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# Mechanisms of Microglial Activation by Amyloid Precursor Protein and its Proteolytic Fragments

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## 1 Reactive Microglia are a Characteristic Histopathology of Alzheimer's Disease Brains

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease (Selkoe, 2005). Histologically, it is characterized by the deposition of extracellular senile plaques composed primarily of beta amyloid (A $\beta$ ) peptides and intracellular inclusions, termed neurofibrillary tangles, made up of primarily hyperphosphorylated tau protein (Braak and Braak, 1997a, b; Grundke-Iqbal et al., 1986; Selkoe, 2001). In addition, AD brains demonstrate significant neuron loss and abundant gliosis (McGeer et al., 1986). The mechanisms by which these pathology occur, however, is debatable. It has been hypothesized that inflammatory events contribute to both the histological and behavioral progression of disease (Akiyama et al., 2000). The histological data demonstrating gliotic changes in AD brains as compared to age-matched controls certainly supports the notion that microglia, in particular, may mediate the changes that are observed. Reactive microglia with swollen bodies and shortened, thickened processes are histologically identified in close association with the fibrillar or congophilic plaques in the AD brain (Itagaki et al., 1989; Miyazono et al., 1991). Although the percentage of microglia associated with fibrillar plaques is greater, they are also localized, in a more ramified phenotype, with the diffuse plaques (Itagaki et al., 1989; Mattiace et al., 1990; Sasaki et al., 1997). These data suggest that microglia develop a specific reactive phenotype in association with plaques as A $\beta$  undergoes a transition from a nonfibrillar to fibrillar, congophilic conformation (Sheng et al., 1997). In fact, some studies suggest that microglia are involved in the earliest stages of plaque deposition perhaps even dictating where plaques are depositing in the brain (Griffin et al., 1995; Sheng et al., 1995, 1998). Moreover, AD brains have increased protein levels of several proinflammatory mediators commonly associated with reactive microgliosis, including cytokines: interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$ , activated complement components, and cyclooxygenase (COX)-2 when compared to controls (Akiyama et al., 2000; Dickson et al., 1993; Eikelenboom et al., 1989; Lutermaier et al., 2000; Mrazek and Griffin, 2000; O'Banion et al., 1997; Strauss et al., 1992; Xiang et al., 2006;). Strikingly similar observations have been made while

examining transgenic mouse models of disease over the last decade. The majority of the mouse models that have been created over-express human mutant forms of the amyloid precursor protein (APP) and/or mutant forms of the proteins responsible for gamma secretase cleavage of APP, presenilin (PS) 1 and PS2. These animal models have consistently demonstrated that reactive microgliosis occurs in association with fibrillar plaque formation as detected histologically with multiple immuno-markers (Morgan et al., 2005). Collectively, a voluminous body of data strengthens the proposition that APP and its proteolytic fragments are involved in not just plaque deposition but also the reactive microgliosis observed in AD brains.

## 2 Amyloid Precursor Protein and its Relationship to Alzheimer's Disease

APP is a ubiquitously expressed type I transmembrane protein that structurally resembles a cell surface receptor (Kang et al., 1987). The x-ray and crystal structure of the extracellular domain suggests that the protein can homodimerize in a cis (on the same cell surface) or trans (opposing cell surfaces) fashion (Rossjohn et al., 1999; Wang and Ha, 2004). Indeed, multimerization of APP occurs in neuronal cell lines basally (Scheuermann et al., 2001) and following ligand dependent stimulation (Lu et al., 2003). Furthermore, cross-linking APP with antibodies against the extracellular domain stimulates changes in intracellular signaling in vitro reminiscent of ligand dependent-receptor activation (Hashimoto et al., 2003; Okamoto et al., 1995). APP binds to extracellular matrix components including collagen (Behr et al., 1996) and laminin (Kibbey et al., 1993) as well as proteoglycans (Williamson et al., 1995) suggesting a role in mediating cell adhesion. A role as an adhesion receptor is further supported by the fact that APP levels increase on the neurite surface of differentiating neurons (Hung et al., 1992) and localize to points of focal adhesion in cell culture (Sabo et al., 2001). The short cytoplasmic tail contains a Y(682)ENPTY(687) (695 numbering) motif commonly employed by cell surface receptors as a docking site for SH2 and PTB domain containing proteins. Not surprisingly, several adaptor proteins including FE65, X11, JIP-1b and Shc have reported associations with this domain in a variety of different paradigms further supporting its role as a cell surface receptor (Borg et al., 1996; Bressler et al., 1996; Matsuda et al., 2001; Tarr et al., 2002).

