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REVIEW

Mechanisms of amyloid plaque pathogenesis

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Abstract The first ultrastructural investigations of Alzheimer's disease noted the prominence of degenerating mitochondria in the dystrophic neurites of amyloid plaques, and speculated that this degeneration might be a major contributor to plaque pathogenesis. However, the fate of these organelles has received scant consideration in the intervening decades. A number of hypotheses for the formation and progression of amyloid plaques have since been suggested, including glial secretion of amyloid, somal and synaptic secretion of amyloid-beta protein from neurons, and endosomal–lysosomal aggregation of amyloid-beta protein in the cell bodies of neurons, but none of these hypotheses fully account for the focal accumulation of amyloid in plaques. In addition to Alzheimer's disease, amyloid plaques occur in a variety of conditions, and these conditions are all accompanied by dystrophic neurites characteristic of disrupted axonal transport. The disruption of axonal transport results in the autophagocytosis of mitochondria without normal lysosomal degradation, and recent evidence from aging, traumatic injury, Alzheimer's disease and transgenic mice models of Alzheimer's disease, suggests that the degeneration of these autophagosomes may lead to amyloid production within dystrophic neurites. The theory of amyloid plaque pathogenesis has thus come full circle, back to the intuitions of the very first researchers in the field.

Keywords Alzheimer's disease · Amyloid-beta protein · Autophagy · Axonal transport · Mitochondria · Prion diseases · Traumatic brain injury

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Introduction

Deposits of extracellular amyloid with closely associated neuronal and glial pathology are commonly identified with Alzheimer's disease, but amyloid plaques are found in many other conditions, including transmissible spongiform encephalopathies and traumatic brain injury. Amyloid plaques also commonly occur with aging in the absence of disease, injury or dementia. Plaques form in the cerebral cortex of aged primates [72, 184, 194], and in many non-primate species, but only rarely in aged rodents [257]. Animal models of amyloid pathology, created by inserting Alzheimer's disease genes into mice, have rapidly expanded our knowledge in recent years, warranting a reconsideration of the mechanisms of amyloid plaque pathogenesis.

Amyloid is any proteinaceous polymer having a beta-pleated sheet conformation that accumulates extracellularly (for reviews see [205, 275]). In transmissible spongiform encephalopathies, such as mad cow disease, the amyloid is composed primarily of prion protein rather than the amyloid-beta (Aβ) peptide of Alzheimer's disease. A number of prion diseases, including Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker disease, kuru, and scrapie, exhibit amyloid plaque pathology similar to that of aging and Alzheimer's disease [139]. A number of other cellular proteins may form amyloid in the brain, and all of these amyloids induce pathological changes [10, 31, 57, 168].

Amyloid plaques can result from traumatic brain injury in which axonal damage is distributed diffusely throughout the brain. Organelle accumulation in disrupted axons over a period of a few days post-injury leads to axotomy and plaque formation in animal models of traumatic injury [33, 219, 229]. Likewise in humans, traumatic brain injury with diffuse axonal damage leads to plaques containing Aβ protein [97, 218]. There is also evidence that amyloid plaques

accumulate in the cerebral cortex of athletes involved in violent sports such as football and boxing [107, 177, 200].

The fact that insoluble extracellular deposits of fibrillar protein accumulate in a similar pattern in so many different conditions provides interesting clues to the mechanisms of pathogenesis. Pathogenesis likely involves a site of particular vulnerability that is disrupted by a variety of insults. Although amyloid is assembled from cellular proteins, where this assembly takes place is currently unknown. As reviewed below, several loci have been proposed for amyloid polymerization, including glia cells, neuronal lysosomes, and extracellular fluid, but the current evidence does not unequivocally endorse any of these loci. The early hypotheses of Fischer and Bonfiglio maintained that amyloid derives from degenerating axons (reviewed in [78]), and this alternative is reconsidered in light of the recently recognized importance of disrupted axonal transport in amyloid pathology [40, 77, 201, 226].

Amyloid plaque morphologies

Plaques are frequently identified by light microscopy using methods specific for fibrillar amyloid such as thioflavin-S or Congo Red staining. The commonly used descriptors "primitive" and "cored" describe the two main types of amyloid plaques revealed by this kind of histology and by electron microscopy. Several additional types of amyloid-related protein deposits have been more recently identified by immunohistochemistry (for a recent review see [241]).

Primitive plaques

Primitive plaques are composed of extracellular wisps of amyloid woven among a dense cluster of dystrophic neurites. The "dystrophic" label was given to these grossly swollen neurites because they resemble the spheroid enlargements of axons found in cases of malnutrition and in the infantile neuroaxonal dystrophy of Seitelberger [133]. Primitive plaques are sometimes called "neuritic" plaques because such dystrophic neurites are always present.

The term "dystrophic" is often mistakenly applied to the more fusiform, distorted neurites containing paired helical filaments (neurofibrillary tangles) of tau protein. Neurites with tau tangles are found in plaques in advanced Alzheimer's disease, but they are absent from plaques in early disease stages [14, 41, 163, 232, 241, 265, 295]. Many non-human mammalian species develop amyloid plaques with aging but do not have neurites with tau inclusions [43, 212, 252]. Transgenic mice carrying Alzheimer's disease mutations have amyloid plaques without tau tangles (for reviews see, [70, 221]) while mice engineered to also produce tau tangles initially form amyloid plaques without them [17, 170, 171]. This evidence establishes that plaques can form in the absence of neuritic tau accumulations, and that this type of neurite, while significant to Alzheimer's disease progression, is not a general mechanism of amyloid plaque pathogenesis. In this review, the term "dystrophic neurite" is only used to refer to the globular type of swelling without tau tangles.

The term "neurite" is used because the distorted morphology makes it difficult to unequivocally identify the profiles as axonal or dendritic [148, 151]. However, evidence from transgenic mice demonstrates that most grossly swollen, dystrophic neurites are axons [17, 185, 222, 250, 299]. Dendrites passing through plaques often display spine loss, increased curvature, and a reduction in shaft diameter, while filopodial extensions and swellings are less frequently observed [81, 195]. The dystrophic swellings in plaques are more often diverticular offshoots from unmyelinated axons [63, 195]. Whether these dystrophic axons are degenerating or regenerating has been debated [2, 151, 258], but the fact that axon densities are reduced in plaques appears to favor degeneration [13, 52, 222].

By light microscopy, primitive plaques are observed to be spherical regions of pathology, usually 10–70 μm, but sometimes more than 100 μm, in diameter [6, 24]. Electron microscopy reveals many more small neuritic plaques than are apparent by light microscopic examination [239]. The smallest primitive plaques are clusters of just a few dystrophic neurites in the neuropil and do not involve cell bodies of any kind (Fig. 1). In addition to dystrophic neurites, the plaque region often contains normal-looking neuronal and glial processes, but the density of synapses is greatly reduced from that of normal neuropil [115, 125]. Occasionally, a dystrophic neurite is found to be the presynaptic partner of a synapse [75, 282], but claims that most dystrophic neurites are abnormal synaptic terminals are not supported by the available data. The frequency of synapses on dystrophic neurites in plaques has never been quantified, but immunolabeling for presynaptic proteins reveals that most dystrophic neurites lack the full synaptic machinery [18, 62].

