

CELL SURFACE AMYLOID PROTEINS OF MICROORGANISMS: STRUCTURE, PROPERTIES AND SIGNIFICANCE IN MEDICINE

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This review summarizes data which describe properties of microbial cell surface amyloids proteins. Definitions of amyloids and microbial functional amyloids are given. The review provides numerous examples of research in which the presence of amyloid-like properties in microbial cell surface proteins is demonstrated convincingly. Studies of the important role of pili, curli, tafi and some other bacterial fibrillar proteins in host colonization are reviewed. Data on amyloid proteins of yeast cell surface, their properties and potential association with candidiasis development are summarized. This review also appeals to experts in biology and medicine in an attempt to draw their attention to the issue which is increasingly discussed in scientific work at present, namely to a possible role of bacterial extracellular matrix amyloids and amyloid proteins of eukaryotic microorganism surface, yeast in the first place, in the development of amyloidosis in animals and humans.

Keywords: microbial cell surface, microbial amyloid, functional amyloid, pili, curli, tafi, phenol soluble modulin, adhesin, class I hydrophobin, amyloidosis

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АМИЛОИДНЫЕ БЕЛКИ ПОВЕРХНОСТИ МИКРООРГАНИЗМОВ: СТРУКТУРА, СВОЙСТВА И ЗНАЧЕНИЕ ДЛЯ МЕДИЦИНЫ

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В обзоре суммированы данные, посвященные описанию свойств амилоидных белков поверхности клеток микроорганизмов. Определены понятия «амилоид» и «функциональный амилоид» микроорганизмов. Приведены многочисленные примеры исследований, в которых убедительно показано наличие амилоидных свойств у белков клеточной поверхности микроорганизмов. Рассмотрены работы, демонстрирующие важную роль пилей, курлей, тафи и некоторых других фибриллярных белков бактерий в колонизации организма хозяина. Обобщены данные об амилоидных белках поверхности клеток дрожжей, их свойствах и возможной роли в развитии кандидозов. Обзор также призван привлечь внимание специалистов в области медицины и биологии ко все более активно обсуждаемому в литературе вопросу о возможном участии амилоидов внеклеточного матрикса бактерий, а также амилоидных белков поверхности эукариотических микроорганизмов, в первую очередь дрожжей, в развитии амилоидозов животных и человека.

Ключевые слова: клеточная поверхность микроорганизмов, амилоид микроорганизмов, функциональный амилоид, пили, курли, тафи, фенол-растворимый модулин, адгезин, гидрофобин класса I, амилоидоз

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The human microbiome is composed of an average of 10^{14} microbial cells [1], many of which have amyloid proteins on their surfaces. Some recent studies have lead us to hypothesize that the presence of those amyloids can contribute to the onset and development of many diseases such as systemic amyloidoses

in higher animals and humans, tuberculosis and Alzheimer's disease [2–6].

From a medical perspective, the analysis and deep understanding of processes and molecular mechanisms underlying the assembly of amyloid structures in pro- and

eukaryote microorganisms offer broad opportunities. In the first place, the above-said refers to the elaboration of protection strategies against the negative impact of amyloids on humans and animals. It is important to understand how to most effectively prevent the formation of bacterial biofilms by pathogenic microorganisms or destroy those already formed, and to mitigate the effect of amyloid formation in animals and humans caused by exposure to microbial amyloids.

Amyloids are protein fibrils with cross- β -structure. Composed of monomers, they are β -sheets in which parallel or antiparallel β -strands run perpendicular to the fiber axis. The distance between the neighboring strands inside a β -sheet is 0.47 nm; the one between the neighboring β -sheets is 0.8 to 1.2 nm [7, 8]. Hydrogen bonding between peptide backbones of neighboring strands has an important role in stabilizing the structure of amyloid fibrils. Interactions between lateral groups of amino acid residues of neighboring polypeptides, such as hydrogen bonding, ionic and hydrophobic interactions, and stacking interactions, also contribute to the stabilization of the amyloid structure. High resistance to the fluctuations of such environmental parameters as hydrophobicity, salt concentration, pH, temperature, pressure, exposure to denaturing agents and proteinases is characteristic of amyloids, which is determined by a large number of interactions involved in stabilizing their structure [2, 9–12].

