

Serotonin, hematopoiesis and stem cells

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1 2 3	Serotonin, hematopoiesis and stem cells
4 5 6	Guillemette Fouquet ¹ , Tereza Coman ^{1,2} , Olivier Hermine ^{1,3} and Francine Côté ¹
7	Authors' address
8	1. Institut Imagine, INSERM U1163 - CNRS ERL8254, Paris, France
9	2. Département d'hématologie, Institut Gustave Roussy, Villejuif, France
10 11	3. Service d'hématologie adultes, Hôpital Necker, Paris, France
12	Corresponding author
13	Dr Francine Côté
14	Institut Imagine, INSERM U1163 – CNRS ERL8254
15	24, boulevard Montparnasse
16 17	75015, Paris, France
10	Priorie: +33.1.42.75.42.90
10	
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25	Abbreviations
26	5-HT1 to 5-HT7, names of 7 classes of serotonin receptors;
27	5-HT _{2A} R, 5-HT _{2B} R, 5-HT _{2C} R, specific serotonin receptors;
28	5-HTP, 5-hydroxytryptophan;
29 30	BEU-F and CEU-F Burst-forming Unit Ervthroid and Colony forming Unit Ervthroid
31	CFU-GEMM, CFU-GM, CFU-M, Colony-Forming Unit-Granulocyte, Erythrocyte, Monocyte
32	/Macrophage, Megakaryocyte;
33	En, embryonic day n;
34	HSC, hematopoietic stem cell;
35	HSPC, hematopoietic stem / progenitor cell;
36	KO, KNOCKOUL;
37 38	SEBT serotonin transporter:
30	SSBL selective serotonin reuntake inhibitor
40	TPH, tryptophan hydroxylase:
41	Tph1 and Tph2, isoforms of tryptophan hydroxylase;
42	Tph1 ^{-/-} or Tph1 KO, murine model deficient in peripheral serotonin.
43	
44	Chemical compounds
45	Chemical compounds studied in this article:
46	5-Hydroxytryptophan (PubChem CID: 144);
47	Fluoxetine (PubChem CID: 3386);
48	Kynurenine (PubChem CID: 846);
49	Serotonin (PubChem CID: 5202);

50 Tryptophan (PubChem CID: 6305).

51 Abstract

A large number of studies have focused on the role of serotonin as a neurotransmitter in the central 52 nervous system, although only a small percentage of the body's serotonin (\sim 5%) can be found in the 53 mature brain of mammals. In the gut, the enterochromaffin cells are scattered in the enteric epithelium 54 from the stomach through the colon and produce over 95% of the body's serotonin. Since the 55 generation of tryptophan hydroxylase (Tph1 and Tph2) knockout mice, unsuspected roles have been 56 identified for serotonin synthesized outside the brain. Moreover, the murine model deficient in 57 peripheral serotonin (Tph1-/-) is a unique experimental tool for exploring the molecular and cellular 58 59 mechanisms involving serotonin's local effects through microserotonergic systems. In this review, we 60 focus on peripheral serotonin and its role on progenitor or stem cells as well as on hematopoietic progenitors. We discuss the possible role of serotonin in hematopoietic diseases, and whether 61 62 targeting the serotonergic system could be of therapeutic value for the regulation of normal and 63 pathological hematopoiesis.

64 1. Introduction

65

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine highly conserved throughout evolution. It 66 is derived from the essential amino acid tryptophan, obtained from dietary sources. As a well-known 67 neurotransmitter in the central nervous system (CNS), 5-HT is involved in cognition, attention, 68 emotion, pain, sleep, and arousal, to name a few examples. Yet only a small percentage of the body's 69 5-HT (~5%) can be found in the mature brain of mammals: most (~95%) is found synthesized in the 70 71 gastrointestinal tract [1-3]. The cellular effects of 5-HT are exerted through activation of any of 15 different receptors in 7 different classes $(5-HT_1 \text{ to } 5-HT_7)$ [4]. Through these receptors, 5-HT can 72 73 produce opposing effects that add to the complexity of the serotonergic system. The activity of 5-HT 74 also depends on its extracellular availability, which is partly modulated by the specific membrane 5-HT transporter (SERT). SERT removes secreted 5-HT from the extracellular medium when it is no longer 75 76 required. Treatments with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, by blocking the action of SERT, lead to increased 5-HT extracellular concentrations and signaling [5]. The 77 78 rate-limiting enzyme tryptophan hydroxylase (TPH) that catalyzes conversion of tryptophan into 5-79 hydroxytryptophan (5-HTP), the immediate precursor of 5-HT, is found only in 5-HT-producing cells 80 [6-8].

