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Review Article

Microglial chemotactic signaling factors in Alzheimer's disease

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Abstract: The net migration of microglia induced by deposits of amyloid beta (Aβ) constitutes a chemotactic response of resident neuroimmune brain cells. This process serves to localize clusters of microglia nearby Aβ deposits preparatory to cellular activation and functional responses. Microglial responses to Aβ deposits localized in brain parenchyma and in blood vessels lead to acute and chronic neuroinflammation in Alzheimer's disease (AD) brain. This review summarizes studies on the prominent chemotactic factors MCP-1, MIP-1α and IL-8 and also includes recent work indicating VEGF and fractalkine as chemotactic agents. The possibility that microglial release of MCP-1 may play a role in mediating chemotactic responses of neural progenitor cells is also considered. The plethora of chemotactic factors and their cognate receptors suggests the utility in testing pharmacological modulation of chemotaxis for effects to inhibit chronic neuroinflammation and confer neuroprotection in AD animal models.

Keywords: Chemotactic factors, microglial chemotaxis, Alzheimer's disease (AD), inflammatory responses, AD animal models.

Introduction

Deposition of amyloid-beta peptide (Aβ) initiates a spectrum of cellular responses mediated by the resident neuroimmune cells of brain, microglia [1]. The accumulation of Aβ in brain parenchyma and blood vessels in Alzheimer's disease (AD) leads to mobilization and migration of microglia to regions nearby Aβ deposits. The net movement of microglia to spatial locations associated with Aβ deposits represents a chemotactic response of the neuroimmune cells. The initial chemotaxis of microglial cells serves as a precursor to subsequent activation and functional responses of cells [1-3]. Transient and sustained microglial activation, mediated by a host of cellular receptors and downstream effector pathways, yield respective acute and chronic inflammatory responses. Evidence for subsequent beneficial and more commonly, detrimental effects of microglial activation have been well-documented in AD brain [4, 5].

This review focuses on the most prominent factors that mediate microglial chemotactic responses in AD animal models and in AD brain. A host of chemotactic signaling factors and cellular receptors have been implicated in the cellular response to Aβ deposition [1]. The most common signaling agents include monocyte chemotactic protein (MCP-1), macrophage inflammatory peptide-1α (MIP-1α) and interleukin -8 (IL-8). However, evidence for other putative chemotactic factors, such as vascular endothelial growth factor (VEGF), has been reported [6]. With one exception, this article does not include any discussion of the receptors for the various chemotactic factors. The exception is microglial receptor for VEGF, since this work [7] also includes pharmacological effects on inhibition of receptor. As noted below, few studies have addressed pharmacological modulation of chemotactic factors or their receptors in AD animal models. A detailed review of chemotactic receptors in resident brain cells, including microglia, with relevance to pathology of AD is available [8].

The extent of inflammatory responses in AD have been reported as dependent on the den-

sity of activated microglia in an area-specific manner [9, 10]. Patterns of microglial distribution in response to Aβ stimulation have been documented in AD cortex [11] and transgenic animal models [12]. Analysis of a transgenic animal model has indicated that the migration of microglia to Aβ plaques is rapid (1-2 days) [13]. An important consequence following cellular activation by Aβ is microglial release of additional chemokines that further amplify inflammatory reactivity. For example, as discussed below IL-8 chemokine can enhance inflammatory responses from Aβ-stimulated human microglia [14].

It should be kept in mind that chemotaxis in AD brain is not an isolated process. Indeed a number of studies have emphasized the links between chemotactic activity with microglial activation and functional response such as phagocytosis [1]. Chemotactic activity represents an early event in inflammatory response that is coupled to subsequent complex cellular interactions and processes; however, chemotactic responses are also ongoing and could contribute to neuronal degeneration in environments of chronic neuroinflammation in brain. One conclusion arising from this review is that since a diversity of agents and pathways are involved in chemotactic responses, multiple chemotactic factors could serve as targets for pharmacological inhibition of chronic inflammatory responses and ultimately confer neuroprotection in AD brain.