As already mentioned, clinical interest in APP derives from the fact that its proteolytic processing leads to generation of the A $\beta$  peptides that accumulate as extracellular plaques in AD brains (Masters et al., 1985). Moreover, a variety of APP missense mutations have been identified which result in a rare, autosomal dominant form of AD (Cai et al., 1993; Chartier-Harlin et al., 1991; Hendriks et al., 1992; Mullan et al., 1992; Murrell et al., 1991). The best characterized consequence of these mutations is an alteration in proteolytic processing of APP leading to elevated secretion of the longer A $\beta$  peptide, amino acids 1–42 (Citron et al., 1992, 1994; Scheuner et al., 1996; Suzuki et al., 1994;). This peptide forms the fibrillar core of the amyloid plaques in AD brains (Jarrett et al., 1993). Additionally, the fibrillar

peptide is potentially toxic to neurons in a variety of paradigms (Lorenzo and Yankner, 1996; Pike et al., 1993). These collective data led to the formulation of the amyloid cascade hypothesis which proposed that fibrillization of the amyloid peptide is a key event in the pathophysiology of disease and critically important in the death of neurons leading to dementia (Hardy and Higgins, 1992).

### 3 Fibrillar A $\beta$ is an Activating Stimulus for Microglia

Because A $\beta$  peptide forms the fibrillar core of the senile plaques in both sporadic and autosomal dominant disease, it has been hypothesized that fibrillar plaque deposition represents a mechanistically critical process in disease progression (Hardy and Higgins, 1992; Jarrett et al., 1993). As already mentioned the fibrillar peptides exhibit a direct toxic action on neurons and the biology of this process, although certainly of relevance to AD, is outside of the scope of this discussion. On the other hand, the close association of reactive microglia with amyloid plaques as they transition from diffuse to fibrillar dense core (mature) plaques has suggested that fibrils are direct stimuli for activating microglia. Indeed, a large body of data exists demonstrating that fibrillar peptides stimulate microglia to acquire a reactive, neurotoxic phenotype.

Since peptide stimulation often requires interaction with a cell surface protein, many groups have worked to identify putative A $\beta$  “receptors” on cells within the nervous system. A $\beta$  has been shown capable of interacting with a truly diverse set of cell surface proteins including parent APP (Lorenzo et al., 2000; Van Nostrand et al., 2002; Wagner et al., 2000) the receptor for advanced glycation end products (RAGE) (Yan et al., 1996), scavenger receptor A (El Khoury et al., 1996), CD36 (Coraci et al., 2002; Moore et al., 2002), CD47 (Koenigsnecht and Landreth, 2004),  $\beta$ 1 integrins (Koenigsnecht and Landreth, 2004), glypican (Schulz et al., 1998), *N*-Methyl-D-Aspartate (NMDA) receptors (Bi et al., 2002),  $\alpha$ -7 nicotinic acetylcholine receptors (Wang et al., 2000), serpin-enzyme complex receptor (Boland et al., 1995), *N*-formyl peptide receptor-like (FPRL) 1 (Yazawa et al., 2001), and the insulin receptor (Xie et al., 2002a). Importantly, a number of these studies were performed using microglia and microglial cell lines offering some insight into the mechanism by which the peptide interact with the cell surface of microglia. These studies demonstrate that the A $\beta$  peptide has the potential, particularly in its fibrillar form, to interact with a large array of structurally and functionally distinct proteins suggesting that fibril-cell interactions may be somewhat nonspecific.

An additional direction of research has focused not on the cell surface A $\beta$  interaction but rather the subsequent intracellular signaling response driving acquisition of the reactive phenotype. Although the elucidated pathways have been determined from unique cell systems including primary microglial cultures, microglial cell lines, and monocytic cell lines, there are common aspects of the response. For example, fibrils stimulate a transient increase in activity of a number of tyrosine kinases including Fyn, Lyn, Syk, focal adhesion kinase (FAK), and pyruvate kinase (PYK) in stimulated THP-1 monocytes and primary rodent microglia (Bamberger et al., 2003; Combs et al., 1999, 2001; McDonald et al., 1997, 1998). Subsequent

