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Invited review

Purinergic mechanisms in neuroinflammation: An update from molecules to behavior

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ABSTRACT

The principle functions of neuroinflammation are to limit tissue damage and promote tissue repair in response to pathogens or injury. While neuroinflammation has utility, pathophysiological inflammatory responses, to some extent, underlie almost all neuropathology. Understanding the mechanisms that control the three stages of inflammation (initiation, propagation and resolution) is therefore of critical importance for developing treatments for diseases of the central nervous system. The purinergic signaling system, involving adenosine, ATP and other purines, plus a host of P1 and P2 receptor subtypes, controls inflammatory responses in complex ways. Activation of the inflammasome, leading to release of pro-inflammatory cytokines, activation and migration of microglia and altered astroglial function are key regulators of the neuroinflammatory response. Here, we review the role of P1 and P2 receptors in mediating these processes and examine their contribution to disorders of the nervous system. Firstly, we give an overview of the concept of neuroinflammation. We then discuss the contribution of P2X, P2Y and P1 receptors to the underlying processes, including a discussion of cross-talk between these different pathways. Finally, we give an overview of the current understanding of purinergic contributions to neuroinflammation in the context of specific disorders of the central nervous system, with special emphasis on neuropsychiatric disorders, characterized by chronic low grade inflammation or maternal inflammation. An understanding of the important purinergic contribution to neuroinflammation underlying neuropathology is likely to be a necessary step towards the development of effective interventions.

Contents

Abbreviations: ASC, apoptosis-associated speck-like protein; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BD, bipolar disorder; BBB, blood brain barrier; CNS, central nervous system; DAMPs, endogenous damage-associated molecular patterns; FST, forced swim test; LPS, bacterial lipopolysaccharide; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDD, major depressive disorder; MPC, microglial process convergence; NLRP, nod-like receptor protein; OCD, obsessive compulsive disorder; PAMPs, pathogens-associated molecular patterns; Panx1, pannexin-1 hemichannels; PD, Parkinson's disease; PI3K kinase, phosphoinositide 3 kinase; PKA, protein kinase A; PKC, protein kinase C; sIL-2R, soluble interleukin (IL)-2 receptor; sIL-6R, soluble interleukin (IL)-6 receptor; SM, multiple sclerosis; sTNFR1, soluble tumor necrosis factor receptor type 1; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; TST, tail suspension test.

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1. Introduction – the evolution of the concept of neuroinflammation

The term 'inflammation' was coined by Celsus around the 1st century BC, defined by four cardinal signs; tumor, rubor, calor and dolor (Celsus, 1478) (i.e. oedema, redness, increased temperature and pain in the affected tissue) with a fifth sign, loss of function, attributed to Galen. By the identification of underlying molecular and cellular mechanisms, inflammation now assumes a substantially wider meaning, as a complex biological response to harmful stimuli, composed of three phases: initiation, propagation and resolution (Lister et al., 2007). While the principle functions of inflammation are to limit tissue damage and promote tissue repair (Nathan, 2002), inappropriate inflammatory responses, particularly when chronic, can lead to toxicity and cell loss (Hauss-Wegrzyniak et al., 2002).

The central nervous system (CNS), separated from the periphery by a specialized blood brain barrier (BBB) has long been considered an 'immuno-privileged' region (Carson et al., 2006), protected from systemic immune and inflammatory responses to pathology or injury. Behind the protection of the BBB, however, CNS-specific immune effector cells, particularly microglia (Streit et al., 2004), mediate neuroinflammatory responses to insult in response to a variety of triggers, including toxic metabolites, autoimmunity (Gendelman, 2002) or via the detection of pathogens or endogenous damage-associated molecular patterns (PAMPs and DAMPs) released in response to CNS damage, such as traumatic brain injury (Bernier, 2012). The outcome of a neuroinflammatory response depends, to a large extent, on its severity and duration (Vivekanantham et al., 2015), but pathological neuroinflammation, promoting apoptosis and necrosis and influencing the synaptic and intrinsic membrane properties of neurons (Yirmiya and Goshen, 2011), contributes to a host of CNS pathologies. A central role for neuroinflammation has been reported for primary or secondary neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (SM) amyotrophic lateral sclerosis (ALS), Huntington's disease, stroke and epilepsy (Frank-Cannon et al., 2009). Neuroinflammation has also been recognized as a pathological factor in psychiatric mood disorders, characterized by chronic mild neuroinflammation (Najjar et al., 2013), and developmental neuropsychiatric disorders, such as schizophrenia and autism (Meyer, 2013).

