The protective role of melatonin and metformin against chemotherapy side effects have been also seen in another study involving patients with local advanced breast cancer (see www.clinicaltrial.gov, NCT02506790). Both drugs increase the patient response rate to toremifene treatment, rather than with toremifene alone.

In another recruiting clinical program involving 80 breast cancer patients, the aim was to analyze melatonin in a cream formula against dermatitis that could arise after radiation therapy. Therefore, also in this case, the rationale was to define the importance of melatonin in improving the cancer patient's quality of life (see www.clinicaltrial.gov, NCT03716583).

Always focusing on the analysis of cancer patient's quality of life, melatonin activity has been also documented in the elderly. Indeed, the aim of a recruiting trial with an estimated enrollment of 500 participants was to give melatonin supplementation (in tablet form) for 3 months before bedtime together with standard anticancer treatment to elderly cancer patients with tumor metastasis. The purpose was to analyze if melatonin could represent a beneficial complementary treatment, to reduce fatigue, depression, sleep disturbances, and cognitive impairment (see www.clinicaltrial.gov, NCT02454855).

1.9 | The potential antiviral role of melatonin in the attenuation of coronavirus disease 2019 infection

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) called coronavirus disease 2019 (COVID-19) has spread all

over the world (Bulut & Kato, 2020; Harapan et al., 2020) and although the availability of different antiviral therapy protocols and the mechanical respiratory support, the existence of a specific treatment is not yet known.

As already known, SARS-CoV-2 is mainly transmitted through droplets, direct contact and potentially via the fecal–oral pathway (Gu et al., 2020). Primary viral replication is reported to appear on the upper respiratory tract (nasal cavity and pharynx), with further multiplication in the lower respiratory tract and in the gastrointestinal mucosa, causing a slight viremia (Xiao et al., 2020).

Previous works have reported the positive effects of melatonin in alleviating acute respiratory stress induced by the virus and other pathogens (Yip et al., 2013), therefore allowing to enhance the hypothesis of the potential supportive and adjuvant role of melatonin in treating COVID-19 pandemic infection. Melatonin attenuates the cytokine serum levels and lipoperoxides in patients affected by diabetes mellitus and periodontitis (Bazyar et al., 2019; Sanchez-Lopez et al., 2018), is able to modulate angiogenesis, has preventive effects against myocardial infarction and other cardiac disorders, and is protective against cerebral pathologies (Nduhirabandi et al., 2016). Moreover, melatonin safety has been documented in different studies, and also this property would be highly beneficial in COVID-19 patients. The anti-inflammatory and antioxidant activities of melatonin, with consequent regulation of the expression of important modulators involved in inflammation and oxidation, have also been highlighted in the lung (Maarman, 2017), as well as Vitamin D anti-inflammatory and antioxidant properties. Vitamin D is often used in association with steroid therapy in asthmatic patients (Xystrakis et al., 2006) with a significant reduction of the cytokine storm and regulation of known signaling pathways such as those involving MAPK or AKT. Given all these findings and given the fact that both compounds share similar therapeutic molecular mechanisms, recent work has reported the potential benefits that a synergistic combination of vitamin D and melatonin could have in COVID-19 patients, in terms of prevention and treatment at the pulmonary level (Martin Gimenez et al., 2020). This combination could have a positive value in preventing the activation of signaling cascades involved in the inflammatory processes, in reducing the expression of inflammatory markers as TNF-α and overall, in a perspective of prevention, in preparing the human body to overcome the pathological consequences of COVID-19, reducing also the mortality rate.

1.10 | SRIF and melatonin signaling pathways: Are there similarities?

As previously reported, SRIF and melatonin are two neuroendocrine hormones that mediate through GPCR's different cellular and biochemical processes. Although the origin of these two hormones is different, both are able, at the signal transduction level, to activate PI3K/AKT and MAPK/ERK signaling pathways, considered crucial in the onset and progression of tumors. Both hormones are responsible of adenylyl cyclase inhibition and are capable to positively promote the activity of p53 in different tumor models, thus preventing DNA damage, and to restrain the onset of new blood vessels by inhibiting the proangiogenic factor VEGF and other growth factors.

A relevant aspect reported by Zibolka et al. (2015) is that melatonin could have inhibitory effects on SRIF secretion that can primarily be traced back to MT1-receptor activity. In a human pancreatic δ-cell model, the overexpression of this isoform significantly lowered SRIF secretion level (1 nM melatonin concentration) and at low doses of melatonin suppressed SRIF upregulation levels at low-glucose conditions, pointing to a significant influence of melatonin, and especially of the MT1 receptor, on the regulation of SRIF and insulin release.

Regarding biochemical aspects, SRIF and melatonin receptors share similar structural characteristics and signaling pathways.