to the increase in tyrosine kinase activities, the cells release calcium from intracellular stores (Combs et al., 1999) and a number of serine threonine kinases are activated. For example, members of the mitogen activated protein (MAP) kinase family, extracellular signal regulated kinases (ERKs), c-Jun N-terminal kinase (JNKs), and p38 (Combs et al., 2001; Giri et al., 2003; McDonald et al., 1998) protein kinase C (PKC) (Combs et al., 1999), and RSK1/2 (McDonald et al., 1998) have all been reported to be activated by fibrillar stimulation of monocytes or microglia. In addition, subsequent changes suggestive of altered transcription occur after fibril stimulation including nuclear factor kappa beta (NF $\kappa$ B) activation, increased c-fos levels, and increased phosphorylation of CREB (Combs et al., 2001; McDonald et al., 1998).

It is not surprising, then, that fibrillar A $\beta$  stimulation leads to increased secretion of several proinflammatory molecules from monocytes and microglia. Fibrils stimulate increased protein secretion and/or mRNA levels of several cytokines from human monocyte cell lines, microglial cell lines, primary rodent microglia and primary human, fetal and adult microglia including TNF $\alpha$ , IL-8, IL-6, MCSF, MIP-1 $\alpha$ , IL-1 $\beta$ , matrix metalloproteases 1, 3, 9, 10, and 12 (Combs et al., 2000, 2001, Floden and Combs, 2006; Franciosi et al., 2005; Gasic-Milenkovic et al., 2003; Giri et al., 2003; Lue et al., 2001; Twig et al., 2005; Walker et al., 2001, 2006; Yates et al., 2000). In addition to cytokine secretion, fibrillar A $\beta$  also stimulates secretion of superoxide anion from both human and mouse microglia via increased activity of plasmalemmal NADPH oxidase (Bianca et al., 1999; Wilkinson et al., 2006). Fibrillar stimulation also increases secretion of glutamate (Floden et al., 2005; Noda et al., 1999) and D-serine (Wu et al., 2004) demonstrating that oxidative and excitotoxic species may facilitate microglial mediated neuron death.

However, the identity of the neurotoxic agent(s) generated by A $\beta$  fibril stimulated microglia appears to vary between paradigms ranging from excitotoxins, to cytokines, to oxidative damage dependent death (Banati et al., 1993, 1999; Combs et al., 2001; Floden et al., 2005; Giulian et al., 1995; Ii et al., 1996; Kingham and Pocock, 2001; Li et al., 2004; Monsonego et al., 2003; Tan et al., 2000; Xie et al., 2002b). It is likely that a variety of secreted factors contribute to the eventual loss of neurons that occurs either in the culture paradigms or in vivo following A $\beta$  fibril stimulation of microglia. It will be important to identify which factors, if any, are truly generated by microglia in AD brains to determine the accuracy of in vitro modeling of microglial-dependent inflammatory changes during disease.

## 4 Oligomeric A $\beta$ is an Activating Stimulus for Microglia

One of the criticisms of the amyloid cascade hypothesis, as originally proposed, has long been a clear lack of correlation between dementia rating and the numbers of fibrillar plaques in the brain (Lue et al., 1999; McLean et al., 1999; Morris et al., 1996). Indeed, it has been suggested that synaptic loss and gliosis precede plaque deposition (Martin et al., 1994). A similar observation has been con-

firmed in studies employing mouse hAPP transgenic lines. For example, Westerman et al. (2002) observed cognitively normal aged APP<sub>SWE</sub> mice in spite of high concentrations of insoluble A $\beta$  aggregates leading them to suggest a soluble A $\beta$  form is responsible for neuronal deficit. An additional study using mice overexpressing APP<sub>IND</sub> and APP<sub>SWE,IND</sub> demonstrated decreased presynaptic marker immunoreactivity and impaired synaptic transmission prior to plaque deposition (Hsia et al., 1999). Finally, using APP<sub>IND</sub> and APP<sub>SWE, IND</sub> as well as APP<sub>WT</sub> overexpressing cells Mucke et al. (2000) demonstrated that presynaptic marker immunoreactivity correlates inversely with levels of A $\beta$  and plaque load correlates independently of A $\beta$  levels. Collectively these data suggest that the fibrillar, insoluble form of the peptide may not be the most relevant species for mediating neuronal death/dysfunction.

