



Impact of mast cells in depression disorder: inhibitory effect of IL-37 (new frontiers)

Pio Conti¹ · Alessandro Caraffa² · Gianpaolo Ronconi³ · Chiara M. Conti⁴ · Spiros K. Kritas⁵ · Filiberto Mastrangelo⁶ · Lucia Tettamanti⁷ · Theoharis C. Theoharides⁸

Published online: 16 June 2018

© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

The purpose of this article is to study the involvement of inflammatory mast cells (MCs) in depression which may be inhibited by IL-37. We evaluate mast cells in depression on the basis of our previous experimental data, and using the most relevant studies reported in the literature. Dysfunction of mood, feelings, and thoughts is a major risk factor for several metabolic diseases and may influence the physiology of the body leading to depression. Depression, present in mastocytosis, is an important endogenous process that promotes the activation of meningeal cell receptors through a low-grade neurogenic chronic inflammation, and MCs. Mast cells are localized along meningeal blood vessels and connective tissues, as well as between the ganglion cells and nerve fibers. They are present in the hypothalamus of mammalian brains capable of communication with nerves. MCs are classically activated by binding to IgE cross-link FcεRI high-affinity receptor leading to release a plethora of mediators responsible for the generation of inflammatory cytokines. Corticotropin-releasing hormone (CRH), produced by MCs, has been found in microglial cells where it regulates immune cells and contributes to the pathogenesis of neurodegenerative diseases including depression. Inflammatory cytokines released by MCs aggravate depression and could be partially inhibited by IL-37. A detailed understanding of the interaction between the immune system, including MCs and depression, is necessary in order to address an effective therapy which could include IL-37. As a consequence, the concepts reviewed here have treatment implications.

Keywords Depression · Inflammation · Cytokines · Mast cells · IL-37

✉ Pio Conti
pconti@unich.it

¹ Postgraduate Medical School, University of Chieti-Pescara, Viale Unità d'Italia 73, Chieti 66013, Italy

² University of Perugia, Perugia, Italy

³ Clinica dei Pazienti del Territorio, Policlinico Gemelli, Rome, Italy

⁴ Department of Clinical Psychology, University of Chieti, Chieti, Italy

⁵ Department of Microbiology and Infectious Diseases, Aristotle University of Thessaloniki, Thessaloniki, Macedonia, Greece

⁶ Department of Medical Science and Biotechnology, University of Foggia, Foggia, Italy

⁷ Department of Medical and Morphological Science, University of Insubria, Varese, Italy

⁸ Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA, USA

Approximately 20 million people suffer from depression in the USA. Certain neurological diseases (Parkinson's, Huntington's, and others) can cause depression which leads to changes in the front and temporal lobes and lead to a dysfunction of the executive activity, personality, emotional control, learning, and memory [1]; on the other hand, depression can provoke low-grade neurogenic inflammation [2]. Therefore, inflammation is thought to play an important role in neuropathology, but the factors that promote inflammation are still unclear [3].

Migraine and depression are two neuropathological disorders; in fact, most of the people suffering from migraine also suffer from depression [4]. Neuroinflammatory processes are critical pathophysiologic steps in the development of chronic diseases and etiology of persistent depression. Increased depression associated to inflammation is often linked with the early stages of neuropsychiatric disorders [5]. However, the biological origin of depression remains enigmatic and elusive.

The role of immune cells in modulating the neurological diseases and trafficking in the brain [6] is very important, even though this factor is still understudied.

In recent years, considerable evidence has accumulated showing that depression is one of the major endogenous noxious processes that can provoke persistent activation of meningeal nociceptors and dorsal horn neurons in several neurological pathways [7]. Depression is frequent in mastocytosis, but the initial phase in the development of depression is still unclear. Depression is an important endogenous process that promotes the activation of meningeal cell receptors through a low-grade neurogenic chronic inflammation mechanism including immune cell activation [8]. Depression may stimulate and activate the sensory system and migraine pain pathway, often the cause of adult disability, and is a major risk factor for several metabolic diseases [9]. Therefore, depression is also linked to a broad spectrum of pathological diseases, including neurodegenerative disorders [10]. Moreover, the activation of caudal nucleus, which processes the afferent nociceptive signals, may lead to depression. This pathological condition may initiate a cascade of inflammatory events, for example, tissue damage and/or immune cell infiltration in the cerebral meninges, which represent an anatomical barrier that protects the central nervous system (CNS) [11].

Several lines of evidence indicate that the generation and release of cytokines can influence mast cell (MCs) development and function [12, 13]. Cytokines may exert either pro-inflammatory or anti-inflammatory activities and exhibit a wide range of functions including cell proliferation, angiogenesis, immunity, inflammation, vascular homeostasis, and body weight homeostasis (the dysfunction of which often occurs in depression) [14, 15]. The presence of depression may promote inflammatory cytokine formation which induces MC activation [16].

Mature MCs do not circulate, but are resident in the brain and other tissues [17, 18]. MCs are cellular sensors recognized to be involved in immunity and inflammation [19–21]. In the brain, MCs can significantly contribute to the key features of neurological pathology that may be characterized by

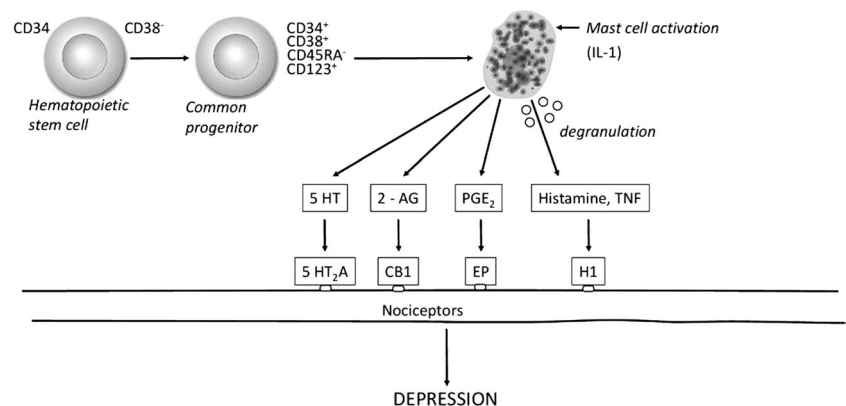
infiltration and activation of other immune cells, such as granulocytes and macrophages, which also contribute to inflammatory states. In proximity to nerve fibers, MCs facilitate the nerve-immune cell cross talk [22]. They are associated with sensory nerves and increase in lesional psoriatic skin, a disease worsened by acute stress, which often provokes the exacerbation of depression [23] (Fig. 1).