Microglial chemotactic factors

MCP-1 (monocyte chemotactic protein)

Increased levels of a host of chemokines are reported in AD, relative to ND (non-demented) individuals [15]. Early work documented active fragment of Aβ induced MCP-1 production from murine microglia and human monocytes [16]. The exposure of cultured human microglia to different forms of Aβ have been found to stimulate cellular production of MCP-1. In particular, microglia isolated from both white and gray matter from AD patients showed marked increases in MCP-1 production following treatment with full length $A\beta_{1-42}$ [17]. Immunohistochemical staining has shown the presence of MCP-1 in activated microglia and in senile plaques in AD individuals [18]. Since the chemokine was absent in immature plaques, the results suggested MCP-1 as a contributing factor in plaque maturation. Gene-array analysis has shown considerable increase in MCP-1 expression with Aβ treatment of cortical human microglia [19]. Induction of MCP-1 was almost 5-fold higher relative to unstimulated microglia an increase second in magnitude only to that reported for the chemokine IL-8 (see below).

Elevated MCP-1 has been measured in cerebrospinal fluid in AD patients relative to controls [20]. Levels of MCP-1 correlated with the age of AD individuals and were upregulated throughout the course of disease. Analysis of a triple transgenic mouse model has found higher MCP-1 levels in entorhinal cortex compared to amounts in control non-transgenic animals [21]. Differences in chemokine levels were evident even at early stages of disease. A correlation between elevated MCP-1 and numbers of activated microglia and macrophages was observed in entorhinal cortical regions in this work. The overall results suggested that MCP-1 could serve as an early chemotactic signal for inflammatory reactivity mediated by neuroimmune cells in AD mice. Use of a different transgenic animal model (Tg2576) has also provided evidence for MCP-1 as a chemotactic signal for microglial accumulation nearby Aβ plaque deposition [22]. The patterns of microglial response indicated clusters of cells associated with Aβ deposits. Finally, MCP-1 has been termed a reliable predictor of disease pathology in a study of brain tissue from AD patients [23]. This study also reported immunostaining analysis that suggested association of the chemokine with neurons, astrocytes and plaques. Overall, MCP-1 has been indicated as a major factor in sustaining chronic neuroinflammation in AD brain.

MIP-1α (macrophage inflammatory peptide-1α)

Early work identified MIP-1α in AD brain tissue [24]. However, this study did not report any difference in overall immunoreactivity for this chemokine between AD and control brains. A similar result was obtained using transgenic animals. Expression of MIP-1α showed no significant differences between Tg2576 mice and aged controls [25]; however, several studies have found exposure of microglia to Aβ increases cell expression of MIP-1α. Gene expression of MIP-1α was more than doubled with $A\beta_{1-42}$ stimulation of human cortical microglia [19]. This same laboratory has also used ELISA to

examine MIP-1α produced by stimulated microglia. Microglia from AD and ND individuals were treated with full-length Aβ and conditioned medium subsequently assessed for chemokine [17]. Both gray and white matter microglia exhibited responses whereby MIP-1α was increased in a dose-dependent manner with Aβ. Interestingly, the patterns of response were similar between AD and ND microglia.

Il-8 (interleukin-8)

IL-8 is commonly associated with chemotactic neutrophil responses but also serves as a prominent factor for migration of microglia. IL-8 gene showed the highest upregulation of any pro-inflammatory factor following full-length Aβ treatment of cortical human microglia [19]. The induction of IL-8 gene was increased more than 10-fold relative to unstimulated human microglia. Functional increases in IL-8 have also been found with exposure of white matter microglia to $A\beta_{1\text{-}42}$ [17]. The chemokine exhibited dose-dependent increases in levels with Aβ treatment of microglia obtained from control and AD patients. Interestingly, magnitudes of IL-8 production were not significantly different between the two groups. The exposure of fetal human microglia to IL-8 has been found to enhance expression and production of pro-inflammatory factors from $A\beta_{1\text{-}42}$-stimulated cells [14]. The pro-inflammatory cytokines TNF-α, IL-1β and IL-6 were significantly upregulated in expression with IL-8 priming of cells compared with microglia exposed only to $A\beta_{1\text{-}42}$; controls in these experiments used reverse peptide $A\beta_{42\text{-}1}$. ELISA also demonstrated enhanced microglial secretion of the pro-inflammatory cytokines with IL-8 priming of $A\beta_{1\text{-}42}$-stimulated cells. Immunocytochemical staining showed IL-8 induced an enhancement in numbers of cyclooxygenase (COX-2) positive microglia. It was suggested that IL-8 could play a role as an enhancement factor in promoting pro-inflammatory micro-environments in AD brain.

