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## Serotonin and the immune system

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### Abstract

The defense against pathogens is mediated by innate and adaptive immune mechanisms that act in periphery and central nervous system (CNS). Outside the CNS, serotonin is found in gastrointestinal tract and enteric nerves, in hematopoietic stem cells, and in particularly high abundance in platelets. Serotonin regulates inflammation and immunity by acting on serotonin receptors that are differentially expressed on immune cells, both in rodents and humans. Serotonin acts as a potent chemoattractant, recruiting innate immune cells to sites of inflammation. Serotonin also alters the production and release of cytokines and cell activation/proliferation. Some immune cells, including mast cells and T-lymphocytes, have the capacity to synthesize and release serotonin, expanding the range of tissues for serotonin signaling.

## 1. Introduction

### 1.1 How do immune cells encounter serotonin?

Although serotonin is largely studied as a neurotransmitter, enterochromaffin cells of the gut produce most of the body's serotonin. These cells express tryptophan hydroxylase TPH1, a rate-limiting enzyme for serotonin production (Walther et al., 2002). A second TPH isoform, TPH2, synthesizes serotonin in CNS, and gut enteric nerves (Walther et al., 2002). Serotonin concentrations in blood and tissues are normally low because of uptake by platelets (<1 nM). Immune cells, however, may encounter serotonin released from enterochromaffin cells in gut mucosa, or from platelets, that accumulate serotonin via the membrane serotonin transporter, SERT (SLC6A4), and then stored in dense granules via the vesicular transporter VMAT-2. In turn, platelets can release this stored serotonin at sites of injury and inflammation. Platelet-derived serotonin is important for attracting innate immune cells such as neutrophils to inflamed tissue (Duerschmied et al., 2013). In addition to platelets, dendritic cells (professional antigen-presenting cells) and B-lymphocytes express SERT and thus, can accumulate and release serotonin. Interestingly, recent studies indicate that some immune cells are capable of serotonin biosynthesis. Mast cells (tissue-resident-cells) in rodents and humans express TPH1 and levels of serotonin are elevated in patients with mastocytosis, who have greatly elevated mast-cell numbers (Kushnir-Sukhov et al., 2007; Nowak et al., 2012). Further, T-lymphocytes (León-Ponte et al., 2007; O'Connell et al., 2006; Urbina et al., 2014) express TPH1 upon mitogen or T-cell receptor activation and can synthesize serotonin. Interestingly, expression of TPH1 and serotonin production is greater in CD8<sup>+</sup> compared with CD4<sup>+</sup> T-cells (Chen et al., 2015).

### 1.2 Serotonin and hematopoiesis

It was proposed that serotonin acts at hematopoietic stem cell progenitors directly or via modulation of bone-marrow microenvironment (Yang et al., 2007). Mice deficient in peripheral serotonin (*Tph1*<sup>-/-</sup>) display morphological and cellular features reminiscent of ineffective erythropoiesis (Amireault et al., 2011). Other data showed that bone-marrow composition of *Htr2B*<sup>-/-</sup> mice displayed a significant increase in Cd11b<sup>+</sup>/Gr<sup>+</sup> cells that represents granulocyte precursors. This is associated with a significant reduction in Cd11b<sup>+</sup>/Cd31<sup>+</sup> population that corresponds to immature endothelial progenitor cells in 5-HT<sub>2B</sub><sup>-/-</sup> mice (Launay et al., 2012). These observations support the hypothesis that serotonin signaling controls differentiation of myeloid precursor cells in the monocyte/macrophage lineages.

### 1.3 Serotonin and the immune tolerance

Acquired peripheral tolerance – defined as a functional state of immunological unresponsiveness to antigenic challenge – is a continuous process that prevents innocuous, nonself antigens from stimulating excessive immunity leading to tissue damage. Peripheral tolerance is established by a number of partly overlapping mechanisms that mostly involve control at the level of T cells, especially by differentiation of naïve CD4<sup>+</sup> helper T cells into induced Treg cells, which give B cells the confirmatory signals they need in order to produce antibodies. One well-documented way to control immunity and tolerance is through regulation of nutrients in microenvironment of immune cells. Best described is tryptophan deficiency mediated by the catabolic enzyme indoleamine 2,3-dioxygenase (IDO), which locally depletes tryptophan and liberates immunoregulatory metabolites known as kynurenines. T-cell activation is exquisitely sensitive to local tryptophan catabolism, and thus IDO exerts profound protective effects in allo-fetal rejection, autoimmunity, and inflammation (Munn and Mellor, 2013). Although IDO is thought to be the major tryptophan-catabolizing enzyme outside of liver, TPH1 shares a similar K<sub>M</sub> (~20 μM) (Mckinney et al.,

2005) and can also potentially exhaust tryptophan to regulate immune tolerance. Indeed, in models of skin allograft tolerance, tumor growth and experimental autoimmune encephalomyelitis (multiple sclerosis), *Tph1* deficiency was shown to break allograft tolerance, to induce tumor remission, and to intensify neuroinflammation independent of downstream product, serotonin (Nowak et al., 2012).