Stress activates the cerebral cortex and stimulates the hypothalamus where corticotropin-releasing hormone (CRH) is released and activates pituitary receptors [24]. CRH, generated by MCs, circulates with plasma and activates adrenal cortex receptors, an effect that provokes the release of cortisol into the circulation [24]. Both cortisol and CRH are involved in depression. In addition, CRH mRNA and its protein are also increased in limbic brain regions where CRH-receptor antagonists show anti-depressant activity [24]. IL-1, a multipotent cytokine, activates postcapillary venules and MCs to release several inflammatory molecules including intercellular adhesion molecule 1 (ICAM-1) and the CC chemokine MCP-1, and CXC IL-8 [25].

The inhibition of inflammatory molecules by an IL-1 antagonist, such as IL-37, can be an anti-depressant mechanism that may cause clinical remission and reverse the pathological condition of depression (Fig. 2).

Cortex, hippocampus, and amygdale are the brain regions particularly associated with stress responses and mood disorders, including depression. MCs have been observed in various brain structures such as hypothalamus, brain side of the blood-brain barrier, thalamus, entorhinal cortex, hippocampus, and leptomeninges which are located around the ganglion and connective tissues and are capable of communication with nerves [26]. MCs circulate as immature cells then mature after they settle in a tissue and in the developing brain [27]. MCs are involved in both innate and adaptive immunity and are activated by binding to IgE cross-link FcεRI, resulting in a variety of responses, including the immediate release of potent inflammatory mediators that provoke hypersensitivity reaction [28]. Human MCs express a functional TrkA receptor tyrosine kinase involved in MC development and/or

Fig. 1 Mast cell development from hematopoietic stem cells. Activation and degranulation leading to depression



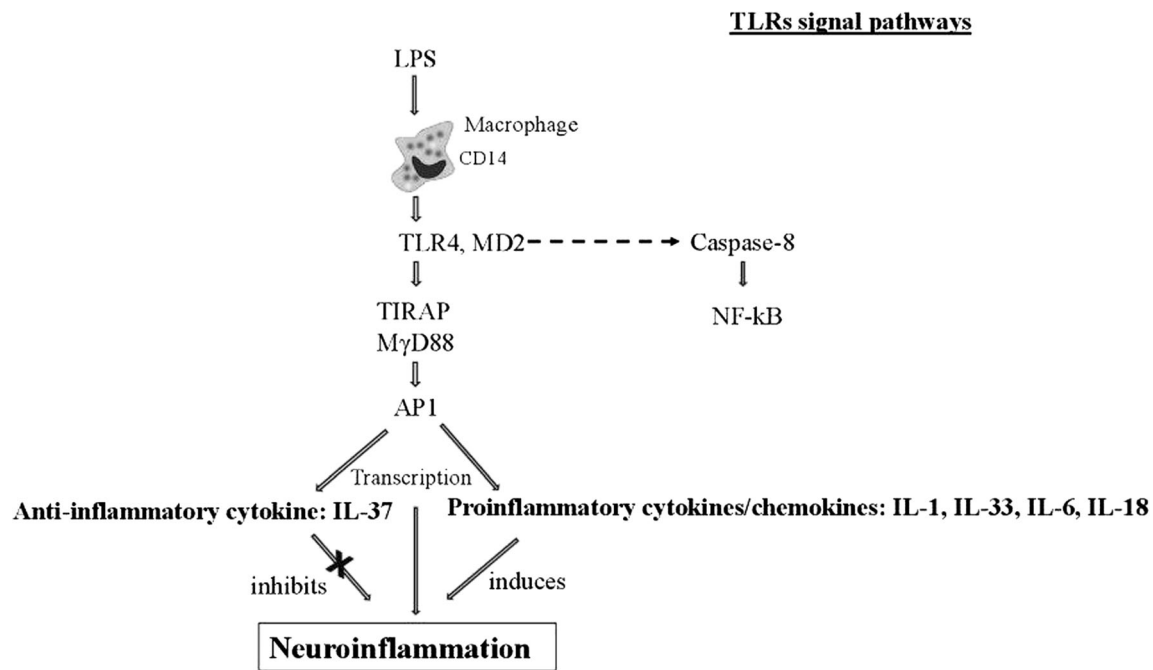


Fig. 2 TLRs may play a role in host defense and neuroinflammation, and are implicated in the pathogenesis of neurological disorders

maturation in humans [29]. FcεRI high-affinity receptor ($K_d = 10^{-10}$ M) MC binds IgE leading to receptor aggregation with an intracellular signal [30]. This cross-linking of FcεRI with IgE or antigen initiates several phosphate transfer reactions through the activation of Src, Syk, and Tec (tyrosine kinase proteins). These phosphorylation events lead to the activation of phospholipase Cγ (PLCγ) which is an important mediator for the intracellular calcium release and protein kinase C (PKC) activity [30]. The formation of inositol triphosphate (IP3) leads to the activation of GTPase which regulates mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, which are involved in a plethora of transcription factors determinant for the cytokines/chemokines, growth factors, and arachidonic acid product generation [30].

MC activation involves nuclear factor κB (NF-κB) and AP-1 stimulation, leading to IL-33, TNF, IL-6, IL-5, IL-4, IL-1, IL-13, and GM-CSF, and various chemokines including MIP-1α, MIP-1β, and MCP-1 [31].

TNF, like biogenic amines and enzymes, also can be stored in the granules and rapidly released after MC receptor activation [32–34]. Therefore, stimulated MCs result in the de novo synthesis and release of cytokine/chemokine and lipid-derived mediators, such as prostaglandin D2, an arachidonic acid cascade inflammatory product [35].