The studies above have employed Aβ stimulation of cultured microglia to examine IL-8 gene expression or production. At present, few studies have investigated differences in levels of IL-8 between AD or control individuals. In one study elevated amounts of IL-8 in cerebrospinal fluid were detected in AD cases compared with controls [20]. Levels of the chemokine were higher with increased age of AD individuals. The finding of enhanced amounts of IL-8 with course of disease suggested a link with neurodegeneration in AD brain.

Fractalkine

Neuronal release of fractalkine is implicated in the induction of microglial inflammatory responses. Microglia express fractalkine receptor CX3CR1 and show chemotactic responses to this factor under a variety of inflammatory conditions. A diminished number of fractalkine positive cells has been reported in cortex and hippocampus of 9-month-old Tg2576 mice [25]; however, older animals showed no significant differences in fractalkine expression relative to wild-type control. ELISA analysis has indicated that levels of fractalkine were increased in AD vs control individuals [26]. Interestingly, mean fractalkine levels were higher in mild to moderate disease cases compared with severe AD. Increased fractalkine in early stage AD has been suggested as a response to enhance microglial activity in order to increase phagocytosis of Aβ plaques [27]. It has also been proposed that modulation of fractalkine may be particularly useful in early stages of AD to moderate disease progression [28].

VEGF (vascular endothelial growth factor)

VEGF is considered the most potent agent to induce angiogenesis, the formation of new blood vessels [29]. VEGF also promotes microglial chemotactic responses mediated by the VEGF subtype receptor, VEGF-1 (also termed Flt-1) [6]. Elevation of VEGF is reported in AD brain [30, 31] with the factor suggested as a prominent activator for vascular remodeling.

Microglial-mediated chemotaxis in response to $A\beta_{1\text{-}42}$ stimulation was investigated both *in vitro* and *in vivo* [7]. In the former case, a transwell migration assay was used to examine microglial chemotaxis in the absence and presence of an anti-VEGF-1 receptor antibody. Cultured human microglia were initially exposed (for 24 hours) to three different stimulus conditions - $A\beta_{1\text{-}42}$, phosphate buffered saline (PBS), and $A\beta_{42\text{-}1}$. Both PBS and $A\beta_{42\text{-}1}$ served as controls in the study. Cell-free conditioned medium from the different treatments were placed in one chamber of a transwell assembly with microglia located in the opposite chamber. The microglia were then subjected to 1 hour treatment with

anti-Flt-1 neutralizing antibody or control IgG. Following a 24 hour incubation time, microglial chemotaxis was determined by counting numbers of cells crossing the membrane into the opposite chamber. The results demonstrated an approximate 5-fold increase in cell chemotaxis for $A\beta_{1-42}$ compared with PBS or $A\beta_{42-1}$. With anti -Flt-1 included with $A\beta_{1-42}$, microglial chemotactic response was decreased by almost 40% compared to response with Aβ alone.