Interestingly, recent data suggests that nonfibrillar A $\beta$  conformations may be more reliable indices of disease progression. An oligomeric form of A $\beta$  has been shown to accumulate in vivo and, more importantly, is elevated in AD brains in correlation with degree of behavioral deficit (Lue et al., 1999; McLean et al., 1999). The oligomeric form of the peptide can vary from dimers to high molecular weight SDS-stable oligomers and also arises in vitro from A $\beta$  secreted into the culture media (Gong et al., 2003; Podlisny et al., 1995; Xia et al., 1997). Importantly, much like their fibrillar derivatives, the oligomers are neurotoxic, stimulate gliosis, produce cognitive dysfunction, and decrease long-term potentiation (LTP) both in vitro and in vivo (Chromy et al., 2003; Cleary et al., 2005; Hu et al., 1998; Klyubin et al., 2005; Lambert et al., 1998; Roher et al., 1996; Walsh et al., 2002; Wang et al., 2002). The low molecular weight dimeric/trimeric multimer of A $\beta$  is reportedly able to mediate reversible inhibition of LTP generation (Klyubin et al., 2005; Walsh et al., 2005), impairment of cognitive dysfunction (Cleary et al., 2005) and microglial-dependent neuron death (Roher et al., 1996). A similar study using monomeric-tetrameric preparations demonstrated robust toxic effects on neuronal cell lines using both A $\beta$ 1-40 and A $\beta$ 1-42 (Dahlgren et al., 2002). Similarly, higher molecular weight multimers have demonstrated direct neurotoxic effects in paradigms ranging from rodent hippocampal slice cultures (Chong et al., 2006) to cell lines (Chromy et al., 2003; Demuro et al., 2005) to human fetal neuron cultures (Deshpande et al., 2006). Not surprisingly, these high molecular weight multimers have been observed to directly bind to neurons in both diseased brains and rodent hippocampal neuron cultures (Kokubo et al., 2005; Lacor et al., 2004). More recently, a dodecamer, A $\beta$ \*56, has been specifically characterized to increase in vivo in the brains of Tg2576 mice correlatively with the appearance of cognitive deficit and induce a reversible spatial memory deficit when microinjected into rat brain (Cleary et al., 2005; Lesne et al., 2006). This plethora of new data has revised the amyloid cascade hypothesis to now state that AD is initiated by neurotoxic stimulation provided by soluble A $\beta$  peptide in its oligomeric rather than fibrillar form (Selkoe, 2002). Unfortunately, the mechanism by which oligomers stimulate neuron loss and glial activation is still unclear.

There is some data demonstrating that increasing oligomer concentrations correlate with microgliosis in vivo in transgenic rodent brains (Gordon et al., 2002;

Koistinaho et al., 2002). In agreement with this observation several *in vitro* studies have begun characterizing the ability of nonfibrillar A $\beta$  peptides to stimulate microglia. Although the culture paradigms as well as multimeric state have varied between laboratories, a common theme with these studies is that oligomeric stimulation promotes acquisition of a proinflammatory phenotype. As already mentioned, while many studies have characterized putative receptors for fibrillar A $\beta$ , it remains unclear how the oligomeric peptides interact with microglia. Using purified cultures of mouse microglia we have observed increased protein phosphotyrosine levels upon stimulation with the low molecular weight dimer/trimer A $\beta$ 1-42 oligomers (unpublished observations). This is similar but not identical to the signaling response initiated by stimulating microglia with fibrillar peptides (Combs et al., 1999). For example, we have not observed any increase in MAP kinase activities upon stimulation with these dimer/trimer oligomers (unpublished observations). There is, however, still a paucity of data describing the extent of the stimulated signaling response in microglia following treatment with not only the low molecular weight dimer/trimer oligomers but also the larger multimers.

On the other hand, the reactive phenotype produced by oligomer stimulation is better characterized. Using rat astrocyte cultures (95–98%astrocytes/2–5% microglia) two different studies demonstrated that the low molecular weight oligomers (White et al., 2005) and soluble A $\beta$  (Hu et al., 1998) stimulate proinflammatory changes including increased protein and mRNA levels of inducible nitric oxide synthase (iNOS) and IL1- $\beta$ , increased iNOS activity, and increased TNF $\alpha$  secretion. In a similar study Manelli et al. (2006) demonstrated that this mixed glia paradigm produced neurotoxins when cocultured with coverslips of primary rat cortical neurons. Although these data do not prove that the changes in proinflammatory protein expression and neurotoxicity are via oligomer-microglia interaction a study by Roher et al. (1996) demonstrated that rat mixed hippocampal neuron-glia cultures exhibited toxicity when treated with low molecular weight oligomers (dimer/trimer) only when microglia were present.