Immediate hypersensitivity reactions occur within seconds after antigen MC activation, leading to dilated blood vessels, edema, and swelling, as a result of leakage of plasma [36], while the late-phase reaction appears at 2 to 20 h later with in situ infiltration of Th2 cells, eosinophils, macrophages, and neutrophils, and may lead to chronic inflammatory diseases [30–37].

MCs stimulate nociceptors, and in particular, C fibers, outside the CNS [38]. These C fibers are small non-myelinated peripheral nerves that survey harmful stimuli. The fibers of the C signals are processed by the CNS and cause the activation of preganglionic neurons and also produce inflammatory clinical effects [38].

Over the past years, a large body of clinical evidence has been presented indicating that depression is correlated to vascular functions that may be linked to the painful phase of migraine [39].

In depression, there is a marked depolarization of neuronal and glial induced in the cerebral cortex in experimental animals or those individuals who have suffered trauma cortical and/or cerebral hemorrhage [40].

Dysfunction of mood, feelings, and thoughts may all influence the physiology of the body and lead to depression [41]. Relaxing leads to a decrease in blood pressure; therefore, the body may emerge from depression and the immune system be restored [42]. Current consensus holds that the way we think and feel can increase the population of disease-fighting immune cells and lower the level of the hormones that raise blood pressure, such as angiotensin II, which also provokes vasoconstriction, sympathetic nervous stimulation, and increases aldosterone biosynthesis [43]. In depression, the brain can generate epinephrine and cortisol; and undergo immune changes associated with decreased blood flow [44]. In fact, depression may induce TLR4 in macrophages, a receptor that recognizes bacterial lipopolysaccharide (LPS) and is localized on CNS microglia [45, 46], inducing neuroinflammation (Fig. 2). Therefore, depression is a noxious stimulus that can activate the meningeal sensory system and the migraine pain

pathway and may increase *c-FOS* expression [47]. The activation of TLR4 causes the production of TNF and the release of IL-1 by promoting neuroinflammation [48]. TLR, a family of evolutionary conserved pattern, is expressed by a variety of cell types of the innate immunity and its activation pathways result in the production and release of various cytokines/chemokines including IL-1, TNF, IL-6, and the chemokines MCP-1 and RANTES [48, 49].

Activation of MCs by IL-1 or TNF induces an NF- κ B signal through their respective specific receptors leading to neuroinflammation (Fig. 3).

In depression and other neurological diseases, there is likely to be a low concentration of the serotonin released by MCs and a dysfunction in its transport [50]. In addition to the serotonergic disorders, it is possible to have hormonal and Na⁺, K⁺, and ATPase dysfunction [51].

Another neurotransmitter that might also be involved in depression is CRH, which is produced by MCs [52]. CRH is a neuropeptide consisting of 41 amino acids and plays a determinant role in mental diseases including stress [53] and chronic fatigue syndrome. Hypothalamus expresses CRH receptor-1 (CRH-R1) along with microglia cells, and the peptide regulates the behavioral and immunologic challenges in stress and depression [54]. CRH binds CRH-R1 in the brain and it has been found in murine microglial cell line where it regulates immune cells, and

the endocrine system [54]. In addition, CRH regulates several neural activities under both physiological and pathological conditions. Activation of microglia cells by CRH may contribute to the pathogenesis of neurodegenerative diseases and glia cell degeneration in neurological disorders such as stress and depression [55].

The two receptors CRH-R1 and CRH-R2 derive from two diverse genes and CRH act biologically through the G protein-coupled receptors via specific binding [56]. CRH-R1 is expressed in brain stem, cerebellum, and cerebral cortex, while CRH-R2 is predominantly expressed in microglia cells [57].

When activated by CRH through CRH-R1, microglia cells release some bioactive molecules, which have biological effects in the brain and mediate several neurological disorders [58]. CRH can provoke either neurotoxic or neuroprotective effects and is implicated in the regulation of neuronal cell survival [59]. It also stimulates the production of the pituitary adrenocorticotrophic hormone (ACTH) triggers cortisol secretion involved in the regulation of neuronal cell survival and growth, an effect that may have therapeutic consequences [60].

CRH regulates the generation of inflammatory IL-1 family members released by MCs, leading to an autocrine effect [61]. The upregulation of these cytokines is due to CRH by enhancement of the intracellular reactive oxygen levels in microglial cells [62].