Because amyloids cause many widely spread incurable diseases (the amyloidoses), they have long been actively explored in humans and animals. Pili (from Latin *pilus* — a hair) were described in the middle of the 20th century in gram-negative and gram-positive bacteria [13]. However, it has been discovered recently that many structures on microbial surfaces are amyloid fibrils. By now, curli (from English a *curl*) or tafi (thin aggregative fimbriae) have been described in such bacteria genera as *Escherichia*, *Neisseria*, *Yersinia*, *Shigella* and *Salmonella* [2, 3, 10, 11, 14–17]. Pili have been described in *Streptococcus* genus, specifically, in *Streptococcus agalactiae*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*, in *Mycobacterium tuberculosis* and other gram-positive bacteria. The assembly mechanisms of these structures and their role in host colonization have been described in sufficient detail [13].

It is well known that amyloids, specifically the so-called class I hydrophobins, are present on the surface of filamentous fungi, such as *Aspergillus fumigatus* [18]. Amyloids are found in microorganisms among structural molecules, adhesins and toxins. Along with the structures mentioned above, a growing list of already described amyloids includes phenol-soluble modulins of *Staphylococcus aureus* [12, 19], adhesins of *Candida albicans* [20, 21], and amyloids formed by TasA protein in *Bacillus subtilis* [22–24].

In the course of study of microbial surface amyloid proteins, the term “functional amyloids” was coined [25]; functional amyloids are amyloid-forming proteins that are not associated with pathologies in microorganisms and perform functions useful for microbial cells. A number of published works have demonstrated that the formation of functional amyloids is possible not just in microorganisms; a supposition has been made that they exist in all domains of the living world and participate in various processes, from biofilm formation in microbial communities to long-term memory regulation in animals [7]. This review will look at some examples of how amyloid proteins of microbial surfaces contribute to the development of diseases in animals and humans, and present some data characterizing the structure of these amyloids and the conditions under which they are formed.

Amyloids participating in the formation of bacterial extracellular matrix

Curli and tafi are the main protein components necessary for the extracellular matrix formation. They are present on the surface of many gram-negative bacteria, including a number of strains of *Escherichia coli*, *Salmonella spp.* and other *Enterobacteriaceae* [10, 11, 14–17]. *E. coli* curli bind to many human proteins, including fibronectin, laminin, type I collagen, major histocompatibility complex class I molecules, plasminogen and some others [26–29], and contribute to pathogenesis facilitating further microbial invasion of the host. [14, 30–32]. Curli are fibrillar structures attached to the bacterial outer membrane at one end. They can be up to several micrometers long and 3 to 4 nm wide. Curli tend to aggregate laterally by forming clusters up to 60 nm in diameter [33]. Curli fibrils are highly resistant to denaturing agents and proteinases but can be depolymerized after the short-term treatment with concentrated formic acid [10, 11, 34]. The data from circular dichroism spectroscopy indicate that the secondary structure of curli fibrils is rich in β -sheets [11]; curli fibrils also interact with amyloid-specific dyes, namely, congo red (CR) and thioflavin T (TT) [11, 27]. This information makes it possible to classify curli as amyloid fibrils [11].

Curli are necessary for bacterial biofilm formation and are the major protein component of the extracellular matrix formed along [33, 35]. It has been shown that curli genes are best expressed at temperatures below 30 °C, low concentration of nutrients, low osmolality and at the stationary growth phase, i.e. under the conditions that *E. coli* and other *Enterobacteriaceae* encounter outside the host. Under such conditions biofilm formation can contribute to bacteria survival [33]. Curli mediate the attachment of bacteria to various surfaces, including plant cells [36, 37], stainless steel [38], glass and plastic [33], and can considerably enhance microbial cell resistance to chlorine [38] and mercuric compounds [39].