In 2003, the generation of TPH knockout (KO) mice revealed the existence of two isoforms of the enzyme derived from two different genes with a high degree of homology in their amino acid sequences. Since then, it has been shown that peripheral or nonneuronal 5-HT is mainly—but not only, as we shall see—synthesized by the Tph1 isoform in enterochromaffin cells of the gastrointestinal tract, whereas Tph2 participates in neuronal 5-HT synthesis. Because 5-HT does not cross the blood-brain barrier, it is believed that each pool has a discrete set of functions [6, 7].

An important key to the understanding of 5-HT functions and advances in our knowledge was the generation of the Tph1 and Tph2 KO murine models. For the last 15 years, the mouse model selectively deficient in peripheral 5-HT (Tph1^{-/-} or Tph1 KO), but having normal brain 5-HT levels, has led to the discovery of complete serotonergic systems in unexpected locations and the identification of unforeseen roles of 5-HT, from early development to adult life [6, 7, 9-15].

This review will focus on peripheral 5-HT, discussing 5-HT synthesis under physiological and pathological states, its role on stem and progenitor cells during development and after, and more specifically its role on hematopoiesis. We will discuss whether modulating 5-HT synthesis and signaling could be a novel tool for the regulation of normal and pathological hematopoiesis.

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100 2. 5-HT synthesis under normal and pathological states

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102 2.1.<u>5-HT synthesis</u>

Enterochromaffin cells are scattered throughout the enteric epithelium and, as previously 103 104 mentioned, produce over 95% of the body's 5-HT. Although earlier studies suggested that enterochromaffin cell activation promotes the release of 5-HT, thereby stimulating gut contractility, 105 106 Tph1^{-/-} mice do not experience much difference in gut contractility [16]. In fact, removal of the mucosa 107 from the colon and hence all release of 5-HT from enterochromaffin cells does not block peristalsis or 108 other major neurogenic motor patterns in the colon [17, 18]. This proves that Tph1 dependent 5-HT synthesis and release from the mucosa is not required for the generation of peristalsis. This leaves 109 fundamental unanswered questions about the role played by the prodigious quantities of 5-HT 110 synthesized in enterochromaffin cells. Once synthesized and released by these cells, 5-HT is secreted 111 112 into the bloodstream, where it is taken up by and accumulates in platelet-dense granules. These granules constitute the main 5-HT reservoir in the organism. As such, 5-HT can be considered a 113 114 pleiotropic hormone. Although blood platelets contain a large amount of 5-HT, they do not have the ability to synthesize it. Several studies have demonstrated that 5-HT is released by circulating 115 platelets in response to signals including contact with damaged endothelium or ischemia [19]. Others 116 have suggested that enterochromaffin cells are used to detect luminal stimuli and couple this to the 117 release of 5-HT [20-24]. 118

119 Recently, Bellono and colleagues [25] have demonstrated that enterochromaffin cells express 120 specific chemosensory receptors that modulate 5-HT-sensitive primary afferent nerve fibers to 121 transduce environmental, metabolic, and homeostatic information from the gut directly to the nervous system. However, this conclusion was based on the use of a 5-HT₃ antagonist and 5-HT₃ receptors 122 123 have been shown to exhibit constitutive activity [26] and potently contribute to the excitability of neurons in the intestinal wall, even when all endogenous 5-HT has been depleted [27]. So, direct 124 evidence that endogenous 5-HT release from enterochromaffin cells acts on any sensory nerves in the 125 aut wall is still lacking. 126

127 Thorough analysis of the Tph1^{-/-} mouse model has demonstrated that 5-HT can also be released by 128 other TPH1-expressing cells, such as pancreatic β cells [9, 10], adipocytes [11], aortic smooth muscle 129 cells [28], breast cells [12], and osteoclasts [13]. Emerging evidence emphasizes the importance of 130 these "microserotonergic systems" (**Figure 1**). Under some conditions, locally restricted 5-HT 131 synthesis may play a predominant role [3], in contrast to the traditional view of gut derived 5-HT as a 132 pleiotropic hormone.