NF κ B signaling

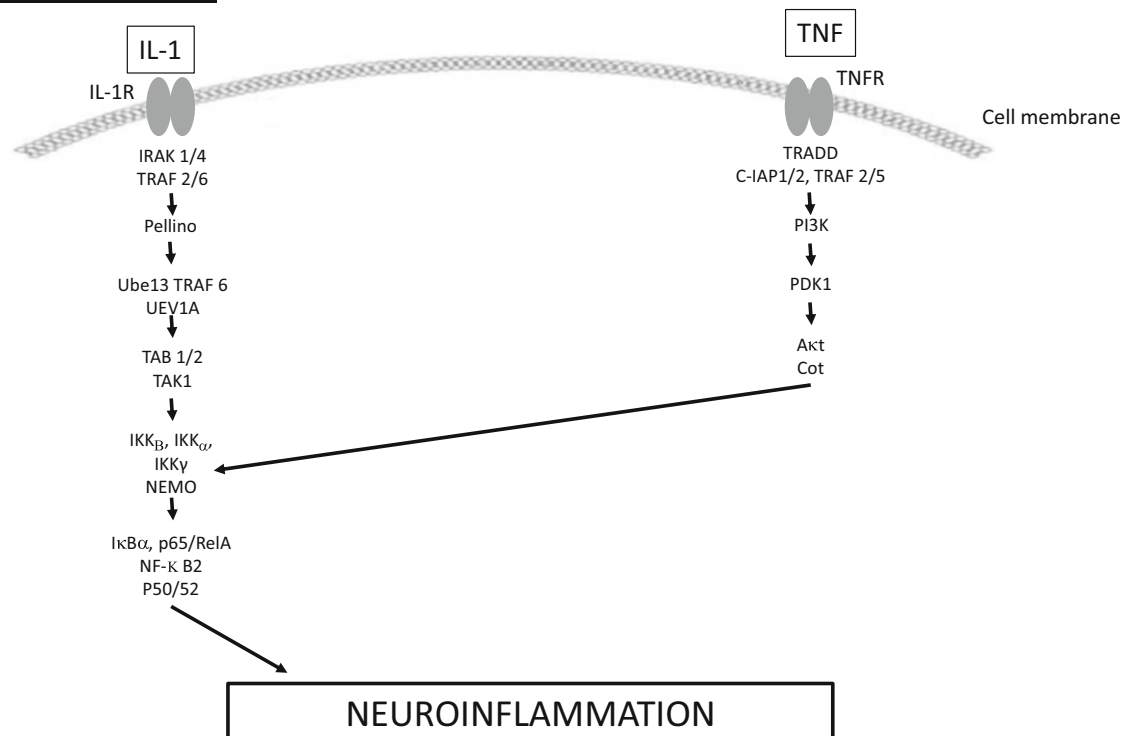


Fig. 3 IL-1 and TNF bind their respective receptors on mast cells and provoke a cascade reaction leading to neuroinflammation, an effect which can be inhibited by IL-37

In addition, stress molecules include CRH and neurotensin (NT) secreted in response to the metabolic burden, and may act in an autocrine manner through MCs [63].

Therefore, the activity of brain MCs is increased by multiple stimuli including cytokines, chemokines, growth factors, CRH, catecholamines, and substance P, which in contact with MCs cause degranulation, an effect increased in acute stress in mice [64]. CRH can increase the activity of brain MCs even if its physiological role remains unclear.

Neuropeptides can activate MCs in a receptor-independent manner by directly activating G proteins [65]. IL-1 family members include IL-33, which is a pleiotropic immunostimulatory cytokine expressed by microglia and astrocytes and a variety of cell tissue types and involved in brain diseases [66]. The body may react to depression similarly to infection and produce inflammatory mediators which can up-regulate genes that code for inflammation, one of the greatest drivers of aging [67, 68]. Moreover, depression may decrease the immune system by reducing the telomerase, the enzyme that repairs and maintains telomeres, and shortens the life span [69]. In addition, shortening telomere plays an important role into immune system problems and other diseases.

Depression may lead to stress (and vice versa) that can augment the cellular damage from highly reactive oxygen atoms such as free radicals [70].

Several cytokines can influence MC development and function by interacting with its receptors [71, 72]. MCs interact with CNS by generating and secreting an array of potent numerous mediators including cytokines/chemokines, lipid-derived factors, and neurotransmitters which are secreted upon receiving an appropriate signal and influence neuronal activity and vascular permeability of CNS [73]. Stress can strongly influence the number of brain MCs, although in some cases of social stress, isolation of the number of MCs in the brain can be decreased [74]. In depression, there may be an increase in sympathetic tone leading to chronic stress with an augmentation of both MC inflammatory compounds released immediately, and later-released products such as cytokines, chemokines, prostaglandins, and leukotrienes [75].

Therefore, the activity of brain MCs can be stimulated by multiple stimuli including chronic stress, psychological stressors, and neurotransmitters such as CRH and substance P (SP).

SP is an undecapeptide, neurotransmitter, belonging to a group of proteins termed tachykinins. SP is an activator of MCs and is a mediator of pain, stress, depression, and other neurological disorders [76]. SP in contact with fibers causes swelling, headache, and inflammation. SP is a potent activator of MCs where it induces the release of VEGF, cytokines/chemokines, and promotes the generation of a number of intracellular molecules such as stored enzymes (i.e., chymase, phospholipases, kinogenases, carboxypeptidase A, and cholinesterase) [76]. Neurotransmitter SP binding MC receptor

provokes degranulation, an effect increased in acute stress in mice [77]. It also induces on MCs the release of certain cytokines such as IL-1, TNF, and IL-33. Pro-inflammatory cytokines, such as IL-1, TNF, IL-6, and IL-33, regulate intracellular communication and are often elevated in a number of neurological conditions [78, 79]. IL-1 regulates IL-6 release and induces generation of several chemokines from neuroendocrine cells, demonstrating that products of the immune system, such as cytokines, may affect neuroendocrine activation, cell proliferation, and inflammation [80].

IL-33 (or IL-1F11) plays an important role not only in asthma, but also in neurological diseases [81]. IL-33 is an IL-1 inflammatory family member synthesized as a peptide precursor cleaved by caspase-1, which acts by binding its receptor T1/ST2, Toll-IL-1 receptor, an orphan member of the IL-1 receptor family [82]. IL-33 activates NF-kappa B and MAP kinase pathways [82]. It is abundantly expressed by endothelial cells and mediates several pathological effects in the brain, provoking and increasing MC numbers without causing degranulation [74]. We previously reported that IL-33 is a strong activator of human MC lines (LAD II cells) with the capacity to stimulate the release of MCP-1, IL-8, TNF, and VEGF at the transcriptional and translational level, an effect that can be seen in neurological diseases, including depression [74].

Depression may also cause migraine and headache through the caspase-1 activation from neurons and NF-κB activation in astrocytes [83]. The inhibition of this cascade abolishes depression-induced MC activation and degranulation and therefore headache. Depression may induce neuronal channel opening and promote activation of nerves via inflammatory cascade joining glia limiting membrane [84]. This is the pathway that triggers when neurons are stressed. Depression can lead to an increase in the number and the activation of brain MCs, suggesting that these cells, as well as being immune cells, can also mediate neuropsychiatric inflammatory diseases and can be regarded as an important target for the management of depression [85].

Stress also causes a series of reactions involving the hippocampus, the amygdala, and hypothalamus, and may lead to depression [86]. On the other hand, depression through stress may stimulate the release of CRH from the hypothalamus, provoking the stimulation of the anterior pituitary gland and therefore the release of ACTH and secretion of cortisol [87].