The first ultrastructural studies of Alzheimer's disease revealed that dystrophic neurites are swollen by abnormal accumulations of filaments, vesicles, tubules and mitochondria [115, 143, 238]. Transitional forms between mitochondria and additional mitochondrial-sized lamellar or dense bodies are obvious, and all of the early investigators, with the exception of Terry et al. [238], speculated that the numerous lamellar and dense bodies were degenerating mitochondria. Krigman et al. [125] further speculated that the degeneration of mitochondria in dystrophic neurites might ultimately lead to cored plaques. These inferences of progressive degeneration were partly motivated by the similarity of dystrophic neurites to axons undergoing Wallerian degeneration after transection [133, 134]. After Suzuki and Terry [233] found that the lamellar and dense bodies

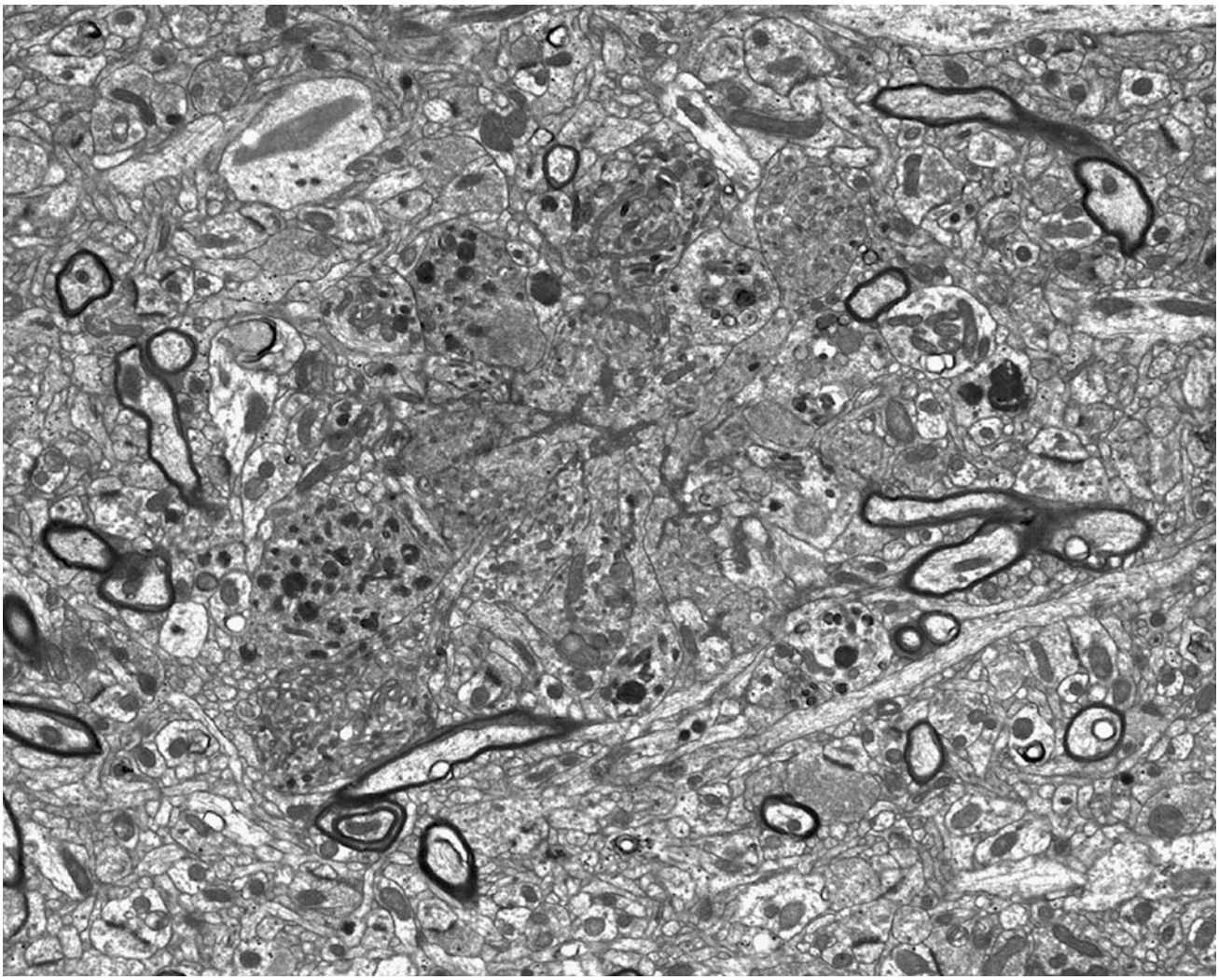

Fig. 1 A primitive neuritic plaque from layer III of prefrontal cortex of a 32-year-old rhesus monkey. Serial section electron microscopy shows that the plaque is a cluster of dystrophic neurites around darker extracellular deposits. This section from the center of the plaque shows the maximum diameter of approximately 12 μm. Surrounding the cluster of dystrophic neurites is normal-looking cortical neuropil in which glial and neuronal cell bodies are absent

contained acid phosphatase, and classified these inclusions as lysosomes, little further consideration was given to their origin or fate until recently.

The terminology used to describe plaque types is not standardized, and some investigators use the term "diffuse plaque" to describe the distribution of amyloid in primitive plaques containing both amyloid fibrils and dystrophic neurites [54, 241, 252]. The adjective "diffuse" has also been applied to many other types of fibrillar and non-fibrillar deposits, so to avoid confusion "diffuse" will be avoided altogether in this review.

Cored plaques

Cored plaques differ from primitive plaques by containing a large central mass of amyloid. The central mass of amyloid makes these plaques easily identifiable with amyloid staining techniques, giving these plaques the moniker "classical". The amyloid core sometimes has a star-shaped appearance with spokes of amyloid extending outward, and it is usually surrounded by a spherical cluster of dystrophic neurites and extracellular wisps of amyloid as in the primitive plaque.

Immediately around the core there may be a layer devoid of amyloid and neuritic processes. Ultrastructural studies reveal that this halo effect is created by glia that enclose the core [110, 150, 223, 257, 270, 296]. Cores of small plaques are enveloped by one or two activated microglia, while large plaque cores are surrounded by processes from dozens of microglia and astrocytes [268]. When cored plaques are not surrounded by dystrophic neurites and wisps of amyloid they are often referred to as compact or "burnt-out"

plaques. Compact plaques are also enveloped by glial cells, in some cases entirely by astrocytes [115, 239].

Non-amyloid deposits

After the Aβ peptide was identified [152], it became possible to further examine the distributions of both fibrillar and non-fibrillar forms of Aβ in Alzheimer's disease using immunohistochemistry. Immunolabeling revealed a more widespread deposition of the Aβ peptide than was seen previously with the classical stains for fibrillar amyloid [234, 281, 291]. Non-amyloid Aβ deposits, often called "diffuse plaques", are frequently seen in the cerebral cortex, cerebellum, and striatum. The morphology of the deposits depends on the characteristics of the tissue. For example in the cerebellum, non-amyloid deposits extend vertically through the molecular layer, often appearing to loosely follow Purkinje neuron dendritic arbors [106, 264].

