Short Conceptual Overview

Niclas Solin*

Amyloid-like fibrils labeled with magnetic nanoparticles

Abstract: A number of human diseases are associated with the formation of insoluble protein aggregates commonly known as amyloid fibrils or amyloid plaques. Similar materials can be prepared *in vitro* resulting in so-called amyloid-like fibrils. Herein is discussed how to prepare such fibrils labeled with magnetic nanoparticles. Such materials have the potential to be used as magnetic probes for magnetic resonance imaging applications.

Keywords: amyloid; magnetic nanoparticles; magnetic resonance imaging; protein.

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Introduction

A number of human diseases are associated with the formation of insoluble protein aggregates commonly known as amyloid fibrils or amyloid plaques (1–3). In all these diseases a normally soluble protein undergoes conformational change followed by aggregation into insoluble fibrils, which gradually accumulate in a variety of organs and tissues. Such fibrils are associated with a number of degenerative diseases including Alzheimer's, Parkinson's and Huntington's diseases (4), as well as various types of amyloidosis (5). Generally, two types of processes are responsible for the formation of amyloid fibrils *in vivo*; one is related to genetic disorders that introduces amino acid residues that destabilizes the native state of a globular protein, making the protein more prone to aggregation; in the other process, a high protein concentration, resulting from overexpression of the protein or dysfunction of the protein breakdown mechanism, enables nucleation and subsequent fibril formation. High protein concentration can also result from external causes as is demonstrated by dialysis related amyloidosis, where a high concentration of β_2-microglobulin leads to deposition of amyloid fibrils (6). Moreover, amyloid fibril deposits have been observed in patients with type II diabetes as well as after insulin infusion and repeated injection (7, 8). It has been demonstrated that material isolated from amyloid plaques can be infectious (9). For example, in animal studies it has been shown that material from isolated amyloid β plaques induce formation of amyloid deposits (10). Interestingly, synthetic amyloid β peptide did not induce plaque formation (10). Moreover, it has been demonstrated that amyloidosis is transmissible (11), and that even synthetic amyloid-like peptides can shorten the lag phase for amyloidosis in mice, when the synthetic peptide was given intravenously at the time of inflammatory induction with silver nitrate (12). These findings are of high relevance as it has been shown that foods, such as foie gras may contain amyloid materials (13). Moreover, it has been demonstrated that ovalbumin may form amyloid-like fibrils under food processing conditions (14). It is thus likely that in our natural and cultural environment we are surrounded by and probably ingest and inhale many different protein assemblies, which may act as a trigger for amyloid fibril formation in a susceptible individual (11). It should be pointed out, however, that currently little is known about these effects in humans.

It should be noted that cases where amyloid structures have beneficial properties for their host organism are known, and a wide variety of organisms, including mammals, employ the amyloid structural motif for constructive purposes ranging from pigment synthesis to secretion of material with the purpose of scaring off predators (1, 15–18). Misfolded proteins formed *in vivo* can thus have both detrimental and beneficial properties for their host organisms.

It is well known that proteins forming amyloid plaques *in vivo* will under appropriate conditions undergo aggregation processes *in vitro* resulting in structures commonly called amyloid-like fibrils. This opens up the possibility of probing the aggregation process in more detail than is possible *in vivo*. It is thus well established that the aggregation process involves a conformational change of the protein. In aqueous solvent, globular proteins

adopt a well-defined three dimensional structure – the native state. As a general rule, in the native state hydrophobic amino acid residues will be buried in the protein interior, whereas the surface is preferentially covered by hydrophilic residues. Moreover, conformational constrains and hydrogen bonding favors the formation of secondary structural elements α-helices, β-strands, and reverse turns. Under denaturating conditions *in vitro* – for example, high temperature or acidic pH – the native state becomes unstable, and the protein will unfold, resulting in the rearrangement of the protein into conformations other than the native state. If this alternative conformation contains β-strands the protein may aggregate into fiber-like geometries known as amyloid-like fibrils when formed *in vitro* (1–3). These fibrils consist of polypeptide chains forming cross β-sheets, with peptide strands oriented perpendicularly to the fiber axis (1–3). Fibrils have typical diameters of approximately 10 nm and lengths in the micrometer range. The interactions mainly responsible for the aggregation of proteins into fibrils are hydrogen bonding between β-strands as well as hydrophobic interactions (3).