Curli assembly is a process strictly regulated by the cell [14, 40]; it involves proteins encoded by at least two operons: *csgABC* and *csgDEFG* in *E. coli* [41]. Curli consist of two homologous proteins, namely, CsgA and CsgB, the main structural component of fibrils being CsgA protein [27]. Purified CsgA forms amyloid fibrils *in vitro* in the absence of other proteins. However, their β -strands are arranged into β -spirals instead of β -sheets. *In vivo* the presence of CsgB is necessary for CsgA amyloid fibril assembly [11, 27, 42]. CsgA secreted by a *csgB* deletion mutant of *E. coli* can polymerize on the surface of CsgB producing cells [11, 14, 27]. This phenomenon is called interbacterial complementation and is widely used in mutation studies aimed at detecting protein genes participating in curli formation [11, 43]. Interbacterial complementation proves that CsgB is a nucleating agent for CsgA polymerization [11].

The majority of CsgBs are localized on the bacterial surface, which indicates that the supposition of CsgB nucleating function is accurate [44]. CsgF provides the proper folding and localization of CsgB nucleator protein and is probably a chaperon-like protein [43]. CsgE periplasmic protein is likely to participate in CsgA secretion and inhibit CsgA polymerization *in vitro* [45] due to the unmediated interaction between CsgE and CsgA molecules [46]. Thus, CsgE can be seen as a CsgA-specific chaperon. The evolving concept of the nucleation properties exhibited by microbial cell surface proteins in the course of amyloid formation allowed some authors to consider microbial-derived amyloid proteins as a real risk factor for amyloidoses and Alzheimer's disease development [47].

The majority of experiments on curli biogenesis and functions were carried out on *E. coli* and *Salmonella spp.* Curli homologues were discovered among the representatives of *Bacteroidetes*, *Firmicutes* and *Thermodesulfobacteria* genera by bioinformatic analysis [48]. *CsgEFG* operons were found in the majority of the bacteria mentioned above with potential CsgA and CsgB homologues, while CsgC and CsgD proteins were often absent. In spite of the fact that many bioinformatic assays are awaiting the experimental confirmation, there are grounds to suppose that structures similar to curli can be more widely spread in biofilm-forming bacteria than it was thought before [49].

Adhesin P1 located on the cell surface of *Streptococcus mutans* that causes dental caries is an amyloid protein [50]. This adhesin induced a shift in the CR dye absorption spectrum, green birefringence in the CR stained sample and a specific TT fluorescence. Using microscopic methods, fibrils were detected in the sample of this adhesin; this, coupled with spectrophotometric assay results, confirmed its amyloid nature [50]. The obtained data indicate that P1 is not the only protein of *S. mutans* cell surface capable of forming amyloids, because the colonies of the bacteria deprived of this adhesin still induced green birefringence after CR staining [50].

Mycobacterium tuberculosis pili are another example of how amyloids of microbial extracellular matrix can possibly contribute to pathology. This microorganism causes tuberculosis that leads to 3 million deaths every year worldwide [2]. Pili on gram-positive *M. tuberculosis* surfaces are not soluble in the chloroform/methanol mix (2:1) and in the sodium dodecyl sulfate-containing buffer (SDS); they also interact with amyloid-specific CR dye, which suggests their amyloid nature [2]. Pilus protein deletion mutants of *M. tuberculosis* exhibited reduced virulence [2]. The researchers explain that pili are capable of binding to laminin, the extracellular matrix protein, thus contributing to the firm adhesion of a microorganism to host tissues. Thus, *M. tuberculosis* uses these amyloid proteins to successfully colonize the host [2]. In the serum of patients with tuberculosis, high titers of antibodies interacting with *M. tuberculosis* pili are found. [2].

Other gram-negative microorganisms that can colonize different human organs and tissues, such as cocci *Staphylococcus aureus*, cause various diseases, from minor skin infections to bacteremia and sepsis. Many of these diseases are associated with biofilm formation in the host [20]. Extracellular amyloid fibrils have been identified in *S. aureus* biofilms. They consist of short peptides called phenol-soluble modulins (PSM) [12].