The Aβ immunoreactivity of non-amyloid deposits often extends over a large region 200 μm or more in diameter [234], which is largely devoid of dystrophic neurites or activated microglia, but occasional dystrophic neurites may be found on close inspection [18, 292]. While most of the immunoreactive region appears to lack amyloid, a sparse distribution of extracellular fibrils is sometimes revealed by electron microscopy [292], by Campbell–Switzer silver staining [241], or by weak thioflavin-S fluorescence [136]. Some investigations have concluded that amyloid fibrils are present in all deposits that are immunoreactive for fibrillogenic forms of the Aβ peptide, which would include most types of "non-fibrillar" deposits [49, 241, 242].

One issue with the identification of non-amyloid deposits is the use of formic acid pretreatment to enhance immunoreactivity [118]. This procedure defibrillates amyloid and solubilizes the constituent peptide, thus precluding amyloid staining by Congo Red or thioflavin-S [231]. Such treatment may also cause diffusion of the amyloid peptide within the tissue sample and may even extract amyloid protein from neurons [48, 174]. It is perhaps not surprising then that non-amyloid deposits are sometimes large, lake-like regions of Aβ immunoreactivity that are either perineuronal or extend beyond a central region of neuritic pathology. However, other investigators report that distributions of Aβ immunoreactivity are little changed by formic acid pretreatment [100, 106].

Numerous studies indicate that the molecular composition of non-amyloid deposits differs from that of primitive and cored plaques [80, 90, 158, 196, 245]. Non-amyloid deposits in the cerebellum, for example, are characterized by a preponderance of Aβ fragments in which the amino-terminal is truncated [100, 131]. This less fibrillogenic molecular profile was confirmed in aged canines [285], a species that develops non-amyloid Aβ deposits but not neuritic plaques [43]. Immunotherapy using antibodies directed at the amino-terminal of Aβ successfully removes fibrillar plaques but not non-amyloid deposits [183], further substantiating the difference in molecular composition. The relative lack of neuritic and microglial pathology in non-amyloid deposits may be related to this different composition.

Do plaque types reflect a progression of pathology?

Based on ultrastructural studies, Terry and Wisniewski [239, 240] proposed that small clusters of dystrophic neurites evolve into larger primitive plaques and, with the continual accumulation of extracellular amyloid, primitive plaques eventually evolve into cored plaques. While this plaque evolution hypothesis is certainly consistent with the structural evidence, it has met with criticism (reviewed in, [5]). An opposite progression has even been proposed, with cored plaques transitioning into primitive plaques to end up as non-amyloid deposits [269].

Struble et al. [230] found that as total plaque density increased in aged monkeys, there was a corresponding increase in cored plaques, suggesting that primitive plaques evolve into cored plaques. Evidence in favor of a plaque progression in Alzheimer's disease has been less conclusive, however. Some studies have reported that primitive plaques precede cored plaques and that cored plaques accumulate as the disease progresses [244], but other studies have reported that primitive plaques increase with duration of the disease while cored plaques do not [54]. Supportive evidence for plaque progression comes from transgenic mice models of Alzheimer's disease and from Down's syndrome.

Transgenic mice expressing pathogenic forms of the Aβ precursor protein (APP) and its proteolytic enzymes exhibit increased production of Aβ from APP. Young mice first develop mostly small primitive plaques, but later numerous cored plaques appear [15, 85, 237]. The sizes of cored plaques and the number of invested microglial cells increase with age, and in the oldest transgenic mice, large plaques are often infiltrated by hypertrophic astrocytic processes [197, 268]. Older mice also exhibit more cored plaques with a "burnt-out" morphology in which dystrophic neurites are largely absent [15].

Down's syndrome is manifested by an extra copy of chromosome 21, which leads to overexpression of APP and early onset of Alzheimer's disease. The numerical density of amyloid plaques increases with age in Down's syndrome [96, 136]. Non-amyloid deposits appear in the second and third decades of life, followed by neuritic and cored plaques in the fourth to fifth decades [87, 91, 136]. Primitive plaques predominate when Alzheimer's disease first

becomes identifiable, but with continued aging there is an increase in cored plaques. Protein aging studies confirm that the amyloid in the cores of classical plaques is older than the amyloid in primitive plaques, and the cores are surrounded by a halo of younger amyloid [9, 65].

Given the multifarious nature of non-amyloid deposits, it is difficult to assign them a specific role in the progression of pathology. Extracellular deposits containing mostly soluble Aβ protein are often assumed to represent the first step in amyloid plaque pathogenesis [53, 210, 234]. The best evidence supporting this contention is usually taken to be the sequence of pathology reported in Down's syndrome [5], but recent evidence from transgenic mice is not confirmatory. Non-amyloid deposits appear months after fibrillar plaques in most transgenic mice with one or more Alzheimer's disease mutations [76, 85, 114, 155, 197, 198]. However, when transgenic mice are engineered to overexpress APP without mutations, similar to Down's syndrome, they initially develop non-amyloid deposits [89]. Non-amyloid deposits in the cerebellum and striatum, which are highly insoluble, do not appear to evolve into neuritic plaques over the course of Alzheimer's disease [286] or over a lifetime with Down's syndrome [147]. The existence of a "pre-amyloid" type of deposit therefore, remains controversial.

Proposed mechanisms of plaque pathogenesis

A key attribute of all plaques is the focal deposition of amyloid in a local, typically spherical, region. The evidence for temporal evolution suggests that primitive plaques mature into cored plaques, and then stabilize as large, spherical areas of pathology around this focus of fibrillar amyloid [36]. Although several different mechanisms for the focal deposition of amyloid have been proposed (Fig. 2), the issue of how plaques form is still unresolved.

