Journal of Experimental and Basic Medical Sciences 2022;3(3):221-226

Review

The Role of Serotonin in Breast Cancer

Büşra Nur Barmanbay[1], İlknur Altuntaş[1], Oytun Erbaş[1]

ABSTRACT

Serotonin (5-hydroxytryptamine, 5-HT) is a hormone that functions as a neurotransmitter as well as a hormone. Recently, the link between 5-HT and metabolic diseases has been revealed. Breast cancer is one of the most common cancers in women throughout the world. Serotonin is a monoamine that is produced and secreted by breast epithelial cells. It is essential for maintaining epithelial homeostasis during pregnancy, lactation, and involution. The role of 5-HT in tumor cell biology in breast cancer is not completely understood. In this review, we focused on the impact of 5-HT on breast cancer.

Keywords: 5-HT, breast cancer, cancer, serotonin

Cancer is a disease caused by cell mutations and uncontrolled cell proliferation.[1-6] Angiogenesis, continuous proliferation, vascularization, metastasis, invasion, self-sufficiency in growth signals, insensitivity to growth inhibition, and unlimited replicative potential are the basic characteristics of cancer cells.[6-9] Breast cancer is one of the most common cancers in women and the main cause of cancer deaths worldwide.[10-15] Every year, 1.7 million new cases of breast cancer are detected. Despite recent advancements, its prevalence is growing.[6,16] Serotonin (5-hydroxytryptamine, 5-HT) is an amine that is produced from tryptophan, an important amino acid.[7] An important neurotransmitter 5-HT functions as a hormone outside of the central nervous system (CNS) and has many receptor subtypes.[10] Serotonin promotes the growth of tumor cells. It also regulates tumor growth by regulating cell proliferation, metastasis, invasion, and angiogenesis.[17,18]

BREAST CANCER

Cancer was detected in evidence of fossilized bone tumors (osteosarcoma) found in Ancient Egyptian mummy research circa 1600 BC. According to the oldest records in 1500 BC it is thought that breast cancer was the first disease to be detected at that time.[1,19] Hippocrates defined cancer between 480 and 370 BC.[20,21] It comes from the Greek word "karkinos (carcinoma)" and is used to describe malignant tumors.[1] The breast is mainly composed of adipose and fibroglandular tissues. In females, the mammary glands[22,23] responsible for lactation are found in the breasts. Mammary glands are composed of 12 to 20 lobes, each of which contains numerous smaller lobules. These smaller lobules have grape-like clusters of alveoli that contain mammary secretory epithelial cells, which produce milk during lactation. Breast cancer is divided into two categories based on the histological characteristics of the tissue.[1,24] Cancer that occurs in the breast lobes is known as lobular carcinoma in situ, while cancer that occurs in the canal structure is known as ductal carcinoma *in situ*.[24,25] Breast cancer is one of the most common cancers in women.[12,26,28,29] Cancer treatment options include surgery, radiation therapy, and chemotherapy.[10,30] Breast cancer susceptibility gene 1 (BRCA1)[31-33] and BRCA2[34-36] is the most important biological breast cancer genes.[6,14,15,24,37] Mutations in these genes cause cancer. The immune system plays an essential role in breast cancer. The immune-inhibitory receptor programmed death 1 (PD-1) and programmed cell

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Büşra Nur Barmanbay. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: busranurbarmanbay1998@gmail.com

Cite this article as: Barmanbay BN, Altuntaş İ, Erbaş O. The Role of Serotonin in Breast Cancer. JEB Med Sci 2022;3(3):221-226.