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136 2.2.5-HT synthesis and hypoxia

137 It is well known that neuronal 5-HT is involved in anxiety and psychological stress control [29-31]. In 138 light of this, it is intriguing that the importance of peripheral 5-HT has mostly been revealed under local 139 stress conditions, for which its synthesis serves an adaptive purpose. Hence it is tempting to consider 140 peripheral 5-HT a stress sensor or adapter.

The mucosa of the gastrointestinal tract is physiologically subject to large variation in blood 141 142 perfusion and therefore partial pressure of oxygen as a function of daily dietary intake [32]. Hypoxiainducible factor 1 α (HIF1 α) plays a central role in regulating the cellular and systemic homeostatic 143 144 response to hypoxia [33]. HIF1a isoforms are present in enterochromaffin cells [34], suggesting that hypoxia is a physiological process at baseline. In enterochromaffin cells, a hypoxia-responsive 145 element (HRE) has been identified in the TPH1 promoter region [35, 36], and 5-HT production and 146 147 secretion are upregulated through a HIF1 α -sensitive mechanism [35]. On the other hand, hyperoxia 148 induced by increasing oxygen to 100% in enterochromaffin cells inhibited HRE-mediated signaling and 149 Tph1 transcription, reduced 5-HT secretion, and significantly lowered HIF1α levels [34]. Beyond physiological conditions, in mice models of intestinal ischemia, 5-HT secretion is upregulated through 150 151 a HIF1α-related mechanism associated with nuclear factor kappa B (NF-κB) pathway activation [37]. Increased 5-HT secretion [38, 39] and decreased levels of SERT have been observed [40], while the 152 number of enterochromaffin cells also increases and most cells exhibit HIF1a [41]. 153

Neuroepithelial bodies (NEBs) in lungs are bronchopulmonary neuroendocrine cells that are the 154 pulmonary counterparts of enterochromaffin cells. Like enterochromaffin cells, they have 155 chemomechanical functions and serve as airway chemoreceptors [34]. When exposed to hypoxia, 156 157 NEBs synthesize and release 5-HT, which activates vagal afferents and participates in the peripheral autonomous regulation of breathing [42]. In a rabbit model of lung transplantation for an ischemia-158 reperfusion study, high levels of 5-HT were released during the first 15 minutes after lung harvesting 159 160 and could be antagonized by 5-HT_{2B/2C} receptor (5-HT_{2B/2C} R) antagonists [43]. It is noteworthy that Tph1 alteration is observed as early as 15–30 minutes after hyper- or hypoxia, suggesting that the 161 162 serotonergic system acts as a first-line adapter [34].

Altogether, 5-HT appears to be a local rapid oxygen sensor that may have broad implications in normal and pathological conditions.

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166 2.3.<u>5-HT synthesis and tissue injury</u>

Peripheral 5-HT has been involved in numerous biological processes, including vasoconstriction and vasodilatation, changes in metabolic rate, temperature control, inflammation, and fibrosis [44]. Consequently, the restorative regeneration of a functional tissue after injury, which most of these biological processes may require, has been linked to 5-HT synthesis and local secretion. 171 The adult mammalian liver is a highly regenerative organ that has been used to study 5-HT 172 synthesis and action after tissue injury. In a partial hepatectomy model, peripheral 5-HT is rapidly 173 mobilized in the remnant liver and enhances regeneration of hepatocytes via 5-HT_{2A}R signaling [14, 45]. Platelet-derived 5-HT is involved in the initiation of liver regeneration through the 5-HT_{2A} and 5-174 HT_{2B} receptors on hepatocytes [46], and it plays a key role in hepatic proliferation after major tissue 175 loss. Surprisingly, the cholangiocytes of the hepatic biliary tract have been reported to synthesize 5-176 177 HT [15] that may be a local source for hepatocyte proliferation. In addition, a complete serotonergic system has been described in sinusoidal hepatic stellate cells that express SERT and release and 178 179 respond to 5-HT via autocrine and paracrine routes [47]. The available data obtained from Tph1^{-/-}, 5-HT_{2B}R KO, or pharmacological agonists and antagonists suggest that 5-HT/5-HT_{2A}R signaling in 180 hepatocytes is proregenerative, whereas 5-HT_{2B}R signaling via hepatic stellate cells in a fibrogenic 181 182 environment is antiregenerative [48].