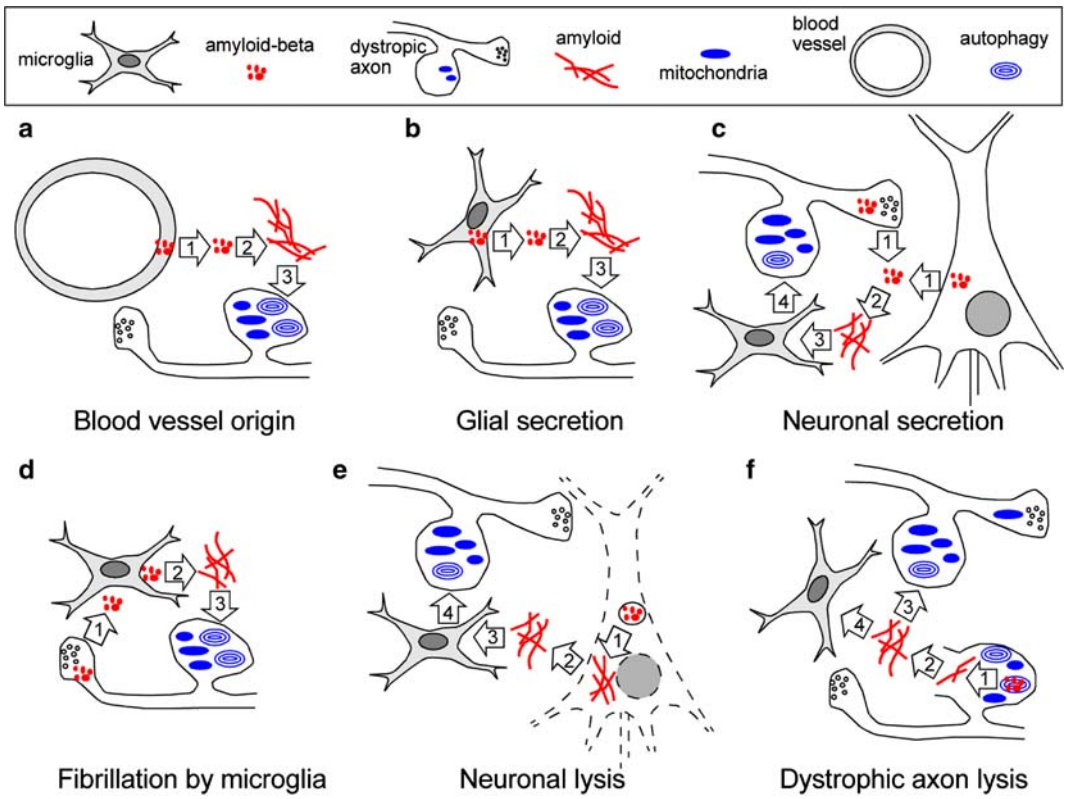

Fig. 2 Competing hypotheses for the locus of amyloid production and the pathogenesis of neuritic plaques. **a** Amyloid deposition is initiated from blood vessels that release Aβ (*1*) which spontaneously fibrillates (*2*) in the perivascular space and creates a toxic environment for axons, leading to dystrophy (*3*). **b** Amyloid deposition is initiated by glia that secrete Aβ (*1*) which spontaneously fibrillates (*2*) and produces axonal dystrophy (*3*). **c** Aβ is secreted from somato-dendritic regions or synaptic terminals of neurons (*1*). The protein spontaneously aggregates (*2*) into amyloid filaments that activate microglia (*3*). Activated microglia secrete toxins that cause axonal dystrophy (*4*). **d** Aβ is secreted by neurons (*1*) and processed extracellularly into amyloid filaments by microglia (*2*). Amyloid toxicity leads to axonal dystrophy (*3*). **e** Aβ or its precursor protein is internalized through endocytosis and aggregated in lysosomal compartments in the cell body of neurons (*1*). Lysis of the cell (*2*) leads to extracellular deposition, which activates microglia (*3*). Activated microglia poison axons leading to dystrophy (*4*). **f** Amyloid is formed in autophagosomes (*1*) trapped in axonal dystrophies and deposited by rupture of the swelling (*2*). Extracellular amyloid leads to the formation of more dystrophies (*3*) by disrupting axonal transport, and provokes a glial reaction (*4*)

Blood vessel origin

Amyloid plaques are frequently accompanied by cerebral amyloid angiopathy in which amyloid is deposited around cerebral and leptomeningeal blood vessels. The cause of cerebral amyloid angiopathy is unknown (for review see [23]), but similarities in the distributions of amyloid angiopathy and plaques suggest that blood vessels might be involved in amyloid plaque formation [4, 58, 260]. The severity of Alzheimer's disease pathology correlates with the severity of co-occurring cerebral amyloid angiopathy [7, 8], and large cored plaques are often in close proximity to blood vessels with amyloid deposits [126, 127], further suggesting that brain amyloid might originate from systemic circulation or from the cells of the blood vessel walls [56, 105]. However, small plaques are frequently far from blood vessels [4, 111], ruling out a nidus of origin involving blood vessels for these plaques.

Neuron-specific expression of Alzheimer's disease mutations in mice causes parenchymal amyloid plaques to form prior to significant perivascular amyloid deposition [197], making it unlikely that Aβ originates from blood or blood vessel walls. Rather, cerebral amyloid angiopathy appears to develop from neuronal APP, since it also occurs in APP-null mice expressing mutant APP only in neurons [25]. In addition, amyloid angiopathy occurs in the thalamus, even though neurons in the thalamus do not express the transgenes, indicating that the transgene products are transported from cortex, possibly by axons [25].

Glial production of amyloid

All cored plaques contain activated microglia that surround and interdigitate with the central mass of amyloid. On single sections, bundles of amyloid are often completely surrounded by microglial profiles, giving the appearance that amyloid lies within membranous compartments in the microglia cytoplasm. This appearance led to the supposition that fibrillar amyloid is secreted by microglia [160, 238]. Some investigators speculated that amyloid fibrils are formed within the endoplasmic reticulum of microglia and exocytosed to the extracellular space [284]. But evidence from serial section electron microscopy shows that the amyloid fibrils in cored plaques that appear to lie within microglia are in fact entirely extracellular [204, 223, 257, 268].

The proteolytic enzymes responsible for production of Aβ from APP, as well as APP itself, are most strongly expressed in neurons [42, 44, 124, 215, 256]. Therefore, glia are unlikely producers of the Aβ that forms plaques. The glial secretion hypothesis was accordingly modified to propose that Aβ from neurons is processed into amyloid at the plasma membrane of microglia cells [148, 165]. Support for this hypothesis comes from studies showing activated microglia in plaques from the onset of amyloid pathology in transgenic mice [88, 197, 224, 268].

The production of amyloid principally at the surface of microglia gives a definite nidus to amyloid plaque formation, every plaque would originate at a microglial cell. But if each microglial cell is independently capable of forming a plaque, it is unclear why large numbers of microglia cluster around single plaque cores [224]. Furthermore, although cultured microglia respond to plaques of synthetic amyloid [98], they do not process synthetic Aβ into amyloid plaques [26]. Another difficulty with this hypothesis is that the earliest amyloid plaques would be expected to be compact plaques produced by activated microglia, which would evolve first into classical plaques, and then into primitive plaques when microglia retract and astrocytes infiltrate the amyloid core [269]. Obviously, this evolution is at odds with the sequence of plaque progression in transgenic mice models of Alzheimer's disease, and some of the earliest, primitive plaques may be devoid of microglia [42, 47, 228].

Microglia and astrocytes may be consumers of amyloid rather than producers, since cultured microglia internalize aggregates of Aβ peptide and rapidly phagocytose plaque cores [51, 66, 181]. There is also some evidence of phagocytosis and digestion of amyloid by microglia in vivo [102, 153, 273], and astrocytes have been shown to migrate to and degrade amyloid plaques [288]. Consistent with consumption of amyloid instead of production, inhibition of microglial responses in transgenic mice leads to more rapid development of amyloid pathology [59, 289].

