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Serotonin and human cancer: a critical view

Mini-review article for the special issue devoted to "70 years of serotonin" of BIOCHIMIE, guest editors: Francine COTE and Cathy VAILLANCOURT

Running title: Serotonin in human carcinogenesis

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Abstract:

Besides its classical functions as a neurotransmitter in the central nervous system, local mediator in the gastrointestinal tract and vasoactive agent in the blood, serotonin has more recently emerged as a growth factor for human tumor cell lines of different origins (carcinomas, glioma and carcinoids). Several data are also available on serotonin involvement in cancer cell migration, metastatic dissemination and tumor angiogenesis. The serotonin-induced signaling pathways that promote tumor progression are complex and only partly understood in some cancer types. The results of several studies showed that serotonin levels in the tumor played a crucial role in cancer progression. A serotonin production and secretion by neuroendocrine cells have been shown in the progression of several solid tumors and the involvement of a serotoninergic autocrine loop was proposed. Specific receptor subtypes are

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associated with different fundamental stages of tumor progression and the pattern of receptors expression becomes dysregulated in several human tumors when compared with normal cells or tissues. Serotonin receptors, selective serotonin transporter and serotonin synthesis pathways are potential chemotherapeutic targets for the treatment of several cancers in which therapeutic approaches are limited. Through several asked questions, this critical mini-review discusses the relevance of the involvement of serotonin in human cancer progression.

Keywords: angiogenesis, carcinogenesis, chemotherapy, neuroendocrine cells, serotonin, SSRI.

Abbreviations: 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; CNS: central nervous system; CSC: cancer stem cells; EC: enterochromaffin cells; HCC: hepatocellular carcinoma; HDAC: Histone deacetylase; MAO: monoamine oxidase; MMP: matrix metalloproteinase; NE: neuroendocrine; NET: neuroendocrine tumor; PaCa cells: pancreatic cancer cells; PC: prostate cancer; SCLC: small-cell lung carcinoma; SERT: selective serotonin transporter; SSRI: selective serotonin reuptake inhibitors; TPH: Tryptophan hydroxylase.

1-Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic monoamine produced from the essential amino-acid tryptophan obtained primarily through diet. Serotonin is mostly located in the periphery of the body and less than 1% of total body serotonin circulates in its free form in the blood [1]. It acts as a neurotransmitter in the central nervous system (CNS), local mediator required for motility in the gastrointestinal tract and vasoactive agent in the blood. The classification of serotonin receptors recognizes 13 receptor subtypes in human, spreading over 7 receptor families that are widely distributed among many organs [2]. Serotonin can exert multiple, sometimes opposing actions, and this is determined by the characteristics of the receptor with which it interacts and the intracellular signaling pathway coupled to it. Within the CNS of vertebrates, a large majority of the cell bodies of serotonergic neurons are located in the nine raphe nuclei of the brain stem, the neurons of the rostral and caudal groups of raphe nuclei giving rise to broad and diffuse projections to the forebrain for the former group and to the hindbrain and spinal cord for the latter one [3]. Serotonin has been linked to a variety of CNS functions and is implicated in many CNS and psychiatric disorders. Consequently, serotonergic systems are targets for a large array of psychoactive compounds including antidepressants, antipsychotics and hallucinogens [4]. Serotonin is also synthesized

and stored in the mucosal enterochromaffin cells (EC) of the gastrointestinal tract and its secretion upon the action of different types of stimuli results in increased absorption by circulating platelets and mast cells that provide a potent reservoir of serotonin. Serotonin released from platelets is critical for normal wound healing in multiple organs [5]. Besides all its already known functions, serotonin has been shown to be a mitogenic factor for a wide range of non-tumoral and tumoral cells in culture and specific receptor subtypes have been associated with the progression of solid tumors [6]. Therefore, serotonin might be involved in one or more fundamental stages of their progression, *ie* growth of the primary tumor, invasion and dissemination up to metastasis.

Through several asked questions, this critical mini-review discusses the relevance of the involvement of serotonin in human cancer progression.

