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Surface-Mediated Supramolecular Self-Assembly of Protein, Peptide, and Nucleoside Derivatives: From Surface Design to the Underlying Mechanism and Tailored Functions

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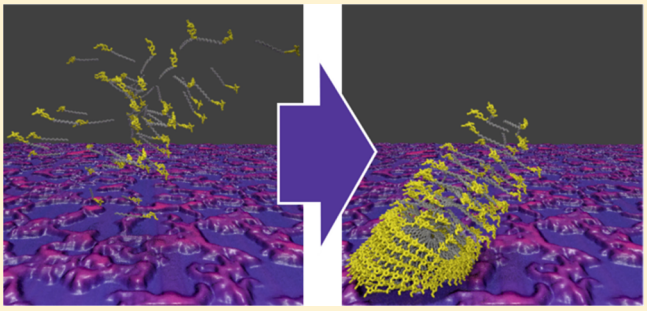
ABSTRACT: Among the many parameters that have been explored to exercise control over self-assembly processes, the influence of surface properties on self-assembly has been recognized as important but has received considerably less attention than other factors. This is particularly true for biomolecule-derived self-assembling molecules such as protein, peptide, and nucleobase derivatives. Because of their relevance to biomaterial and drug delivery applications, interest in these materials is increasing. As the formation of supramolecular structures from these biomolecule derivatives inevitably brings them into contact with the surfaces of surrounding materials, understanding and controlling the impact of the properties of these surfaces on the self-assembly process are important. In this feature article, we present an overview of the different surface parameters that have been used and studied for the direction of the self-assembly of protein, peptide, and nucleoside-based molecules. The current mechanistic understanding of these processes will be discussed, and potential applications of surface-mediated self-assembly will be outlined.



1. INTRODUCTION

Biomimicry and the design of naturally inspired materials through self-assembly was originally a branch of fundamental science but has now become an important concept in nanotechnology. Nature is a master at designing chemically complementary and structurally compatible constituents for molecular self-assembly through molecular selection and evolution. Supramolecular assembly is ubiquitous in nature and underpins the formation of a wide variety of complex biological structures, such as egg shells, pearls, corals, and bone, which use protein-driven templating mechanisms to induce the nucleation and growth of inorganic materials in biomineralization.[1,2] Similar supramolecular organization is observed with organic molecules such as the self-assembly of phospholipids, which can give rise to structures from nanometer to millimeter length scales. Larger molecules such as proteins are also able to form ordered supramolecular structures; individual chaperone proteins, for example, assemble into a well-defined ring structure to sort, fold, and refold proteins.[3]

Self-assembly describes the spontaneous association of numerous individual entities into a coherent organization of structurally well defined and rather stable aggregates joined by noncovalent interactions.[4,5] Typical driving forces for these noncovalent interactions include hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions. Because of the considerable application potential of self-assembled structures in biology, harnessing control of self-assembly in a biological context has attracted significant interest. A number of excellent reviews exist that describe self-assembly as a fundamental strategy for building hierarchical structures in both living systems and for novel advanced materials.[6−10] In particular, it is well established that these self-assembled materials contain the potential to control drug delivery processes and enable the growth and regeneration of cellular tissue, among other possibilities.[11−13] Over the past several decades, considerable effort has been expended in understanding and utilizing ways to control the intermolecular interactions between supramolecular building blocks and direct the self-assembly process to construct complex architectures with tailored functions. Parameters that have been explored for the control of self-assembly include the pH, temperature, nature of the solvent used, and biocatalysts, among others. The importance of surface properties as a means of influencing the self-assembly of materials into architectures with complexity that surpasses that of 2D monolayers is increasingly coming to the forefront as an important additional tool.[14−16]

Surface-mediated multilevel molecular self-assembly that goes beyond traditional monolayer self-assembly and the design of multifunctional nanostructures on the molecular level at an interface is a relatively new research area. Its importance is increasingly recognized because interfacial processes can play