It is well established that amyloid fibril formation shows characteristics of a nucleated growth mechanism, with an initial lag phase followed by a rapid exponential growth phase (1–3, 19). However, the actual mechanism whereby the soluble protein is converted into amyloid-like aggregates is highly complex. A general finding in agreement with a nucleation mechanism is that the addition of preformed amyloid material to a protein solution generally leads to a shortening of the lag phase (1–3). The capacity of globular proteins to form amyloid related structures is believed to be widely spread among proteins (1–3).

Apart from enabling mechanistic studies of protein aggregation, protein aggregation processes *in vitro* are a convenient way to form protein nanowires that have a range of valuable properties, such as high mechanical strength and attractive templating and gelation properties. Protein fibrils are therefore being considered for various applications, for example, in nanotechnology (20, 21), drug delivery (22), or foods (23). Owing to the adverse effects amyloid structures might have, especially when considering that such materials could function as seeds for amyloid formation *in vivo*, it is important to understand the fate of such aggregates *in vivo*. One appealing way would be to use magnetic resonance imaging (MRI), for example, using magnetically labeled amyloid materials prepared *in vitro*. MRI is an appealing technique due to its non-invasive nature and imaging depth and high spatial resolution. Nanoparticles are currently being evaluated as tools for increased contrast enhancement (24–26). MRI of amyloid plaques in the brain is currently heavily investigated (27–31) and attempts have been made to image conditions related to various amyloidosis diseases (32–35). Owing to the possibility of human exposure to various amyloid-like materials, it would be valuable to study the behavior of such materials in animal studies, in order to increase our understanding of the fate of such materials *in vivo*. Such research could benefit from the use of magnetically labeled amyloid materials combined with MRI. In this overview, we will discuss recent developments in the preparation of amyloid-like fibrils labeled with magnetic nanoparticles. This labeling will be called functionalization. Characterization of amyloid materials is traditionally done with a variety of organic molecules such as congo red and thioflavin T (1). Moreover, various thiophene-based probes show high promise as probes for the presence of amyloid materials (36). These molecules have the common feature of a linear shape that enables favorable interactions with the grooves of the pleated β-sheet present in fibrils. Much less is known regarding functionalization of proteins with nanoparticles (37). Much focus has been on studies regarding the influence of nanoparticles on amyloid formation kinetics (38–47). The influence of nanoparticles on amyloid formation kinetics is complex (37–42). Many amyloidogenic proteins interact strongly with surfaces. Accordingly, nanoparticles, which have large surface to volume ratios, are efficient at interacting with such proteins (37). Various nanoparticles have been shown to promote aggregation of proteins into amyloid fibrils (40, 41); other nanoparticles have been shown to inhibit amyloid formation (43); and other nanoparticles do not significantly influence fibrillation kinetics (44, 46). Any observations may be generally rationalized in terms of competing phenomena. Thus, interaction between a protein and nanoparticles will lead to a decrease in concentration of the protein, which slows down or inhibits fibril formation. However, interaction with nanoparticles may also induce conformational changes in proteins, which may lead to an acceleration of protein aggregation (37, 42).

In this short overview, we will focus on composites between amyloid-like fibrils and magnetic iron oxide nanoparticles. Such nanoparticles can be prepared from readily available precursors; moreover, a wide variety of iron oxide nanoparticles are commercially available. A schematic drawing illustrating different approaches for functionalizing amyloids with nanoparticles is shown in Figure 1. Most studies focus on the use of water-soluble iron oxide nanoparticles. By preparing nanoparticles that will interact strongly with amyloid materials, this approach enables the preparation of novel composites between

