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## Serotonin, hematopoiesis and stem cells

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**References:**107

### Abbreviations

5-HT1 to 5-HT7, names of 7 classes of serotonin receptors;  
5-HT<sub>2A</sub>R, 5-HT<sub>2B</sub>R, 5-HT<sub>2C</sub>R, specific serotonin receptors;  
5-HTP, 5-hydroxytryptophan;  
AGM, aorta-gonad-mesonephros;  
BFU-E and CFU-E, Burst-forming Unit Erythroid and Colony forming Unit Erythroid  
CFU-GEMM, CFU-GM, CFU-M, Colony-Forming Unit-Granulocyte, Erythrocyte, Monocyte  
/Macrophage, Megakaryocyte;  
E<sub>n</sub>, embryonic day *n*;  
HSC, hematopoietic stem cell;  
HSPC, hematopoietic stem / progenitor cell;  
KO, knockout;  
MDS, myelodysplastic syndrome;  
SERT, serotonin transporter;  
SSRI, selective serotonin reuptake inhibitor;  
TPH, tryptophan hydroxylase;  
Tph1 and Tph2, isoforms of tryptophan hydroxylase;  
Tph1<sup>-/-</sup> or Tph1 KO, murine model deficient in peripheral serotonin.

### Chemical compounds

Chemical compounds studied in this article:  
5-Hydroxytryptophan (PubChem CID: 144);  
Fluoxetine (PubChem CID: 3386);  
Kynurenine (PubChem CID: 846);  
Serotonin (PubChem CID: 5202);

50 Tryptophan (PubChem CID: 6305).

51 **Abstract**

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

64 **1. Introduction**

65  
66 Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine highly conserved throughout evolution. It  
67 is derived from the essential amino acid tryptophan, obtained from dietary sources. As a well-known  
68 neurotransmitter in the central nervous system (CNS), 5-HT is involved in cognition, attention,  
69 emotion, pain, sleep, and arousal, to name a few examples. Yet only a small percentage of the body's  
70 5-HT (~5%) can be found in the mature brain of mammals: most (~95%) is found synthesized in the  
71 gastrointestinal tract [1-3]. The cellular effects of 5-HT are exerted through activation of any of 15  
72 different receptors in 7 different classes (5-HT<sub>1</sub> to 5-HT<sub>7</sub>) [4]. Through these receptors, 5-HT can  
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  
75 transporter (SERT). SERT removes secreted 5-HT from the extracellular medium when it is no longer  
76 required. Treatments with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, by  
77 blocking the action of SERT, lead to increased 5-HT extracellular concentrations and signaling [5]. The  
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].

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

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

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

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99

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

101

### 102 2.1. 5-HT synthesis

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

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  
122 system. However, this conclusion was based on the use of a 5-HT<sub>3</sub> antagonist and 5-HT<sub>3</sub> receptors  
123 have been shown to exhibit constitutive activity [26] and potently contribute to the excitability of  
124 neurons in the intestinal wall, even when all endogenous 5-HT has been depleted [27]. So, direct  
125 evidence that endogenous 5-HT release from enterochromaffin cells acts on any sensory nerves in the  
126 gut wall is still lacking.

127 Thorough analysis of the Tph1<sup>-/-</sup> mouse model has demonstrated that 5-HT can also be released by  
128 other TPH1-expressing cells, such as pancreatic  $\beta$  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.