## **2. Serotonin and the innate immune response**

Innate immune system function involves monocytes, macrophages, dendritic cells, neutrophils, eosinophils, mast cells and natural killer cells that act immediately in the area of infection, leading to destruction of pathogens. Innate immunity is primarily responsible for recognizing and eradicating “non-self” molecules presented by pathogens, and is therefore confined to recognizing extracellular pathogens (bacteria vs. viruses). This response is nonspecific with respect to particular invaders, but provides immediate host defense against pathogens via pattern recognition by toll-like receptors (TLRs). Pathogen-associated molecular patterns (e.g. peptidoglycans, bacterial lipopolysaccharides-LPS, double-stranded viral RNAs) bind TLRs on antigen-presenting cells, namely, dendritic cells and macrophages. Antigen-presenting cells then phagocytose pathogens and display pathogen-derived peptides via the major histocompatibility complex (MHC) on their cell surface for recognition by leukocytes of the “adaptive” immune system. Antigen-presenting cells also secrete pro-inflammatory cytokines (e.g., IL1 $\beta$ , IL-6, TNF $\alpha$ ), prostaglandins, and histamine, which further activate physiological responses, alerting the body to infection/invasion. In addition to cellular protective mechanisms, innate immunity also includes the complement system, activated by foreign substances, antigen–antibody complexes (classical pathway), and Gram-negative bacteria (alternative pathway). This system leads to cell lysis, increased vascular permeability (allowing antibodies, innate immune cells, and fluid to enter tissues), and chemotaxis. The complement system also helps to activate antigen-presenting cells, namely, dendritic cells and B-cells during specific immune responses. Innate immunity also functions to communicate the presence of pathogens to cells involved in adaptive immune responses (Baganz and Blakely, 2013). The local environment and the presence of stimulatory signals determine whether monocytes acquire dendritic cell or macrophage characteristics and functions. Serotonin receptors are expressed by a broad range of inflammatory cell types.

### **2.1 Serotonin and neutrophils**

Neutrophils are the most abundant white blood cells and serve an essential role in innate immunity, particularly against bacteria. Duerschmied and colleagues (2013) reported that *Tph1*<sup>-/-</sup> mice show mild leukocytosis, i.e. elevated white blood cells (WBC) numbers compared with wild-type (WT) mice, which is primarily driven by an elevated neutrophil count. Despite this, 50% fewer leukocytes rolled on unstimulated mesenteric venous endothelium of *Tph1*<sup>-/-</sup> mice. After LPS treatment, diminished rolling in *Tph1*<sup>-/-</sup> mice resulted in reduced firm adhesion of leukocytes and neutrophil extravasation into lung, peritoneum and skin wounds was also reduced. Serotonin alone did not induce neutrophil migration *in-vitro*, suggesting that endothelial adhesion was the primary deficit. Consequently, survival from LPS-induced endotoxic shock was improved in *Tph1*<sup>-/-</sup> mice.

Acute fluoxetine treatment increased plasma serotonin concentrations and promoted leukocyte-endothelial interactions *in-vivo*, suggesting that serotonin participates in acute inflammation. E-selectin is a cell adhesion molecule expressed only on endothelial cells activated by cytokines, and plays an important part in inflammation. E-selectin is upregulated on endothelial cells in the presence of serotonin, possibly explaining the observed increase in

leukocyte-endothelial interactions. Whether SSRI use in humans alters leukocyte recruitment remains to be investigated (Herr et al., 2014).

In conclusion, platelet serotonin promotes recruitment of neutrophils in acute inflammation; however, the nature of serotonin receptor(s) underlying these effects is unknown.

## 2.2 Serotonin and monocytes

Monocytes are the largest type of leukocyte and can differentiate into macrophages and myeloid lineage dendritic cells. In human monocytes (CD14<sup>+</sup>), mRNA expression of 5-HT<sub>1E</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors is detectable (Dürk et al., 2005). In LPS-stimulated human blood monocytes, serotonin modulates the release of IL-1 $\beta$ , IL-6, IL-8/CXCL8, IL-12p40 and TNF- $\alpha$ , but has no effect on the production of IL-18 and IFN- $\gamma$ . Moreover, serotonin modulates mRNA levels of IL-6 and IL-8/CXCL8, but not of IL-1 $\beta$  and TNF- $\alpha$ . Interestingly, 5-HT<sub>1E</sub> and 5-HT<sub>2A</sub> receptor agonists do not modulate the LPS-induced cytokine production in human monocytes (Dürk et al., 2005). Instead, serotonin modulates cytokine production via activation of 5-HT<sub>3</sub>, 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors. Pharmacologic experiments suggested that signaling through the 5-HT<sub>3</sub> receptor up-regulates LPS-induced production of IL-1 $\beta$ , IL-6 and IL-8/CXCL8, but not that of TNF- $\alpha$  and IL-12p40. Furthermore, activation of the Gs-coupled 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors increases secretion of IL-1 $\beta$ , IL-6, IL-12p40 and IL-8/CXCL8, but in contrast, inhibits LPS-induced TNF- $\alpha$  release.

