BRAIN RESEARCH 1628 (2015) 288–297

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Brain Research

Research Report

How microglia kill neurons

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ARTICLE INFO

Article history:
Accepted 24 August 2015
Available online 2 September 2015

Keywords:
Inflammation
Cell death
Nitric oxide
Phagocytosis
Neurodegeneration
Neurotoxicity

ABSTRACT

Microglia are resident brain macrophages that become inflammatory activated in most brain pathologies. Microglia normally protect neurons, but may accidentally kill neurons when attempting to limit infections or damage, and this may be more common with degenerative disease as there was no significant selection pressure on the aged brain in the past. A number of mechanisms by which activated microglia kill neurons have been identified, including: (i) stimulation of the phagocyte NADPH oxidase (PHOX) to produce superoxide and derivative oxidants, (ii) expression of inducible nitric oxide synthase (iNOS) producing NO and derivative oxidants, (iii) release of glutamate and glutaminase, (iv) release of TNFα, (v) release of cathepsin B, (vi) phagocytosis of stressed neurons, and (vii) decreased release of nutritive BDNF and IGF-1. PHOX stimulation contributes to microglial activation, but is not directly neurotoxic unless NO is present. NO is normally neuroprotective, but can react with superoxide to produce neurotoxic peroxynitrite, or in the presence of hypoxia inhibit mitochondrial respiration. Glutamate can be released by glia or neurons, but is neurotoxic only if the neurons are depolarised, for example as a result of mitochondrial inhibition. TNFα is normally neuroprotective, but can become toxic if caspase-8 or NF-κB activation are inhibited. If the above mechanisms do not kill neurons, they may still stress the neurons sufficiently to make them susceptible to phagocytosis by activated microglia. We review here whether microglial killing of neurons is an artefact, makes evolutionary sense or contributes in common neuropathologies and by what mechanisms.

This article is part of a Special Issue entitled SI: Neuroprotection.

Abbreviations: BDNF, brain-derived neurotrophic factor; casp8, caspase 8; Cox-2, cyclooxygenase-2; CXCL1, chemokine (C-X-C motif) ligand 1; CX3CR1, CX3C chemokine receptor 1; DAP12, DNAX-activation protein 12; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HMGB1, high-mobility group protein B1; HSP60, heat shock protein 60; IGF1, insulin-like growth factor 1; INF-γ, interferon-γ; IL, interleukin; LPS, lipopolysaccharide; mito, mitochondria; MERTK, Mer tyrosine kinase; MFG-E8, milk fat globule-EGF factor 8 protein; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; NOS, nitric oxide synthase; iNOS, inducible NOS; MMP-9, matrix metallopeptidase 9; PHOX, phagocytic NADPH oxidase; PS, phosphatidylserine; RIP1, receptor-interacting protein 1; RIP3, receptor-interacting protein 3; MLKL, mixed lineage kinase domain-like protein 1; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; TNFα, tumour necrosis factor alpha; TLR, toll-like receptor; VNR, vitronectin receptor; XIAP, X-linked inhibitor of apoptosis protein.

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http://dx.doi.org/10.1016/j.brainres.2015.08.031
0006-8993/

1. Introduction

There is evidence that brain inflammation and/or activated microglia contribute to acute pathologies such as stroke, trauma and meningitis, psychiatric diseases such as schizophrenia, depression and autism, and neurodegenerative diseases such as AIDS dementia, multiple sclerosis, Alzheimer's disease, Parkinson's disease and motor neuron disease (Bal-Price and Brown, 2001; Bal-Price et al., 2002; Klegeris et al., 2007; Lucas et al., 2006; McNaught and Brown, 1998; Zipp and Aktas, 2006). These pathologies have different causes and consequences, but they all involve brain inflammation, and there is evidence that blocking inflammation can either delay onset or reduce symptoms (Klegeris et al., 2007; Lucas et al., 2006; Zipp and Aktas, 2006; Block et al., 2007; Brown and Bal-Price, 2003; Wyss-Coray, 2006). In general, inflammation may have beneficial and/or detrimental effects in any particular disease and in any particular phase of a disease. The beneficial effects are mainly due to elimination of pathogens, clearing debris, recruiting other cells, aiding repair and providing neurotrophins; and the detrimental effects may be unintended side-effects of the beneficial processes (Klegeris et al., 2007; Lucas et al., 2006; Zipp and Aktas, 2006; Block et al., 2007; Brown and Bal-Price 2003; Wyss-Coray 2006).