Neuronal secretion of Aβ

Neurons in culture secrete Aβ, and extracellular, soluble Aβ peptide has been proposed to be sufficient to initiate plaque formation [209]. In a simple version of this hypothesis, abnormal proteolysis of APP at the surface of neurons releases Aβ peptide directly into the extracellular space. However, the proteolytic enzymes that generate Aβ from APP appear to operate in intracellular compartments rather than at the neuron plasma membrane (for reviews see [217, 276]). Many different compartments have been proposed as principal sites of pathogenic cleavage prior to secretion, including rough endoplasmic reticulum, golgi secretory apparatus, and endosomes that recycle to the plasma membrane. Whatever the compartment, non-fibrillar deposits generated by the secretion of soluble Aβ would be centered on neurons, in agreement with data showing some Aβ immunoreactivity centered on the cell bodies and primary dendrites of neurons in Alzheimer's disease and aging [178, 179, 271]. In the cerebella of Alzheimer's disease patients, non-fibrillar deposits are often closely associated with accumulations of Aβ inside the somata and dendrites of Purkinje neurons [264].

In conflict with the hypothesis that the neuron soma is the primary nidus of amyloid plaque formation, many amyloid plaques are not centered on neuron cell bodies. As shown by electron microscopy, small plaques are often located in the synaptic neuropil and involve only neurites and glial processes without any neuronal cell bodies or large proximal dendrites (Fig. 1). The soma is often not the nidus of plaque formation even when it is the source of Aβ. This is evident in mice with genetic constructs designed to secrete Aβ through the golgi pathway. In these mice amyloid plaques form in the molecular layers of the cerebellum and hippocampus rather than only in cell body layers [154].

APP is trafficked down the axon [108, 123], suggesting that Aβ is produced in synaptic terminals rather than in the somato-dendritic compartment. One hypothesis based on this idea is that normal synaptic transmission secretes Aβ, which if not cleared quickly leads to pathogenesis [211]. Recent experiments in transgenic mice demonstrate that extracellular levels of Aβ rise with epileptiform activity and decrease when synaptic transmission is blocked [38]. Additional support for an axonal locus of production comes from studies in transgenic mice showing that the transection of axons of the perforant pathway to the hippocampal dentate gyrus reduces the amount of Aβ protein deposited in this brain region [135, 213, 254]. Unlike somatic secretion however, there is no obvious nidus of fibrillation with synaptic secretion. Synaptic release of soluble peptide would disperse Aβ widely throughout the neuropil of the cerebral cortex.

Spontaneous extracellular fibrillogenesis

One proposal for how soluble Aβ triggers plaque pathogenesis is that the peptide spontaneously begins to form fibrils as the extracellular concentration of Aβ reaches high levels [53, 210, 241]. To explain the formation of a neuritic plaque, it is assumed that the extracellular amyloid attracts microglia, which release molecules toxic to nearby axons and dendrites, causing them to swell and degenerate. Since microglia and amyloid precede dystrophic neurites in this hypothesis, it is in conflict with the sequence of plaque progression discussed above.

Although solutions of synthetic Aβ spontaneously fibrillate in vitro under certain conditions, the extent to which this happens in vivo is unclear. Comparable concentrations of Aβ peptide are found in the extracellular fluid of normal mice and transgenics with amyloid pathology [37], and this concentration appears to be orders of magnitude less than the concentration required for spontaneous fibrillation in vitro [141, 180]. Moreover, the presence of a high concentration of Aβ appears to be insufficient for both fibrillation and plaque pathogenesis in vivo, since intracerebral injections of Aβ rarely produce plaques [156, 214, 277 but see 216].

Additional evidence indicates that oligomerization begins intraneuronally, with secretion of soluble oligomers rather than monomers of Aβ [263]. Pathogenesis may require this prior aggregation of Aβ into oligomers or protofibrils, since the Aβ peptide is much less toxic to neurons than these multimers (reviewed in [262]). Experiments with transgenic mice suggest that soluble Aβ oligomers may be involved in the cognitive decline of Alzheimer's disease [39, 137], but there is still little evidence for the formation of focal, neuritic amyloid plaques directly from these oligomers. Intracerebral injections of Aβ dimers, oligomers or polymers at physiological concentrations produces little or no seeding of amyloid plaques, even in transgenic mice predisposed to amyloid pathology [156]. However, injection of extracts from brains with extant amyloid pathology does seed plaques, suggesting that factors in addition to Aβ protein are involved in plaque pathogenesis [11, 109, 156].

Neuronal accumulation and lysis

Several groups proposed that Aβ aggregation within the cell bodies of neurons is prerequisite to deposition in the extracellular space (for reviews see [78, 129, 276, 279]). In Down's syndrome, granular accumulations of Aβ can be seen in neuronal cell bodies prior to the appearance of plaques or perineuronal deposits [82, 162], and Aβ peptide accumulates in a granular pattern in the cell bodies of neurons in Alzheimer's disease [46, 79]. Transgenic mice with amyloid pathology also exhibit intraneuronal granules of Aβ immunoreactivity [15, 171, 278, 280]. In mice with highly accelerated pathology, fibrillar amyloid accumulates in neurons along with Aβ prior to deposition of the protein in the extracellular space [169].

Aβ could accumulate inside any of the intracellular compartments where it is cleaved from APP but not secreted. Two likely candidates are endoplasmic reticulum [86, 247], and lysosomes [29, 30, 182]. To reach the lysosomal pathway, Aβ might be produced inside endosomes by proteolytic processing of internalized APP, or Aβ might be endocytosed from an extracellular pool of soluble protein [119]. Normal processing of endosomal compartments would then lead to aggregation of the Aβ within lysosomes.

Amyloid plaques might be created when lysosome-laden neurons die and release amyloid into the extracellular space [46, 74]. In this hypothesis, every plaque is centered on a dying neuron. Although there is evidence for somal and lysosomal remnants in some plaques [28, 30, 46], plaques are not necessarily concentrated in cell body layers, and transgenic mice engineered to accumulate Aβ in neuronal somata exhibit neurodegeneration but not plaques [130]. Further emphasizing that somata are not niduses of all plaques, non-transgenic brain tissue grafted into transgenic mice develops amyloid plaques before the rest of the

hippocampus even though the neurons expressing amyloidogenic mutations reside outside the graft [157].

As noted above, many small plaques are clusters of dystrophic axons and amyloid in neuropil distant from cell bodies (Fig. 1). Consequently, the somal accumulation hypothesis has been extended to include the possible transportation of amyloid-filled endosomes or lysosomes from the soma into neurites [74, 78], where they would presumably accumulate as the lamellar and dense bodies in dystrophic swellings. Dystrophic axonal swellings are often far from the soma, and while evidence shows that endosomal and lamellar bodies are retrogradely transported along axons to the soma [94], there is little evidence for anterograde transportation of lysosomes to distal axons.

Disruption of axonal transport

Disruption of fast axonal transport leads to focal swellings filled with organelles [95, 251], which resemble Wallerian degeneration [267]. Similarities to Alzheimer's disease pathology led many investigators to surmise that disrupted axonal transport is responsible for the formation of dystrophic neurites in amyloid plaques [69, 115, 134, 192, 240]. Terry and Wisniewski [240], in the vein of Fischer and Bonfiglio, suggested that the earliest precursor of a senile plaque was an axonal swelling, but the mechanism by which an axonal swelling might serve as a nidus of amyloid deposition and plaque formation has remained elusive. Renewed interest in this possibility (as exemplified by [77, 226]) is largely due to recent findings in transgenic mice models of Alzheimer's disease.

