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Initiating Mechanisms of Surgery-induced Memory Decline: The Role of HMGB1

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Introduction

We will review (i) how High Mobility Group Box Protein 1 (HMGB1) engages with the innate immune system following the aseptic trauma of surgery, (ii) how engagement of the innate immune system results in postoperative neuroinflammation (PONI) and postoperative cognitive decline (POCD), and finally we propose (iii) putative treatments targeting these processes to limit cognitive decline.

Damage Associated Molecular Patterns and the Innate Immune System

Matzinger's "danger" – subsequently known as "damage" - model of the immune system accounts for observations that are not explained by Burnet's original "self-nonself" model [1]. Necrotic cells, or cells in profound distress, release damage-associated molecular patterns (DAMPS) into the circulation. DAMPs are naturally-occurring intracellular constituents that include S100 proteins, heat-shock proteins and HMGB1. Similar to sepsis, in which release of bacterial DNA – known as pathogen-associated molecular patterns [2] – alerts the organism to invasion by "nonself", so too can DAMPs notify the host's innate immune system that tissue damage is present in order to initiate healing processes. DAMPS are recognized by pattern recognition receptors (PRR) [3,4]; among PRRs, toll-like receptors (TLRs) play a key role in recognizing disparate ligands and triggering signals along different pathways. Once PRRs are ligated the immune system initiates the synthesis and release of inflammatory mediators.

High Mobility Group Box Protein 1

HMGB1 is a ubiquitous nuclear protein encoded on human chromosome 13q12-13. It was initially identified over 30 years ago with a particular focus on its importance in transcription regulation stabilizing nucleosome formation and acting as a transcription factor-like protein that regulates the expression of several genes [5], including p53, p73, the retinoblastoma family, members of the Rel/nuclear factor-κB (NF-κB) family, and nuclear hormone receptors [6]. Later studies have since recognized its cytokine-like potential [7]. HMGB1 can mediate systemic inflammatory responses by stimulating a variety of cells including monocytes, smooth muscle cells, tumor cells, dendritic cells, neutrophils and mesoangioblast stem cells, promoting inflammation, angiogenesis, and enhancing hematopoietic stem-cell migration [8]. Emerging evidence indicates that HMGB1 is also an essential mediator of severe systemic inflammation (SSI) [9,10].

HMGB1 can be released into the extracellular space either by an active process, once it is acetylated in the nucleus, or by a passive process in which it diffuses out of the necrotic cells. Various stimuli can activate monocytes, tissue macrophages, NK or even mature myeloid dendritic cells to secrete HMGB1 [5]. Depending on the ambient redox state the cysteine residues of HMGB1 may become oxidized thereby dictating the subsequent signaling [11,12]. HMGB1 contains three conserved cysteines that are sensitive to oxidation: Cys23, Cys45 (located in Box A), and Cys106 (located in Box B) [12]. Cys-23 and Cys-45 can easily form a disulfide bond under relatively mild oxidative conditions giving rise to "disulfide HMGB1". Cys-106 remains in the reduced state until it is exposed to a large amount of reactive oxygen species, typically from activated leukocytes, thereby forming "sulfonated HMGB1" [6]. When released into the extracellular space, HMGB1 is initially in the reduced state but becomes oxidized by the extant environmental conditions that initiated its release. The disulfide form of HMGB1 binds to TLR2, TLR4 and receptor for advanced glycation end-products (RAGE). Signaling through these receptors leads to activation of NF-κB, that is pivotal for the proinflammatory pathway, thereby increasing the synthesis and release of cytokines [13]. As triggering of PRRs on inflammatory cells by disulfide HMGB1 generates more reactive oxygen species, further oxidation generates sulfonated HMGB1 thereby resolving inflammation [14]. Interestingly, while extracellular disulfide HMGB1 leads to the synthesis and release of tumor necrosis factor (TNF)α, intracellular HMGB1 may silence TNFα during SSI, as seen in sepsis and other disseminated acute inflammatory processes [15]; evidence for this role comes from studies involving the depletion of HMGB1 in which RelB dissociates from the promoter region and negatively regulates the expression of TNF-α [16]. In addition, loading of HMGB1 at the TNF-α gene locus correlates with the presence of H3K9me2 [15], which implies that histone methyltransferase G9a and its partner protein GLP may also play roles in the regulation of SSI [17]. Recent observations indicate that the G9a/GLP complex is also involved in the maintenance of imprinted DNA methylation [18], the potential epigenetic mechanisms associated with SSI may also include DNA methylation.