S. aureus or *S. epidermidis* PSMs have many functions [51–54]. It has been shown that in their fibrillar form PSMs are necessary for *S. aureus* to provide biofilm stability against various dispersing (biofilm degrading) agents and physical impact [12]. The authors of that work believe that the inhibition of phenol-soluble modulins export is a promising research area that can contribute to preventing diseases induced by pathogenic staphylococci. The search for minor molecules – amyloid polymerization inhibitors – is one of the ways that can lead to the development of drugs for staphylococci elimination on the stage of biofilm formation [49].

Bacillus subtilis pili are an important component of biofilm extracellular matrix formed by the bacteria on hard surfaces and at water–air interface [55]. This microorganism is not pathogenic, however, it is widely spread and can be found in soil, air, water and food. The main protein subunit of *B. subtilis* pili is TasA protein [22, 56]. Fibrils formed by TasA *in vitro* are very similar to *B. subtilis* pili morphologically [22]; at the same time

they interact with amyloid-specific dyes such as CR and TT, are rich in β -sheets, as suggested by CD-spectroscopy, and can be depolymerized only after the incubation in the presence of formic acid [22]. It should be noted that TasA was first identified as a secreted protein and a protein of *B. subtilis* spore surfaces with distinct antibacterial properties [57, 58]. Antibodies used in the diagnosis of neurodegenerative diseases recognize both metastable intermediates generated in the course of amyloid fibril formation and TasA oligomers, which suggests a possible structural similarity of these two oligomer types [22, 59, 60]. Antibodies used in the diagnosis of neurodegenerative diseases in humans recognize TasA oligomers [22, 59, 60], which suggests their immunological similarity.

Amyloids forming amphipathic membranes on microbial cell surfaces

Hyphae, spores and fruiting bodies of many fungi are covered with amphipathic (i.e., having both hydrophilic and hydrophobic areas) rodlet layers that form a mosaic of parallel fibrils 5 to 12 nm wide [18]. Those amphipathic layers do not dissolve when boiled in the presence of 2 % SDS and 1 M NaOH, and dissociate into monomers only when treated with formic or trifluoroacetic acids [9]. The main and probably the only component of fungal rodlet layers is class I hydrophobins [61, 62]. The polymerization of hydrophobins is most effective at interfaces with high surface tension, such as liquid-air interface; agents reducing surface tension also reduce the rate of hydrophobin polymerization *in vitro* [63].

Hydrophobins are a large family of low molecular weight proteins (7–9 kDa) found in fungi [61]. This family got its name due to being rich in hydrophobic amino acid residues [9]. Hydrophobin encoding genes are present in many fungi. Class I hydrophobins are typical functional amyloids because they have a role in spore and fruiting body formation; they are also important for adhesion to the host cell surface and protection against the host immune system [18, 64]. Thus, in the infection caused by filamentous fungi *Arthroderma benhamiae* (dermatophytes, i.e., surface mycosis pathogens in humans and animals), hydrophobin HypA has a masking function and protects the microorganism from the host immune system. Deletion of the hydrophobin gene leads to a rapid wetting of fungal filaments and conidia, which induces increased activation of granulocytes, neutrophils and dendritic cells and is accompanied by elevated titers of interleukins IL-6, -8, -10 and tumor necrosis factor TNF- α [65]. RodA hydrophobin, a component of the rodlet layer that covers pathogen spores, contributes to the development of the infection induced by another filament fungus *Aspergillus fumigatus* that can lead to invasive aspergillosis. In the experiments on animals the spores of the mutant strain with deleted RodA or $\Delta laeA$ mutant containing 60 % less hydrophobins, were susceptible to macrophage phagocytosis [66].