133

134

135

### 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.

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

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

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

### 166 2.3.5-HT synthesis and tissue injury

167 Peripheral 5-HT has been involved in numerous biological processes, including vasoconstriction  
168 and vasodilatation, changes in metabolic rate, temperature control, inflammation, and fibrosis [44].  
169 Consequently, the restorative regeneration of a functional tissue after injury, which most of these  
170 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<sub>2A</sub>R signaling [14,  
174 45]. Platelet-derived 5-HT is involved in the initiation of liver regeneration through the 5-HT<sub>2A</sub> and 5-  
175 HT<sub>2B</sub> receptors on hepatocytes [46], and it plays a key role in hepatic proliferation after major tissue  
176 loss. Surprisingly, the cholangiocytes of the hepatic biliary tract have been reported to synthesize 5-  
177 HT [15] that may be a local source for hepatocyte proliferation. In addition, a complete serotonergic  
178 system has been described in sinusoidal hepatic stellate cells that express SERT and release and  
179 respond to 5-HT via autocrine and paracrine routes [47]. The available data obtained from Tph1<sup>-/-</sup>, 5-  
180 HT<sub>2B</sub>R KO, or pharmacological agonists and antagonists suggest that 5-HT/5-HT<sub>2A</sub>R signaling in  
181 hepatocytes is proregenerative, whereas 5-HT<sub>2B</sub>R signaling via hepatic stellate cells in a fibrogenic  
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  
185 (PAH), it has been reported that NEBs may be the major source of 5-HT [49]. Additionally, Tph1  
186 expression in pulmonary epithelial cells is higher in patients with idiopathic PAH, and it has been  
187 hypothesized that activation of extracellular signal-regulated kinases (ERKs) and reactive oxygen  
188 species following 5-HT internalization promotes the proliferation of arterial fibroblasts and pulmonary  
189 arterial smooth muscle cells [50, 51]. Whether hypoxia or other factors—including certain drugs (e.g.,  
190 methysergide, a 5-HT<sub>1</sub>R agonist and 5-HT<sub>2</sub>R antagonist [52], methotrexate [53] or bleomycin [54],  
191 mostly 5-HT<sub>2</sub>R family antagonists—are triggers of modified 5-HT signaling remains unknown.  
192 However, these reports highlight that 5-HT is particularly sensitive to local tissue injury in several  
193 models.

194

### 195 **3. 5-HT, embryogenesis and stem cells**

196

#### 197 **3.1. 5-HT and embryogenesis**

198 In mice, once they have formed in the aorta-gonad-mesonephros (AGM) region by embryonic day  
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  
203 blood cells for the organism as a whole. The extrinsic and intrinsic regulatory factors controlling  
204 hematopoietic stem/progenitor cells development are still not completely understood. It is also not  
205 clear whether such factors act in a locally restricted paracrine fashion, or if stem cell production and  
206 homeostasis can be remotely modulated—for instance, hormonally. Finally, the search for novel

207 regulators is an ongoing challenge for the development of therapeutic approaches in regenerative  
208 medicine.

209 Among its many roles, 5-HT is a powerful mitogen that has been shown to promote neuro- [60-62]  
210 and angiogenesis [63, 64]. During embryonic development in mice, where the mitogenic action of 5-  
211 HT is particularly important, several studies have reported the presence of components of the  
212 serotonergic system [65, 66], including 5-HT<sub>2B</sub>R and SERT as early as E8 [7] and E9 [4]. These data  
213 indicate that 5-HT is needed by the embryo before the latter is capable of synthesizing it. It has also  
214 been shown that serotonergic drugs have the ability to interfere with development [67]. For instance,  
215 5-HT dose-dependently stimulates the migration of neural crest cells in culture through the 5-HT<sub>1A</sub> and  
216 5-HT<sub>2B</sub> receptors in mice. In addition, 5-HT uptake inhibitors have been shown to inhibit neural crest  
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,  
222 syncytiotrophoblasts, and fetal capillaries expressed TPH1 in mouse and human placenta throughout  
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  
225 in the placenta and *de novo* placental synthesis of 5-HT throughout pregnancy. Whether 5-HT is of  
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.

228

### 229 3.2.5-HT and stem cells

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

242 Another cell-autonomous serotonergic system can be found in bone, where Chabbi-Achengli et al.  
243 identified 5-HT as a regulator of osteoclast differentiation and function [13]. Interestingly, they found  
244 that 5-HT was synthesized by osteoclast precursors, suggesting that 5-HT may be important not only  
245 for mature cells, but also for precursor cells.