doi: 10.5606/jebms.2022.1031

Received : November 11, 2022
Accepted : November 27, 2022
Published online : January 30, 2023

death-ligand 1 (PD-L1)[38-41] cause the tumor to escape the immune system.[38] Breast cancer is a disease that causes malignant tumors as a result of the excessive proliferation of epithelial cells lining the lobules and ducts. Breast tumors are the first epithelial tumors to take the form of cancer stem cells.[10] The mammary gland's effectiveness also renders it defenseless against breast disorders such as mastitis and cancer. These disorders are caused by a malfunction in the main homeostatic regulatory system that regulates mammary gland development and function.[7] Since tumors have different characteristics, various molecular states are classed as a single disease in the diagnosis and treatment of breast cancer. Breast cancer stem cells are resistant to treatment. Therefore, breast cancer recurrence is considered. It is essential to target these cells in order to eliminate the symptoms of breast cancer.[10] Breast cancers are divided into various subtypes based on the expression of estrogen receptor (ER) and progesterone receptor (PR) and the presence of human epidermal growth factor receptor 2 (HER2)-negative cells.[10,11,13] Breast cancers are classified into three types: hormone-sensitive, HER2-positive, and triple-negative breast cancer (TNBC/ER negative, PR negative, and HER2 negative).[42] Triple-negative breast cancer is the most severe subtype, with a high risk of recurrence, aggressiveness, a poor prognosis, poor differentiation, and few treatment choices.[11,13,24,43]

SEROTONIN

Serotonin, like epinephrine, is a biogenic monoamine that has been remarkably conserved throughout evolution.[44.45]Serotonin is important in the many functional brain mechanisms that underlie aggression, appetite, mood swings, motor abilities, pain, and sleep.[46,47] In 1948, 5-HT was isolated and described by Rapport et al.[45] and Gaddum and Hameed [48] revealed the existence of 5-HT in the brain in 1954 and demonstrated that 5-HT had a function in the gut.[49] Serotonin was named after the Latin word *serum* and the Greek word *tonic*.[45] Tryptophan hydroxylase (TPH), a rapidly restrictive enzyme with two isoforms TPH1 and TPH2, converts tryptophan, a necessary amino acid, to 5-HTP in mammals.[45,47,50] The TPH1 is expressed mostly in the pineal gland, pancreatic beta-cells, and enterochromaffin cells of the intestine. The THP2 is expressed by neurons in the CNS. Enterochromaffin cells in the gut are the most abundant source of 5-HT in the body, accounting for 90-95% of 5-HT expression.[48,51,52] Serotonin has long been known to play an important function in platelet aggregation and vasoconstriction, but 5-HT has lately been shown to play other roles in metabolism.[47] Presynaptic neurons in the raphe nucleus generate and store 5-HT in vesicles in the adult brain. E14 produces a high level of 5-HT in some tissues as a supplement to the raphe nucleus; these tissues are enterochromaffin and myenteric cells in the pineal gland and intestine.[52-54]

Serotonin is a neurotransmitter and peripheral signaling molecule that influences hemostasis, immune function, gastrointestinal physiology, and other physiological systems. Many 5-HT receptors are found in endocrine, cardiovascular, immunological, and gastrointestinal tissues. Many diseases have been linked to serotonin, including gastrointestinal disorders, cardiac arrhythmia, hypertension, depression[55], anxiety, schizophrenia, obsessive-compulsive disorders, addiction, and Parkinson's disease.[56,57] Serotonin regulates and functions the brain in many ways, including appetite, sleep, memory and learning, temperature regulation, mood, behavior, cardiovascular function, muscle contraction, endocrine regulation, neuronal and glial cell development, and control of the synaptic connection.[58,59] It is essential for controlling all brain activities, and defects in the serotonergic system can lead to the development of a variety of mental and neurological disorders.[18,57,60] It has numerous important effects on serotonin vascular biology, vascular resistance, and blood pressure regulation, as well as hemostasis and platelet function.[60] The quantity of 5-HT in the blood ranges between 0.7 μM and 2.5 μM.[51] The fact that 5-HT is released by platelets is critical for the healing process in normal organ damage.[61] Serotonin acts on cells by activating a random one of 15 different receptors from seven different families (5-HT1 to 5-HT7), each with its own signal transduction mechanism and functional role.[44,56] The serotonin reuptake transporter (SERT) is another essential 5-HT receptor involved in the uptake and clearance of 5-HT into the cell.[7] It is encoded by the SLC6A4 (17q11.1-q12) gene in humans. It is a monoamine transporter protein that transports 5-HT into cells. It is also known as sodium-dependent 5-HT transporter.[51] Serotonin is a cancer-activating agent.[51,62] Inhibition of tumor development and angiogenesis is achieved by 5-HT's stimulation of dopamine. There is insufficient data on the expression of 5-HT and dopamine receptors in cancer.[63] Serotonin's autocrine/paracrine activity is a critical homeostatic variable in mammary gland development. Many of the effects of 5-HT in breast tissue are aided by the 5-HT7 receptor, which has been suggested to be significant.[7] Serotonin has