Other studies have used purified cultures of microglia to characterize the effects of oligomer stimulation on activation. A recent report showed that A $\beta$ 1-42 monomer-24mer preparations stimulate rat microglia cultures to secrete IL-1 $\alpha$  and interferon- $\gamma$  (IFN- $\gamma$ ) (Lindberg et al., 2005). A similar study by Takata et al. (2003) showed that rat microglia cultures increase secretion of TNF $\alpha$ , IL-6, and nitric oxide upon stimulation with low molecular weight A $\beta$ 1-40 oligomers. Even the A $\beta$ 25-35 fragment in its nonfibrillar form has recently demonstrated the ability to activate rat microglia to increase TNF $\alpha$  secretion (Hashioka et al., 2005). Using a dimer/trimer preparation of A $\beta$ 1-42, we have observed a similar activating response using cultures of purified mouse microglia. Oligomer stimulation results in increased expression of CD68, increased secretion of IL-6, TNF $\alpha$ , keratinocyte chemoattractant chemokine (KC), and decreased secretion of monocyte chemoattractant protein-1 (MCP-1) (Floden and Combs, 2006; unpublished observations). Moreover, these low molecular weight species are toxic to neurons only in the presence of microglia similar to prior work (Roher et al., 1996; unpublished observations). Therefore, although oligomeric peptides have direct effects on neuron activity and viability these collected studies above suggest that oligomeric



peptides, much like their fibrillar counterpart, may mediate a portion of their detrimental effects through microglia activation. It remains to be seen whether different multimeric states have unique stimulatory abilities for microglia.

## **5 The N-terminal Secreted Fragment of APP, sAPP, is an Activating Stimulus for Microglia**

It is now appreciated that additional cleavage products of APP besides the A $\beta$  peptides also mediate distinct, physiologic effects on cells. APP can be processed along two distinct, competing pathways to release a large secreted N-terminal portion of the protein (sAPP). ADAM 10 and TACE are involved in alpha secretase cleavage of APP resulting in generation of a soluble, 612 amino acid, N-terminal fragment of APP (sAPP $\alpha$ ) which is released into the extracellular space (Esch et al., 1990; Haass et al., 1991; Sinha and Lieberburg, 1999; Weidemann et al., 1989). The aspartic proteases, BACE1 and BACE2, represent the beta secretase activities responsible for generation of sAPP $\beta$  required for the proteolytic processing to generate the A $\beta$  peptides (Bennett et al., 2000; Sinha et al., 1999; Vassar et al., 1999). Much like, the fibrillar form of A $\beta$ , sAPP has a host of effects on neurons. For example, sAPP $\alpha$  has direct protective effects on cultured neurons in response to excitotoxic challenge that is a hundred fold more protective than sAPP $\beta$  (Barger and Mattson, 1997; Furukawa et al., 1996). This effect involves increased guanylate cyclase activity and increased NF $\kappa$ B activation as well as decreased NMDA receptor-mediated calcium influx (Barger and Mattson, 1995, 1996; Furukawa et al., 1996; Furukawa and Mattson, 1998). In addition, sAPP $\alpha$  has a demonstrated ability to stimulate increased neurite outgrowth in neuronal cells via a tyrosine kinase stimulated signaling response (Jin et al., 1994; Mook-Jung and Saitoh, 1997).

Almost paradoxically, sAPP $\alpha$  also has a demonstrated ability to robustly stimulate microglial activation. Although the signaling pathway is not completely determined, it has been demonstrated that sAPP $\alpha$  stimulation of microglia involves increased MAP kinase activities. Specifically, treatment of rat microglia with sAPP $\alpha$  leads to increased levels of active ERKs, p38 kinase, and JNKs (Bodles and Barger, 2005). In addition, sAPP $\alpha$  or sAPP $\beta$  stimulation of primary microglia as well as the N9 microglia cell line increases NF $\kappa$ B activity (Barger and Harmon, 1997). As might be expected, these changes lead to increased expression or activity of a host of proinflammatory products including iNOS and IL-1 $\beta$ , and reactive oxygen species (Barger and Harmon, 1997; Barger et al., 2000; Bodles and Barger, 2005; Li et al., 2000). Importantly, the production of proinflammatory proteins is dependent upon activity of JNK and p38 kinases and not ERKs since specific inhibitors of JNK and p38 MAP kinases but not ERKs attenuate the sAPP $\alpha$ -induced increase in iNOS protein levels and activity (Bodles and Barger, 2005). Besides cytokine secretion, sAPP $\alpha$  also stimulates microglia to secrete glutamate via the cystine-glutamate antiporter (Barger and Basile, 2001; Ikezu et al., 2003).

