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Review

Resolution of inflammation and mood disorders

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ABSTRACT

Relationship between mood disorders and inflammation is now well-documented, although molecular mechanisms are not understood. Previously mostly pro-inflammatory cytokines of immune system (IL-6, TNF, etc.) were taken into account. However, recent understanding of resolution of inflammation as an active process drew attention to mediators of resolution, which include both proteins and ω-3 and ω-6 polyunsaturated fatty acids derivatives (resolvins, cyclopentenone prostaglandins, etc.). This review takes into account new data on resolution of inflammation and action of mediators of resolution in models of depression. New facts and ideas about mechanisms of chronic inflammation onset are considered in relation to mood disorders. Basic control mechanisms of inflammation at the cellular level and the role of resolution substances in regulation of depression and other mood disorders are discussed. Signaling systems of innate immunity located in non-immune cells and their ability to generate substances that affect an onset of depression are reviewed. A novel hypothesis of depression as a type of abnormal resolution is proposed.

1. Introduction

Mood disorders, first of all depression, are recognized among the most significant diseases and an increase in their burden is expected in the nearest future according to WHO data ("Sixty-fifth World Health Assembly Resolution: the global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level", 2012). Thus improvement of the disease diagnostics, understanding mechanisms of mood disorder occurrence and development of effective therapy are currently of high importance. Intensive research of the recent years opens up new pages in mood disorder studies. There are many hypotheses about molecular mechanisms underlying an onset of depression (Cai et al., 2015; Dantzer et al., 2008; Deak et al., 2017; Dean and Keshavan, 2017; Krishnan and Nestler, 2008; Massart et al., 2012). Neuroendocrine interrelations are noted in etiology of these diseases (see, for example, (Krishnan and Nestler, 2010; Ménard et al., 2017; Russo and Nestler, 2013)). Pathogenic mechanisms of depression are associated with a functional deficiency of the serotonergic system that interacts with the noradrenergic, dopaminergic, cholinergic, glutamatergic and GABAergic systems (Krishnan and Nestler, 2008; Russo and Nestler, 2013). Correction of abnormal neurochemical pathways underlies action of most classical antidepressants. Noteworthy, therapy with existing antidepressants brings positive results in just 30–50% of cases (Ménard et al., 2017; Trivedi et al., 2006). This implies that depression is provided by a number of molecular mechanisms with similar manifestations. Low efficiency of antidepressant treatment makes researchers turn to search of novel possible mechanisms. Over the past three decades, many studies have been carried out in the area of interconnections between mood disorders, innate immunity and inflammatory processes, they have been summarized in several recent reviews (Dantzer, 2018; Krishnan and Nestler, 2008; Ménard et al., 2017; Russo and Nestler, 2013).

Alterations in communication pathways between the immune system and the nervous system can be attributed to many pathological conditions (Dantzer, 2018). Acute inflammation causes sickness behavior and chronic inflammatory processes (so called chronic low-grade inflammation) that are related to mood disorders. As in other structures, inflammation in the central nervous system (CNS) plays a dual role, i.e., it can be neuroprotective or neurotoxic. Moreover, low grade inflammation can cause brain dysfunctions over months, years, or during lifetime (Hohlfeld et al., 2007). This emphasizes need for detailed examination of inflammation as a common phenomenon of an organism response to external stimuli. Traditionally inflammation referred to as an innate immune response and nervous system processes were not viewed as a single system. Currently understanding of this

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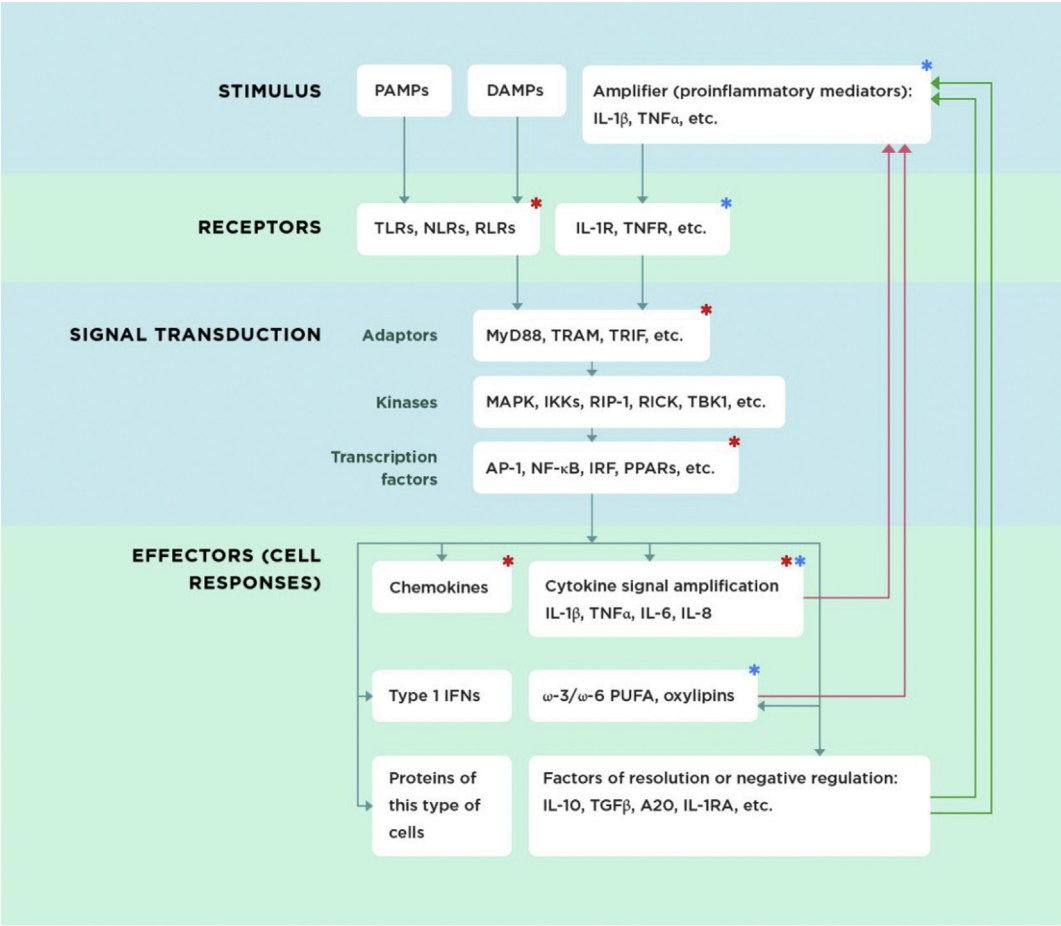