Amyloids as a part of yeast cell walls: adhesins and glucantransferase Bgl2p

The development of systemic amyloidosis in mice injected with *Candida sp.* lyophilized cells is well known, but is not widely discussed [67]. The authors of that article emphasized that amyloid depositions could occur in experimental animals as a response to casein, albumin, bacteria or *E. coli* endotoxin administration [68–71]; but after the injections had been cancelled, amyloid depositions started to reduce gradually or

disappeared. [72, 73]. Laboratory mice injected with *Candida sp.* lyophilized cells died of systemic amyloidosis within 400 days after the last injection [67]. Separate experiments showed that injecting mice with *Candida sp.* intracellular matter did not cause amyloidosis. The authors concluded that amyloidosis development was stimulated by cell walls components [67].

Bioinformatic analysis of *Saccharomyces cerevisiae* yeast proteome detected the abundance of amyloidogenic proteins in cell walls [74]. Als proteins (from *agglutinin-like sequence*) are the example of well described proteins of yeast cell surfaces with amyloid properties [20, 21, 75]. In *Candida albicans* genome eight ALS genes were detected, each of them encoding the protein that consists of a signal sequence necessary for the protein secretion, three tandem immunoglobulin (Ig)-like domains, a T-domain rich in threonine, a various number of 36-amino-acid-long glycosylated tandem repeats (TR), a highly glycosylated stem domain and a signal sequence of glycosylphosphatidylinositol anchor attachment protein that ensures protein covalent attachment to the cell wall glucan [76]. Ig-like domain ensures binding to a substrate; T-domain is necessary for proper folding of Ig-like domain and secretion TR increases affinity of Ig-like region to ligands and can promote yeast aggregation independent of Ig-like region. Due to the presence of stem domain, active regions are at a considerable distance from the stem wall [76].

In spite of the intense glycosylation, Als family proteins are low soluble and form amyloid fibrils even at low concentrations when purified [20]. The conformation of N-terminal regions of Als1p (Ig-fragment) and Als5p (Ig-T-fragment) proteins in a solution has been studied [76]. The obtained data indicated that in both cases β -sheets were prevailing elements of a secondary structure of the polypeptide of interest [76]. It was also shown that Als5p, Als1p and Als3p had a highly conserved potentially amyloidogenic region (PAR) in T-domain [20].

Interestingly, PARs were detected in amino acid sequences of both Als proteins and yeast adhesins of different families [75]. Peptides containing those PARs formed fibrils that interacted with amyloid-specific dyes, and according to the CD-spectroscopy assay had a secondary structure rich in β -sheets [75]. Amyloid formation is likely to be a very common phenomenon [75].

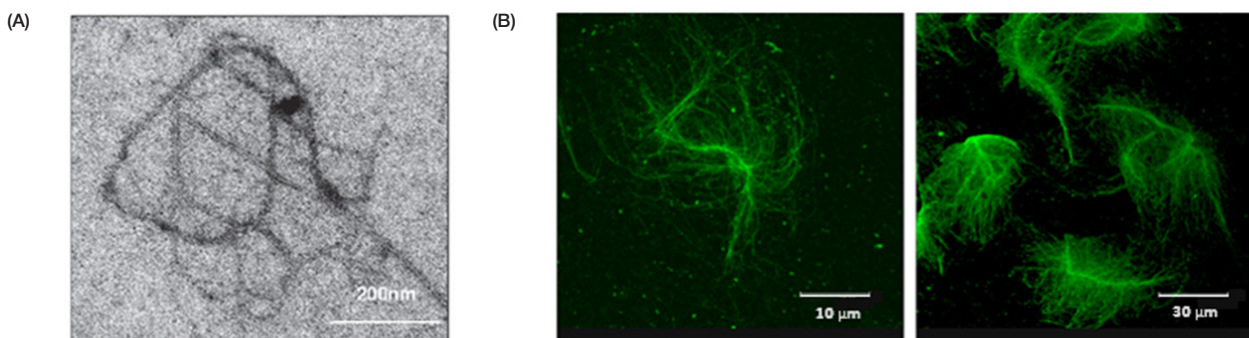
The opportunistic yeast pathogen *C. albicans* forms biofilms facilitating colonization of host tissues and making *C. albicans* cells extremely resistant to antimicrobial treatment [77, 78]. An important role in the pathogenesis and biofilm formation is played by Als-adhesins described above, along with many other adhesins produced by *C. albicans* [78, 79]. Some Als-