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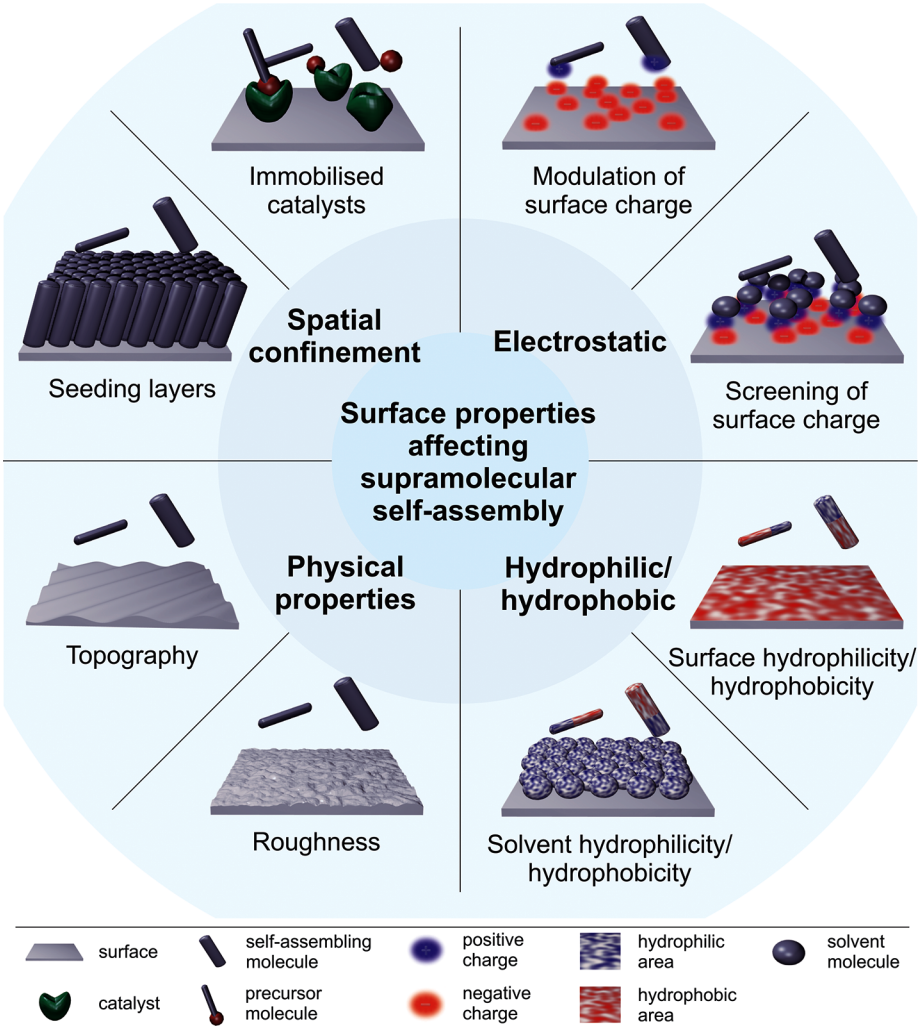

Figure 1. Overview of the surface properties that have been implicated in surface-mediated self-assembly processes.

a key role in the self-assembly process with the potential to cause subtle changes in structure and composition. Self-assembly can cause dramatic changes in the performance of a supramolecular material. Surface-directed self-assembly is crucial not just for understanding the self-assembly formation mechanism but also as a versatile approach to controlling and directing the properties of novel materials.

The history of surface-mediated self-assembly dates back to the well-defined monomolecular films described by Langmuir at the gas–liquid interface[17] and by Blodgett on a solid substrate.[18] Since then, a variety of techniques have been developed to direct self-assembly at the interface, including the Langmuir–Blodgett technique,[19] self-assembled monolayers (SAM),[20] and layer-by-layer (LbL) assembly.[21−23] While a number of articles and reviews have been published on the self-assembly at the interface,[24−33] they are predominantly focused on these monolayer-type structures formed on a material surface.

Research moving beyond the monolayer space of interfacial self-assembly and exploring the effect of surfaces on molecular organization at larger distances from the interface has seen considerable progress in recent years. The effect of surfaces on the self-assembly of de novo-designed organic molecules has been reviewed in the past.[14−16] It is notable that among the efforts to investigate surface-mediated self-assembly, the design of new molecules that fit or adapt to the properties of a surface, often selected because of its inherent crystal structure, is a central strategy.

Biomolecules such as proteins, peptides, and biologically derived molecules, including de novo-designed peptides or nucleotides, that are able to self-assemble often cannot be subjected to the modulation of their chemical structure at will because this may interfere with their other biological functions. These biomolecules may, however, provide other useful functionalities such as a higher specificity of their interactions and the ability to undergo multivalent binding. Although these properties provide intriguing possibilities to control biomolecule self-assembly, nonspecific interactions between self-assembling biomolecules and surfaces are equally important because they are almost ubiquitously present in any system and can have a profound influence on the supramolecular structures formed. It is therefore critical to understand, and perhaps control, the self-assembly behavior of such biomolecules at the interface to a surface in terms of both specific and nonspecific interactions.

This feature article aims to illustrate and summarize recent advances in understanding and controlling the surface-mediated formation of supramolecular self-assemblies from biomolecules or biologically derived molecules (protein, peptide, and nucleoside-based molecules) into architectures