recently emerged as a growth factor in malignancies such as carcinomas, gliomas, and carcinoids. There is evidence that 5-HT has a role in cancer cell invasion, metastatic expansion, and tumor angiogenesis. The signaling pathways by which serotonin promotes cancer progression are unclear, and only a fraction of some cancers are understood.[48,51,61] Anticancer effects of serotonin receptor antagonists have been observed in numerous malignancies, including bladder cancer, prostate cancer, breast cancer, colorectal cancer, carcinoid, and small-cell lung cancer.[48]

THE LINK BETWEEN BREAST CANCER AND SEROTONIN

Serotonin is a neurotransmitter, growth factor, and hormone that has a variety of physiological functions. It has recently been demonstrated to be a metabolic hormone that influences glucose homeostasis and obesity, with a link between circulating 5-HT levels and metabolic disturbances.[47] Breast cancer is the most frequent type of cancer in women worldwide, with few prognostic markers identified. During pregnancy, lactation, and involution, serotonin acts as a local regulator to modify epithelial homeostasis.[48,61] One of the local factors produced and secreted by breast epithelial cells is monoamine 5-HT as shown in Figure 1. It has been demonstrated that it acts as a 5-HT stimulator in the development of breast cancer.[43] The molecular goals of selective antagonists are expressed in 5-HT-producing breast tumors and breast cancer cell lines, indicating that 5-HT necessarily plays a functional role in these cells.[10] The bioactive level of 5-HT in the mammary gland is actively regulated by means of TPH, SERT, and monoamine oxidase.[7] Except for cancer cells, serotonin has been observed in many studies to have only a weak effect on cell growth. 5-HT's 5-HT1 and 5-HT2 receptors act on cell growth.[61] Serotonin is known to be effective in tumor development, metastasis, and cancer types.[17,48,64]

Serotonin receptors are expressed in breast cancer tissues, and this expression is also related to estrogen and HER2 receptor expression.[65] Epithelial homeostatic balance has to do with the progression of breast cancer in the mammary gland. Serotonin 5-HT2A receptors trigger the tumor formation structure of breast cells.[17,48,61] The function of serotonin can change with environmental factors and drugs.[51] In breast cancer, 5-HT plays a crucial role in tumor development by stimulating the proliferation of breast cancer cells and activating the characteristics of the cellular environment in which it interacts to keep unsuitable cells alive.

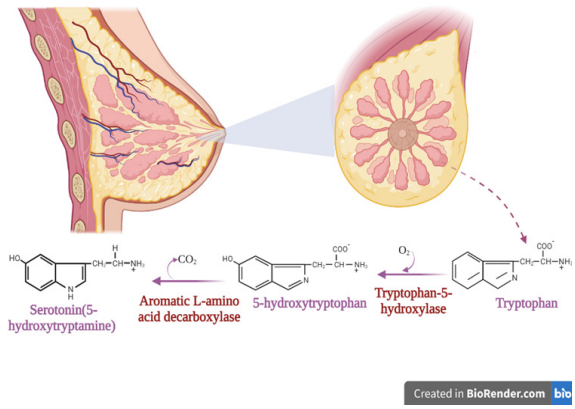

Figure 1: Serotonin synthesis and enzymes in breast tissue.