Based upon the identity of the secretory products described above, it is not surprising that the secretions from sAPP $\alpha$  or sAPP $\beta$  stimulated microglia are toxic to

rodent neuron cultures (Barger and Basile, 2001; Barger and Harmon, 1997; Ikezu et al., 2003). The toxicity can be prevented by a superoxide dismutase (SOD) mimetic, MnTBP, specific inhibitors of neuronal nitric oxide synthase (nNOS), specific inhibitors of iNOS, and the NMDA receptor antagonist, MK-801 (Barger and Basile, 2001; Ikezu et al., 2003). Taken together, these data suggest that sAPP-stimulated microglia induce neuron death via combined oxidative and excitotoxic mechanisms. Therefore, although alpha secretase cleaved APP, sAPP $\alpha$ , is a demonstrated neurotrophic factor, it can also drive microglia to acquire a reactive, neurotoxic phenotype. It remains to be seen which of these opposing actions will dominate the *in vivo* function of sAPP.

## 6 Full Length APP can Act as a Proinflammatory Receptor on Microglia

We have thus far reviewed the accumulating data describing the ability of APP proteolytic fragments to stimulate microglial activation. Far less information is available regarding the function of full length APP in microglia. This is somewhat surprising since microglia serve as the second major producer of A $\beta$  peptides behind neurons (Banati et al., 1993). It is relevant to discuss microglial APP in the context of this discussion since work by ourselves as well as others has suggested that it behaves as a proinflammatory receptor on monocytes and microglia. It has been known for some time that APP mRNA can be found within microglia of human brains (Schmechel et al., 1988). However, it has also been reported that plaque associated microglia in the AD brain have no detectable APP mRNA (Scott et al., 1993). The more definitive assessment of protein, however, has confirmed that microglia not only express APP but also upregulate protein levels in response to particular stimuli. *In vitro* cultures of purified rat microglia have verified they can express all isoforms of APP (Haass et al., 1991; LeBlanc et al., 1991). However, basal APP levels are low compared to neurons and very little of the protein is localized to the plasmalemma (Haass et al., 1991; LeBlanc et al., 1991). Not surprisingly, then, *in vitro* rat microglia studies have demonstrated that very little to no A $\beta$  peptide or sAPP is generated by microglia (Haass et al., 1991; LeBlanc et al., 1991). These data suggest that the holoprotein may function differently in microglia compared to neurons.

However, other *in vitro* studies have demonstrated that APP protein levels are readily upregulated in microglia upon specific stimulation. For instance, human monocytes differentiated to macrophage *in vitro* increase their APP protein levels (Bauer et al., 1991). Microglia cultures stimulated with activating ligands like lipopolysaccharide (LPS) or prostaglandin E2 (PGE2) also increase APP, particularly on the cell surface (Pooler et al., 2004; unpublished observations). Using a mouse microglia line, BV-2, Monning et al. (1995) have demonstrated that when microglia express cell surface APP they are fully capable of secreting sAPP fragments. More importantly, this occurs in response to microglial adhesion to extracellular substrates like fibronectin and poly-L-lysine (Monning et al., 1995).



Perhaps the most compelling microglial APP data is derived from a series of *in vivo* studies demonstrating that APP immunoreactivity increases acutely and transiently within microglia following a variety of insults. For instance, transection of facial or sciatic nerves in rats results in increased microglial APP immunoreactivity within 6 h post lesion not only in the affected nucleus but also in areas of afferent projection (Banati et al., 1993). Lesion of the entorhinal cortex in rats produced a similar, transient profile of increased microglial APP immunoreactivity in the dentate gyrus (Banati et al., 1994). However, microglial APP expression is also responsive to a broader range of insults beyond axotomy. Both an experimental autoimmune encephalomyelitis (EAE) model as well as a transient ischemia model in mice result in an elevation of microglial APP immunoreactivity that lasts for several days-weeks (Banati et al., 1995a, b). Collectively, these data, together with the observation that the structure of APP resembles a cell surface receptor (Kang et al., 1987), suggest that APP has a role in regulating acquisition of a reactive phenotype in microglia.