Transgenic mice with amyloid pathology exhibit swellings along the lengths of axons long before amyloid deposition is detectable [227, 250]. These non-synaptic, non-terminal axonal swellings are filled with mitochondria, vesicles, and mitochondrial-sized lamellar and dense bodies, consistent with disrupted axonal transport. Furthermore, reduced expression of microtubule motor proteins in these mice increases the number of axonal swellings, as well as the number of amyloid plaques later in the disease, reinforcing the supposition that disrupted axonal transport contributes to the formation of amyloid plaques [227].

Traumatic brain injury produces axonal swellings similar in appearance to plaque dystrophic neurites [33, 219, 229], and these swellings are believed to arise as a result of impaired axonal transport (reviewed in [22, 190]). Axon swellings appear within 1–2 h post-injury and demonstrate intense APP immunoreactivity, consistent with interruption of the normal axonal transport of this protein [186, 218]. Some swellings also exhibit immunoreactivity for Aβ peptide and stain for fibrillar amyloid, suggesting that amyloid plaques are sequelae of the deposition of amyloid from axon swellings after traumatic injury [34, 186].

APP-immunoreactive dystrophic neurites that resemble those of traumatic injury are likewise found in the amyloid plaques of Alzheimer's disease [42, 44, 112, 153, 215]. Some investigators hypothesize that extracellular amyloid causes structural injury to axons in the same manner as traumatic injury [117, 287]. However, evidence for amyloid inside axon swellings following traumatic injury also supports the opposite relationship, namely that dystrophic neurites in plaques produce amyloid.

Autophagic production of amyloid

Dystrophic axons clearly accumulate APP, and cleavage of APP to Aβ protein likely occurs within these swellings as well, because the enzymes responsible for this proteolysis also accumulate there [21, 34, 248, 299]. One candidate compartment for this proteolysis is the early endosome. Although there is scant evidence for significant endocytosis within dystrophic neurites of amyloid plaques, endosomes might be trafficked into dystrophic swellings from the distal axon [166]. However, immuno-electron microscopy of Aβ has thus far failed to localize the Aβ protein to clearly identifiable endosomal compartments within dystrophic neurites [120–122, 235, 236].

Another candidate site for Aβ production in dystrophic neurites is within autophagic vacuoles, which have recently been implicated in Alzheimer's and other neurodegenerative diseases (for review see [202]). Analysis of biopsy material reveals that Alzheimer's disease brains contain many more autophagosomes than normal brains [167], and a similar abnormal accumulation of autophagosomes occurs in transgenic mice with amyloid pathology [297]. The majority of these autophagosomes are concentrated in the dystrophic neurites of amyloid plaques, but a few are found in the somato-dendritic compartment. These autophagic vacuoles appear to be a prominent locus of Aβ production [297, 298]. In cultured cells overexpressing APP, suppression of autophagy reduces Aβ secretion while induction of autophagy increases Aβ release [297].

The substrate of autophagy is unclear, but recent data indicate that autophagocytosis of mitochondria is increased in Alzheimer's disease [161]. Autophagocytosis followed by lysosomal processing is the major degradative pathway for mitochondria, a process sometimes abbreviated as "mitophagy" (for reviews see [20, 116]). Moreover, the autophagocytosis of mitochondria would account for the transitional forms between normal mitochondria and the lamellar bodies in dystrophic neurites of amyloid plaques [63, 239, 283]. Amyloid may be produced by dysfunctional mitophagy, and this possibility is supported by immuno-electron microscopy showing that APP accumulates in the mitochondria and lamellar bodies of dystrophic neurites [17, 50, 112, 148, 215]. Proteolytic enzymes necessary for

the production of Aβ from APP have also been identified in mitochondria and autophagosomes [84, 297, 298], as have the Aβ peptide and its oligomers [27, 120, 121, 144, 146, 218, 293, 297].

A synthesis of mechanisms

One curious aspect of most proposed mechanisms of plaque formation is that the central cellular pathology of primitive plaques, the dystrophic neurite, plays no role in pathogenesis (Fig. 2). Dystrophic neurites are often considered to be an incidental consequence of amyloid deposition or microglial activation, but not active participants in plaque pathogenesis. In other words, most hypotheses assume that extracellular Aβ peptide and microglial activation are all that is needed to create a classical amyloid plaque. The data discussed above, however, suggests that plaques form in close conjunction with amyloid protein processing in dystrophic neurites. When considered in synthesis with the mechanisms of disrupted axonal transport, mitochondrial malfunction and oxidative stress, autophagy, impaired lysosomal processing, and intraneuronal production of Aβ, all of which have been implicated in Alzheimer's disease, the dystrophic neurite is a likely nidus of plaque pathogenesis (Fig. 2f).

Dystrophic axons are antecedents of pathology

The data from traumatic injury, Alzheimer's disease and transgenic mice, discussed above, are consistent with axonal dystrophy playing a key role in plaque formation. Numerous studies report that the smallest amyloid deposits are closely associated with dystrophic neurites [15, 176, 199, 227, 283]. In addition, isolated dystrophic neurites are found widely scattered throughout the cortical neuropil in all conditions leading to amyloid pathology, including normal aging [113, 149], traumatic brain injury [218, 229], prion diseases [140], and Alzheimer's disease [41, 167, 215, 227, 283].

Any insult that disassembles axonal microtubules and disrupts retrograde transport would be an additional candidate for initiating plaque pathogenesis, due to the expected formation of dystrophic swellings. This would include excitotoxic injury for example, since high concentrations of extracellular potassium and glutamate have been shown to disrupt axonal transport and induce dystrophic swellings [92, 93]. Relatively few studies have made an association between amyloid plaques and excitotoxic injury, but there is evidence that mediators of excitotoxicity such as hypoxia/ischemia can result in the initial stages of amyloid pathogenesis [32, 104, 189, 255].

Amyloid plaques might also be expected as an outcome of any number of pathological conditions in which dystrophic neurites commonly occur (for reviews see [103, 140]). However, depositions of amyloid are not consistently found in most of these conditions, emphasizing that additional factors are involved, such as overproduction of fibrillogenic fragments of APP. In familial Alzheimer's disease, the genetic defects leading to overproduction of fibrillogenic Aβ protein may cause relatively benign axonal dystrophies to become potent seeds of pathology. Likewise, in late-onset, sporadic forms of Alzheimer's disease, the increased frequency of axonal dystrophies with aging may conspire with other factors to increase the probability of amyloid plaque formation.

Mitophagy follows disruption of axonal transport

The organelles that accumulate most during inhibition of retrograde axonal transport are mitochondria [251], because these organelles are normally trafficked from the distal axon to the soma for lysosomal degradation after they become metabolically dysfunctional [188]. Dystrophic neurites in plaques likewise accumulate large numbers of mitochondria, which are metabolically compromised but unable to reach the soma for lysosomal processing [15, 63]. These stranded mitochondria consequently enter a mitophagic pathology leading to production of large numbers of autophagosomes. Autophagosomes might also be trafficked into dystrophic swellings from the distal axon, along with endosomes and amyloid-related proteins, since autophagosomes are also retrogradely transported [94]. In any case, the large numbers of mitochondria, and the transitional forms between these mitochondria and the autophagic vacuoles, indicate that mitochondria are the main substrate of autophagy in dystrophic neurites [63, 115, 233, 239, 240].