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

251 In a mice model of multiple sclerosis, Ghareghani et al. found that the SSRI fluvoxamine  
252 significantly increased cell viability and proliferation of neural stem cells [77]. Physiological  
253 concentrations of fluvoxamine induced remarkably efficient differentiation of neural stem cells into  
254 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-HT<sub>2</sub> and 5-HT<sub>7</sub>  
257 receptors [78]. They demonstrated that pulp-derived stem cells were able to synthesize, catabolize,  
258 and store 5-HT, even though a bulk release of 5-HT by platelets upon pulp injury seemed essential for  
259 pulpal stem cell-based dental repair. They suggested that within the pulp, 5-HT and dopamine  
260 receptor-dependent signaling act in concert to impose stem cell quiescence and/or regulate the  
261 balance between self-renewal and differentiation. In response to pulp injury, and through a systemic 5-  
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.

264

#### 265 **4. 5-HT and hematopoiesis**

266

##### 267 4.1. 5-HT and hematopoietic stem cells

268 Little is known regarding the mechanism of action of 5-HT during hematopoiesis. As discussed  
269 below, it was long ago hypothesized that 5-HT had a strong erythropoietic effect in mice through  
270 stimulation of the 5-HT<sub>2</sub> receptor family [79, 80]. Since then, several studies have considered its action  
271 on hematopoietic stem/progenitor cells. Some suggested a molecular interrelation of neuronal and  
272 hematopoietic signaling mechanisms in primary human CD34<sup>+</sup> hematopoietic stem and progenitor  
273 cells [81]. In particular, the presence of the 5-HT<sub>1F</sub>R on CD34<sup>+</sup> cells suggested a possible neuronal  
274 regulation of immature hematopoietic progenitors [82].

275 Along that line, during embryogenesis, 5-HT has been found to impact HSCs in mice [83] and  
276 zebrafish [84]. Surprisingly, in zebrafish, Kwan et al. showed that 5-HT synthesis induced by a stress  
277 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  
281 glucocorticoid–glucocorticoid receptor activity. Lv et al., using the Tph2<sup>-/-</sup> mouse model, proposed that  
282 5-HT synthesized by Tph2 in the AGM regulates hematopoietic stem/progenitor cells survival [83].  
283 Both studies argue that a Tph2 neuronal signal was responsible for the development of hematopoietic  
284 stem/progenitor cells during early embryonic development. In contrast, Kirouac et al reported that HSC  
285 expansion correlated with G-protein–coupled receptor neurotransmitter signaling (especially the 5-  
286 HT<sub>2</sub>R family), giving further support to the concept of microserotonergic systems. Specifically, an  
287 endogenous serotonergic signal of nonneuronal origin produced by hematopoietic progenitor cells  
288 may be acting as an autocrine/paracrine factor to regulate the fate of hematopoietic progenitors  
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  
291 CD34<sup>+</sup> cells, yielding early stem/progenitors (CD34<sup>+</sup>, CFU-GEMM) and multi-lineage–committed  
292 progenitors (BFU-E/CFU-E, CFU-GM, CFU-M) [86]. Additionally, 5-HT stimulates bone marrow  
293 stromal cell formation [86]. A few studies have further shown that neurotransmitters such as dopamine  
294 or 5-HT can improve *in vitro* proliferation and *in vivo* engraftment of hematopoietic stem/progenitor  
295 cells [85-88]. In a xenograft model, 5-HT has been shown to increase proliferation and mobility of  
296 human CD34<sup>+</sup> 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.

298

#### 299 4.2.5-HT and hematopoietic progenitors

300

##### 301 *Erythroid progenitors and megakaryocytes*

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

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

316 The hypothesis that 5-HT could play a role in erythropoiesis was proposed decades ago. In 1970,  
317 Lowly et al. demonstrated that subcutaneous administration of 5-HT in mice led to an increase in  
318 hematocrit that was erythropoietin (EPO)-dependent [79]. More recently, studies have also suggested  
319 the presence of Tph1 in erythroid progenitors, promoting their self-renewal [93-96]. Analysis of Tph1<sup>-/-</sup>  
320 mice led to important findings about the role of 5-HT in erythropoiesis and red blood cell (RBC)  
321 survival [97-99]. It was demonstrated that as young adults, peripheral 5-HT-deficient mice developed  
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<sup>-/-</sup> 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<sub>2A</sub> and 5-HT<sub>2B</sub>  
328 receptors identified on erythroid precursors in mice [76].