Serotonin increases the rate of cell proliferation and provides the advantage of promoting the proliferation of breast cancer cells by providing an escape from apoptosis. Breast cancer cells produce a lot of 5-HT, and free 5-HT plasma levels are used as an early detection marker in breast cancer. The biology of serotonin in breast cancer cells is not yet fully known, and also the mechanisms by which 5-HT is thought to induce carcinogenesis have not yet been resolved too.[66] Serotonin levels are known to play a very important role in tumor growth.[48] Selective serotonin reuptake inhibitors (SSRIs)[67] are known to increase the likelihood of malignancy.[68] Serotonin increases the proliferation rate of cancerous cells and is known to provide proliferative benefits to breast cancer cells by providing an escape from apoptosis.[66] The effect of 5-HT, which acts as an oncogene, on tumor growth has not yet been resolved. This can be explained by the fact that tissue-specific expression of 5-HT receptors is carried out. The effect of serotonin on the stimulation of mitosis division is dose-dependent, while higher doses promote cell proliferation, and lower doses cause tumor vessels to shrinkage and inhibit tumor growth. There are many 5-HT receptor-directed drugs, such as SSRIs, which are used in the treatment of central nervous system patients, and are being evaluated for use as anticancer agents. Selective serotonin reuptake inhibitors increase the level of 5-HT in the synaptic gap and plasma but do not contribute to tumor formation.[48] The complex function of serotonin in the vessels is the result of its combination with many different receptors. The vasoconstrictive effects of the agonists of 5-HT and 5-HT in the blood vessels feeding the tumor tissue are under the control of the arterioles and thus are effective in reducing

the development of malignants that are altered by controlling the tumor blood flow. Different receptors of serotonin are located in the blood vessels that feed tumors. The 5-HT1D and 5-HT2B receptors are very much expressed in all the inner surface cells of the vessels in the good and bad tumor tissues. Immunohistochemical analyses of samples obtained from breast cancer patients revealed the expression of 5-HT1A and 5-HT2B receptors in the blood vessels of malignant and non-malignant cancer cells.[18] The effect on the tumor vascular system is a mixed process and depends on its interaction with 5-HT receptors.[48] Serotonin, 5-HTR1B, and 5-HTR2B receptors stimulate tumor angiogenesis through interaction. Cancer cells are able to stimulate the proliferation of tumor cells through 5-HT receptors.[63] High levels of 5-HTR2B receptor are expressed in endothelial cells of breast, kidney, and pancreatic cancers.[66] Antagonists of serotonin receptors have been found to inhibit the proliferation of cancer cells, but the suitability of the use of the 5-HT receptor for pharmacotherapy is not certain.[18] The 5-HTR2B antagonists expressed in breast cancer are LY272025 and SB-206553 molecules.[70,71] Selective serotonin reuptake inhibitors slow tumor growth.In cancer cells, 5-HT is used to increase the expression of this molecule, which is an immune inhibitor expressed as PD-L1. This immunoinhibitory molecule binds to T cells, which are immune cells. Thus, they can escape from T cells that are programmed to destroy their cancerous cells. Studies have shown that SSRIs inhibit this mechanism. Such antidepressants cause immune cells to recognize and destroy cancer cells again.[69] Serotonin promotes the development of cancer by affecting cancer cells by enabling the proliferation of cancer cells through cell cycle progression, autophagy, and the suppression of apoptosis.[51]