### 2.2.1 Serotonin and monocyte to macrophage differentiation

Serotonin upregulates the activity of peritoneal macrophages, and increases the *in-vitro* activity of phagocytosis in a concentration-dependent manner via 5-HT<sub>1A/7</sub> receptors and nuclear factor  $\kappa$ B (NF- $\kappa$ B) (Freire-Garabal et al., 2003). Gene expression profiling of pro-inflammatory M1 (GM-CSF) and anti-inflammatory M2 (M-CSF) macrophages revealed that 5-HT<sub>2B</sub> and 5-HT<sub>7</sub> receptor mRNAs are preferentially expressed by M2 macrophages, whereas the 5-HT<sub>7</sub> receptor is the only serotonin receptor expressed in M1 macrophages (de Las Casas-Engel et al., 2013). The 5-HT<sub>2B</sub> receptor is preferentially expressed by anti-inflammatory M2 macrophages, and is also detected *in-vivo* in liver Kupffer cells, and in tumor-associated macrophages. Expression of 5-HT<sub>2C</sub> receptors also occurs in alveolar macrophages, where serotonin induces a rise in intracellular Ca<sup>2+</sup> concentration and an increased expression of CCL2 (MCP-1) mRNA (Mikulski et al., 2010). LPS, the archetypal macrophage-activating stimulus that signals via TLR4, was shown to regulate expression of 5-HT<sub>2B</sub> receptors (20 fold over basal 24h after LPS) in mouse macrophages. 5-HT<sub>2B</sub> receptor mRNA is increased 20-fold in murine thioglycollate-elicited peritoneal macrophages, compared to bone marrow macrophages (Lattin et al., 2008). Serotonin inhibits LPS-induced release of pro-inflammatory cytokines, upregulates expression of macrophage M2 polarization-associated genes and reduces expression of M1-associated genes. Only 5-HT<sub>7</sub> receptors mediate inhibitory action of serotonin on the release of pro-inflammatory cytokines. Both 5-HT<sub>2B</sub> and 5-HT<sub>7</sub> receptors mediate the pro-M2 skewing effect of serotonin. Blockade of both receptors during *in-vitro* monocyte-to-macrophage differentiation preferentially modulates acquisition of M2 polarization markers (de Las Casas-Engel et al., 2013).

Natural killer cells are large lymphocytes with innate killing capacity. Addition of serotonin to mixtures of target-cells and CD56<sup>+</sup> natural killer-enriched human mononuclear cells strongly augmented natural killer cell cytotoxicity via 5-HT<sub>1A</sub> receptors. This effect was indirect and involved serotonin signaling at accessory monocytes. The cytotoxicity-enhancing effect of serotonin was additive to that induced by IFN- $\alpha$ , IFN- $\gamma$ , or IL 2, but not to histamine (Hellstrand and Hermodsson, 1987).

### 2.2.2 Serotonin and microglia

In mice, it has been established that serotonin is an important regulator of microglia, the brain resident macrophages, which are derived from yolk sac hematopoietic stem cell precursors. In the presence of serotonin, microglial processes moved more rapidly towards a lesion, which is considered a chemotactic response. Similarly, chemotactic response of cultured microglia to ATP is enhanced by serotonin. Phagocytic activity determined by the uptake of microspheres reveals that serotonin application decreases phagocytic activity of amoeboid microglia. Expression of microglial 5-HT<sub>2B</sub>, 5-HT<sub>5A</sub> and 5-HT<sub>7</sub> receptors was shown by qPCR analysis of RNA isolated from primary cultured and acutely isolated adult microglia (Krabbe et al., 2012; Kolodziejczak et al., 2015). The presence of functional serotonin receptors was confirmed by patch clamp experiments in cultured and amoeboid neonatal microglia. This was also recently established by two-photon microscopy, showing that microglial processes moved rapidly toward the source of serotonin via activation of the 5-HT<sub>2B</sub> receptor (Kolodziejczak et al., 2015). Modulation of microglial functions like phagocytosis and migration is fundamental for CNS since microglia can influence the balance of synaptogenesis and neuronal death during development and in pathology.