A novel protocol was used to determine chemotaxis *in vivo* [7]. Briefly, microglia were isolated from rat brain and infected with an enhanced green fluorescent protein (EGFP) expressing lentivirus. The EGFP-labelled microglia were exposed to control or anti-Flt-1 antibody medium and stereotactically injected into the corpus callosum region in two groups of rats (labeled control and anti-Flt-1 antibodies). Both animal groups had previously (3 days prior) received stereotaxic injection of $A\beta_{1-42}$. A third animal group received EGFP-microglia incubated with control antibody and that had previously (3 days prior) been injected with reverse peptide $A\beta_{42-1}$; this group thus served as a control with no chemotactic stimulus. The extent of EGFP immunoreactivity was then determined in three areas between injected EGFP and Aβ peptide (forward or reverse) and used as a measure of microglial mobility. The results showed equivalent EGFP immunoreactivity for all animal groups in the region adjacent to the site of EGFP injection. For the area most distant from EGFP injection (i.e. closest to Aβ peptide injection site) minimal expression of EGFP-labelled microglia was evident for microglia plus control antibody (reverse peptide injection) and microglia plus anti-Flt-1 antibody ($A\beta_{1-42}$ injection). On the other hand, the group with control antibody with $A\beta_{1-42}$ injection exhibited considerable EGFP-positive microglia in this area. An intermediate region showed a graded response between sites closest to and further away from EGFP injection. Another component of this study showed $A\beta_{1-42}$ injection with anti-Flt-1 antibody was associated with an increased number of granule cell layer neurons relative to Aβ peptide injection with control antibody. Thus, the effects of anti-Flt-1 treatment included neuroprotection in Aβ-injected hippocampus.

The conclusion from the *in vitro* and in *vivo* studies was that $A\beta_{1-42}$ could serve as a chemotactic stimulus for microglia via activation of the subtype VEGF receptor, Flt-1. Furthermore, antagonism of Flt-1 acted to inhibit microglial chemotactic activity and increased neuronal viability in the AD animal model.

Chemotaxis of neural progenitor cells (NPC) in vivo

Microglial release of chemotactic factors has been implicated in the net migration of NPC in the $A\beta_{1-42}$ injection animal model [32]. The effects of transplantation of NPC on cellular properties and processes were investigated in control PBS and $A\beta_{1-42}$ intra-hippocampal injected rats. The transplanted NPC were identified *in vivo* from green fluorescent (GFP) previously added to cultured cells via lentiviral vector. Transplantation of NPC into a specific region of hippocampus followed 3 days after animals were injected with PBS or $A\beta_{1-42}$ in dentate gyrus. Immunostaining analysis for NPC spatial intra-hippocampal expression was carried out at one-week post-NPC transplantation.

The results demonstrated a 3-fold increase in migration of NPC from transplantation to injection site of Aβ over control. Thus, the pattern of NPC staining suggested a chemotactic response to $A\beta_{1-42}$. A possible explanation for the findings was that Aβ-activated resident microglia were stimulated to produce chemokines such as MCP -1 and IL-8, as reported in cultured cell experiments [17]. Upregulation of the chemokines in the vicinity of $A\beta_{1-42}$ may have provided a net driving force for migration of NPC. Previous work has reported increased migration of stem cells induced by chemokine (MCP-1) released from microglia [33]. Interestingly, NPC transplantation attenuated microgliosis and provided neuroprotection in the Aβ-injection animal model. One suggestion for the overall findings was that NPC-mediated production of neurotrophic factors could directly and indirectly block microglial activation and modulate levels of chemotactic stimuli.

Other chemotactic factors in AD

The factors discussed above are the most prominent agents inducing chemotactic responses in AD brain; however, a number of other agents are candidates for induction of microglial chemotactic responses in AD brain. For example, macrophage-colony stimulating factor (M-CSF) is reported to increase microglial

migration after cellular exposure to Aβ [4]. The number of factors that evoke net migration of microglia in AD brain suggest the utility of pharmacological modulation of chemotaxis as a putative neuroprotective strategy. Surprisingly, this point has not been extensively addressed in experimental work. Few studies have examined effects of the inhibition of cellular production of chemotactic factors in AD animal models. Chemotactic receptors, not a focus of this review, also remain largely unstudied as specific drug targets in AD brain. As noted above, antagonism of microglial VEGF receptor was found to reduce microgliosis and neuronal loss in $A\beta_{1-42}$ injected rat brain [7].

Conclusions

Microglial chemotaxis represents an early response to amyloid deposition in AD brain. Importantly, ongoing chemotactic activity could contribute to chronic neuroinflammation in the progression of disease. The most prominent chemotactic factors have been considered in this article. These factors, together with their specific receptors, constitute an extensive array of targets for pharmacological intervention in animal models of AD. Inhibition of microglial-mediated chemotactic activity may serve as a strategy to protect neurons in environments of chronic neuroinflammation.

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