protein fibrils and magnetic nanoparticles. However, a challenging aspect for amyloid detection based on magnetic nanoparticles is to design nanoparticles that will bind to the amyloid structural motif selectively in the presence of other bioanalytes. By contrast, if this challenge is met, this method will provide a powerful means to image amyloid structures *in vivo*. An alternative approach is to functionalize the protein with nanoparticles prior to fibril formation, thereby enabling monitoring of the aggregation process of the protein by magnetic probes. Thus, this overview will be divided into two sections depending on the method of preparation of the amyloid-nanoparticle material: one section focuses on the functionalization of preformed amyloid-like fibrils by water-soluble nanoparticles, this section also discusses fibrillation in the presence of water-soluble nanoparticles; the other section focuses on other functionalization methods, where the protein is functionalized prior to fibril formation. These different methods are illustrated schematically in Figure 1.

Functionalization with water-soluble nanoparticles

Mahmoudi and co-workers investigated the effect of surface coating of iron oxide nanoparticles on amyloid β aggregation kinetics (42). Interestingly, they found that whereas lower concentrations of nanoparticles inhibited fibrillation, a higher concentration increased the rate of fibrillation. Moreover, they found that positively charged nanoparticles promoted fibrillation to a higher degree than negatively charged particles (42). Transmission electron microscopy (TEM) images demonstrate that amyloid-like fibrils are stained by nanoparticles. Bellova and co-workers investigated the effect of electrostatically stabilized Fe_3O_4 nanoparticles on the fibrillation of hen egg lysozyme and found that nanoparticles inhibit amyloid formation, and that they even could disassemble already formed fibrils (43).

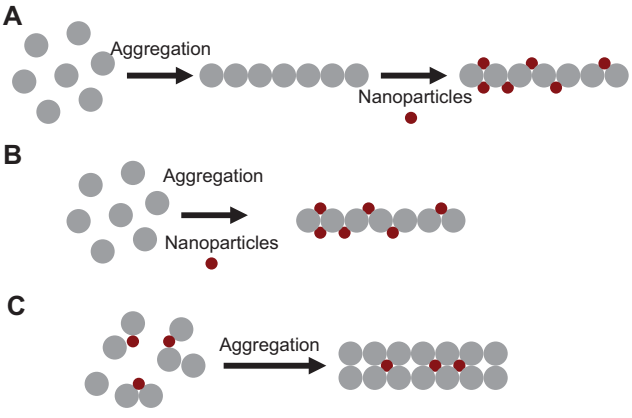

Figure 1 Schematic drawing of different methods for preparation of functionalized amyloid-like fibrils.
(A) Amyloid-like fibrils are formed and then functionalized with nanoparticles. (B) Protein and nanoparticles are mixed and the protein aggregates in the presence of nanoparticles. (C) The protein and hydrophobic nanoparticles are mixed prior to dissolving the materials. Owing to the hydrophobic effect, the material stays together during protein aggregation and forms an amyloid-like material incorporating nanoparticles.

The interaction between maghemite iron oxide nanoparticles and amyloid fibrils, as well as the influence of iron oxide nanoparticles on protein aggregation was investigated by Skaat and co-workers (44). Human insulin amyloid-like fibrils were prepared by heating protein at 65°C at pH 1.6. The resulting fibrils were then treated with magnetic nanoparticles, which resulted in efficient coverage of fibrils by nanoparticles. The authors also investigated the effect of nanoparticles on fibrillation kinetics and showed that no significant influence on fibrillation kinetics was obtained. The interaction of preformed fibrils and iron oxide nanoparticles was demonstrated by TEM images. Moreover, the authors demonstrated by cryo-TEM that the aggregate between fibers and nanoparticles exist in solution and is not an artifact from drying of the sample on the TEM grid. The authors demonstrated the magnetic separation of such magnetically labeled materials by magnetic fields. Skaat and co-workers also prepared fluorinated core shell iron oxide nanoparticles and found that these particles slowed down fibrillation kinetics of insulin (45). Moreover, Skaat and co-workers have prepared fluorescent maghemite nanoparticles (due to the inclusion of fluorescent dyes in nanoparticles), which were used as multimodal imaging agents for detection of amyloid β aggregation (46). Again, it was found that nanoparticles have no effect on the kinetics of amyloid β aggregation. The nanoparticles stained amyloid-like fibrils efficiently as demonstrated by TEM images and fluorescence microscopy. Examples are shown in Figure 2.