Postoperative Neuroinflammation and Postoperative Cognitive Decline (Figure 1)

The discharge of proinflammatory cytokines into the circulation is responsible for the disruption of the blood brain barrier (BBB) integrity [19]. The pathways that lead to neuroinflammation and cognitive decline after infection seem to be different from those following aseptic surgical trauma [20]. After aseptic peripheral surgery,

the release of monocyte chemotactic protein-1 (MCP-1) in the hippocampus is responsible for attracting chemokine C-C motif receptor 2-expressing cells into the brain [21]. In the active state, the translocated monocytes, now macrophages, synthesize and release a variety of pro-inflammatory cytokines that are capable of disrupting long-term potentiation, the neurobiologic correlate of memory. Depletion of bone marrow-derived macrophages (BM-DM) reduces, PONI and POCD [21]. Interestingly, depletion of BM-DM does not affect surgery-induced upregulation of hippocampal MCP-1 suggesting that it originates from cells other than BM-DM, mostly likely activated microglia [8,22]. Chronic neuroinflammation with persistently activated microglia in the hippocampus can disrupt neuronal networks required for learning and memory [23].

N-Methyl-D-aspartate (NMDA) receptors are highly concentrated in the hippocampus, playing an important role in neuroplasticity and long-term potentiation is crucially dependent on these receptors [24,25]; PONI can lead to a reduction in the number of these receptors [26]. During early stages of neuroinflammation dysfunction at the NMDA-glutamate synapse may disrupt accuracy of information processing, while in the later stages of neuroinflammation it may progress to neuronal degeneration [27,28].

Putative, additional, mechanisms whereby proinflammatory cytokines induce a long-lasting effect on cognitive function may be due to disruption of specific neural circuits [29], neurogenesis [30] as well as epigenetic modifications [31].

Possible Targets for Therapeutic Interventions of Postoperative Cognitive Decline

Changes in subcortical white matter [31], brain plasticity [32], as well as information-processing circuits within the hippocampus are features related to aging [33]. Further, declines in immune function [34] within this population lead to increased neuroinflammation and coincide with cognitive decline [35], making this patient population particularly vulnerable to POCD. With an ever-aging surgical population, postoperative delirium (POD), an easily diagnosed form of POCD, has reached epidemic proportions in the US. According to National Hospital Survey Data for 2010 more than 19 million in-patients over the age of 65% had surgery. With a quoted incidence of POD in this age group of between 15-53% [32], this translates into up to 10 million POD sufferers each year. While POD is usually short-lived, its occurrence may presage long-term problems that are associated with longer hospital stays, higher morbidity and mortality, higher risks of institutionalization, cognitive decline/dementia, and poorer overall outcomes [33-36]. Average health care costs per day survived among patients with delirium have been estimated to be more than 2.5 times those of patients without delirium, leading to increased cost of care of between $38–152 billion/year [37].