It is known that 5-HT has a role in the mammary gland process.[48,61] Serotonin supports the development of cancer by affecting cancer cells by acting in the cell cycle, autophagy, and apoptosis processes.[51] Serotonin is one of the underlying causes of many diseases. The fact that serotonin underlies other metabolic diseases has also recently emerged. [47] One of these diseases is cancer.[43,62,51] Serotonin, which exists in the structure of the mammary gland, serves in breast cancer. It is, which plays a role in breast development, also effective in the development of cancerous tissue in breast cancer. It has functions such as the development of cancerous tissue, the formation of angiogenesis, and escape from apoptosis. Breast cancer is so much in its structure that it can produce a lot of 5-HT. This is used as an early diagnosis of breast cancer by looking at the free 5-HT levels in the plasma. It is clear that serotonin has a negative function in cancer, but this complex mechanism has not been fully solved.[66] A solution to prevent the negative effect of serotonin in cancer has not been definitively found. The biggest reason why the mechanism of serotonin in cancer cannot be solved is the tissue-specific expression of 5-HT. For example, the effect of high levels of 5-HT on cancer supports tumor cell proliferation, while low amounts of 5-HT prevent the development of tumor tissue by contracting the vascular structure in cancerous tissue.[48] Although antagonists of 5-HT inhibit the development of cancer, information on their use as a treatment is not conclusive.[18] The task of antagonists is to bind to a receptor and replace the compound that stimulates the receptor to which it binds, preventing the result that occurs when that receptor is stimulated. These are LY272025 and SB-206553, known antagonists of the highly expressed 5-HTR2B receptor in breast cancer.[70,71] However, these antagonists do not have studies in breast cancer. Studies on antagonists of 5-HT receptors in breast cancer are insufficient. Studies on 5-HT antagonists in cancer should be conducted. Deeper studies should be done on the antagonists of the 5-HT receptors that are specialized in breast cancer.

In conclusion, 5-HT is involved in cancer, but this mechanism has not been solved. Serotonin has a role in breast cancer, with highly expressed 5-HT being used as a marker for early detection. No solution has been found to prevent serotonin's role in cancer. Since serotonin is such a deep issue as cancer, studies on the relationship between 5-HT and cancer are therefore scarce. Although serotonin antagonists have been shown to prevent the development of cancer, their use for treatment is not certain. More studies on serotonin antagonists should be done.

Acknowledgments

The figure used in this review was created with BioRender (BioRender.com).

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Sudhakar A. History of Cancer, Ancient and Modern