Neurons contain many neuropeptides, such as neurotensin, angiotensin II, SP, and CRH, substances capable of influencing the response of immune cells, including MCs [88]. ACTH produced by the pituitary gland acts on the adrenal cortex, which releases glucocorticoids, immunosuppressive and anti-inflammatory compounds, stimulating the cytokines IL-10, IL-4, IL-1 receptor antagonist (IL-1RA), and lipocortin and inhibiting the transcription of inflammatory cytokines, including IL-1, TNF, IL-6, and IL-33 [89, 90]. However, IL-10

augments both the number and the size of MCs grown in vitro from precursors isolated from infected mice in the presence of IL-3 and IL-4 [91, 92]. Therefore, IL-10 inhibits Th1-released immune functions and is one of the most important cytokines capable of affecting MC development and differentiation [78, 93].

These studies reveal a novel role for MCs and their mediators in modulating brain inflammation and neurological diseases, such as depression and migraine, and hold much promise for therapeutic intervention.

IL-37, MCs, and depression

Some decades ago, we reported that IL-1 plays a crucial role in a broad spectrum of inflammatory diseases including various infectious, neoplastic, and immunologic challenges, and inflammatory disorders. It has been reported that IL-1 stimulates IL-6 and mediates inflammation without degranulation and releasing protease tryptase in normal human umbilical cord blood-derived MCs [94]. In fact, in experimental animals, it appears that IL-6 is significantly high immediately after depression. Therefore, stress and depression induce inflammation in the periphery, a response that may be transient.

In addition, IL-1 induces its own gene expression and may be part of a self-amplification or an autocrine growth factor in inflammatory disorders [95]. Specific therapies that inhibit IL-1 help to better understand the pathological role of inflammation mediated by this cytokine.

IL-37, formerly termed IL-1 family member 7 (IL-1F7), its precursor form has a caspase-1 site and is similar to IL-1 α and IL-33 [96]. IL-37 shares critical amino acid residues with IL-18 and binds low-affinity IL-18R α . It protects the experimental animals against LPS challenge which is a strong activator of mast cells. IL-37 is a natural inhibitor of immune responses and inflammation and acts as a cytokine with intracellular as well as extracellular functionality.

A large body of evidence has emerged linking cytokine/chemokine profile, stress, and depression. Stress and depression lead to an increase of the number of inflammatory cells, including MCs, with the release of IL-1, IL-6, TNF, and the chemokine monocyte chemoattractant protein (MCP)-1, eotaxin, and RANTES [97].

Since IL-1 activates MCs mediating inflammation in many disorders including stress and depression, we propose that IL-37, a strong inhibitor of IL-1, may exert an anti-inflammatory effect and a therapeutic function in these disorders.

Reduced inflammation may also be associated with decreased leukocyte recruitment and the decrease release of IL-1 β and TNF α , and an increase of IL-10, which is also an anti-inflammatory cytokine.

IL-37 applied in the inflamed tissues shows marked reduction of inflammation, and has a therapeutic potential for the

regulation of stress and depression-induced inflammatory response, and for protection against tissue injury.

Here, we report for the first time that depression may lead to MC activation and inflammation mediated by IL-1 and inhibited by IL-37. However, the function, the tolerability, and the safety of this new anti-inflammatory cytokine remain to be determined.

Author contribution Pio Conti, thought and wrote the paper.

Alessandro Caraffa, worked in the laboratory and contributed to the results.

Gianpaolo Ronconi, worked in the laboratory and contributed to the results.

Chiara M. Conti, took care of the neurological part.

Spiros K. Kritas, contributed to the discussion of the results.

Filiberto Mastrangelo, contributed to the discussion of the results.

Lucia Tettamanti, contributed to the discussion of the results.

Theoharis C. Theoharides, he corrected the manuscript and gave important suggestions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J. Detecting depression in Parkinson disease: a systematic review and meta-analysis. *Neurology*. 2016;87(4):426–37.
- Hayley S, Audet MC, Anisman H. Inflammation and the microbiome: implications for depressive disorders. *Curr Opin Pharmacol*. 2016;29:42–6.
- Conti P, Kempuraj D. Important role of mast cells in multiple sclerosis. *Mult Scler Relat Disord*. 2016;5:77–80.
- Yang Y, Ligthart L, Terwindt GM, Boomsma DI, Rodriguez-Acevedo AJ, Nyholt DR. Genetic epidemiology of migraine and depression. *Cephalalgia*. 2016;36(7):679–91.
- Mitchell RH, Goldstein BI. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. *J Am Acad Child Adolesc Psychiatry*. 2014;53(3):274–96.
- Bittner S, Ruck T, Schuhmann MK, Herrmann AM, Maati HM, Bobak N, et al. Endothelial TWIK-related potassium channel-1 (TREK1) regulates immune-cell trafficking into the CNS. *Nat Med*. 2013;19(9):1161–5.
- Zhao J, Levy D. Modulation of intracranial meningeal nociceptor activity by cortical spreading depression: a reassessment. *J Neurophysiol*. 2015;113(7):2778–85.
- Dalkara T, Zervas NT, Moskowitz MA. From spreading depression to the trigeminovascular system. *Neurol Sci*. 2006;27(Suppl 2):S86–90.
- Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. *Pain*. 2013;154(Suppl 1):S44–53.
- De Berardis D, Di Iorio G, Acciavatti T, Conti C, Serroni N, Olivieri L, et al. The emerging role of melatonin agonists in the treatment of major depression: focus on agomelatine. *CNS Neurol Disord Drug Targets*. 2011;10(1):119–32.
- Swardfager W, Winer DA, Herrmann N, Winer S, Lanctôt KL. Interleukin-17 in post-stroke neurodegeneration. *Neurosci Biobehav Rev*. 2013;37(3):436–47.