183 Several respiratory diseases characterized by pulmonary fibrosis have been linked to 5-HT 184 deregulation. However, in some conditions, like acute postoperative pulmonary arterial hypertension (PAH), it has been reported that NEBs may be the major source of 5-HT [49]. Additionally, Tph1 185 expression in pulmonary epithelial cells is higher in patients with idiopathic PAH, and it has been 186 hypothesized that activation of extracellular signal-regulated kinases (ERKs) and reactive oxygen 187 188 species following 5-HT internalization promotes the proliferation of arterial fibroblasts and pulmonary arterial smooth muscle cells [50, 51]. Whether hypoxia or other factors-including certain drugs (e.g., 189 methysergide, a 5-HT₁R agonist and 5-HT₂R antagonist [52], methotrexate [53] or bleomycin [54], 190 mostly 5-HT₂R family antagonists—are triggers of modified 5-HT signaling remains unknown. 191 192 However, these reports highlight that 5-HT is particularly sensitive to local tissue injury in several models. 193

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195 3. 5-HT, embryogenesis and stem cells

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197 3.1.<u>5-HT and embryogenesis</u>

In mice, once they have formed in the aorta-gonad-mesonephros (AGM) region by embryonic day 198 199 10.5 (E10.5), hematopoietic stem/progenitor cells migrate to the yolk sac and later to the placenta, 200 expanding in the fetal liver before colonizing the bone marrow prior to birth [55-57]. The placenta has 201 been recognized as a site of hematopoiesis supporting the development of hematopoietic stem cells 202 (HSCs) [58, 59]. But as an animal matures, bone marrow assumes the task of forming the majority of blood cells for the organism as a whole. The extrinsic and intrinsic regulatory factors controlling 203 204 hematopoietic stem/progenitor cells development are still not completely understood. It is also not clear whether such factors act in a locally restricted paracrine fashion, or if stem cell production and 205 homeostasis can be remotely modulated-for instance, hormonally. Finally, the search for novel 206

regulators is an ongoing challenge for the development of therapeutic approaches in regenerativemedicine.

Among its many roles, 5-HT is a powerful mitogen that has been shown to promote neuro- [60-62] 209 210 and angiogenesis [63, 64]. During embryonic development in mice, where the mitogenic action of 5-HT is particularly important, several studies have reported the presence of components of the 211 serotonergic system [65, 66], including 5-HT_{2B}R and SERT as early as E8 [7] and E9 [4]. These data 212 213 indicate that 5-HT is needed by the embryo before the latter is capable of synthesizing it. It has also been shown that serotonergic drugs have the ability to interfere with development [67]. For instance, 214 215 5-HT dose-dependently stimulates the migration of neural crest cells in culture through the 5-HT_{1A} and 5-HT_{2B} receptors in mice. In addition, 5-HT uptake inhibitors have been shown to inhibit neural crest 216 217 cell migration and ectomesenchyme proliferation in complete embryos cultured in vitro, causing severe 218 craniofacial malformations and suggesting that 5-HT acts as a morphogen [67].

219 Some reports argue for a role played by maternally derived 5-HT during development, whereas 220 others suggest a role played by placentally derived 5-HT [66, 68, 69]. Recently, Laurent and 221 colleagues used immunohistochemistry to demonstrate that villous and extravillous cytotrophoblasts, syncytiotrophoblasts, and fetal capillaries expressed TPH1 in mouse and human placenta throughout 222 223 pregnancy [70]. Within an organ, the presence of 5-HT synthesis, uptake, and receptors is proposed 224 as a complete serotonergic system. The data therefore demonstrated the presence of such a system in the placenta and *de novo* placental synthesis of 5-HT throughout pregnancy. Whether 5-HT is of 225 226 maternal (paracrine) or placental (autocrine) origin during embryonic development-and whether an 227 interaction between these two sources exists—is still a subject of debate.