329  
330

## 331 **5. 5-HT in hematopoietic diseases and future applications for SSRI therapy**

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

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

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

344

### 345 5.1.5-HT and hematopoietic stem cell stimulation

346 Autologous or allogeneic hematopoietic stem cell transplantation (HSCT) are major therapies for  
347 several hematologic and some non-hematologic malignant disorders. Most autologous and nearly 3/4  
348 of allogeneic HSCT are performed with HSC collected in the peripheral blood after mobilization. It is  
349 therefore important to properly mobilize donors, to obtain a sufficient amount of CSH for the

350 transplant. However, up to 30% of healthy donors or patients are failing standard mobilization [100].  
351 Interestingly, a report has suggested the involvement of dopaminergic or adrenergic neurotransmitters  
352 in the regulation of hematopoietic stem and progenitor cell, precisely on motility, proliferation and  
353 repopulation [88]. Indeed, norepinephrine has been shown to increase the mobilization of HSC and to  
354 induce the downregulation of CXCL12, a chemokine essential for maintaining stem cells within the  
355 bone marrow. The use of a  $\beta$ -2-adrenergic agonist augmented this mobilization [88].

356 As discussed before, 5-HT has a role in cardiac valve remodeling through bone marrow  
357 mobilization of endothelial progenitors [75], and has been shown to increase proliferation and mobility  
358 of human CD34<sup>+</sup> cells [88]. Hence SSRI treatment might have clinical applications on HSCs therapies  
359 where increase 5-HT level may help mobilization and/or engraftment of HSCs for autologous or  
360 allogeneic HSCT [85-88]. SSRI treatment could also help to improve HSC function, since some data  
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.

365

#### 366 5.2.5-HT, anemia and depression

367 Anemia is a debilitating, highly prevalent condition with heterogeneous causes and widely varying  
368 prognoses. As mentioned before, we demonstrated that erythroid precursors are sensitive to 5-HT  
369 [99]. In parallel, it is known that 5-HT affects mood, and that low levels are associated with the onset  
370 of depression. Furthermore, varying levels of its precursor, tryptophan, are likely to influence 5-HT  
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  
373 publication by Vulser and colleagues showing a robust association between depression and anemia,  
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.

378

#### 379 5.3.5-HT and myelodysplastic syndromes related anemia

380 Myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal hematopoietic stem cell  
381 disorders characterized by dysplastic changes in the bone marrow, ineffective hematopoiesis resulting  
382 in cytopenias, and an increased risk of developing acute myeloid leukemia. MDSs are sporadic  
383 diseases affecting predominantly the elderly, with a median age of diagnosis of over 70 years, and  
384 generally having a poor prognosis.

385 MDSs were found to be associated with greater tryptophan breakdown and higher kynurenine  
386 levels, implying that enhanced tryptophan metabolism and elevated levels of kynurenine metabolites  
387 in patients' sera could inhibit hematopoietic progenitor amplification [102]. This enhanced breakdown  
388 of tryptophan may have an impact on hematopoiesis through a reduction in 5-HT synthesis, as it has  
389 been documented in patients with anemia of inflammation [103].

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

394

#### 395 5.4.5-HT, myelodysplastic syndromes and inflammation

396 In MDSs, apoptosis and immune deregulation have been shown to play a role in the development  
397 of medullary hypoplasia and cytopenia. SSRI, by decreasing pro-inflammatory cytokines such as IL-6,  
398 TNF $\alpha$  and IFN $\gamma$ , could be beneficial in several situations where inflammation is deleterious, such as  
399 MSDs but also other inflammatory diseases.