Inflammation can damage the brain in a variety of ways, including: (i) inflammation in the vascular wall may drive atherosclerosis, leading to stroke and vascular dementia, (ii) inflammation in the blood brain barrier may compromise barrier function and allow thrombin, albumin and antibodies into the brain, (iii) inflammation and/or blood brain barrier breakdown may recruit/allow lymphocytes, monocytes and neutrophils into the brain (Engelhardt and Ransohoff, 2005), (iv) antibodies generated against brain antigens may induce immune attack as occurs in multiple sclerosis, (v) inflammation may induce brain oedema (swelling), (vi) some types of inflammation may suppress neurogenesis, (vii) cytokines may inflammatory activate astrocytes, which may then kill neurons, and (vii) pathogens, protein aggregates, damaged neurons and/or cytokines may inflammatory activate microglia, which may then kill neurons. It is this last type of damage, common to many brain pathologies, that we shall be concerned with here.

2. Microglia and their 'activation' states

Microglia, the brain's main resident macrophages, are the predominant immune cells in the healthy brain, and main regulators of brain inflammation (Block et al., 2007; Ransohoff and Perry, 2009). The healthy, non-inflamed brain contains almost entirely 'resting' microglia, which are highly ramified, with a small, static cell body, but with dynamic and branched processes actively seeking out signs of pathogens or damage in the brain (Hanisch and Kettenmann, 2007). When microglia detect such signs, they become 'activated' (Fig. 1). Activation is normally accompanied by partial retraction of processes to the cell body, proliferation, and expression and release of pro-inflammatory cytokines, including TNFα, IL-1β, IL-6 and IFN-γ. These cytokines recruit and activate other microglia. In fact in the inflamed brain, most microglia will encounter pro- or anti-inflammatory cytokines, or chemokines or other chemotactic factors first before they encounter a pathogen or damaged neuron, and this first encounter will 'prime' or programme their response to subsequent encounters (Perry and Holmes, 2014). Highly activated microglia may completely retract processes to the cell body producing rounded ('amoeboid') microglia that are highly mobile and phagocytic.

Microglia can be 'activated' into a variety of states, of which the best characterised are the M1 or classically activated state (induced by pro-inflammatory cytokines and/or TLR activation) and the M2 or alternatively activated state (induced by IL-4) (Ransohoff and Perry, 2009; Chhor et al., 2013). This classification is derived from the Th1 (releasing IFN-γ) and Th2 (releasing IL-4) responses of T cells, which was then extended to macrophages as M1 (induced by

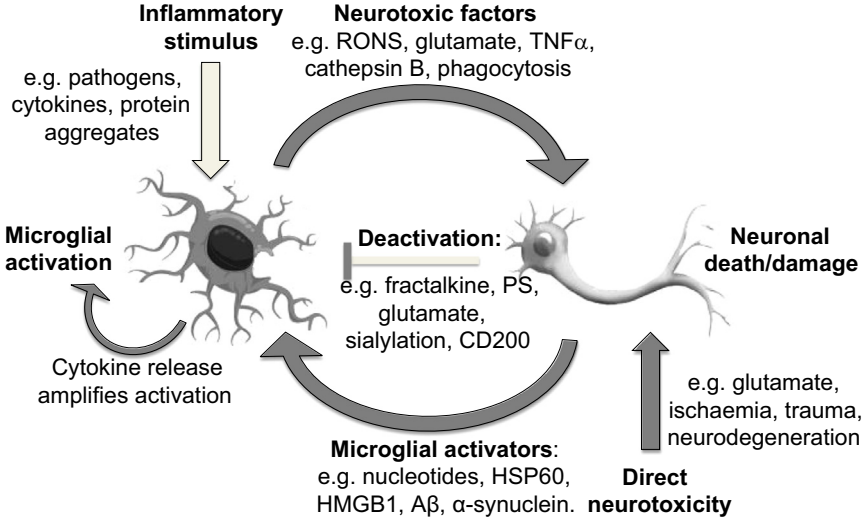

Fig. 1 – Factors regulating neuroinflammation and associated neurotoxicity. Microglia are activated by inflammatory stimuli, amplified by cytokine release, causing release of neurotoxic factors that damage or kill neurons. This or direct neurotoxicity may further activate microglia. However, the potential vicious cycle can be deactivated by a variety of factors or resolution of the original stimuli.