For imaging applications where the magnetically labeled amyloid-like fibrils are to be used as models that allow monitoring of amyloid materials, it is desirable to have strong non-reversible interactions between nanoparticles and amyloid-like fibrils. Otherwise, nanoparticles may dissociate from the amyloid structure, resulting in non-labeled materials. Therefore, it is appealing to prepare structures where amyloidogenic proteins or the corresponding antibodies are conjugated to nanoparticles. For example, Skaat and co-workers have prepared

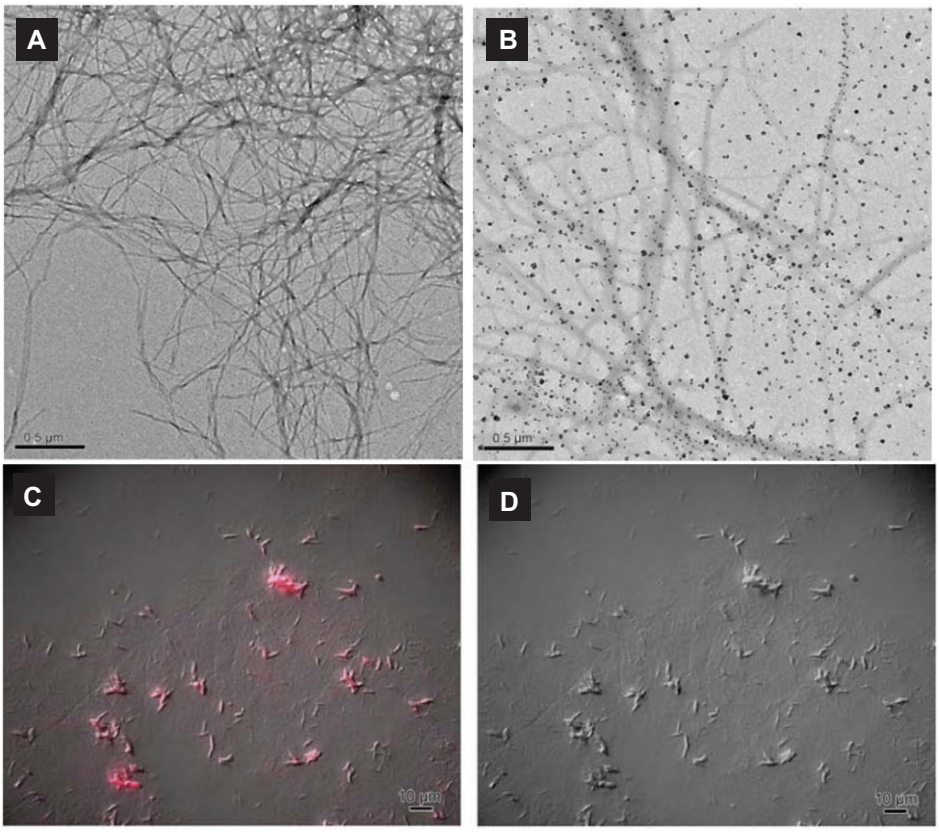

Figure 2 TEM and fluorescence microscopy images of amyloid-like fibrils labeled with fluorescent magnetic nanoparticles. (A) TEM image of amyloid β fibrils. (B) TEM image of amyloid β fibrils stained with magnetic nanoparticles. (C) Fluorescence microscope image of fibrils stained with multimodal nanoparticles. (D) Corresponding microscope image. Reproduced, with permission from Elsevier, from (46).

fluorescently labeled iron oxide nanoparticles conjugated to amyloid β (47). They investigated the influence of such nanoparticles on the aggregation of amyloid β and found that nanoparticles accelerate fibril formation. The resulting aggregates were characterized by TEM and fluorescence microscopy, demonstrating the formation of amyloid materials incorporating nanoparticles. By attaching a short peptide sequence, corresponding to a hydrophobic domain in amyloid β, to the nanoparticles, they could slow down amyloid formation. Again, these reported materials may enable monitoring of protein aggregates or protein aggregation *in vivo* by MRI. In a study by Wadghiri and co-workers, amyloid β was conjugated to iron oxide nanoparticles (48). The authors could use these nanoparticles to image amyloid plaques by means of μMRI. Moreover, Sillerud and co-workers could show that conjugation of an anti-amyloid β antibody to iron oxide nanoparticles enabled binding of nanoparticles and contrast enhanced imaging of Alzheimer's amyloid plaques (49).