400 Consistently, a neuro-inflammatory response is detected in a large number of patients suffering  
401 from depression, with features including an increase of pro-inflammatory cytokines (IL-1, IL-6, TNF $\alpha$ )  
402 [105, 106]. This neuro-inflammatory response, along with the observation that many symptoms  
403 developed in chronic inflammation are similar to the symptoms presented by depressive patients (lack  
404 of movement, indifference, self-neglect and reduced intake of food), led to the inflammatory and  
405 neurodegeneration hypothesis of major depression [105, 107]. This data supports the hypothesis that  
406 SSRIs could be of interest in various inflammatory diseases.

407

## 408 **Discussion and conclusion**

409 Animal models play a crucial role in helping us understand basic cellular biological phenomena.  
410 Since the discovery of the second Tph isoform, an important key to the understanding of 5-HT  
411 functions both in the CNS and in the periphery has been the use of KO mice models. Detailed analysis  
412 of the mouse model selectively deficient in peripheral 5-HT (Tph1<sup>-/-</sup> or Tph1 KO) suggested that local  
413 physiological serotonergic networks might exist not exclusively in the gut but also in the placenta and  
414 the bone marrow, where they would be involved in hematopoietic stem/progenitor cells proliferation.  
415 However, the possibility that gut-derived 5-HT or neuronal 5-HT exerts an activity on hematopoietic  
416 stem/progenitor cells proliferation during early embryonic development is not excluded. Albeit within  
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

420 source of 5-HT acting directly on 5-HT receptors present on HSCs does not require an intermediate  
421 signal such as the one observed in zebrafish embryos where 5-HT synthesized by Tph2 in the CNS  
422 regulates embryonic HSPC production via a glucocorticoid receptor signaling [84].

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

444 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.

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448 **Legend Figure 2.** General overview of hematopoiesis and potential benefits of the increase of 5-HT  
449 levels by SSRIs.