As discussed above, autophagosomes appear to be a principal site of Aβ generation in Alzheimer's disease, but direct evidence of amyloid production by autophagosomes in dystrophic neurites is still lacking. Amyloid fibrillogenesis in vitro has been shown to have an intermediate stage involving a 5 nm-wide protofibril [3,261], and recent ultrastructural evidence reveals that clusters of autophagosomes in some dystrophic neurites degenerate into loose bundles of 5 nm filaments [63]. This suggests that amyloid fibrillogenesis may occur in some dystrophic neurites (Fig. 3), but verification of the molecular nature of these filaments awaits further studies.

Amyloid disrupts axonal transport and neurite integrity

Extracellular amyloid protein has detrimental effects on neuron integrity. Multimers of Aβ are toxic to neurons [67, 132, 142], and in high enough concentration Aβ peptide can kill cultured neurons, possibly due to the spontaneous formation of such aggregates [45]. Significantly, application

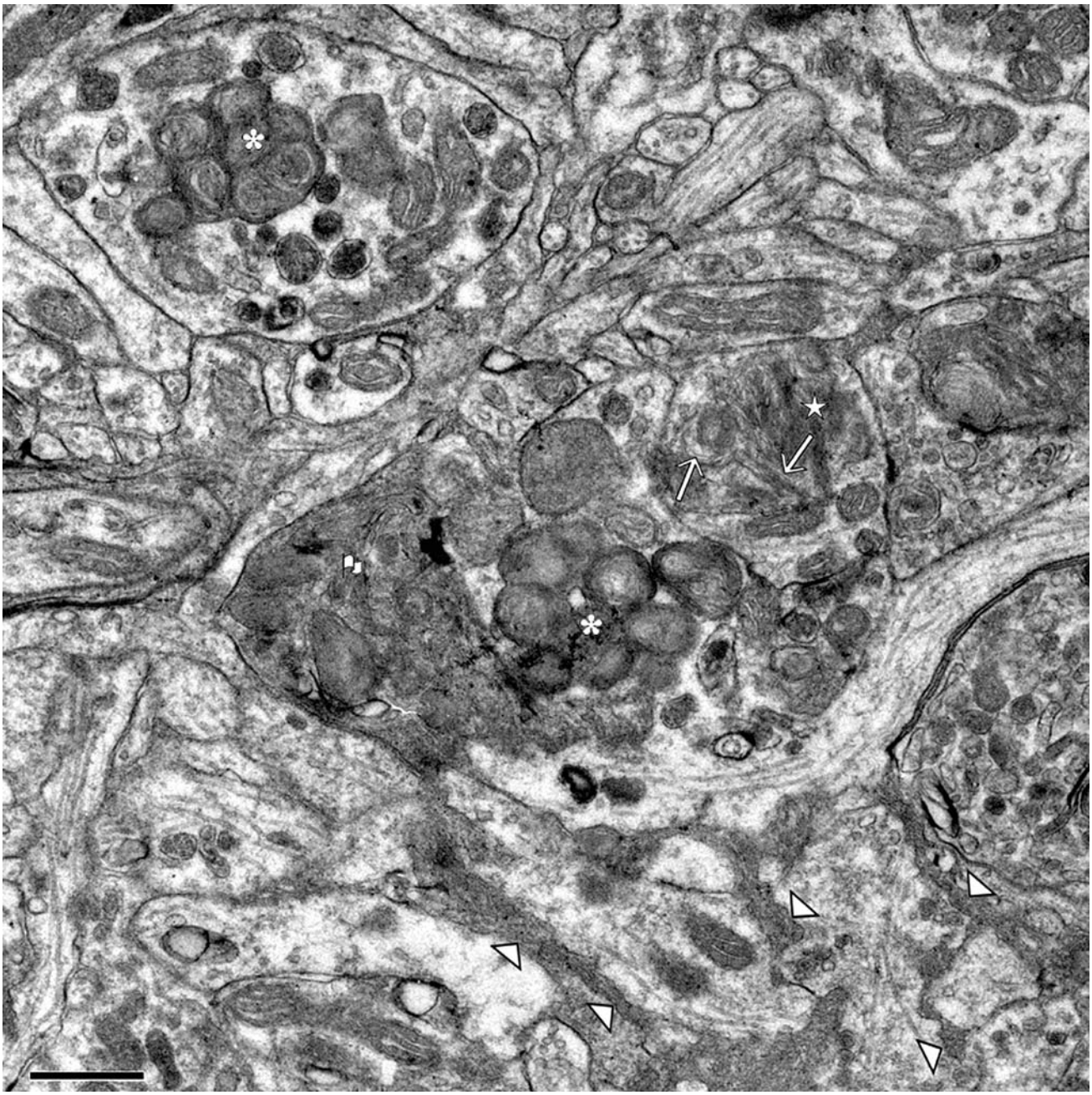

Fig. 3 Dystrophic neurites in a primitive neuritic plaque from layer III of prefrontal cortex of a 32-year-old rhesus monkey. Degenerated mitochondria form lamellar bodies that in advanced stages of degeneration form tight clusters (*asterisks*). These clusters appear to degenerate further (*star*) into loose 5 nm-wide filaments within the cytoplasm (*arrows*). Dystrophic neurites with accumulations of filaments and degenerated organelles form a dense matrix (*flag*) that is similar in appearance to the filamentous material found in the extracellular spaces of the plaque (*arrowheads*). Scale bar: 0.5 microns

of Aβ protein to the axons of cultured neurons induces local swelling and degeneration [99, 187, 220], consistent with the evidence that extracellular amyloid protein disrupts axonal transport [92] and strands mitochondria [203]. The disruption of axonal transport may be due to the formation of calcium-permeable channels by multimers of Aβ [141], since a pathological influx of calcium can completely disassemble microtubules [64, 207, 266].

The effects of intracellular amyloid on neuronal integrity are less well established, but it has been shown that intracellular accumulation of Aβ can lead to loss of membrane integrity and eventual neuron degeneration [55, 130, 294]. Internal aggregation of Aβ could thus lead to disintegration of a dystrophic neurite and spilling of its cytoplasmic contents into the extracellular space, as proposed by Kawai et al. [112], Chen et al. [34], and others. Neuritic lysis in

plaques is consistent with evidence of neuronal cytoplasmic and organellar proteins, mRNAs, and membranous organelles among the extracellular amyloid of plaques [28, 30, 63, 73, 138, 191, 193]. These spilled cytoplasmic contents may be part of the plaque seeding mechanism, which would help explain why brain extracts, but not synthetic amyloids, seed plaques [156].