12. Robuffo I, Toniato E, Tettamanti L, Mastrangelo F, Ronconi G, Frydas I, Caraffa A, Kritas SK, Conti P. Mast cell in innate immunity mediated by proinflammatory and antiinflammatory IL-1 family members. *J Biol Regul Homeost Agents*. 2017;31(4):837–42.
13. Conti P, Caraffa AI, Kritas SK, Ronconi G, Lessiani G, Toniato E, Theoharides TC. Mast cell, pro-inflammatory and anti-inflammatory: Jekyll and Hyde, the story continues. *J Biol Regul Homeost Agents*. 2017;31(2):263–7.
14. Toniato E, Frydas I, Robuffo I, Ronconi G, Caraffa AI, Kritas SK, Conti P. Activation and inhibition of adaptive immune response mediated by mast cells. *J Biol Regul Homeost Agents*. 2017;31(3):543–8.
15. Conti P, Kempuraj D, Kandere K, Di Gioacchino M, Barbacane RC, Castellani ML, et al. IL-10, an inflammatory/inhibitory cytokine, but not always. *Immunol Lett*. 2003;86(2):123–9.
16. Raison CL. The promise and limitations of anti-inflammatory agents for the treatment of major depressive disorder. *Curr Top Behav Neurosci*. 2016;31:287–302.
17. Kasperska-Zaiac A, Grzanka A, Damasiewicz-Bodzek A, Bieniek K, Skrzypulec-Frankel A, Stencel-Gabriel K, Sikora-Zydek A. Elevated plasma IL-8 concentration is related to severity of systemic inflammation in chronic spontaneous urticaria. *J Biol Regul Homeost Agents*. 2017;31(4):957–61.
18. Conti P, Shaik-Dasthagirisab Y. Atherosclerosis: a chronic inflammatory disease mediated by mast cells. *Cent Eur J Immunol*. 2015;40(3):380–6.
19. Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med*. 2012;18(5):693–704.
20. Nakayama S, Yokote T, Hiraoka N, Nishiwaki U, Hanafusa T, Nishimura Y, et al. Role of mast cells in fibrosis of classical Hodgkin lymphoma. *Int J Immunopathol Pharmacol*. 2016;29(4):603–11.
21. Eskandari N, Tashrif F, Bastan R, Andalib A, Yousefi Z, Peachell PT. Cyclic nucleotide phosphodiesterase isoforms in human basophils and mast cells. *Int J Immunopathol Pharmacol*. 2016;29(4):654–65.
22. Petra AI, Panagiotidou S, Stewart JM, Conti P, Theoharides TC. Spectrum of mast cell activation disorders. *Expert Rev Clin Immunol*. 2014;10(6):729–39.
23. Theoharides TC, Rozniecki JJ, Sahagian G, et al. Impact of stress and mast cells on brain metastases. *J Neuroimmunol*. 2008;205(1–2):1–7.
24. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008;358(1):55–68.
25. Tailor A, Tomlinson A, Salas A, Panés J, Granger DN, Flower RJ, et al. Dexamethasone inhibition of leucocyte adhesion to rat mesenteric postcapillary venules: role of intercellular adhesion molecule 1 and KC. *Gut*. 1999;45(5):705–12.
26. Buhner S, Schemann M. Mast cell-nerve axis with a focus on the human gut. *Biochim Biophys Acta*. 2012;1822(1):85–92.
27. Theoharides TC, Doyle R, Francis K, Conti P, Kalogeromitros D. Novel therapeutic targets for autism. *Trends Pharmacol Sci*. 2008;29(8):375–82.
28. Marichal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, Tsai M, et al. A beneficial role for immunoglobulin E in host defense against honeybee venom. *Immunity*. 2013;39(5):963–75.
29. Tam SY, Tsai M, Yamaguchi M, Yano K, Butterfield JH, Galli SJ. Expression of functional TrkA receptor tyrosine kinase in the HMC-1 human mast cell line and in human mast cells. *Blood*. 1997;90(5):1807–20.
30. Galli SJ, Kalesnikoff J, Grimaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as “tunable” effector and immunoregulatory cells: recent advances. *Annu Rev Immunol*. 2005;23:749–86. Review
31. John AE, Zhu YM, Brightling CE, Pang L, Knox AJ. Human airway smooth muscle cells from asthmatic individuals have CXCL8 hypersecretion due to increased NF-kappa B p65, C/EBP beta, and RNA polymerase II binding to the CXCL8 promoter. *J Immunol*. 2009;183(7):4682–92.
32. Taracanova A, Alevizos M, Karagkouni A, Weng Z, Norwitz E, Conti P, Leeman SE, Theoharides TC. SP and IL-33 markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. *Proc Natl Acad Sci USA*. 2017;114(20):E4002–9.
33. Savi E, Peveri S, Cavaliere C, Masieri S, Montagni M. Laboratory tests for allergic diagnosis. *J Biol Regul Homeost Agents*. 2018;32(1 Suppl 1):49–60.
34. Incorvala C, Cavaliere C, Frati F, Masieri S. Allergic rhinitis. *J Biol Regul Homeost Agents*. 2018;32(1 Suppl 1):61–6.
35. Taketomi Y. Emerging roles of phospholipase A2s in mast cell biology. *Yakugaku Zasshi*. 2014;134(11):1179–89. Review
36. Theoharides TC, Donelan JM, Papadopoulou N, Cao J, Kempuraj D, Conti P. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol Sci*. 2004;25(11):563–8.
37. Haselden BM, Larché M, Meng Q, Shirley K, Dworski R, Kaplan AP, et al. Late asthmatic reactions provoked by intradermal injection of T-cell peptide epitopes are not associated with bronchial mucosal infiltration of eosinophils or T(H)2-type cells or with elevated concentrations of histamine or eicosanoids in bronchoalveolar fluid. *J Allergy Clin Immunol*. 2001;108(3):394–401.
38. Yu S, Kollarik M, Ouyang A, Myers AC, Undem BJ. Mast cell-mediated long-lasting increases in excitability of vagal C fibers in guinea pig esophagus. *Am J Physiol Gastrointest Liver Physiol*. 2007;293(4):G850–6.
39. Levy D. Endogenous mechanisms underlying the activation and sensitization of meningeal nociceptors: the role of immunovascular interactions and cortical spreading depression. *Curr Pain Headache Rep*. 2012;16(3):270–7.
40. Dietz RM, Weiss JH, Shuttleworth CW. Contributions of Ca²⁺ and Zn²⁺ to spreading depression-like events and neuronal injury. *J Neurochem*. 2009;109(Suppl 1):145–52.
41. Paulus MP, Yu AJ. Emotion and decision-making: affect-driven belief systems in anxiety and depression. *Trends Cogn Sci*. 2012;16(9):476–83.
42. Ba D, Takeichi N, Kodama T, Kobayashi H. Restoration of T cell depression and suppression of blood pressure in spontaneously hypertensive rats (SHR) by thymus grafts or thymus extracts. *J Immunol*. 1982;128(3):1211–6.
43. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. *J Am Soc Nephrol*. 1999;10(Suppl 12):S258–65.
44. Zheng Y, Song T, Zhang L, Wei N. Immunomodulatory effects of T helper 17 cells and regulatory T cells on cerebral ischemia. *J Biol Regul Homeost Agents*. 2018;32(1):29–35.
45. Cazareth J, Guyon A, Heurteaux C, Chabry J, Petit-Paitel A. Molecular and cellular neuroinflammatory status of mouse brain after systemic lipopolysaccharide challenge: importance of CCR2/CCL2 signaling. *J Neuroinflammation*. 2014;11:132.
46. Liu Y, Yan H, Shao F, Li QH, Cui M. Correlation between childhood eczema and specific IgG antibody level. *J Biol Regul Homeost Agents*. 2018;32(2):341–4.
47. Moskowitz MA, Nozaki K, Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. *J Neurosci*. 1993;13(3):1167–77.
48. Fallach R, Shainberg A, Avlas O, Fainblut M, Chepurko Y, Porat E, et al. Cardiomyocyte toll-like receptor 4 is involved in heart dysfunction following septic shock or myocardial ischemia. *J Mol Cell Cardiol*. 2010;48(6):1236–44.
49. Chen Y, Liu ZH, Lin ZH, Shi XZ. Eyes in pituitary disorders. *J Biol Regul Homeost Agents*. 2018;32(1):97–9.