2- What are the arguments for the involvement of serotonin in human cancer progression?

In vitro, serotonin exhibits a **growth stimulatory effect** on several types of human tumor cell lines *ie* carcinoma [prostate, bladder, small-cell lung (SCLC), colorectal, bile duct, trophoblast, breast, hepatocellular (HCC)], glioma and carcinoids (Fig. 1). With the exception of glioma and carcinoid tumor, in many studies only a slight stimulatory effect of serotonin on cell growth was observed [6]. More often the effect of serotonin on cell growth is mediated through 5-HT_1 and 5-HT_2 receptors and less frequently through 5-HT_3, 5-HT_4, 5-HT_6 and 5-HT_7 receptors. Many studies have focused on the action of serotonin on prostate cancer (PC) and suggested that this action is mediated through several receptor subtypes that are present at various tumor stages, 5-HT_{2B} in the initial stages of tumorigenesis, 5-HT_{1A} and 5-HT_{1B} in aggressive PC with high Gleason grades (4 and 5) and 5-HT_{1A} in PC cells metastasized to human lymph nodes and bones [6, 7]. Serotonin activates the two interrelated MAP kinase and PI3K/Akt signaling pathways to induce proliferation, migration and differentiation in PC cell lines [8]. However, the results regarding prostate carcinoma are inconsistent probably due to the involvement at high serotonin concentrations of other serotonin receptor subtypes that have lower affinity for serotonin [6]. *In vitro*, serotonin is a potent mitogen for neoplastic placental cells and stimulation of two choriocarcinoma cell lines by a selective agonist of 5-HT_{2A} receptor activates MEK-ERK1/2 and JAK2-STAT3 signaling pathways [6]. The expression of various 5-HT receptors is involved in HCC progression and serotonin promotes proliferation of serum-deprived HCC cells through a complex cross-talk between signaling pathways including Wnt/β-catenin signaling and activation of mTOR downstream targets

[6,9]. Sometimes, as it was shown in the SCLC (5-HT_{1A} and 5-HT_{1D}), the mitogenic action of serotonin seemed to involve a complex time course interaction between the signaling pathways of several receptor subtypes [6]. Immunohistochemical and Western blot analysis demonstrated the presence of 5-HT receptors in cultured cells and sometimes quantitative RT PCR revealed that their mRNA was expressed. Often, as a proof of principle of *in vitro* experimental results, microarray and immunohistochemistry were used to study 5-HT receptor expression in tumor biopsies and compared to normal tissue. In contrast, several genetic studies support a tumor suppressor role for the human *HTR1B* gene during lung, renal, oral, osteo carcinogenesis and non-Hodgkin lymphomas [6].