*In-vitro* analyses revealed that stimulation of 5-HT<sub>7</sub> receptors in human microglial cell lines results in an increase in IL-6 expression in these cells, an effect blocked by antagonizing 5-HT<sub>7</sub> receptors (Mahé et al., 2005). As mentioned previously, one of the major functions of microglia is to respond to disruptions in homeostatic states through the release of proinflammatory cytokines. *In vitro* studies using murine microglia cell line showed that microglia can release cytokines, including IL-1 $\beta$ , in exosomes by a process that is not yet fully understood (Glebov et al., 2015). Serotonin also plays an important role in the ability of microglia to release exosomes, which is dependent on increases in cytosolic Ca<sup>2+</sup> elicited through 5-HT<sub>2</sub> and 5-HT<sub>4</sub> receptor activation (Glebov et al., 2015). In this manner, serotonin may ultimately be able to regulate cytokine release and immune processes within the CNS similarly to immune function in the periphery. The release of these cytokines may then act in a concerted manner to modulate other aspects of serotonin neurotransmission, such as SERT-mediated serotonin clearance or exocytotic serotonin release (Robson et al., 2017).

Microglia are implicated in pathogenesis of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS; motoneuron disease; Lou Gehrig's or Charcot's disease). During neurodegeneration, microglial activation is accompanied by infiltration of circulating monocytes, leading to production of multiple inflammatory mediators in spinal cord. The 5-HT<sub>2B</sub> receptor expressed in microglia, is upregulated in spinal cord of three different transgenic mouse models of ALS. In mutant SOD1 mice, this upregulation was restricted to cells positive for CD11b, a marker of mononuclear phagocytes. Ablation of 5-HT<sub>2B</sub> receptor in transgenic ALS mice expressing mutant SOD1 resulted in increased degeneration of mononuclear phagocytes, as evidenced by fragmentation of Iba1-positive cellular processes (El Oussini et al., 2016). This was accompanied by decreased expression of key neuroinflammatory genes but also loss of expression of homeostatic microglial genes. Importantly, the dramatic effect on mononuclear phagocytes of 5-HT<sub>2B</sub>-receptor ablation was associated with acceleration of disease progression. In a large cohort of ALS patients, the C allele of SNP rs10199752 in *HTR2B* was associated with longer survival. Moreover, patients carrying one copy of the C allele of SNP rs10199752 showed increased 5-HT<sub>2B</sub> receptor mRNA expression in spinal cord and displayed less pronounced degeneration of Iba1 positive cells than patients carrying two copies of the more common A allele. Thus, the 5-HT<sub>2B</sub> receptor is able to limit degeneration of spinal cord mononuclear phagocytes, most likely microglia, and slows disease progression in ALS (El Oussini et al., 2016).

### 2.3 Serotonin and dendritic cells

Dendritic cells are potent antigen-presenting cells endowed with the unique ability to initiate adaptive immune responses upon inflammation. Inflammatory processes are often associated with an increased production of serotonin, which operates by activating specific receptors. However, functional role of serotonin receptors in regulation of dendritic cell functions is poorly understood. Platelet activation was reported in patients with various allergic disorders. Platelet-derived factors may influence monocytic differentiation into dendritic cells. Indeed, serotonin alters differentiation of monocytes into dendritic cells (triggered by granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4), leading to dendritic cells with reduced expression of co-stimulatory molecules and CD1a, and higher expression of CD14. These serotonin-triggered dendritic cells exhibit significantly reduced stimulatory activity toward allogenic T-cells. However, they show enhanced cytokine-producing capacity, including for IL-10 but not IL-12. Serotonin-induced alteration of dendritic cells phenotype and reduction in antigen-presenting capacity are mediated via 5-HT<sub>1E</sub>/5-HT<sub>7</sub> receptors (Katoh et al., 2006).

Immature dendritic cells preferentially express mRNA for 5-HT<sub>1B</sub>, 5-HT<sub>1E</sub> and 5-HT<sub>2A/2B</sub> receptors. The 5-HT<sub>1B/1E</sub> and 5-HT<sub>2A/2B</sub> receptor stimulation induces intracellular Ca<sup>2+</sup> mobilization via Gi/Gq proteins in immature, but not mature, dendritic cells. The mRNA expression level of ligand-gated cation channel 5-HT<sub>3</sub> and the GPCR 5-HT<sub>2A</sub> receptors are not modified during maturation. Serotonin stimulates 5-HT<sub>3</sub>-dependent Ca<sup>2+</sup> influx in both immature and mature dendritic cells. Mature dendritic cells mostly express 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors and their activation induces cAMP elevation. Functional studies indicate that activation of 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors enhances the release of the cytokines IL-1 $\beta$  and IL-8, while reducing secretion of IL-12 and TNF- $\alpha$  in mature dendritic cells (Idzko et al., 2004). Expression of 5-HT<sub>7</sub> receptor as well as its downstream effectors Cdc42 are upregulated in dendritic cells upon maturation. In addition, basal activity of 5-HT<sub>7</sub> receptors is required for proper expression of the chemokine receptor CCR7, which is a key factor that controls dendritic cell migration. 5-HT<sub>7</sub> receptor enhances chemotactic motility of dendritic cells *in-vitro* by modulating their directionality and migration velocity (Holst et al., 2015).