50. Conti P, Shaik-Dasthagirisahab YB. Mast cell serotonin immunoregulatory effects impacting on neuronal function: implications for neurodegenerative and psychiatric disorders. *Neurotox Res*. 2015;28(2):147–53.
51. Cloix JF, Crabos M, Grichois ML, Meyer P. An endogenous digitalis-like compound extracted from human urine: biochemical and chemical studies. *Can J Physiol Pharmacol*. 1987;65(8):1522–7.
52. Kalantaridou S, Makriganakis A, Zoumakis E, Chrousos GP. Peripheral corticotropin-releasing hormone is produced in the immune and reproductive systems: actions, potential roles and clinical implications. *Front Biosci*. 2007;12:572–80.
53. Kehne J, De Lombaert S. Non-peptidic CRF1 receptor antagonists for the treatment of anxiety, depression and stress disorders. *Curr Drug Targets CNS Neurol Disord*. 2002;1(5):467–93.
54. Ramirez K, Niraula A, Sheridan JF. GABAergic modulation with classical benzodiazepines prevent stress-induced neuro-immune dysregulation and behavioral alterations. *Brain Behav Immun*. 2016;51:154–68.
55. Yirmiya R, Rimmerman N, Reshef R. Depression as a microglial disease. *Trends Neurosci*. 2015;38(10):637–58.
56. Dogra S, Sona C, Kumar A, Yadav PN. Epigenetic regulation of G protein coupled receptor signaling and its implications in psychiatric disorders. *Int J Biochem Cell Biol*. 2016;77(Pt B):226–39.
57. Webster EL, Lewis DB, Torpy DJ, Zachman EK, Rice KC, Chrousos GP. In vivo and in vitro characterization of antalarmin, a nonpeptide corticotropin-releasing hormone (CRH) receptor antagonist: suppression of pituitary ACTH release and peripheral inflammation. *Endocrinology*. 1996;137(12):5747–50.
58. Du F, Yin L, Shi M, Cheng H, Xu X, Liu Z, et al. Involvement of microglial cells in infrasonic noise-induced stress via upregulated expression of corticotropin releasing hormone type 1 receptor. *Neuroscience*. 2010;167(3):909–19.
59. Martin B, Lopez de Maturana R, Brennenman R, Walent T, Mattson MP, Maudsley S. Class II G protein-coupled receptors and their ligands in neuronal function and protection. *NeuroMolecular Med*. 2005;7(1–2):3–36.
60. Watts AG. Glucocorticoid regulation of peptide genes in neuroendocrine CRH neurons: a complexity beyond negative feedback. *Front Neuroendocrinol*. 2005;26(3–4):109–30.
61. Theoharides TC, Alysandratos KD, Angelidou A, Delivanis DA, Sismanopoulos N, Zhang B, et al. Mast cells and inflammation. *Biochim Biophys Acta*. 2012;1822(1):21–33.
62. Yang Y, Hahm E, Kim Y, Kang J, Lee W, Han I, et al. Regulation of IL-18 expression by CRH in mouse microglial cells. *Immunol Lett*. 2005;98(2):291–6.
63. Hoseini RF, Jabbari F, Rezaee A, Rafatpanah H, Yousefzadeh H, Ariaee N, et al. House dust mite sublingual-swallow immunotherapy in perennial rhinitis: a double-blind, placebo-controlled Iranian study. *J Biol Regul Homeost Agents*. 2018;32(1):83–8.
64. Singh LK, Boucher W, Pang X, Letourneau R, Seretakis D, Green M, et al. Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of corticotropin-releasing hormone receptors. *J Pharmacol Exp Ther*. 1999;288(3):1349–56.
65. Ramkissoon SH, Patel HJ, Taborga M, Rameshwar P. G protein-coupled receptors in haematopoietic disruption. *Expert Opin Biol Ther*. 2006;6(2):109–20.
66. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*. 2005;54(10):1481–91.
67. Norcini Pala A. HIV, depression and compliance: the mediating role of cytokines. A review of the international literature. *Riv Psichiatri*. 2013;48(6):432–40.
68. Silvestre FJ, Lauritano D, Carinci F, Silvestre-Rangil J, Martinez-Herrera M, Del Olmo A. Neuroinflammation: Alzheimer's disease and periodontal disease: is there an association between the two processes? *J Biol Regul Homeost Agents*. 2017;31(2 Suppl 1):189–96.
69. Schaakxs R, Wielaard I, Verhoeven JE, Beekman AT, Penninx BW, Comijs HC. Early and recent psychosocial stress and telomere length in older adults. *Int Psychogeriatr*. 2016;28(3):405–13.
70. Anderson G, Maes M. Oxidative/nitrosative stress and immunoinflammatory pathways in depression: treatment implications. *Curr Pharm Des*. 2014;20(23):3812–47.
71. Matin N, Tabatabaie O, Falsaperla R, Pavone P, Serra A, Cocuzza S, et al. Efficacy and safety of omalizumab in paediatric age: an update of literature data. *J Biol Regul Homeost Agents*. 2016;30(2):579–84.
72. Tettamanti L, Caraffa A, Mastrangelo F, Ronconi G, Kritas S, Frydas I, et al. Different signals induce mast cell inflammatory activity: inhibitory effect of vitamin E. *J Biol Regul Homeost Agents*. 2018;32(1):13–9.
73. Dines KC, Powell HC. Mast cell interactions with the nervous system: relationship to mechanisms of disease. *J Neuropathol Exp Neurol*. 1997;56(6):627–40.
74. Theoharides TC, Asadi S, Patel AB. Focal brain inflammation and autism. *J Neuroinflammation*. 2013;10:46.
75. Milano S, Arcoleo F, Dieli M, D'Agostino R, De Nucci G, D'Agostino P, et al. Ex vivo evidence for PGE2 and LTB4 involvement in cutaneous leishmaniasis: relation with infection status and cytokine production. *Parasitology*. 1996;112(Pt 1):13–9.
76. Theoharides TC, Zhang B, Kempuraj D, Tagen M, Vasiadi M, Angelidou A, et al. IL-33 augments substance P-induced VEGF secretion from human mast cells and is increased in psoriatic skin. *Proc Natl Acad Sci U S A*. 2010;107(9):4448–53.
77. Liu N, Wang LH, Guo LL, Wang GQ, Zhou XP, Jiang Y, et al. Chronic restraint stress inhibits hair growth via substance P mediated by reactive oxygen species in mice. *PLoS One*. 2013;8(4):e61574.
78. Yan T. Role of anti-inflammatory cytokines in pathogenesis of pediatric mycoplasma pneumoniae pneumonia. *J Biol Regul Homeost Agents*. 2016;30(2):541–5.
79. Abd El-Aal AA, Hassan MA, Gawdat HI, Ali MA, Barakat M. Immunomodulatory impression of anti and pro-inflammatory cytokines in relation to humoral immunity in human scabies. *Int J Immunopathol Pharmacol*. 2016;29(2):188–94.
80. Kaushik DK, Thounaojam MC, Kumawat KL, Gupta M, Basu A. Interleukin-1 β orchestrates underlying inflammatory responses in microglia via Krüppel-like factor 4. *J Neurochem*. 2013;127(2):233–44.
81. Franca RF, Costa RS, Silva JR, et al. IL-33 signaling is essential to attenuate viral-induced encephalitis development by downregulating iNOS expression in the central nervous system. *J Neuroinflammation*. 2016;13(1):159.
82. Dinarello CA. Overview of the interleukin-1 family of ligands and receptors. *Semin Immunol*. 2013;25(6):389–93.
83. Karatas H, Erdener SE, Gursay-Ozdemir Y, Lule S, Eren-Kocak E, Sen ZD, et al. Spreading depression triggers headache by activating neuronal Panx1 channels. *Science*. 2013;339(6123):1092–5.
84. Msghina M, Gonon F, Stjärne L. Paired pulse analysis of ATP and noradrenaline release from sympathetic nerves of rat tail artery and mouse vas deferens: effects of K⁺ channel blockers. *Br J Pharmacol*. 1998;125(8):1669–76.
85. Graziottin A, Skaper SD, Fusco M. Mast cells in chronic inflammation, pelvic pain and depression in women. *Gynecol Endocrinol*. 2014;30(7):472–7.
86. Morales-Medina JC, Dumont Y, Quirion R. A possible role of neuropeptide Y in depression and stress. *Brain Res*. 2010;1314:194–205.