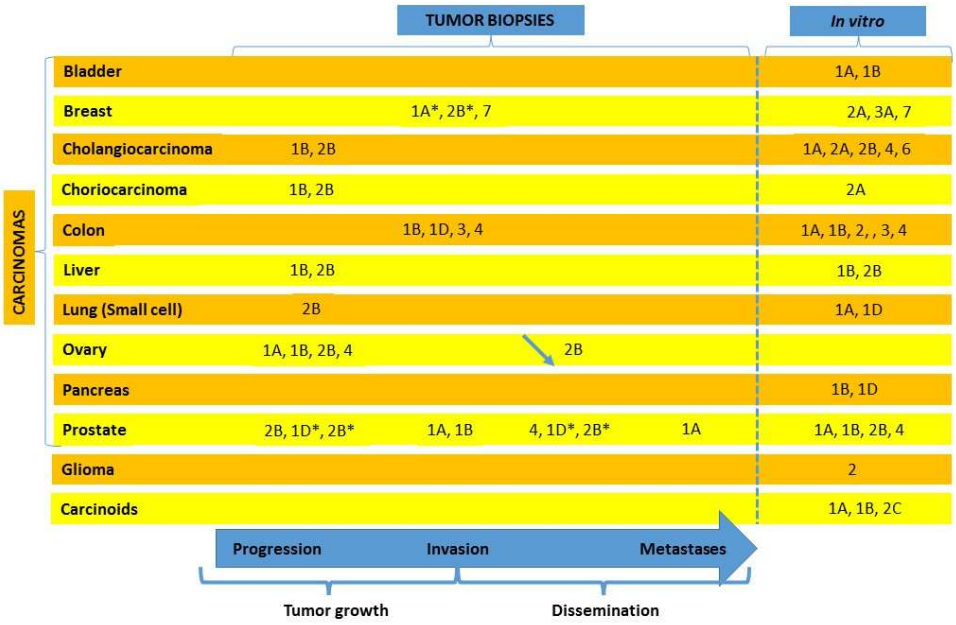

Figure 1: Expression of serotonin receptors in human cell lines and cancer biopsies according to tumor progression. * Expression in endothelial cells of the tumor vasculature.

Among the few studies that have linked serotonin to **cancer cell differentiation,** in LNCaP PC cells, serotonin was related with a differentiation and acquisition of neuroendocrine (NE) phenotype [8].

Several data are available on serotonin involvement in **cancer cell migration** and **metastatic processes**. Serotonin promoted the invasiveness of certain PC cells and 5-HT_{1A} receptor was shown to be involved in PC cell migration [8]. Serotonin also potently

stimulated migration and invasion of various human glioma cell lines [10]. In triple-negative breast cancer cells, a highly aggressive subtype of breast cancer, serotonin promoted proliferation and a strong invasion via 5-HT_7 receptors and increased the protein expression of TPH1 suggesting that the monoamine promotes cancer progression through an autocrine loop. Interestingly, downstream signaling molecules responsible for transmitting signals from 5-HT_7 receptor differed during invasion and proliferation: 1) Gαs-linked generation of cAMP, Gβγ-activated kinase signaling (Src/ERK and PI3K/Akt) and matrix metalloproteinase-9 (MMP-9) during invasion and 2) Gβγ-activated PI3K/Akt signaling during proliferation [11]. 5-HT_{1D} receptor is overexpressed in colorectal cancer biopsies and modulates human colorectal tumor cells invasion/migration *in vitro* by regulating Axin1/β-catenin/ LEF1/TCF4/MMP-7 signaling pathway [12]. Moreover, 5-HT_{1B} and 5-HT_{1D} receptors are also overexpressed in pancreatic cancer cells (PaCa cells) where they play an important role in the regulation of the proliferation and invasion of these tumor cells [13]. The data of the studies are consistent with the following tumor PaCa cells 5-HT_{1B} and 5-HT_{1D} receptors signaling pathways associated with tumor progression: 1) the two receptors mediate β1-integrin activity to recruit a Src–FAK complex promoting proliferation and migration; 2) the two receptors overexpression promotes the activation of urokinase plasminogen activator receptor (uPAR) and of MMP-2, facilitating invasion; 3) they stimulate the expression of the zinc finger transcriptional regulator of epithelial-mesenchymal transition (Snail and ZEB1) which, in turn, repress the expression of epithelial markers (claudin-1 and E-cadherin) supporting the proliferation and invasiveness [13]. An autocrine proliferation role of serotonin was suggested in human carcinoid cells mediated through 5-$HT_{1A,\ 1B}$ receptors inhibition of cAMP production in pancreatic tumor and 5-HT_2 receptor induced phosphorylation of ERK1/2 and activation of JNK pathway in bronchopulmonary NET and small intestinal NET [6]. In contrast, 5-HT_{2B} receptor expression decreased during dissemination of ovarian tumor cells supporting a tumor suppressor role for serotonin during the invasive step of carcinogenesis [14]. A correlation was shown between 5-HT_{1A} receptor expression, invasiveness of PC3 and DU145 cells and metastatic PC to human lymph nodes and bones [7, 8]. Moreover, in 159 bone metastases from a spectrum of primary carcinomas and sarcomas, expression of serotonin in combination with tumor necrosis factor receptor 1 is correlated with poor survival [15].