Functionalization with hydrophobic nanoparticles

Another method to prepare proteins functionalized with nanoparticles is to employ hydrophobic nanoparticles capped with alkyl chains such as oleic acid (50). The combination of such materials with hydrophilic proteins seems problematic due to the orthogonal solubility of nanoparticles and proteins. Globular proteins are, of course, hydrophilic and soluble in aqueous media; by contrast, hydrophobic nanoparticles are naturally insoluble in aqueous media. However, this orthogonal solubility can be turned to an advantage by utilizing a mechanochemical approach (50, 51). By mixing the proteins and hydrophobic material in solid form, prior to addition of solvent, a composite material can be formed. When dissolved in aqueous acid and heated, this material still assembled into amyloid-like structures (50). Owing to the hydrophobic effect, the hydrophobic material remains associated with protein

molecules throughout the aggregation process, thereby ending up associated with amyloid-like structures. To prepare insulin fibrils incorporating iron oxide nanoparticles, bovine insulin was mixed with a toluene solution of iron oxide nanoparticles, and the mixture was gently ground while the toluene evaporated. This was followed by grinding for an additional 5 min. Upon addition of 25 mM HCl, a rust-colored solution was obtained that formed fibrillar materials when heated. The functionalization method is extremely facile; however, a drawback is an irregular distribution of the nanoparticles in the resulting protein materials. In Figure 3A is shown a TEM image of a sample not fibrillated, which shows an irregular distribution of protein and nanoparticles. By contrast, the TEM image of the heated sample (Figure 3B) shows fibrillar material, with an irregular distribution of nanoparticles within the fibers. The fibers have an unusually wide diameter and seem to display a high degree of branching. However, the fibrils can be stained by thioflavin T, which demonstrates their amyloid character. The materials were also characterized by electron tomography, which demonstrated the location of the nanoparticles within the protein fibrils (Figure 3C, D).

For the utilization of these materials for MRI applications, it is important to know their magnetic relaxation properties. Accordingly, the resulting materials were investigated regarding magnetic resonance properties. These measurements demonstrated that relaxation time is influenced by the protein aggregation state. Thus, a comparison of the relaxation times for non-aggregated and aggregated solutions showed that transverse relaxivity r_2 increased from 52 s/mM to 152.4 s/mM, whereas longitudinal relaxivity r_1 remained largely unaffected (50).

Owing to the facile preparative method, it should be possible to prepare amyloid-like materials labeled with, for example, both magnetic nanoparticles and fluorescent molecules, by combining the two approaches demonstrated in Refs. (50) and (51).

Summary and outlook

There has been a growing interest in developing methods to visualize amyloid plaques *in vivo* in mice by MRI, using methods that could eventually be applied to humans