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3.2.<u>5-HT and stem cells</u>

There are a large variety of stem cells. Having the potential to self-renew and the ability to 230 231 differentiate, stem cells play essential roles at multiple stages of development. In the early embryo, pluripotent stem cells are progenitors of all tissues; whereas, later in development, tissue-restricted 232 233 stem cells give rise to cells with highly specialized functions. Stem cells are the focus of fascinating investigations in science and medicine because of their potential to regenerate and repair damaged 234 235 tissue [71]. And in hematology, stem cells are widely used for treatments such as bone marrow or peripheral stem cell transplantation [72]. As mentioned before, 5-HT plays a role in embryogenic 236 237 development, and it also seems to have broad regenerative properties, as discussed below [46, 73, 238 74].

239 Matsuda et al. demonstrated that mouse mammary glands are able to synthesize 5-HT and 240 contain a complex serotonergic regulatory system [12]. This local serotonergic system appears to play 241 an important role in the development of mammary gland and homeostatic control of lactation. Another cell-autonomous serotonergic system can be found in bone, where Chabbi-Achengli et al. identified 5-HT as a regulator of osteoclast differentiation and function [13]. Interestingly, they found that 5-HT was synthesized by osteoclast precursors, suggesting that 5-HT may be important not only for mature cells, but also for precursor cells.

Similarly, Ayme-Dietrich et al. established the role of 5-HT in cardiac valve remodeling through bone marrow mobilization of endothelial progenitors that express 5-HT_{2B}R, in mice and humans [75]. These cells can be recruited in the cardiac valve, where they are responsible for valve lesions. This discovery parallels findings concerning pulmonary hypertension, in which a similar mechanism involving bone marrow progenitors had previously been demonstrated [76].

In a mice model of multiple sclerosis, Ghareghani et al. found that the SSRI fluvoxamine significantly increased cell viability and proliferation of neural stem cells [77]. Physiological concentrations of fluvoxamine induced remarkably efficient differentiation of neural stem cells into oligodendrocytes, astrocytes, and neurons.

255 Moreover, in mouse pulp-derived stem cell lines and in a rat model of pulp injury, Baudry et al. 256 described a major role for 5-HT in stem cell-mediated dental repair through the 5-HT₂ and 5-HT₇ receptors [78]. They demonstrated that pulp-derived stem cells were able to synthesize, catabolize, 257 and store 5-HT, even though a bulk release of 5-HT by platelets upon pulp injury seemed essential for 258 259 pulpal stem cell-based dental repair. They suggested that within the pulp, 5-HT and dopamine receptor-dependent signaling act in concert to impose stem cell guiescence and/or regulate the 260 balance between self-renewal and differentiation. In response to pulp injury, and through a systemic 5-261 262 HT/dopamine "damage" signal, receptor-bearing stem cells involved in dentin reparation would be 263 forced to leave their quiescent state and differentiate in order to participate in dentin repair.

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265 4. 5-HT and hematopoiesis

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267 4.1.<u>5-HT and hematopoietic stem cells</u>

Little is known regarding the mechanism of action of 5-HT during hematopoiesis. As discussed below, it was long ago hypothesized that 5-HT had a strong erythropoietic effect in mice through stimulation of the 5-HT₂ receptor family [79, 80]. Since then, several studies have considered its action on hematopoietic stem/progenitor cells. Some suggested a molecular interrelation of neuronal and hematopoietic signaling mechanisms in primary human CD34⁺ hematopoietic stem and progenitor cells [81]. In particular, the presence of the 5-HT_{1F}R on CD34⁺ cells suggested a possible neuronal regulation of immature hematopoietic progenitors [82].

Along that line, during embryogenesis, 5-HT has been found to impact HSCs in mice [83] and zebrafish [84]. Surprisingly, in zebrafish, Kwan et al. showed that 5-HT synthesis induced by a stress signal in the brain promoted the formation of blood at a rather distant site (dorsal aorta) [84]. During