We have begun work in support of this hypothesis by characterizing the signaling response stimulated by plasmalemmal APP in primary mouse microglia and the human monocytic cell-line THP-1 (Sondag and Combs, 2004, 2006). Utilizing two different stimulation paradigms we have found that APP is associated with a classic tyrosine kinase-based proinflammatory signaling response leading to acquisition of a reactive phenotype in these cells. By plating these cells onto a type I collagen substrate we have modeled  $\beta 1$  integrin-mediated adhesion-dependent activation. In addition we have used an antibody, 22C11, against the N-terminus of APP to cross-link cell surface APP to simulate ligand binding. Both paradigms stimulate increased protein phosphotyrosine levels in microglia and THP-1 cells indicative of increased tyrosine kinase activity. APP pull-down co-immunoprecipitations have shown that the Src family tyrosine kinase, Lyn, and the tyrosine kinase, Syk, are recruited to a complex with APP upon substrate adhesion or antibody cross-linking (Sondag and Combs, 2004). In addition, substrate adhesion but not antibody cross-linking recruits APP to a multireceptor signaling complex with  $\beta 1$  integrin along with Syk and Lyn (Sondag and Combs, 2004). Subsequent to increased tyrosine kinase activity, we observed activation of the MAP kinase family following both adhesion and antibody cross-linking (Sondag and Combs, 2004, 2006).

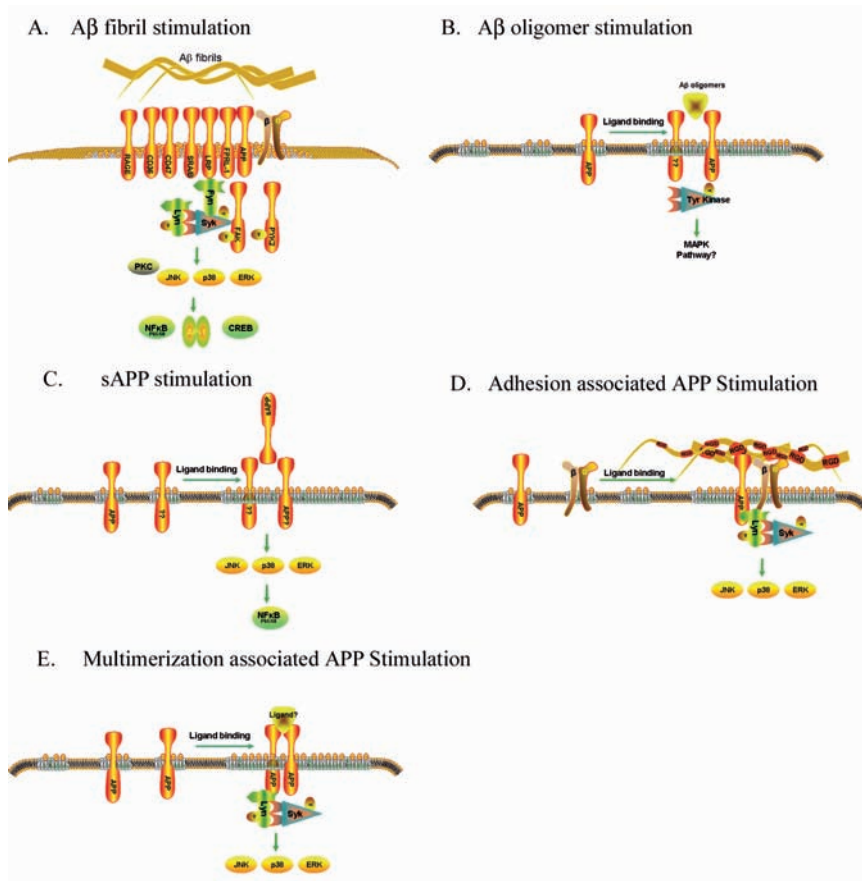
Not surprisingly, adhesion-dependent activation of THP-1 cells stimulates an increase in protein levels of a plethora of proinflammatory markers including COX-2, CD36, iNOS, and IL-1 $\beta$ . However, the more interesting observation is that these changes in protein levels were dependent upon expression of APP and the subsequent increase in tyrosine and MAP kinase activities induced upon ligand binding (Sondag and Combs, 2004). We extended this observation to define the behavior of THP-1 cells and microglia following antibody cross-linking of APP. As with the adhesion studies, the stimulated increase in proinflammatory protein levels was dependent upon recruited tyrosine and MAP kinase activities. Moreover, APP cross-linking increased cytokine secretion by the THP-1 cells and microglia. Most notably, cross-linked cells increased secretion of IL-1 $\beta$  and IL-6 in a tyrosine kinase dependent manner (Sondag and Combs, 2006). Because antibody-mediated receptor cross-linking is expected to influence endocytic events we also determined whether APP was