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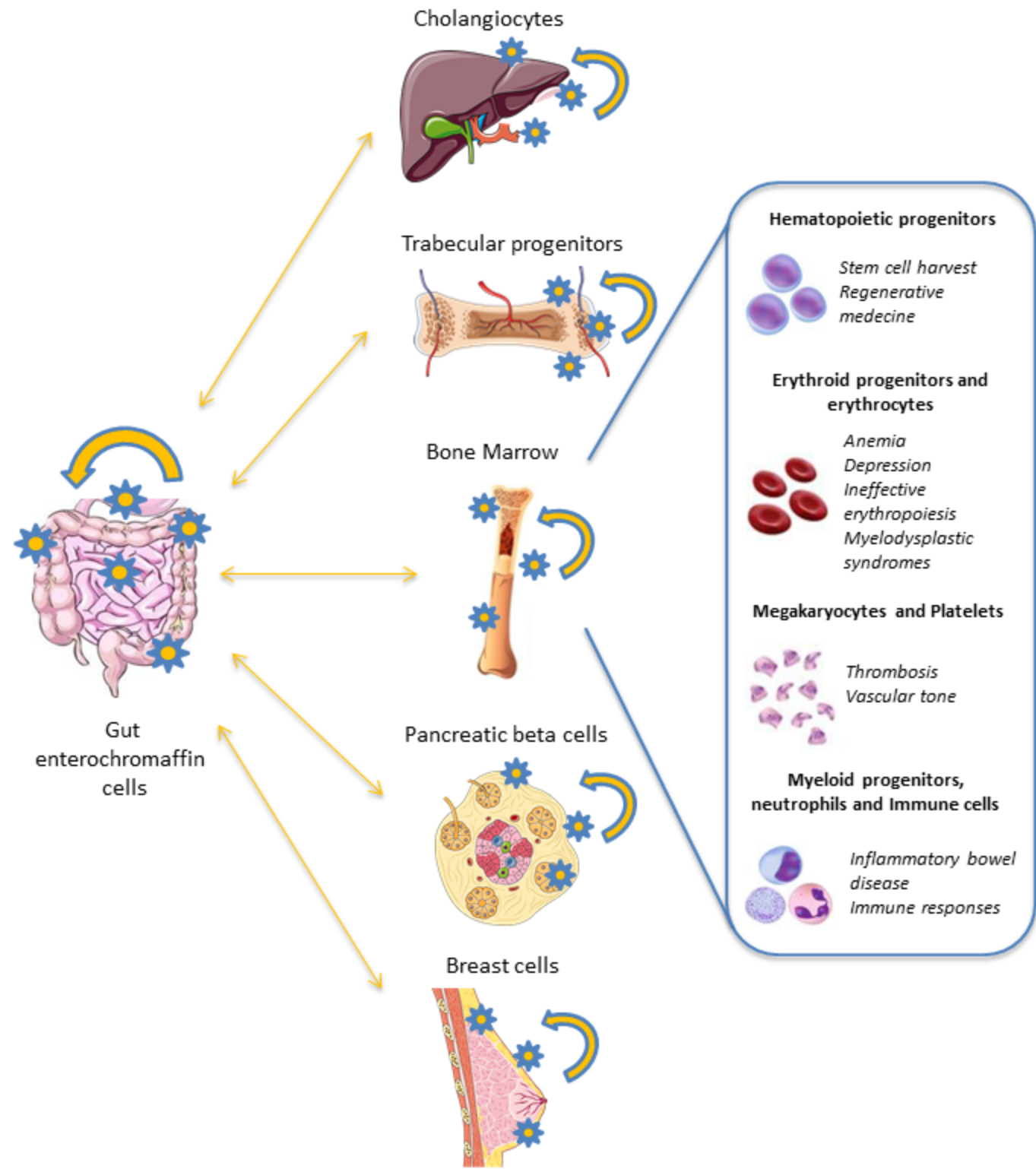
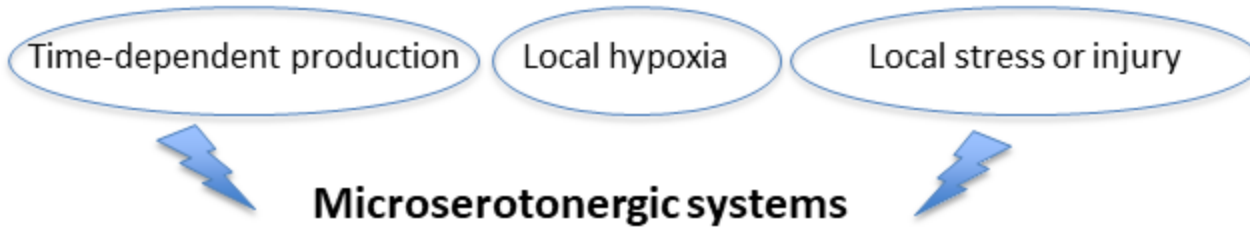
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