Pathogenesis involves local positive feedback

To account for the focal nature of plaque growth, the primary pathogenic mechanism likely involves local positive feedback between the damage caused by extracellular amyloid and the intracellular production of amyloidogenic proteins. Of the mechanisms considered (Fig. 2), only the production and release of amyloid from dystrophic neurites due to dysfunctional mitophagy appears to fully satisfy this condition. In this scenario, the neuritic plaque is generated by a chain reaction of pathology in a local region of the neuropil, as proposed by Wisniewski and Terry [283], Stokin and Goldstein [226], and others. Rupture of an amyloid-laden swelling would expose neighboring healthy axons to the toxic effects of amyloid, disrupt microtubule-based transport, and cause them to become dystrophic. Such a process would explain why dystrophic neurites are clustered tightly together in plaques [18, 259].

Studies of neuritic plaques in transgenic mice reveal that both human and mouse Aβ is present, with human Aβ concentrated in amyloid cores due to the fibrillogenic transgenes and wild-type mouse Aβ concentrated more in the dystrophic neurites [253], consistent with extracellular amyloid causing swellings and Aβ production in neighboring axons. The rapid formation of neuritic plaques in just a few days, as observed by in vivo imaging studies of transgenic mice [71], indicates that a positive feedback mechanism is responsible for plaque formation. Moreover, the swelling of neurites in plaques recovers just as rapidly upon removal of extracellular amyloid [19, 71, 206], consistent with a restoration of axonal transport.

Intracellular amyloid accumulation

The implication is that dystrophic axons with localized accumulations of APP precede amyloid plaques, as observed [227]. However, as mentioned above, intraneuronal aggregations of Aβ in somata and axon initial segments also precede extracellular Aβ deposition [169]. What is the relationship between the Aβ formed in dystrophic neurites to that accumulating in the somata of neurons? One possibility is that neuronal cell bodies endocytose Aβ that has been released from nearby dystrophic axons. This is consistent with data showing that the intrasomal Aβ accumulation is cleared after immunotherapy removes extracellular deposits [172].

Another possibility is that intracellular Aβ production in dystrophic neurites contributes directly to accumulation in the cell body, by the retrograde transportation of autophagosomes formed in dystrophic neurites [297]. Such an explanation is more parsimonious than supposing that lysosomes migrate from somata to distal dystrophic neurites. This possibility is also supported by electron microscopic evidence that the clusters of lamellar bodies, normally found in axonal dystrophies where normal microtubule-based transport is disrupted, are also occasionally found nearby in the non-dystrophic part of the axon where retrograde transport is possible (e.g. Fig. 2b of [63]). Another interpretation of the finding that immunotherapy clears both plaques and intraneuronal Aβ [172], would be that removal of extracellular amyloid allows the recovery of dystrophic neurites (as shown in [19]) and so removes the intracellular source of Aβ from the lysosomal pathway.

Role of glia in plaque pathogenesis

The progressive deposition of amyloid from dystrophic neurites would activate glia to migrate into the developing plaque. As plaques accumulate extracellular amyloid, microglia invade the amyloid deposit and perhaps facilitate its compaction into a central mass by removing cellular debris. A plaque may stop growing when neighboring neurites are no longer easily disrupted by exposure to amyloid, due to enclosure of amyloid by glia and reduced exposure of healthy neurites to amyloid protofibrils. Amyloid plaques appear to be remarkably stable once mature [12, 36, 101, 145].

Astrocytes may participate in the removal of amyloid plaques, as evidenced by plaque-like regions of gliosis, 40–100 μm in diameter, with little extracellular amyloid and few dystrophic neurites. These “remnant” or “vanishing” plaques as they are sometimes called, are composed of numerous astrocytes with intracellular granules of Aβ immunoreactivity [68, 243, 246, 290]. They appear to be the final resolution of cored plaques because their density increases with disease duration in Alzheimer’s disease [175]. Because astrocytes accumulate Aβ in this manner during advanced stages of amyloid pathology, it has been further suggested that these Aβ-laden astrocytes might serve as secondary niduses for plaque formation by cell lysis [164, 165].

Relationship of dystrophic neurites to non-amyloid deposits

Each dystrophic neurite may experience a unique life history that depends, in part, on the accumulation and processing of amyloidogenic proteins. Many axons may swell but remain intact, while others may generate highly disruptive aggregates of Aβ. Dystrophic neurites accumulating

non-fibrillogenic, but relatively insoluble, fragments of Aβ, may disgorge their contents without triggering additional neuritic degeneration, glial activation, or plaque growth. For example, a type of deposit known as a "cotton–wool plaque" is associated with particular presenilin-1 mutations that predispose neurons to produce amino-terminal truncated fragments of Aβ [128, 225]. Accumulations of amino-terminal truncated forms of Aβ have been seen in single dystrophic neurites scattered throughout the neuropil in Alzheimer's disease [90], substantiating the idea that particular types of dystrophic neurites are niduses of non-amyloid deposits.

Relevance to other brain amyloid pathologies

Remarkably, the above synthesis appears to also account for the formation of amyloid plaques by the proteins involved in prion disease and in the familial British and Danish dementias. Like APP, prion protein is trafficked along the axon and accumulates in dystrophic neurites along with mitochondria and APP [16, 61, 140, 173]. The amyloidogenic proteins in familial British and Danish dementias show similar properties, including fast axonal transportation [35] and accumulation in dystrophic neurites [1]. Like Aβ protein, multimers of these other proteins are also toxic to neurons, possibly by acting as calcium ionophores that disrupt microtubules [57, 168]. Thus, amyloid plaques in a variety of diseases may be produced by dystrophic axons that accumulate amyloidogenic protein. This common mechanism of pathogenesis is supported by data showing that the different types of amyloidogenic proteins are often deposited together in plaques [61, 83, 159, 208, 249].

Amyloidogenic proteins subject to axonal trafficking may also be contributors to cerebral amyloid angiopathy. Axons appear to play a role in delivering the amyloid protein that leads to angiopathy, as mentioned above [25]. Whether some type of axonal secretion is involved remains unclear, but dystrophic swellings are found adjacent to the perivascular amyloid [25]. Amyloid angiopathy is also found in leptomeningeal vessels outside of the neuropil, which is much less likely to have a direct neuronal origin. Non-neuronal hypotheses for amyloid angiopathy include diffusion of Aβ along perivascular drainage pathways [274], microglial or smooth muscle production of amyloid [271, 272], and few others [23].

Conclusions

Amyloid deposits in the brain may be produced through multiple mechanisms (Fig. 2), but recent data support the intuitions of the early ultrastructural investigators that degenerating mitochondria in dystrophic axons are significant contributors to amyloid pathology. Rupture of a dystrophic neurite that contains amyloid protofibrils may seed a neuritic plaque, particularly when this occurs in a region dense with unmyelinated axons susceptible to further disruption by the deposited amyloid. Of course, secreted soluble Aβ might contribute to further plaque growth once a plaque is seeded [60], and some plaques may be seeded by lysis of cell bodies or other mechanisms. Further investigations into the processes of degeneration in dystrophic axons across the full spectrum of conditions exhibiting amyloid pathology are needed to fully explicate the role of this common aspect in the development and progression of disease.

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