Treatment Methods. J Cancer Sci Ther. 2009 Dec 1;1:1-4.
2. Hajdu SI. A note from history: landmarks in history of cancer, part 2. Cancer. 2011 Jun 15;117:2811-20.
3. Liotta LA, Kohn EC. Cancer's deadly signature. Nat Genet. 2003 Jan;33:10-1.
4. Hausman DM. What Is Cancer? Perspect Biol Med. 2019;62:778-84.
5. Gyamfi J, Kim J, Choi J. Cancer as a Metabolic Disorder. Int J Mol Sci. 2022 Jan 21;23:1155.
6. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144:646-74.
7. Pai VP, Marshall AM, Hernandez LL, Buckley AR, Horseman ND. Altered serotonin physiology in human breast cancers favors paradoxical growth and cell survival. Breast Cancer Res. 2009;11:R81.
8. Sevinç S, Erbaş O. Effects of DNA Methylation on Cancer and Aging. JEB Med Sci 2020;1:126-30.
9. Yaman G, Çini N, Altuntaş İ, Erbaş O. What Does CRISPR Technology Provide to Cancer Treatments? JEB Med Sci 2021;2:41-9.
10. Gwynne WD, Shakeel MS, Girgis-Gabardo A, Hassell JA. The Role of Serotonin in Breast Cancer Stem Cells. Molecules. 2021 May 26;26:3171.
11. Xie QE, Du X, Wang M, Xie F, Zhang Z, Cao Y, et al. Identification of Serotonin as a Predictive Marker for Breast Cancer Patients. Int J Gen Med. 2021 May 19;14:1939-48.
12. Slepicka PF, Cyrill SL, Dos Santos CO. Pregnancy and Breast Cancer: Pathways to Understand Risk and Prevention. Trends Mol Med. 2019 Oct;25:866-81.
13. Nicolás-Morales ML, Luisa-Sanjuan A, Gutiérrez-Torres M, Vences-Velázquez A, Ortuño-Pineda C, Espinoza-Rojo M, et al. Peptide-Based Vaccines in Clinical Phases and New Potential Therapeutic Targets as a New Approach for Breast Cancer: A Review. Vaccines (Basel). 2022 Aug 3;10:1249.
14. Arslan Ates E, Turkyilmaz A, Alavanda C, Yildirim O, Guney AI. Multigene Panel Testing in Turkish Hereditary Cancer Syndrome Patients. Medeni Med J. 2022 Jun 23;37:150-58.
15. Angeli D, Salvi S, Tedaldi G. Genetic Predisposition to Breast and Ovarian Cancers: How Many and Which Genes to Test? Int J Mol Sci. 2020 Feb 8;21:1128.
16. Busby J, Mills K, Zhang SD, Liberante FG, Cardwell CR. Selective serotonin reuptake inhibitor use and breast cancer survival: a population-based cohort study. Breast Cancer Res. 2018 Jan 19;20:4.
17. Ye D, Xu H, Tang Q, Xia H, Zhang C, Bi F. The role of 5-HT metabolism in cancer. Biochim Biophys Acta Rev Cancer. 2021 Dec;1876:188618.
18. Sarrouilhe D, Clarhaut J, Defamie N, Mesnil M. Serotonin and cancer: what is the link? Curr Mol Med. 2015;15:62-77.
19. Hajdu SI. A note from history: landmarks in history of cancer, part 1. Cancer. 2011 Mar 1;117:1097-102.
20. Ben-Dror J, Shalamov M, Sonnenblick A. The History of Early Breast Cancer Treatment. Genes (Basel). 2022 May 27;13:960.