adhesins form amyloid structures [20, 21, 75], which probably contributes to *C. albicans* cell autoaggregation and *C. albicans* interaction with extracellular matrix proteins (fibronectin, laminin, type IV collagen) and other mammalian peptide ligands, cells of other yeast species and bacterial cells [76, 78]. The ability of *Candida sp.* to attach to the mucosal surfaces of different organs and to synthetic materials surfaces by means of surface adhesins is an important factor in the pathogenicity of these fungi that contributes to the development of the infection. This property is most conspicuous of *C. albicans* yeast [80, 81].

Glucantransferase Bgl2p is another protein of yeast cell wall (CW) exhibiting amyloid properties. It is a small (31.5-34 kDa depending on the yeast species) conserved major noncovalently bound protein. Its presence in the CW has been detected in many yeast species, such as *S. cerevisiae*, *C. albicans*, *A. fumigatus* [82–84]. Bgl2p of *S. cerevisiae* is highly homologous to Bgl2p of *C. albicans*. Antibodies against *S. cerevisiae* Bgl2p react with *C. albicans* Bgl2p [82, 85]. Bgl2p of the CW is resistant to trypsin and proteinase K and cannot be extracted from it when treated with 1% SDS solution in water at 37 °C, in contrast to other noncovalently bound polysaccharide backbone proteins of the CW [86].

Bgl2p extracted from *S. cerevisiae* CW can form structures with fibrillar morphology [86, 87] clearly seen in microscopic assays (see the figure below). Bgl2p protein extracted from the CW induced specific fluorescence of TT and exhibited a circular dichroism spectrum characteristic of a protein rich in β -structure [86, 88], which also indicated the amyloid nature of the structures formed by Bgl2p. The ability of Bgl2p to fibrillize at different pH values was also studied using isolated proteins and synthetic peptides with potential amyloidogenic determinants predicted in the Bgl2p sequence by a bioinformatic assay [87]. It was shown that Bgl2p extracted from the cell wall formed fibrils at neutral and mildly acidic pH values, while in mildly alkaline media it lost its ability to form amyloid fibrils [87]. The mechanism of Bgl2p formation in the cell wall and its physiological role in the functioning of yeast are yet to be discerned [89].

Presumably, Bgl2p has a crucial role in pathogenic yeast virulence, since BGL2 gene deletion reduces the infecting ability of those microorganisms [82]. Jang et al. found that *C. albicans* Bgl2p also functions as an adhesin and ensures cell attachment to the immobilized saliva components [85]. It was shown that antibodies to *C. albicans* Bgl2p are a diagnostic biomarker of systemic candidiasis, and their high levels correlate with the reduced death probability, which may be related to the protective function of these antibodies [90].



Photomicrograph of glucantransferase Bgl2p samples extracted from *Saccharomyces cerevisiae* yeast cells. (A) — electronic microscopy. Negative staining[86]. (B) — fluorescent microscopy. Staining with antibodies against Bgl2p [87]

CONCLUSIONS

When describing amyloid proteins of microbial surfaces, we did not review the articles dedicated to such amyloids as chaplins, microcins and harpins, because their role in human and animal pathogenesis has not yet been identified or studied. Still, the studies of the amyloid structures and formation mechanisms, which are actively carried out in a number of big research centers and laboratories in Russia and abroad, hold promise for important discoveries in this field. We think it necessary to pay close attention to the analysis of a possible role of

amyloids and other microbial cell surface components in the development of diseases with vague etiology. Microorganisms are abundant in the bodies of higher eukaryotes including humans. For many animals microorganisms are essential. The number of microbial cells can be significantly higher than the number of host cells [1]. Components of microbial cell surfaces including amyloid proteins are in permanent contact with host cells and liquids. One should not underestimate the potential role of these molecules, localized on the surface of both pro- and eukaryotic microorganisms, in the metabolism of animals and humans including pathogenic mechanisms.

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