Fig. 1. Intracellular signaling pathways of pattern recognition receptor. Activation of receptors (TLR, NLR, etc) induces a number of signaling pathways, the pathways are comprised of protein adaptors (MyD88, TRAM, etc.), kinases (MAPKs, IKKs, etc.) and transcription factors (AP-1, NF-κB, etc). Transcription factors bind to specific sites of DNA and activate synthesis of effector molecules, different cytokines, chemokines and lipid mediators, which have both pro- and anti- inflammatory effects.

Abbreviations: PAMP - pathogen-associated molecular patterns; DAMP - Damage-associated molecular patterns; IL-1β - interleukin 1 beta; TNFα - tumor necrosis factor alpha; IL-1R - interleukin-1 receptor; TNFR - tumor necrosis factor receptor; TLRs - toll-like receptors; NLRs - nucleotide-binding oligomerization domain-like receptors; RLRs - RIG-I-like receptors; MyD88 - Myeloid differentiation primary response 88; TRAM - trif-related adaptor molecule; TRIF - TIR-domain-containing adapter-inducing interferon-β; MAPK - mitogen-activated protein kinase; IKK - IκB kinase; RIP-1 - receptor interacting protein 1; RICK - Rip-like interacting caspase-like apoptosis-regulatory protein kinase; TBK1 - TANK-binding kinase 1; AP-1 - activator protein 1; NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells; IRF - interferon regulatory factors; PPARs - peroxisome proliferator-activated receptors; IL-6 - interleukin 6; IL-8 - interleukin 8; PUFA - polyunsaturated fatty acids; IFNs - interferons; TGF-β - transforming growth factor beta; A20 - zinc finger protein A20.

problem is changing and balance between the immune system and the central nervous system is being under consideration (see review (Dantzer, 2018)).

Over the past ten years, significant breakthrough was made in study of inflammation (Medzhitov et al., 2012; Medzhitov and Horng, 2009; Nathan and Ding, 2010; Serhan, 2017a). First of all, it became clear, that resolution of inflammation is an active process that can be actively controlled. Moreover, unbalanced positive and negative feedback loops of innate immune regulatory pathways can result in chronic inflammation. The aim of this publication will be to provide a review of contemporary literature in order to present the latest scientific data regarding the role of resolution processes of innate immune responses in pathology of depression and other mood disorders. We have carried out a comprehensive search in the Pubmed/MEDLINE electronic databases from the very beginning until March 1, 2018. The terms we looked for included: “Resolution”, “Inflammation”, “Innate immunity” cross-referenced with “mood disorders”, “depression”. The articles were taken into account and included in our study based on their overall quality of methodology. In spite of huge amount of reviews and original research papers concerning connection between the keywords “inflammation”, “depression”, “mood disorders”, relatively few data connected resolution of inflammation with mood disorders. This represents a gap between two branches of current scientific knowledge. Therefore, we add section about basic regulatory mechanisms of inflammation at the cellular level and examine the role of resolution substances in regulation of depression and other mood disorders. A role of innate immune signaling pathways presented in non-immune cells in production of substances that affect onset of depression and other psychiatric disturbances is discussed.

2. Modern view on innate immunity and inflammation

2.1. Basic principles of inflammation

The innate immune system is the first line of host defense (Medzhitov and Janeway, 2000; Takeda and Akira, 2015). In narrow sense, it represents a number of mechanisms and adaptations that prevent invasion of pathogens of various nature (viruses, bacteria, multicellular parasites etc.). In broad sense innate immunity serves to protect a host from a homeostasis alteration no matter of its cause.