21. Yan SH. An early history of human breast cancer: West meets East. Chin J Cancer. 2013 Sep;32:475-7.
22. McGhee DE, Steele JR. Breast Biomechanics: What Do We Really Know? Physiology (Bethesda). 2020 Mar 1;35:144-56.
23. Jesinger RA. Breast anatomy for the interventionalist. Tech Vasc Interv Radiol. 2014 Mar;17:3-9.
24. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017 Oct 2;50:33.
25. Subramani R, Lakshmanaswamy R. Pregnancy and Breast Cancer. Prog Mol Biol Transl Sci. 2017;151:81-111.
26. Rivenbark AG, Coleman WB. Field cancerization in mammary carcinogenesis - Implications for prevention and treatment of breast cancer. Exp Mol Pathol. 2012 Dec;93:391-8.
27. Gadaleta E, Thorn GJ, Ross-Adams H, Jones LJ, Chelala C. Field cancerization in breast cancer. J Pathol. 2022 Jul;257:561-74.
28. Nathanson SD, Detmar M, Padera TP, Yates LR, Welch DR, Beadnell TC, et al. Mechanisms of breast cancer metastasis. Clin Exp Metastasis. 2022 Feb;39:117-37.
29. Yücel U, Erbaş O. The role of oxytocin and prolactin in breast carcinogenesis and breast cancer prognosis: a mini-review. D J Tx Sci 2022;7:7-13.
30. Çağlar O, Özyılmaz E. Effect of Quercetin in Hepatocellular Carcinoma. Research & Reviews in Health Sciences, 2020;311-28.
31. Fu X, Tan W, Song Q, Pei H, Li J. BRCA1 and Breast Cancer: Molecular Mechanisms and Therapeutic Strategies. Front Cell Dev Biol. 2022 Mar 1;10:813457.
32. Jin TY, Park KS, Nam SE, Yoo YB, Park WS, Yun IJ. BRCA1/2 Serves as a Biomarker for Poor Prognosis in Breast Carcinoma. Int J Mol Sci. 2022 Mar 29;23:3754.
33. Park SS, Uzelac A, Kotsopoulos J. Delineating the role of osteoprotegerin as a marker of breast cancer risk among women with a BRCA1 mutation. Hered Cancer Clin Pract. 2022 Apr 13;20:14.
34. Kim M. Cost-effective BRCA Testing in Advanced Ovarian Cancer. Ann Lab Med. 2023 Jan 1;43:3-4.
35. Casaubon JT, Kashyap S, Regan JP. BRCA 1 and 2. 2022 Jul 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
36. Edaily S, Abdel-Razeq H. Management Strategies of Breast Cancer Patients with BRCA1 and BRCA2 Pathogenic Germline Variants. Onco Targets Ther. 2022 Jul 27;15:815-26.
37. Woods RW, Salkowski LR, Elezaby M, Burnside ES, Strigel RM, Fowler AM. Image-based screening for men at high risk for breast cancer: Benefits and drawbacks. Clin Imaging. 2020 Mar;60:84-9.
38. Babayakalı A, Erbaş O. PD-1, PD-L1 mechanism and cancer treatment. D J Tx Sci 2021;6:1-8.
39. Sasmal P, Kumar Babasahib S, Prashantha Kumar BR, Manjunathaiah Raghavendra N. Biphenyl-based small molecule inhibitors: Novel cancer immunotherapeutic agents targeting PD-1/PD-L1 interaction. Bioorg Med