Serotonin can induce oriented migration in immature but not in LPS-matured dendritic cells via activation of 5-HT<sub>1B/1E</sub> and 5-HT<sub>2A/2B</sub> receptors. Accordingly, serotonin also increases migration of pulmonary dendritic cells to draining lymph nodes *in-vivo*. By binding to 5-HT<sub>3</sub>, 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors, serotonin up-regulates production of the pro-inflammatory cytokine IL-6. Additionally, serotonin influenced chemokine release by human monocyte-derived dendritic cells: production of the potent T-helper cells Th1 chemoattractant IP-10/CXCL10 was inhibited in mature dendritic cells, whereas CCL22/MDC secretion was up-regulated in both immature and mature dendritic cells. Furthermore, dendritic cells matured in the presence of serotonin switched to a high IL-10 and low IL-12p70 secreting phenotype. Consistently, serotonin favored the outcome of a Th2 immune response both *in-vitro* and *in-vivo* (Müller et al., 2009). A recent study using *Htr7*<sup>-/-</sup> mice confirmed 5-HT<sub>7</sub> receptor expression in CD103<sup>+</sup>CD11c<sup>+</sup> dendritic cells found in colon (and spleen), and its importance in immune activation and gut inflammation (Kim et al., 2013). Lack of endogenous serotonin *in-vitro* and *in-vivo* was associated with an impaired Th2-priming capacity of bone marrow dendritic cells (Dürk et al., 2013).

Interestingly, like platelets, dendritic cells can take up serotonin from the microenvironment and the antidepressant, fluoxetine, inhibits this uptake. Expression of serotonin transporter (SERT) is regulated by dendritic cell maturation, exposure to microbial stimuli, and physical interactions with T-cells. Significantly, serotonin sequestered by dendritic cells is stored within LAMP-1+ vesicles and subsequently released via Ca<sup>2+</sup>-dependent exocytosis, as confirmed by amperometric recordings (O'Connell et al., 2006).

## 2.4 Serotonin and eosinophils

Asthma is an inflammatory disease of the lung characterized by airways hyper-responsiveness, inflammation, and mucus hyperproduction. Notably, allergic asthma is characterized by infiltration of eosinophils, and plasma levels of serotonin are elevated in symptomatic asthma patients. Serotonin levels are increased in bronchoalveolar lavage fluid of mice and people with asthma after allergen provocation. TPH1 deficiency and TPH1 inhibition reduced all cardinal features of allergic airway inflammation. Transfusion of platelets from wild type and TPH1-deficient mice revealed that only platelets containing serotonin enhanced allergic airway inflammation.

Serotonin is well known to be involved in lung inflammatory processes. There is solid evidence that serotonin contributes to this eosinophil recruitment. Indeed, serotonin alone can stimulate *in-vitro* migration of murine and human eosinophils (Boehme et al., 2004; Kang et al., 2013). Although several serotonin receptor subtypes are expressed, 5-HT<sub>2A</sub> is the most prominent, and 5-HT<sub>2A</sub> receptor antagonists inhibit serotonin-induced, but not eotaxin-induced migration. Further, eosinophils roll in response to serotonin in venules under conditions of physiological shear stress (Boehme et al., 2004; Kang et al., 2013). Signaling via 5-HT<sub>2A</sub> receptors is associated with changes in cell shape/morphology via activation of specific intracellular signaling molecules (ROCK, MAPK, PI3K and the PKC-calmodulin pathway) (Kang et al., 2013).

In the ovalbumin mouse model of allergic inflammation, inhalation of the 5-HT<sub>2</sub> receptor agonist (R)-DOI prevents the development of many key features of allergic asthma, including airways hyper-responsiveness, mucus hyperproduction, airways inflammation, and pulmonary eosinophil recruitment. The 5-HT<sub>2A</sub> receptors participate thus in allergic airways disease (Nau et al., 2015).