Angiogenesis processes contribute for primary tumor progression and also for metastasis in colonized tissues. It was recently reported that serotonin at concentrations lower than those seen in human serum activates in human endothelial cells the angiogenic

Src/PI3K/AKT/mTOR/p70S6K phosphorylation signaling [16]. Using *in vitro* models, serotonin stimulates the proliferation of endothelial cells *via* activation of 5-HT_1, 5-HT_2 and 5-HT_3 receptors and proliferation of aortic smooth muscle cells *via* 5-HT_2 receptors suggesting that the monoamine is also involved in tumor behavior by affecting angiogenesis [17]. Moreover, serotonin exerts complex actions on blood vessels, dependent on its interaction with a multiplicity of receptors and several serotonin receptors have been localized on the blood vessels feeding human tumors. Thus, 5-HT_{1D} and 5-HT_{2B} receptors were shown to be highly expressed in vascular endothelial cells in both benign and malignant prostate tissues [7, 18]. Immunohistochemical analysis of patients with breast ductal carcinoma, revealed the expression of 5-HT_{1A} and 5-HT_{2B} receptors in blood vessel-related cells of malignant and non-malignant specimens [19].

3- Are serotonin levels sufficient to act on tumor progression in human?

Platelets and platelet activation have been linked to tumor progression and angiogenesis [20]. Moreover, thrombocytosis at the time of diagnosis was associated with a shorter survival in many types of solid tumors [21]. In the thrombotic environment of tumors, platelet aggregation frequently occurs and leads to significant release of serotonin, which may constitute one of the mechanisms of tumor progression and angiogenesis. Such platelet-derived serotonin level present in tumor microenvironment would be much higher than the blood serotonin level of normal healthy subjects which is about 0.7 µM (below the age of 16 years) and 0.4 µM (above the age of 16 years) [22].

Moreover, serotonin production and secretion by neuroendocrine (NE) cells have been shown in the progression of several types of solid tumors (prostate carcinoma, urinary bladder carcinoma, SCLC, carcinoid tumors). Nicotine stimulates the release of serotonin by NE cells in SCLC suggesting an involvement of a serotoninergic autocrine loop in the control of proliferation. The 30-50 10^{-9} M serotonin concentration found in the medium after nicotinic stimulation was compatible with this mechanism [23]. Increased serotonin secretion is also found in carcinoid tumors which are slow-growing NE tumors (NET) of the diffuse NE system. The involvement of an autocrine proliferation role of serotonin is also suggested in human carcinoid cells and serotonin levels in blood (15-20 times higher than in control subjects) and tumor tissue are compatible with such a mechanism [24]. In cases of liver metastases, serotonin reaches the systemic circulation bypassing hepatic inactivation, and engenders the relatively uncommon carcinoid syndrome. In human cholangiocarcinoma cell lines, a dysregulation of the cellular machinery responsible for the metabolism of serotonin

was observed and resulted in an increased production and secretion of the monoamine at levels compatible with stimulation of tumor cells. These results were further confirmed *in vivo* and on human biopsies [25]. During breast carcinoma progression, TPH1 expression augments which corresponds to an increase in serotonin biosynthetic capacity [26]. All these results show that serotonin levels in the tumor play a crucial role in cancer progression. Serotonin produced by NE cells may also act on the growth, differentiation of neighboring cells through paracrine mechanisms and may facilitate tumor recurrence and metastases, correlated with poor prognosis and shortened patient survival.

Serotonin and its metabolites have been already used as tumor markers of carcinoid tumors and carcinoid syndrome and serotonin was further proposed as a potential diagnostic and prognostic marker for other tumor types [6].

4-Is tumor progression accompanied by changes of serotonin receptor expression?