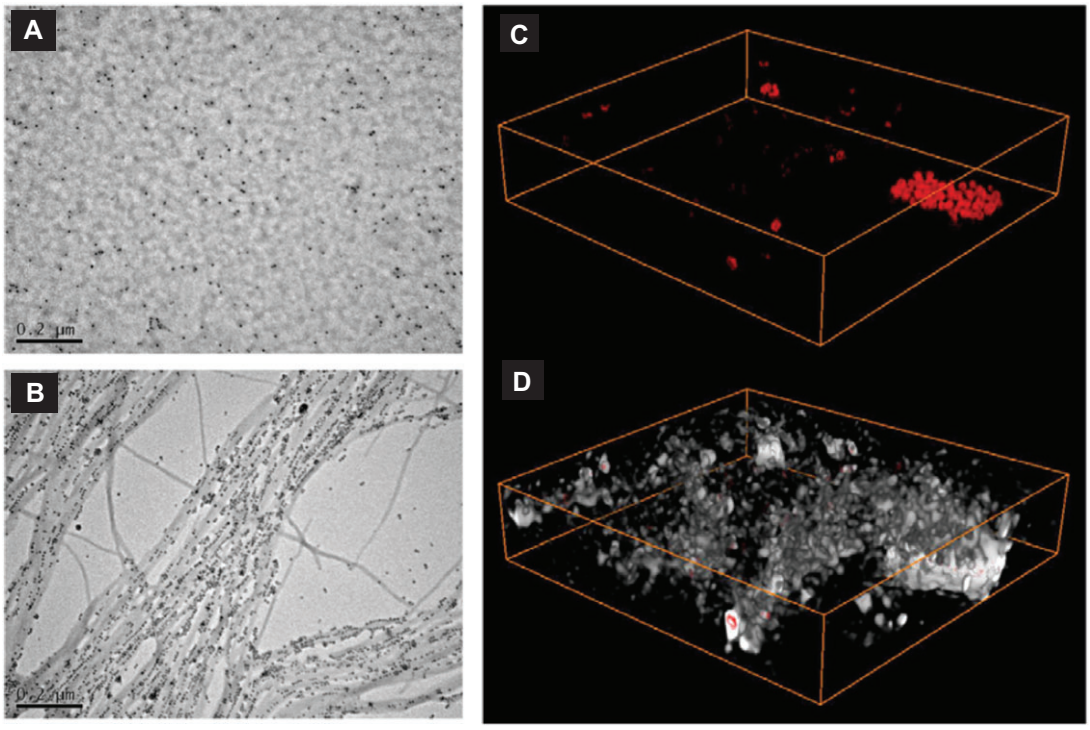

Figure 3 TEM and electron tomography images of investigated materials.
(A) TEM image of a non-fibrillated sample of bovine insulin grinded with iron oxide. (B) Corresponding image of the fibrillated material. (C) Electron tomography image of high contrast area (imaged in red), corresponding to nanoparticles. (D) Electron tomography image with a lower contrast threshold, showing protein material in gray. The image in (C) is overlaid, demonstrating that the nanoparticles are residing within the protein material. Reproduced, with permission from Elsevier, from (50).

(48). MRI has a high spatial resolution which may allow for detection of early stages of amyloid deposition, which would enable early diagnosis and treatment. It is thus of great interest to prepare magnetic probes such as magnetic nanoparticles for amyloid detection. A variety of methods exist to prepare amyloid-like materials labeled with magnetic nanoparticles. One method involves the use of water-soluble nanoparticles that interact with amyloidogenic proteins or protein aggregates. Such nanoparticles are appealing to use as magnetic probes for the presence of amyloid plaques, which could in principle enable efficient MRI of amyloid deposits *in vivo*. However, at present it is challenging to achieve selective binding of magnetic nanoparticles to amyloid plaques in a biological setting. If magnetic nanoparticles coated with substituents that enable selective binding to amyloid plaques can be developed, this technique would be appealing for diagnosis of amyloid plaques by MRI (48). By contrast, with magnetic nanoparticles discussed in this overview such selective interactions between amyloid plaques and magnetic nanoparticles are difficult to achieve. Therefore, an alternative approach is to use amyloid-like materials prelabeled with magnetic nanoparticles that can be used for mechanistic studies. Assuming that the magnetically labeled amyloid-like structures have similar properties to non-labeled amyloid materials, such studies can provide information on the fate of amyloid structures *in vivo*, using non-invasive MRI. For example, labeled material could be used in animal studies providing information on the fate of ingested amyloid materials (13). Magnetic nanoparticles covalently attached to amyloid-like structures are suitable for such applications. Another example of a suitable material is amyloid-like fibrils labeled with hydrophobic nanoparticles (50). Such materials are readily prepared from commercially available starting materials and are thus efficient to use for proteins available in large quantities.

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