## 2.5 Serotonin and mast cells

Mast-cells have the capacity to synthesize and accumulate serotonin (Kushnir-Sukhov et al., 2007). In turn, this stored serotonin can be released upon IgE cross-linking. Further, mast cells express mRNA for multiple serotonin receptors, including 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors (Kushnir-Sukhov et al., 2006). Serotonin can induce mast-cell adherence to fibronectin and stimulate cell migration. However, there is no evidence that serotonin degranulates mast cells or modulates their activation by IgE. Mast cells from 5-HT<sub>1A</sub> receptor knockout mouse (*Htr<sub>1A</sub><sup>-/-</sup>*) do not respond to serotonin indicating a principal role for this receptor. Importantly, serotonin attracts mast cells to sites of inflammation; injection of serotonin into the skin enhances accumulation of mast cells in wild type but not in 5-HT<sub>1A</sub> receptor-null mice.

## 3. Serotonin and adaptive immunity

The response of a second immune system division, termed adaptive, or specific, immune system, occurs within hours of an infection and involves antigen-specific recognition and destruction of pathogens by T and B-lymphocytes. The two components of adaptive immune system involve cell-mediated and humoral immunity. Cell-mediated immunity is carried out by T-cells located in thymus, lymph nodes, and circulation. Antigen presenting cells that migrate to lymph nodes will prime and educate T-cells as to the nature of the pathogen. T-cells then proliferate and differentiate into, for example, CD4<sup>+</sup> T-helper inflammatory cells (Th1) that activate macrophages, CD4<sup>+</sup> Th2 cells that aid antibody responses, or CD8<sup>+</sup> cytotoxic cells that target-cells infected with intracellular microbes. The second component of adaptive immunity involves the contributions of B-cells, located in lymph tissue, spleen and in the circulation. Upon stimulation, B-cells become plasma cells (with or without the



help of Th2) that produce and secrete antibodies (immunoglobulins). Memory T and B-cells recognize specific antigens and respond quickly. Thus, adaptive immune system is distinguished from innate immune system by its ability to identify, remember, and eliminate pathogens that have been designated as non-self. Adaptive immunity is triggered at the immune synapse, where peptide major histocompatibility complexes and co-stimulatory molecules expressed by dendritic cells are physically presented to T-cells (Baganz and Blakely, 2013).

The mRNA expression of serotonin receptors in lymphoid tissues of the rat, *ex-vivo* isolated spleen, thymus, and peripheral blood lymphocytes includes that of 5-HT<sub>1B</sub>, 5-HT<sub>1F</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub>. Mitogen-stimulated spleen cells additionally express mRNA corresponding to the 5-HT<sub>3</sub> receptor (Stefulj et al., 2000). In rhesus macaque, SERT positive cells were found among CD4<sup>+</sup>, CD3<sup>+</sup>, and CD3<sup>+</sup>CD4<sup>+</sup> lymphocytes respectively (Yang et al., 2007). Fluoxetine significantly increases number of lymphocytes expressing SERT, and stimulates an enrichment of CD8<sup>+</sup> T-cells, decreasing CD4<sup>+</sup>/CD8<sup>+</sup> ratio. Fluoxetine administration elevates the levels of IL-4 at 1, 2 and 3 weeks; and of IL-2, at 2 and 3 weeks. IL-4/IL-2 ratio is significantly increased in fluoxetine group respecting the controls and is similar during 3 weeks of treatment (Fazzino et al., 2009). Therefore, serotonin may have multiple actions in lymphoid tissues.

### 3.1 Serotonin and T-lymphocytes

There is long standing evidence that serotonin can influence T-cell activation. Notably, mice treated with an irreversible inhibitor of TPH1, para-chlorophenylalanine, exhibit a reduction in the number of CD25-positive T-cells (León-Ponte et al., 2007; Young et al., 1993), suggesting that serotonin contributes physiologically to T-cell activation. T-cells have the capacity to synthesize serotonin and levels of TPH1 expression increase following T-cell activation (Chen et al., 2015; León-Ponte et al., 2007; O'Connell et al., 2006; Urbina et al., 2014). Conceivably, TPH1 activity in T-cells could act to exhaust tryptophan as proposed for mast cells (Nowak et al., 2012). On the other hand, serotonin produced by T-cells might act in an autocrine or paracrine manner. Indeed, T-cells express the type 1 vesicular monoamine transporter (VMAT1) responsible for vesicular storage of serotonin, and VMAT1 expression increases following T-cell activation concomitant with TPH1. Further, Ca<sup>2+</sup> elevations in T-cells can trigger secretion of serotonin. Interestingly, levels of TPH1 and monoamine oxidase A, the principal catabolic enzyme for serotonin are greater in CD8<sup>+</sup> compared to CD4<sup>+</sup> T-cells suggesting a specific biological role for serotonin synthesis in this T-cell subset (Chen et al., 2015).