The studies on serotonin involvement in tumor progression suggest that its receptors might react in a tissue-specific manner. They may also suggest that the biological response to serotonin could be determined by the combined effect of several receptors but also that serotonin receptor expression could change during this phenomenon. An immunohistochemical analysis of patients with breast cancer was performed in a tissue microarray and showed that the tightly regulated pattern of serotonin receptors becomes dysregulated in a complex way in human breast cancer cells, with ectopic expression of some isoforms and suppression of others, but without correlation with tumor grade [19, 26]. The 5-HT_{1B}, $_{1F}$, $_{2B}$, $_{3C}$ and $_{7}$ types were shown to be down-regulated and all the others up-regulated in human cholangiocarcinoma cell lines compared with the H69 human cholangiocyte cell line [25]. Moreover, 5-HT_{1B} and $_{2B}$ receptors were significantly overexpressed in tumor tissue compared with the nontumoral adjacent liver [27]. In ovarian cancer, 5-HT_{1A}, $_{1B}$, $_{2B}$ and $_{4}$ receptors were strongly expressed in benign and non-invasive cancer cells of patients and decreased in invasive malignant cells. Moreover, decreased expression of 5-HT_{2B} strongly correlated to the dissemination of the disease [14]. Two contradictory studies showed the differential expression of 5-HT receptors in HCC tissues and their corresponding non-tumor tissues, 2-HT_{2B} being the only to be overexpressed in HCC in the two studies [9, 27]. The action of serotonin on prostate carcinoma is mediated through several receptor subtypes that are present at various tumor stages. 5-HT_{2B} receptor expression was associated with the initial stages of prostate tumor. A strong expression of 5-HT_{1A} and 5-HT_{1B} receptors was shown in PC with high grades. And 5-HT_{1A} receptors were also demonstrated in PC cells metastasized

to human lymph nodes and bones. 5-HT_4 receptor expression was found predominantly in high-grade tumors suggesting that this receptor subtype may facilitate cell growth in an androgen-depleted environment [6, 18]. Thus, a systematic analysis of the modulation of serotonin receptor expression during progression of various cancers could be very instructive in order to develop an effective directed pharmaco-therapy.

5-Can serotonin system-directed pharmaco-therapy affect cancer progression?

Serotonin system might represent an interesting chemotherapeutic target for the prevention and treatment of several cancers in which therapeutic approaches are limited (hormone refractory prostate carcinoma, HCC, glioma and carcinoid syndrome) and in SCLC characterized by early metastases which cannot be surgically resected. Serotonin receptors, selective serotonin transporter (SERT) and serotonin synthesis pathways are potential molecular targets in cancer directed pharmaco-therapy. The pharmacology of serotonin and serotonin receptors is highly developed and numerous safe and effective serotonin-targeting drugs are available, some of them being currently used in the treatment of CNS disorders. In several *in vitro* studies, the notion of serotonin receptor-directed pharmaco-therapy has emerged (hormone refractory prostate carcinoma, carcinoma of the urinary bladder, breast cancer, SCLC, colorectal carcinoma and carcinoid). The results of these studies show that 5-HT receptor antagonists inhibit cancer cell growth through various effects (cell cycle arrest, cytotoxicity and tumor cells apoptosis). However, the use of serotonin receptor antagonists as anticancer agents in human is actually limited due to the side effects of these compounds [6].

Octreotide LAR, which was known as an inhibitor of serotonin release and able to lengthen progression of well-differentiated metastatic NET has no effect on survival in patients with metastatic midgut NET (PROMID trial) [28]. In patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide, a TPH inhibitor, telotristat ethyl is currently developed in clinical trials to treat patients by reducing the serotonin production within the metastatic NE cells (TELECAST phase 3 trial) [29].

The incidence of depression is greatly enhanced in patients with cancer and there is a debate about whether antidepressant medications must be avoided or are safe in patients with cancer [30, 31]. Indeed, SSRI, the most commonly prescribed drugs for treating depression, elevates the serotonin levels in the synaptic cleft by blocking serotonin re-uptake. As a side effect, higher levels of serotonin that result from SSRI antidepressant medication treatment could contribute to the growth of tumors. Interestingly, genetic variations in the *SLC6A4* gene, which codes for the SERT, seem to contribute to poor survival in colorectal cancer

patients [32]. In contrast, fluoxetine, and a range of SSRIs, are known to have antiproliferative and cytotoxic effects at high concentrations in several cancer cells. Thus, the secondary mechanisms of action associated with these drugs began to be studied to repurposing them as first-line anticancer drugs or to combine them with standard chemotherapies [33].