The main cellular effectors of neuroinflammation are astrocytes and microglia, as well as perivascular monocytes and macrophages invading to sites of insult from the circulation (Yamasaki et al., 2014). In addition, neurogenic neuroinflammation, the direct contribution of neuronal activity, is a unique feature of the nervous system (Xanthos and Sandkuhler, 2014). Chronic neuroinflammation involves the sustained activation of glial cells, chronic release of pro-inflammatory cytokines, increased permeability of the BBB and recruitment of systemic immune effector cells into the CNS (O'Callaghan et al., 2008).

Neuroinflammatory cascades rely on the activation of an inflammasome, a protein complex, consisting of caspase-1, apoptosis-associated speck-like protein (ASC) and nod-like receptor protein (NLRP1 or NLRP3) (Martinon et al., 2002). The inflammasome is the principle source of mature proinflammatory cytokine IL-1β, with caspase-1 activity necessary for the proteolytic cleaving of pro–IL-1β (Gross et al., 2011). While NLRP inflammasomes are activated by the recognition of PAMPs or DAMPs (Bernier, 2012), the identification of host-derived DAMPs has become a major project, necessary for uncovering the pathway from insult to pathology.

The NLRP3 inflammasome and its downstream pathway has been recognized as a central mediator of systemic inflammation and a key mechanistic link between psychological stress and the emergence of depression and other psychiatric illnesses (Iwata et al., 2013). Much evidence has accumulated that ATP, found at higher extracellular concentrations following insult, potently induces NLRP-mediated IL-1β processing (Burnstock, 2008) and that its metabolite, adenosine, is also heavily involved in the modulation of this signaling pathway. ATP and other nucleotides, such as UTP are released from induced cells and provide "find-me" and "eat-me" signals contributing to different phases of neuroinflammation by activating purinoceptors (Di Virgilio et al., 2009). Purinergic involvement in neuroinflammatory processes include the mediation of early events such as chemotaxis, microglia activation and the secretion of pro-inflammatory cytokines, phagocytosis, reactive astrogliosis and repair mechanisms such as neurogenesis.

Here we review the current understanding of the role of purinergic signaling in mediating the three phases of inflammation, the effect of the neuroinflammatory response on neuronal survival and functionality and the etiology and progression of CNS disease. Because the role of purinergic mechanisms in neurodegenerative diseases, such as AD, PD, SM, ALS and neuropathic pain is widely covered by other articles in this special issue; see (Burnstock, 2015), we will emphasize selected aspects which highlight the purinergic regulation of astrocytic and microglial cellular neuroinflammatory responses and their peculiar role in psychiatric disorders. Further elucidation of the participation of purinergic receptors in neuroinflammation will lead to a better of understanding of its role in neuropathology and may also pave the way towards more targeted and innovative therapies to combat CNS disorders.

1.1. The role of P2X receptors in neuroinflammation

P2X receptors are ligand-gated cation channels, rendered permeable to Na^+, K^+ and Ca^{2+} upon the binding of ATP (Abbracchio et al., 2009). Seven P2X subunits are expressed in the brain (P2X1-7), with P2X1-5 combining to form functional receptors with a heterotrimeric or homotrimeric quaternary structure, P2X6 forming only as a part of heterotrimeric receptors and P2X7 forming only homotrimers (North, 2002). Each combination of subunits forms a functional channel with different affinities for ATP and different desensitization dynamics conferring a variety in physiological responses to ATP; while P2X1 and P2X3 receptors desensitize within hundreds of milliseconds, P2X2 and P2X4 receptors desensitize an order of magnitude slower, and P2X7 receptors show very little desensitization, even over minutes (North and Jarvis, 2013). Both levels of subunit expression and receptor composition vary according to cell type and brain region. ATP-affinity and receptor function are also modulated by phosphorylation state and a host of allosteric and non-allosteric modulators, including heavy metals and reactive oxygen species (Coddou et al.,

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