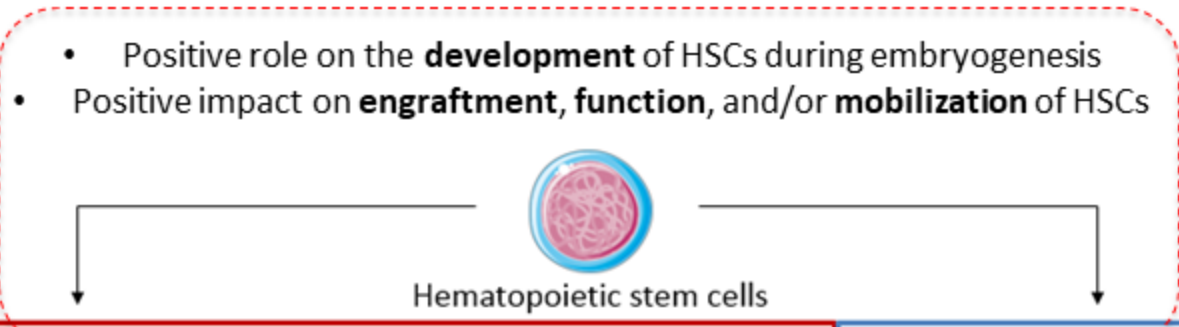
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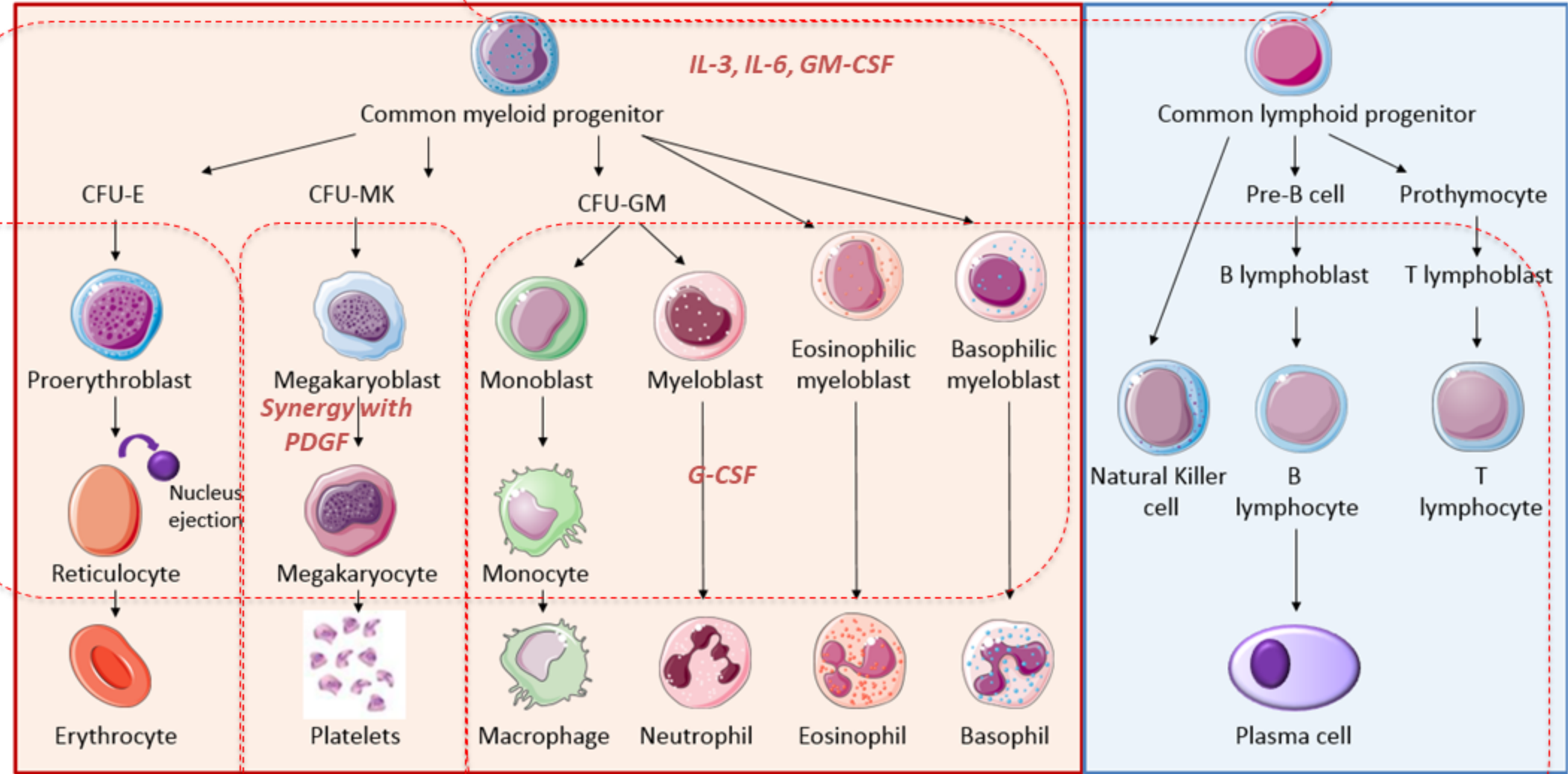
729