87. Thomson M. The physiological roles of placental corticotropin releasing hormone in pregnancy and childbirth. *J Physiol Biochem.* 2013;69(3):559–73.
88. De Souza EB. Corticotropin-releasing factor receptors: physiology, pharmacology, biochemistry and role in central nervous system and immune disorders. *Psychoneuroendocrinology.* 1995;20(8):789–819.
89. Hu GZ, Yang SJ, Hu WX, Wen Z, He D, Zeng LF, et al. Effect of cold stress on immunity in rats. *Exp Ther Med.* 2016;11(1):33–42.
90. Félix NM, Goy-Thollot I, Walton RS, Gil SA, Mateus LM, Matos AS, et al. Effects of etomidate in the adrenal and cytokine responses to hemorrhagic shock in rats. *Eur J Inflamm.* 2016;14:147–61.
91. Moor KW, O'Garra A, de Waal Malefyt R, et al. Interleukin-10. *Annu Rev Immunol.* 1993;11:165–90.
92. Liu QL, Huang L, Zhao QJ, Li Q, He Z. Relationship between serum interleukin-17 level and inflammatory bowel disease. *J Biol Regul Homeost Agents.* 2016;30(1):181–8.
93. dar T, Edden Y, Shteingart S, Ben Ya'acov A, et al. Portal hypertension is associated with modulation of regulatory T cells. *Eur J Inflamm.* 2016;14:40–7.
94. Kandere-Grzybowska K, Letourneau R, Kempuraj D, Donelan J, Poplawski S, Boucher W, et al. IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. *J Immunol.* 2003;171(9):4830–6.
95. Schindler R, Ghezzi P, Dinarello CA. IL-1 induces IL-1. IV. IFN-gamma suppresses IL-1 but not lipopolysaccharide-induced transcription of IL-1. *J Immunol.* 1990;144(6):2216–22.
96. Dinarello CA, Bufler P. Interleukin-37. *Semin Immunol.* 2013;25(6):466–8. <https://doi.org/10.1016/j.smim.2013.10.004>.
97. Wood JD. Neurotransmission at the interface of sympathetic and enteric divisions of the autonomic nervous system. *Chin J Physiol.* 1999;42(4):201–10.