Chem. 2022 Sep 13;73:117001.
40. Shergold AL, Millar R, Nibbs RJB. Understanding and overcoming the resistance of cancer to PD-1/PD-L1 blockade. Pharmacol Res. 2019 Jul;145:104258.
41. Tanaka T, Kutomi G, Kajiwara T, Kukita K, Kochin V, Kanaseki T, et al. Cancer-associated oxidoreductase ERO1-α promotes immune escape through up-regulation of PD-L1 in human breast cancer. Oncotarget. 2017 Apr 11;8:24706-18.
42. Leoncikas V, Wu H, Ward LT, Kierzek AM, Plant NJ. Generation of 2,000 breast cancer metabolic landscapes reveals a poor prognosis group with active serotonin production. Sci Rep. 2016 Jan 27;6:19771.
43. Gautam J, Banskota S, Regmi SC, Ahn S, Jeon YH, Jeong H, et al. Tryptophan hydroxylase 1 and 5-HT7 receptor preferentially expressed in triple-negative breast cancer promote cancer progression through autocrine serotonin signaling. Mol Cancer. 2016 Nov 21;15:75.
44. Fouquet G, Coman T, Hermine O, Côté F. Serotonin, hematopoiesis and stem cells. Pharmacol Res. 2019 Feb;140:67-74.
45. Rapport MM, Green AA, Page IH. Crystalline Serotonin. Science. 1948 Sep 24;108:329-30.
46. Quick MW. Regulating the conducting states of a mammalian serotonin transporter. Neuron. 2003 Oct 30;40:537-49.
47. Jones LA, Sun EW, Martin AM, Keating DJ. The ever-changing roles of serotonin. Int J Biochem Cell Biol. 2020 Aug;125:105776.
48. GADDUM JH, HAMEED KA. Drugs which antagonize 5-hydroxytryptamine. Br J Pharmacol Chemother. 1954 Jun;9:240-8.
49. Green AR. Neuropharmacology of 5-hydroxytryptamine. Br J Pharmacol. 2006 Jan;147 Suppl 1:S145-52.
50. Pawluski JL, Li M, Lonstein JS. Serotonin and motherhood: From molecules to mood. Front Neuroendocrinol. 2019 Apr;53:100742.
51. Karmakar S, Lal G. Role of serotonin receptor signaling in cancer cells and anti-tumor immunity. Theranostics. 2021 Mar 11;11:5296-12.
52. Trowbridge S, Narboux-Nême N, Gaspar P. Genetic models of serotonin (5-HT) depletion: what do they tell us about the developmental role of 5-HT? Anat Rec (Hoboken). 2011 Oct;294:1615-23.
53. Bocchio M, McHugh SB, Bannerman DM, Sharp T, Capogna M. Serotonin, Amygdala and Fear: Assembling the Puzzle. Front Neural Circuits. 2016 Apr 5;10:24.
54. Bliziotes M. Update in serotonin and bone. J Clin Endocrinol Metab. 2010 Sep;95:4124-32.
55. Kayabaşı Y, Güneş B, Erbaş O. Serotonin Receptors and Depression. JEB Med Sci 2021;2:240-6.
56. Matsuda M, Imaoka T, Vomachka AJ, Gudelsky GA, Hou Z, Mistry M, et al.Serotonin regulates mammary gland development via an autocrine-paracrine loop. Dev Cell. 2004 Feb;6:193-03.
57. De Deurwaerdère P, Di Giovanni G. Serotonin in Health and Disease. Int J Mol Sci. 2020 May 15;21:3500.
58. Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. J Neurochem. 2007 Feb;100:857-73.
59. Beliveau V, Ozenne B, Strother S, Greve DN, Svarer C, Knudsen GM, et al. The structure of the serotonin system: A PET imaging study. Neuroimage. 2020 Jan 15;205:116240.
60. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu Rev Med. 2009;60:355-66.
61. Sarrouilhe D, Mesnil M. Serotonin and human cancer: A critical view. Biochimie. 2019 Jun;161:46-50.
62. Wu KK. Cytoguardin: A Tryptophan Metabolite against Cancer Growth and Metastasis. Int J Mol Sci. 2021 Apr 26;22:4490.
63. Peters MAM, Meijer C, Fehrmann RSN, Walenkamp AME, Kema IP, de Vries EGE, et al. Serotonin and Dopamine Receptor Expression in Solid Tumours Including Rare Cancers. Pathol Oncol Res. 2020 Jul;26:1539-47.
64. Pereyra D, Starlinger P. Reply to: "Intra-platelet serotonin in prognosis of tumorigenesis: Friend or foe?". J Hepatol. 2018 Jun;68:1334-5.
65. Warchal SJ, Dawson JC, Shepherd E, Munro AF, Hughes RE, Makda A, et al. High content phenotypic screening identifies serotonin receptor modulators with selective activity upon breast cancer cell cycle and cytokine signaling pathways. Bioorg Med Chem. 2020 Jan 1;28:115209.
66. Sola-Penna M, Paixão LP, Branco JR, Ochioni AC, Albanese JM, Mundim DM, et al. Serotonin activates glycolysis and mitochondria biogenesis in human breast cancer cells through activation of the Jak1/STAT3/ERK1/2 and adenylate cyclase/PKA, respectively. Br J Cancer. 2020 Jan;122:194-08.
67. Kılıç N, Erbaş O. Antidepressant Drugs, Biological Clocks, and Cancer: Is There a Relation. JEB Med Sci 2021;2:298-01.
68. Boursi B, Lurie I, Haynes K, Mamtani R, Yang YX. Chronic therapy with selective serotonin reuptake inhibitors and survival in newly diagnosed cancer patients. Eur J Cancer Care (Engl). 2018 Jan;27.
69. Schneider MA, Heeb L, Beffinger MM, Pantelyushin S, Linecker M, Roth L, et al. Attenuation of peripheral serotonin inhibits tumor growth and enhances immune checkpoint blockade therapy in murine tumor models. Sci Transl Med. 2021 Sep 15;13:eabc8188.
70. Papageorgiou A, Denef C. Stimulation of growth hormone release by 5-hydroxytryptamine (5-HT) in cultured rat anterior pituitary cell aggregates: evidence for mediation by 5-HT2B, 5-HT7, 5-HT1B, and ketanserin-sensitive receptors. Endocrinology. 2007 Sep;148:4509-22.
71. Niture S, Gyamfi MA, Kedir H, Arthur E, Ressom H, Deep G, et al. Serotonin induced hepatic steatosis is associated with modulation of autophagy and notch signaling pathway. Cell Commun Signal. 2018 Nov 8;16:78.