HSC renewal, engraftment, developpement



Myelodysplastic syndromes



- Promotion of erythropoiesis
- Correction of ineffective erythropoiesis
- Correction of anemia in depression
- Correction of anemia in MDS

Ineffective erythropoiesis, Anemia

Promotion of megakaryo-poiesis and proplatelet formation

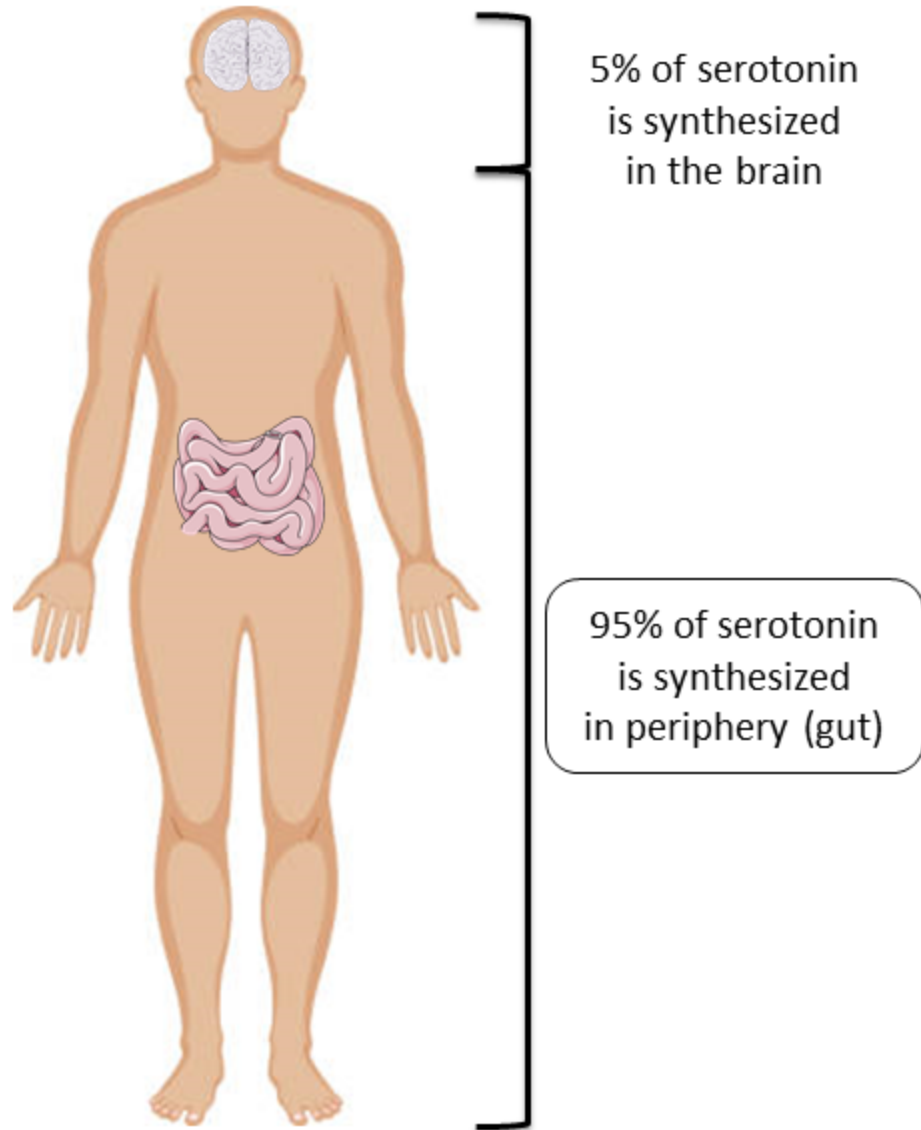
Hemostasis, Thrombosis

Immunomodulatory properties

Immunity, Inflammation

EPO: erythropoietin  
 PDGF: platelet-derived growth factor  
 G-CSF: granulocyte-colony stimulating factor  
 GM-CSF: granulocyte macrophage-colony stimulating factor  
 IL-3: interleukin 3  
 IL-6: interleukin 6

### Traditional view of 5-HT system



### New aspects: 5-HT microserotonergic systems