278 early zebrafish development, hematopoietic stem/progenitor cells proliferation may be modulated by 279 distant neurotransmitter activity, such as a hypoxic stress-induced central serotonergic 280 neurotransmitter acting on Tph2 via the hypothalamic-pituitary-adrenal/interrenal (HPA/I) axis and local glucocorticoid-glucocorticoid receptor activity. Lv et al., using the Tph2^{-/-} mouse model, proposed that 281 5-HT synthesized by Tph2 in the AGM regulates hematopoietic stem/progenitor cells survival [83]. 282 Both studies argue that a Tph2 neuronal signal was responsible for the development of hematopoietic 283 284 stem/progenitor cells during early embryonic development. In contrast, Kirouac et al reported that HSC expansion correlated with G-protein-coupled receptor neurotransmitter signaling (especially the 5-285 286 HT₂R family), giving further support to the concept of microserotonergic systems. Specifically, an endogenous serotonergic signal of nonneuronal origin produced by hematopoietic progenitor cells 287 may be acting as an autocrine/paracrine factor to regulate the fate of hematopoietic progenitors 288 289 through 5-HT receptors [85].

290 In vitro stimulation with 5-HT is able to induce the expansion of cultured human umbilical cord blood CD34⁺ cells, yielding early stem/progenitors (CD34⁺, CFU-GEMM) and multi-lineage-committed 291 progenitors (BFU-E/CFU-E, CFU-GM, CFU-M) [86]. Additionally, 5-HT stimulates bone marrow 292 stromal cell formation [86]. A few studies have further shown that neurotransmitters such as dopamine 293 or 5-HT can improve in vitro proliferation and in vivo engraftment of hematopoietic stem/progenitor 294 295 cells [85-88]. In a xenograft model, 5-HT has been shown to increase proliferation and mobility of 296 human CD34⁺ cells derived from cord blood or circulating blood after mobilization with granulocyte-297 colony stimulating factor (G-CSF) [88], suggesting an additional role for 5-HT in HSC mobilization.

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4.2.5-HT and hematopoietic progenitors

301 Erythroid progenitors and megacaryocytes

302 It has been assumed for a long time that progenitors for platelets (megakaryocytes) and erythroid cells (Burst-Forming Unit and Colony Forming Unit aka BFU-E and CFU-E) differentiate from a shared 303 304 precursor, namelv the megakaryocyte-erythroid progenitor (MEP). Although recently immunophenotyping strategies have permitted the identification of specific intermediate progenitor 305 306 populations in erythro-megakaryopoiesis (73), it is tempting to suggest that the serotonergic system may be implicated in the two lineages. In fact, the first hematopoietic cells studied in connection with 307 the serotonergic system were megakaryocytes, due to the well-known link between 5-HT and 308 platelets. In mice and humans [89, 90], it was found that 5-HT promoted mitogenesis in 309 310 megakaryocytes through 5-HT₂ receptors and exerted an antiapoptotic effect on the megakaryocyte lineage [86]. Further studies demonstrated that 5-HT promoted megakaryopoiesis and proplatelet 311 312 formation through ERK signaling and F-actin reorganization [91]. The contribution of 5-HT signaling pathways via the 5-HT_{2B}R present on hematopoietic stem cell (c-Kit+) in the bone marrow also 313

314 revealed an intrinsic role on c-Kit+ progenitors in the context of hypoxia-induced vascular remodeling
315 as observed in pulmonary hypoxia [76, 92].

The hypothesis that 5-HT could play a role in erythropoiesis was proposed decades ago. In 1970, 316 317 Lowly et al. demonstrated that subcutaneous administration of 5-HT in mice led to an increase in hematocrit that was erythropoietin (EPO)-dependent [79]. More recently, studies have also suggested 318 the presence of Tph1 in erythroid progenitors, promoting their self-renewal [93-96]. Analysis of Tph1-/-319 320 mice led to important findings about the role of 5-HT in erythropoiesis and red blood cell (RBC) survival [97-99]. It was demonstrated that as young adults, peripheral 5-HT-deficient mice developed 321 322 macrocytic anemia due to ineffective bone marrow erythropoiesis, with hampered progression of 323 precursors towards terminal differentiation and shortened survival of mature RBCs [99]. In vitro 324 experiments with isolated Tph1^{-/-} erythroid precursors showed they have a decreased proliferative 325 capacity that is restored by addition of 5-HT [99], suggesting they possess the capacity to synthesize 326 5-HT. The local production of 5-HT within bone marrow is an intense field of research. This locally 327 produced 5-HT could act as a paracrine or autocrine agent, possibly activating the 5-HT_{2A} and 5-HT_{2B} receptors identified on erythroid precursors in mice [76]. 328

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5. 5-HT in hematopoietic diseases and future applications for SSRI therapy

The data discussed above suggest that 5-HT exerts a local effect through microserotonergic systems, that it has regenerative properties possibly arising from a direct role on progenitor or stem cells, and that its action on progenitor or stem cells is required mainly after an injury. As we have seen, all these findings can be applied to the hematopoietic system, in normal and pathological hematopoiesis.