A schematic signaling pathway could be exemplified as follows: agonist (such as somatostatin or melatonin) GPCR binding induces a conformational change in the receptor that triggers signaling downstream outputs involving the heterotrimeric G protein activation. Subsequently, the G-proteins mediate the production of second messengers, including cyclic-AMP, inositol trisphosphate and calcium flux, as common signaling routes.

Of note, a peculiar signaling pathway for somatostatin is exclusively driven by SST3 which is able to induce p53/Bax pathways, causing apoptosis activation. In a recent study in which primary cells from nonfunctioning pituitary tumors patients have been treated with the first SST3-agonist peptides, it was observed a clear increase of caspase activity, which is likely translated into an increase of apoptosis (Vazquez-Borrego et al., 2020). Other recent studies have suggested that the SST3 activation induces antiproliferative or proapoptotic cell-specific effects. In particular, SST3 can especially induce apoptosis in MCF-7 and cell cycle arrest in the MDA-MB-231 breast cancer cell line (S. A. War et al., 2015) and the same pathway can be triggered by melatonin in breast cancer cells (Gatti et al., 2017).

Additionally, SST1 (as well as SST3 or SST4, but not SST2 e SST5) inhibits the activity of sodium/hydrogen exchanger 1 via a PTX-independent mechanism as observed in SST1-neuroblastoma cells (Pola et al., 2003) occurring in increased intracellular acidification (C. Y. Lin et al., 2003) which is able to inhibit the rho-GTPases dependent-cell migration (Buchan et al., 2002).

Further studies need to be assessed to clarify the potential biomolecular correlation between SRIF and melatonin, also with the aim to give a rationale in their potential synergistic use in blocking or slowing down oncogenesis and neovascularization processes.

2 | CONCLUSIONS

The purpose of this review was to highlight the biological aspects and the therapeutic potential of two molecules, SRIF and melatonin, displaying both high affinity for GPCRs and their role in controlling cancer development processes and maintenance.

GPCRs, most likely expressed in every organ in the human body as numerous studies have shown, open new therapeutic options with

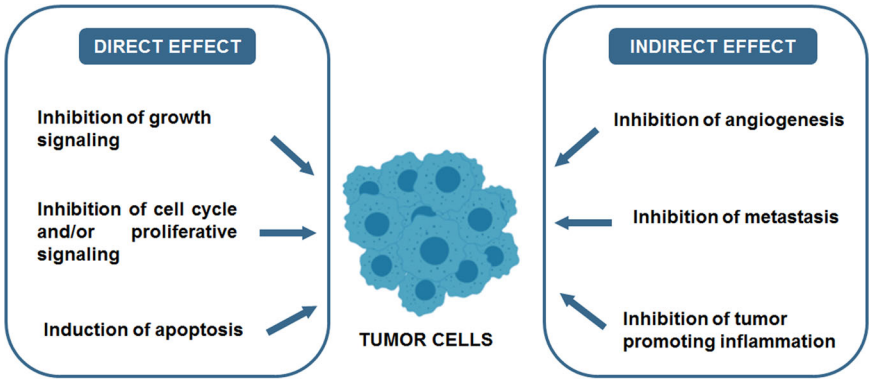

FIGURE 3 Direct and indirect effects of both somatostatin and melatonin on different cancer hallmarks. For details, see the text

novel combination therapies, both in preclinical and in clinical trials. Targeting multiple signaling networks with combination therapy, such as the administration of SRIF analogs with other therapeutic agents as GH receptor antagonists, or therapeutic adjuvants such as melatonin could improve the outcome for cancer treatment. Indeed, in addition to the already known role of SRIF receptors in the modulation of several psychiatric and neurological disorders, specific receptor subtypes have been seen to be associated with the control of tumor development and the regulation of relevant cellular processes such as apoptosis and angiogenesis.

At the same time, literature data reported that also melatonin could have the potential to be an adjuvant of cancer treatments, reinforcing the therapeutic outcomes and limiting the drug and radiation collateral effects. In clinical trials, melatonin showed the capacity to further potentiate the pharmacological effect of several chemotherapeutics, improving the overall cancer patient quality of life. Therefore, the involvement of both SRIF and melatonin in activating different anticancer strategies and processes such as pro-survival signaling and angiogenesis inhibition could represent a new frontier in therapeutic treatments (Figure 3).

Despite the current understanding of the mechanisms involved in GPCR signaling, much remains to be learned about the correlation underlying the signaling pathways of different GPCRs, their heterodimerization, internalization, and distribution pattern in various tumor cells.

The development of specific and more potent SRIF analogs will further highlight the role of SRIF in cancer treatment, in addition to the therapeutic capacity of melatonin, especially in clinical trials, for the formulation of promising therapeutic protocols.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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