A screen for serotonin receptor subtypes in murine T-cells revealed expression of three subtypes; naïve T-cells selectively express 5-HT<sub>7</sub> receptors while following T-cell activation there is a strong upregulation of 5-HT<sub>1B</sub> and 5-HT<sub>2A</sub> receptors (León-Ponte et al., 2007). Significantly, exogenous serotonin induces rapid phosphorylation of extracellular signal-regulated kinase-1 and -2 (ERK1/2) and IκBα in naïve T-cells that is inhibited by preincubation with a selective 5-HT<sub>7</sub>-receptor antagonist. Thus, serotonin signaling via 5-HT<sub>7</sub> receptor may contribute to early T-cell activation. Yin et al. (2006) showed that 5-HT<sub>1B</sub> receptor antagonists impaired the proliferation of helper CD4<sup>+</sup> T-cells in mouse and human. Inoue et al. (2011) showed that a 5-HT<sub>2A</sub> receptor agonist enhanced Concavalin-A induced activation of murine CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, whereas a 5-HT<sub>2A</sub> receptor antagonist blocked T-cell receptor mediated IL-2 and IFN-γ production. Consistent with these data, Akiyoshi et al. (2006) showed that treatment with a 5-HT<sub>2A</sub> receptor antagonist enhanced the survival of cardiac allograft in mice. Thus, these mouse data strongly support involvement of a trio of serotonin receptors (5-HT<sub>7</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>2A</sub>) during early and late stage T-cell activation.

Interestingly, the 5-HT<sub>2B</sub> receptor is expressed in human T-cells. Gene expression profiles during human CD4<sup>+</sup> T-cell differentiation, identified the 5-HT<sub>2B</sub> receptor with 10-fold greater expression in CD3<sup>high</sup>CD4<sup>+</sup>CD8<sup>-</sup> SP4 thymocytes over intrathymic T progenitor cells, CD3<sup>-</sup>CD4<sup>+</sup>CD8<sup>+</sup> ‘double positive’ thymocytes (ITTP), CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> CD45RA<sup>+</sup>CD62L<sup>+</sup> ‘naive’ T-cells from cord blood (CB4) and CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> CD45RA<sup>+</sup>CD62L<sup>+</sup> ‘naive’ T-cells from adult blood (AB4) (Lee et al., 2004). Further, 5-HT<sub>2B</sub> receptors are differentially expressed among Th subsets. In human umbilical cord blood, Th cells cultured in the presence of cytokines promoting Th2 differentiation were found to increase 5-HT<sub>2B</sub> receptor expression along with 50 Th2 differentially expressed genes (Aijö et al., 2012).

Rheumatoid arthritis is a chronic disease that results in a disabling and painful condition as it progresses to destruction of the articular cartilage and ankylosis of the joints. Although the cause of the disease is still unknown, evidence argues that autoimmunity plays an important part. There are increasing but contradictory views regarding serotonin being associated with activation of immuno-inflammatory pathways and the onset of autoimmune reactions. Studies have shown that platelets can have a role in rheumatic diseases. In patients with rheumatoid arthritis, IL-1-containing platelet-derived vesicles called microparticles are abundant in arthritic joint fluid. Platelets also serve as a source of prostaglandins that contribute to synovial inflammation. Furthermore, serotonin released by platelets helps drive persistent vascular permeability that characterizes the microvasculature of inflamed synovium. Therefore, platelets have a distinct role in autoimmunity (Boilard et al., 2012). In mice, induction of arthritis triggers a robust increase in serotonin content in the paws combined with low inflammation. In *Tph1*<sup>-/-</sup> mice with arthritis, a significant increase in osteoclast differentiation and bone resorption was observed with an increase in IL-17 levels in the paws and in Th17 lymphocytes in draining lymph nodes, whereas T-regulatory cells were dampened. *Ex-vivo* serotonin and agonists of 5-HT<sub>2A/2B</sub> receptors restored IL-17 secretion from splenocytes and Th17 cell differentiation in *Tph1*<sup>-/-</sup> mice. Serotonin plays thus a fundamental role in arthritis through regulation of Th17/T-regulatory cell balance and osteoclastogenesis (Chabbi-Achengli et al., 2016).

Serotonin may also modulate migration of human T-cells. Human, but not mouse T-cells, express functional 5-HT<sub>3</sub> receptors. 5-HT<sub>3</sub> receptor agonists selectively decrease T-cell migration towards gradients of the chemokine CXCL12, but not to other chemokines such as CCL2 and CCL5. Interestingly, CXCL12 is highly expressed on vascular endothelium and inhibits T-cell migration across endothelium and extravasation. In transmigration experiments, 5-HT<sub>3</sub>-receptor stimulation reverses this effect of endothelial-bound CXCL12 on T-cell migration (Magrini et al., 2011). These data suggest that serotonin can stimulate trafficking of T-cells from blood to tissues.