cleaved into A $\beta$  peptides following stimulation. Cross-linking stimulated a selective release of A $\beta$ 1–42 compared to A $\beta$ 1–40 from the monocytes. However, A $\beta$ 1–42 secretion was independent of the increase in tyrosine and MAP kinase activities we had observed since inhibition had no effect on stimulated A $\beta$ 1–42 secretion. Therefore, secretase control of APP metabolism was independent of the tyrosine kinase based activation pathway. Our results thus far have suggested that APP has a common function in monocytes and microglia that is important in acquisition of a reactive phenotype. More importantly, it appears that the protein can act as an independent receptor, as in the case of antibody cross-linking, or it can be recruited into a multi-receptor signaling complex, as in the case of adhesion dependent activation. This novel signaling mechanism by which monocytes and microglia generate A $\beta$  peptides could be a relevant contribution to plaque pathology in AD and vascular amyloidosis. Collectively, these results strengthen existing data that suggest microglial-derived APP can contribute to amyloid production in AD (Bauer et al., 1991).

Although we have demonstrated a rather robust role for APP in monocyte/microglial activation as a single receptor or within a multi-receptor complex, it is not clear how APP is involved in activating these cells *in vivo*. While it is easy to imagine APP participating in adhesion-mediated activation of microglia adhering to extracellular matrix, it is more difficult to envision how APP can behave as an independent proinflammatory receptor. This is largely due the fact that an agonist ligand for the extracellular domain of APP is not yet known. One interesting possibility is that the A $\beta$  peptide itself can behave in an autocrine fashion to interact with APP to mediate clustering and subsequent signal transduction. Interestingly, A $\beta$  has already been demonstrated to bind to the extracellular region of APP (Chung et al., 1999; Lorenzo et al., 2000; Shaked et al., 2006; Van Nostrand et al., 2002; Wagner et al., 2000) offering the possibility of a proinflammatory feed-forward pathway in which A $\beta$ -APP interaction leads to increased APP-dependent proinflammatory signaling that results in further A $\beta$  production. Alternatively, *in vitro* studies have shown that membrane-bound APP can form homodimers leading to the speculation that full-length APP can be its own ligand acting in a *cis* (same cell) or *trans* (opposing cell) fashion (Lu et al., 2003; Rossjohn et al., 1999; Scheuermann et al., 2001; Wang and Ha, 2004). Therefore, although it is well accepted that APP processing to A $\beta$  peptide is an important contribution to plaque formation in AD (Citron et al., 1992, 1994; Jarrett et al., 1993; Masters et al., 1985; Scheuner et al., 1996), it is possible that APP has a multi-faceted role in the progression of this disease particularly as a proinflammatory receptor on microglia.

In conclusion, although reactive microglia are a histological hallmark in the AD brain, their contribution to neuron death and cognitive decline remains unclear. In addition, the stimulus for their reactivity is also not defined. A large collection of data demonstrates that proinflammatory changes occur in not only AD brains but also its animal models. These data offer hope that attenuating microgliosis will offer benefit against disease conditions. However, before this can be approached in a specific fashion it is important to define not only the source of reactivity but also the subtle differences in activation phenotype that surely must exist *in vivo*. For example, there is a well recognized association of a certain reactive microglial phenotype with mature, dense core plaques and fibrillar A $\beta$  peptides are activating ligands for microglia. However, as illustrated above, it is also clear that nonfibrillar

forms of the peptide as well as the secreted N-terminus and full length APP itself, all have the capacity to stimulate microglia to acquire unique, reactive phenotypes. It remains to be seen which of these species, if any, has the most significant role in promoting microglial activation in AD.



Comparison of Modes of Microglial Activation by APP and its Proteolytic Fragments.

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