The question that arises is whether the potential source of 5-HT in the bone marrow could be used as a mitogen to regulate hematopoietic stem/progenitor cells maintenance and regeneration after various types of injury. In addition, as it has been demonstrated that 5-HT plays an important role on different hematopoietic lineages, we might wonder whether SSRI treatment could have an impact on the engraftment, function, and/or mobilization of HSCs.

We will next discuss the possible role of 5-HT in hematopoietic diseases, as well as potential future applications for SSRI therapy (**Figure 2**).

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345 5.1.<u>5-HT and hematopoietic stem cell stimulation</u>

Autologous or allogeneic hematopoietic stem cell transplantation (HSCT) are major therapies for several hematologic and some non-hematologic malignant disorders. Most autologous and nearly 3/4 of allogeneic HSCT are performed with HSC collected in the peripheral blood after mobilization. It is therefore important to properly mobilize donors, to obtain a sufficient amount of CSH for the transplant. However, up to 30% of healthy donors or patients are failing standard mobilization [100]. Interestingly, a report has suggested the involvement of dopaminergic or adrenergic neurotransmitters in the regulation of hematopoietic stem and progenitor cell, precisely on motility, proliferation and repopulation [88]. Indeed, norepinephrine has been shown to increase the mobilization of HSC and to induce the downregulation of CXCL12, a chemokine essential for maintaining stem cells within the bone marrow. The use of a β -2–adrenergic agonist augmented this mobilization [88].

As discussed before, 5-HT has a role in cardiac valve remodeling through bone marrow 356 mobilization of endothelial progenitors [75], and has been shown to increase proliferation and mobility 357 358 of human CD34⁺ cells [88]. Hence SSRI treatment might have clinical applications on HSCs therapies where increase 5-HT level may help mobilization and/or engraftment of HSCs for autologous or 359 allogeneic HSCT [85-88]. SSRI treatment could also help to improve HSC function, since some data 360 361 suggest a positive impact of 5-HT on HSCs' proliferation or differentiation [86]. This beneficial effect 362 might also be related to a positive effect of 5-HT on the bone marrow microenvironment [86]. This 363 could be of importance in several situations leading to a differentiation blockade, such as drug-induced 364 agranulocytosis, or in autoimmune or chemotherapy-induced bone marrow aplasia.

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5.2.5-HT, anemia and depression

Anemia is a debilitating, highly prevalent condition with heterogeneous causes and widely varying 367 prognoses. As mentioned before, we demonstrated that erythroid precursors are sensitive to 5-HT 368 [99]. In parallel, it is known that 5-HT affects mood, and that low levels are associated with the onset 369 of depression. Furthermore, varying levels of its precursor, tryptophan, are likely to influence 5-HT 370 371 availability. In addition, it has long been hypothesized that the kynurenine pathway of tryptophan 372 metabolism mediates both genetic and environmental mechanisms of depression. The recent publication by Vulser and colleagues showing a robust association between depression and anemia, 373 374 is of further support of the emerging link between lower 5-HT levels and anemia [101].

375 SSRI therapy could therefore find an application in several clinical situations where correction of 376 anemia is challenging, or where anemia impacts the patients' quality of life. The use of SSRI with the 377 aim of correcting both anemia and depression could be a very promising strategy.

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5.3.5-HT and myelodysplastic syndromes related anemia

Myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by dysplastic changes in the bone marrow, ineffective hematopoiesis resulting in cytopenias, and an increased risk of developing acute myeloid leukemia. MDSs are sporadic diseases affecting predominantly the elderly, with a median age of diagnosis of over 70 years, and generally having a poor prognosis. MDSs were found to be associated with greater tryptophan breakdown and higher kynurenine levels, implying that enhanced tryptophan metabolism and elevated levels of kynurenine metabolites in patients' sera could inhibit hematopoietic progenitor amplification [102]. This enhanced breakdown of tryptophan may have an impact on hematopoiesis through a reduction in 5-HT synthesis, as it has been documented in patients with anemia of inflammation [103].