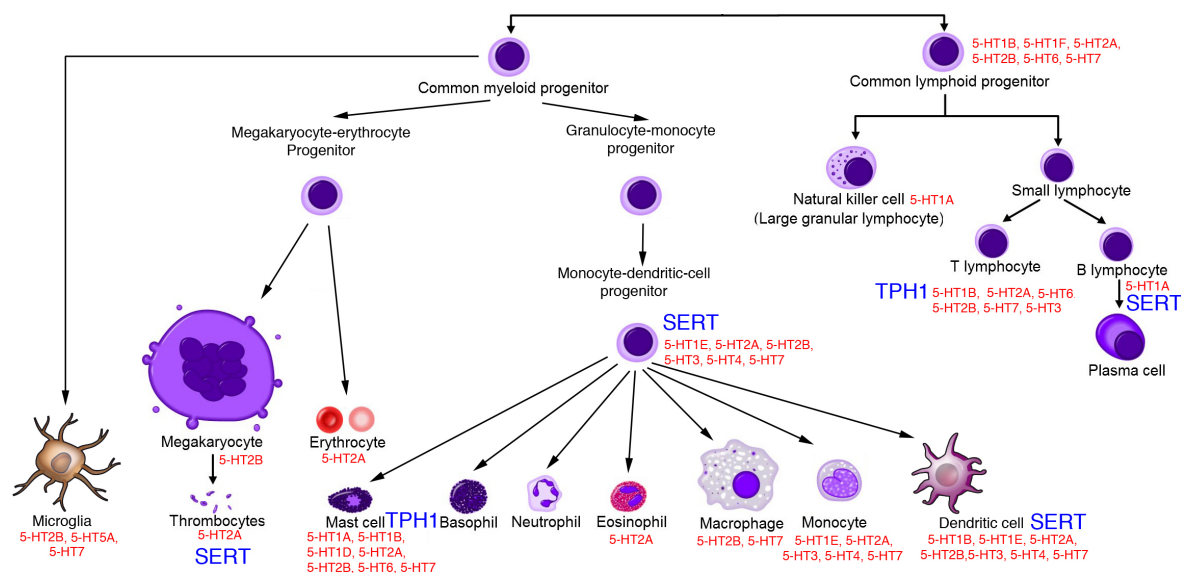
### 3.2 Serotonin and B-lymphocytes

B-lymphocytes have the capacity to sense and take up serotonin. Serotonin increases mitogen-stimulated CD19<sup>+</sup> B-lymphocyte proliferation in a concentration- and time-dependent manner. These effects are reproduced by a 5-HT<sub>1A</sub>-receptor agonist. Serotonin-induced increases in proliferation are blocked by 5-HT<sub>1A</sub> receptor antagonists. Moreover, LPS-activated mouse spleen cells express specific binding sites for 5-HT<sub>1A</sub> receptor, suggesting that serotonin upregulates mitogen-stimulated B-lymphocyte proliferation through 5-HT<sub>1A</sub> receptors (Iken et al., 1995). Further, mitogen-activated B-lymphocytes express higher levels of 5-HT<sub>1A</sub> receptor mRNA and protein than resting cells. This upregulation is seemingly dependent upon NF-κB transcription factors, as specific inhibitors of this pathway prevent the increase in mRNA expression for the 5-HT<sub>1A</sub> receptor (Abdouh et al., 2001).

B-lymphocytes express SERT and uptake of serotonin leads to apoptosis of Burkitt lymphoma cells (Serafeim et al., 2002). Serotonin may induce apoptosis via intracellular serotonylation-signaling pathway. Further, long-term treatment with SSRIs in humans leads to enhanced (~30%) numbers of B-lymphocytes (Hernandez et al., 2010). Interestingly, higher doses of SSRIs directly promote apoptosis of Burkitt lymphoma cells by inhibiting DNA synthesis, whereas normal peripheral and tonsillar B-cells are relatively resistant to SSRI-induced apoptosis (Serafeim et al., 2002). SERT has been detected in a variety of B-cell lines (Meredith et al., 2005), revealing SERT as a potential target for a broad range of B-cell malignancies.

### Concluding remarks

Serotonin regulates inflammation and immunity by acting on serotonin receptors that are differentially expressed on immune cells, both in rodents and humans. Serotonin acts as a potent chemoattractant, recruiting innate immune cells to sites of inflammation. Serotonin also alters production and release of cytokines and cell activation/proliferation. Some immune cells, including mast cells and T-lymphocytes, have the capacity to synthesize and release serotonin, expanding the range of tissues for serotonin signaling.



**Figure1-Relationships between hematopoietic cells and serotonin system.** Cells of the hematopoietic system are depicted, with arrows indicating lineage relatedness with in blue the serotonin markers SERT and TPH1 and in red the distribution of receptors.

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