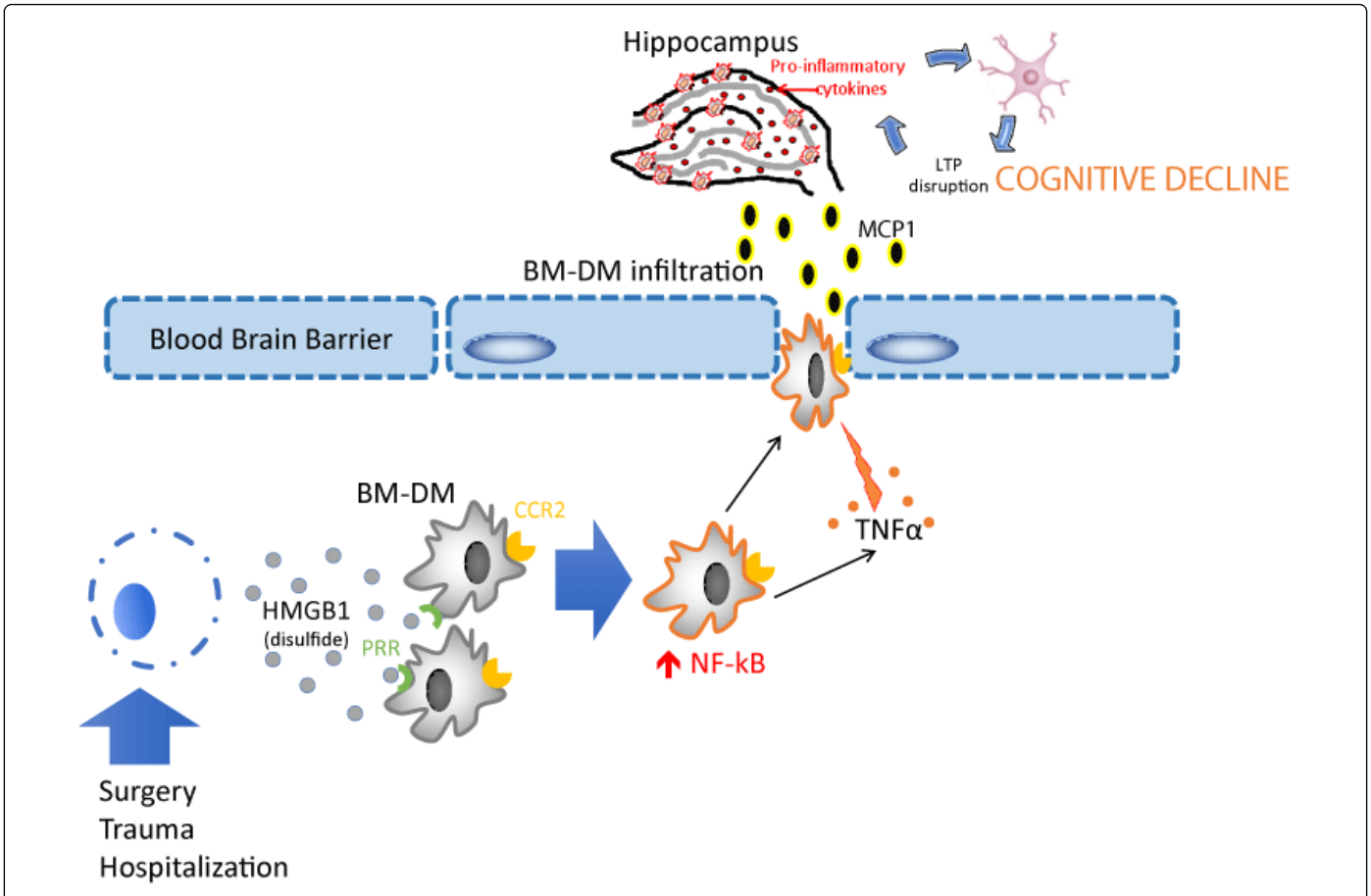

Figure 1: Represents the pathways from peripheral trauma to cognitive dysfunction.

Beyond the numbers that describe the scale of the problem and its healthcare costs is the immense burden that POD places on the patient for whom "staying sharp" was noted to be the most highly desired commodity with aging [38]. For the patient's care-giver, apart from the distress of watching their beloved's cognitive deterioration is the need to provide alternatives to overcome the patient's deficits in activities of daily living.

For these reasons therapeutic interventions are urgently required to address this serious condition. Tracking the precise biological and cellular pathways involved in postoperative memory deficits are decisive components in mapping appropriate interventions to prevent this postoperative complication. The detection of HMGB involvement in the initiation of the surgery-induced PONI, provides an opportunity for manipulating the function of HMGB1 and modifying DAMP signaling. Pre-surgical administration of HMGB1 antibody is able to halt the neuroinflammatory response to surgery by attenuating MCP-1 production [8]. Further studies are needed to determine whether this form of immunotherapy represents a viable option for preventing POD.

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