In patients with lower-risk MDSs, where anemia is a major sign, Rivero et al. observed greater overall survival among patients treated with SSRIs, including fluoxetine [104]. The authors suggest that SSRI administration could exerts a cytokine regulatory effect leading to improved ineffective hematopoiesis, such that low-risk myelodysplastic patients may benefit from SSRI treatment.

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5.4.5-HT, myelodysplastic syndromes and inflammation

In MDSs, apoptosis and immune deregulation have been shown to play a role in the development
 of medullary hypoplasia and cytopenia. SSRI, by decreasing pro-inflammatory cytokines such as IL-6,
 TNFα and IFNγ, could be beneficial in several situations where inflammation is deleterious, such as
 MSDs but also other inflammatory diseases.

Consistently, a neuro-inflammatory response is detected in a large number of patients suffering from depression, with features including an increase of pro-inflammatory cytokines (IL-1, IL-6, TNFα) [105, 106]. This neuro-inflammatory response, along with the observation that many symptoms developed in chronic inflammation are similar to the symptoms presented by depressive patients (lack of movement, indifference, self-neglect and reduced intake of food), led to the inflammatory and neurodegeneration hypothesis of major depression [105, 107]. This data supports the hypothesis that SSRIs could be of interest in various inflammatory diseases.

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408 Discussion and conclusion

409 Animal models play a crucial role in helping us understand basic cellular biological phenomena. Since the discovery of the second Tph isoform, an important key to the understanding of 5-HT 410 functions both in the CNS and in the periphery has been the use of KO mice models. Detailed analysis 411 of the mouse model selectively deficient in peripheral 5-HT (Tph1^{-/-} or Tph1 KO) suggested that local 412 physiological serotonergic networks might exist not exclusively in the gut but also in the placenta and 413 414 the bone marrow, where they would be involved in hematopoietic stem/progenitor cells proliferation. However, the possibility that gut-derived 5-HT or neuronal 5-HT exerts an activity on hematopoietic 415 stem/progenitor cells proliferation during early embryonic development is not excluded. Albeit within 416 417 an organ or a specific cell type, local Tph enzymatic activity, followed by endogenous production of 5-418 HT and the presence of serotonergic components (receptors, SERT) are of importance and support 419 the view that 5-HT is a monoamine with a paracrine/autocrine function. Hence, a locally derived source of 5-HT acting directly on 5-HT receptors present on HSCs does not require an intermediate
 signal such as the one observed in zebrafish embryos where 5-HT synthesized by Tph2 in the CNS
 regulates embryonic HSPC production via a glucocorticoid receptor signaling [84].

Whether peripheral 5-HT could be considered as a stress sensor or adapter and whether targeting 423 the serotonergic system could be of therapeutic value are questions of high interest, still some 424 questions remain unanswered. One concern can be how to specifically increase 5-HT concentration 425 426 locally, for instance in the bone marrow for the development of HSCs. Available molecules include 5-HT receptors specific agonists and antagonists, or SSRI, however whether these drugs could increase 427 428 extracellular concentrations and signaling of 5-HT in the bone marrow remains unknown. Timing is also an important concern as it seems that 5-HT is critical at specific checkpoints, or after an injury. 429 Altogether, the serotonergic system may be a promising therapeutic target with broad regenerative 430 431 capacity to regulate stem cell maintenance and regeneration following various types of injury.

432

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439

440 **Figure legends.**

441 **Graphical abstract**. Traditional view and new aspects of 5-HT synthesis.

- 442
- 443 **Legend Figure 1.** Microserotonergic systems.
- 5-HT synthesis during a specific period may be viewed as a stress sensor or adapter to local injury.
- 445 Peripheral 5-HT may be involved in the proliferation/maturation/survival of hematopoietic stem and
- 446 progenitor cells through a local serotonergic system present in the bone marrow.
- 447
- Legend Figure 2. General overview of hematopoiesis and potential benefits of the increase of 5-HT
 levels by SSRIs.

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Traditionnal view of 5-HT system

New aspects: 5-HT microserotonergic systems



5% of serotonin is synthesized in the brain

is synthesized in periphery (gut)