Cancer Stem Cells (CSC) have recently been identified in several solid tumors, including prostate, breast, colon, ovary, pancreas and glioma. CSC are clonal tumor-forming chemotherapy and radiotherapy-resistant, indefinite self-renewing cells which are suggested to cause tumor relapse and metastasis. Using an *in vitro* approach, unanticipated results showed that a SSRI (sertraline), a 5-HT_{1B} agonist (CGS-12066) and a 5-HT_{2C} agonist (tegaserod) killed all glioma neural stem cell lines tested [34]. Therefore, future studies are needed to show if the development of specific therapies targeting the serotonin system in CSC could be used for treatment of resistant solid tumors.

6-Conclusion

What is the relevance to consider whether serotonin is involved in human cancer progression? Most of the results were obtained *in vitro* and proofs of principles are still needed *in vivo* for many tumors. With the exception of glioma and carcinoid cells, in which a strong stimulatory effect of serotonin on cell growth was observed *in vitro*, in many other studies, serotonin has a slight effect. The effects of serotonin on glioma CSC and on glioma cell proliferation, migration and invasion request further studies [10, 34]. The data available on the involvement of serotonin in the progression of carcinoid tumors and in the development of the carcinoid syndrome are more prevalent and an inhibitor of TPH is currently developed in trials to treat patients by reducing the serotonin production within the metastatic NE cells [29].

The results of many studies showed that serotonin levels in the tumor play a crucial role in cancer progression and a serotoninergic autocrine loop is proposed in several cancers. Serotonin produced by NE cells may also facilitate tumor recurrence and metastases and is correlated with poor prognosis and shortened patient survival. The crucial unsolved point in many studies is whether the serotonin concentration in the primary tumor or in the metastases is compatible with its involvement in cancer progression and angiogenesis.

Studies suggest that specific serotonin receptors are involved in different fundamental stages of carcinogenesis but also that serotonin receptor expression could change during this phenomenon (Fig. 1). Thus, a systematic analysis of the modulation of serotonin receptor

expression during cancer progression would be instructive to develop an effective directed pharmaco-therapy. The use of serotonin receptor antagonists as anticancer agents in human is currently limited due to their side effects. Thus, the selective killing of a tumor cell population, without affecting normal tissues is a challenge for serotonin receptor-directed pharmaco-therapy. 5-HT_{1A} receptor being involved in the growth of carcinoid and many human tumor types (prostate, bladder, SCLC, colorectal, cholangiocarcinoma), it would be of prime interest to develop novel molecules to target it specifically [35]. Likewise, in pancreatic cancer, which is one of the most lethal human cancers, targeting the 5-$HT_{1B/1D}$ receptors with new selective antagonists is a therapeutic option to be explored for the future [13]. 5-HTT gene, which codes for SERT, is epigenetically downregulated by histone deacetylases (HDAC) in several types of human cancer, suggesting that HDAC inhibitors, which are expected to decrease the serotonin levels in the micro-environment of the tumor cells, may be used for therapeutic purposes [36]. Moreover, the development of specific therapies targeted at serotonin system in CSC and the use of SSRIs as cytotoxic drugs could be a new hope for treating resistant tumors.

More *in vivo* studies are needed to explore the role of the serotoninergic system in cancer and to elucidate whether serotonin is a major factor or an epiphenomenon in tumor progression and its relevance as a chemo-therapeutic target.

Conflict of interest

None declared

Author contributions

DS wrote and edited the manuscript, conceived and designed the major ideas developed in the manuscript. MM prepared the figure and made substantial, direct and intellectual contribution to the work. All authors read and approved the final manuscript.

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Highlights :

Serotonin is a growth factor for several human carcinomas, glioma and carcinoids

Serotonin is also involved in cancer cell migration, metastasis and angiogenesis

The levels of the monoamine in the tumor play a crucial role in cancer progression

Serotonin receptor expression becomes dysregulated in several cancers

Serotonin system is a potential chemotherapeutic target for the treatment of cancers