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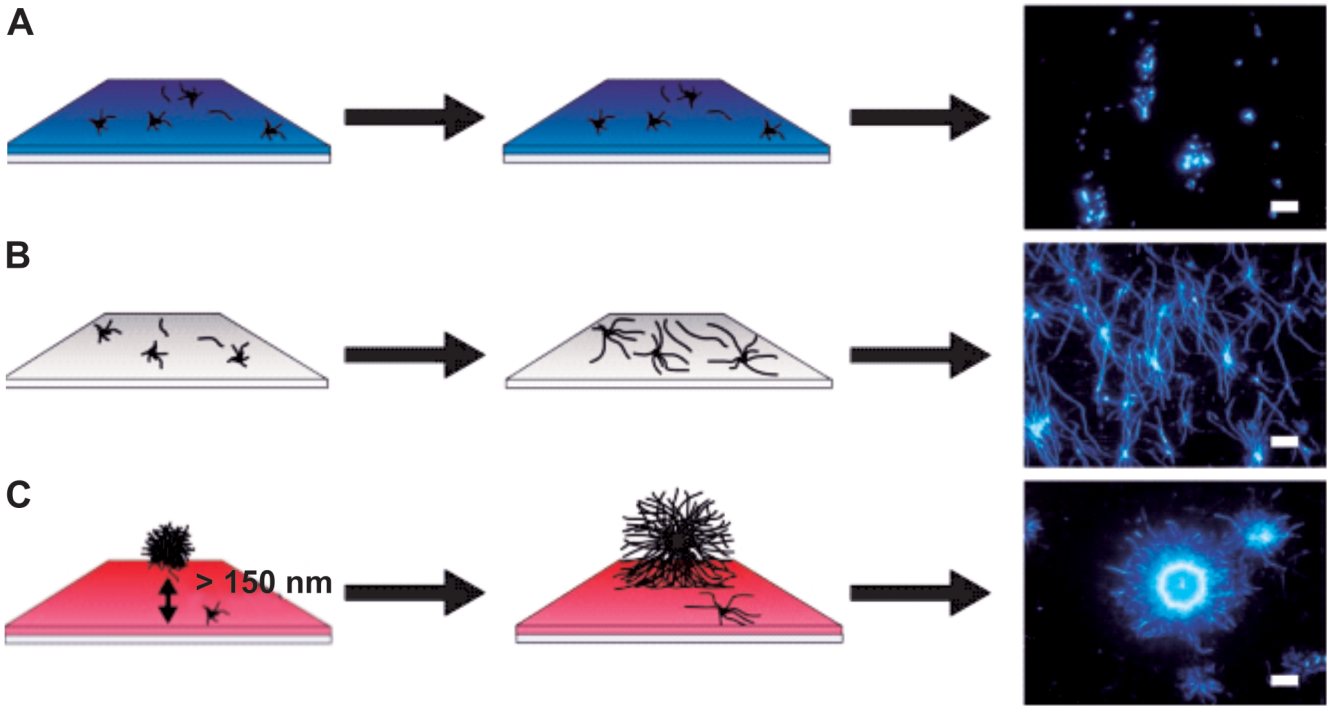

Figure 2. Schematic representation of the surface-dependent fibril growth of amyloid β (1−40). (A) The positively charged surface traps negatively charged fibrils too strongly to allow effective fibril growth. (B) The moderately negatively charged surface interacts weakly with the negatively charged fibrils, allowing fibril edges to be exposed and enabling fibril growth. (C) A strongly negatively charged PEI/PVS surface gives rise to spherulitic aggregates. Scale bars represent 10 μm. Reproduced with permission from ref 42. Copyright 2006, Journal of Biological Chemistry.

with a hierarchical complexity that is higher than that of single monolayers and that have an impact on the properties of materials that are not in direct contact with the interface. Supramolecular self-assembly involved with the Langmuir−Blodgett, SAM, and LbL techniques and the surface-mediated self-assembly of other molecules are beyond the scope of this feature article.

In this feature article, we will first discuss the various surface parameters that have been used in the past to control the self-assembly of proteins, peptide,s and nucleosides and their derivatives on a surface. In an attempt to classify these approaches more systematically, we have structured these reports according to the predominant surface parameter that influences the self-assembly process, electrostatic interactions, hydrophilic/hydrophobic interactions, surface topology and roughness, and surface confinement of self-assembly-induced events (Figure 1). These will include nonspecific interactions such as the surface polarity, general surface charge, and surface roughness as well as more specific interactions such as enzymatic catalysis and the influence of geometrically structured chemical heterogeneity. These discussions will be followed by a consideration of the underlying mechanisms that govern the surface-mediated interactions to draw together communal strategies and generalize the principles that lead from surface design to controlled self-assembly. Finally, a brief outline of current applications of these strategies will be presented.

2. ELECTROSTATIC INTERACTIONS

2.1. Modulation of Surface Charge. *2.1.1. Control over Self-Assembled Structure at the Interface.* Electrostatic interactions between a material surface and the self-assembling molecule have been extensively investigated in the context of protein adsorption because this is a key factor in the formation of amyloid fibrils, a self-assembly-driven protein aggregation process that leads to a number of severe pathologies.[34−36] While biological materials and interfaces would be the most relevant to study in the context of amyloidosis, developing mechanistic concepts from these systems is analytically challenging. Therefore, simpler surfaces such as mica with well-defined physical properties have been used to study the effect of surfaces on amyloid fibril formation and binding to the interface.

Different types of material surfaces have been shown to influence the types of structures formed by peptides and proteins. Whitehouse et al. investigated the peptide CH_3CO-QQRFQWQFEQQ-$CONH_2$ (P_{11}-2), which was designed to form twisted tapes and higher-order structures in solution due to the chirality of individual peptide molecules.[37] P_{11}-2 can self-assemble at the water−mica interface into planar tapes at concentrations well below the critical concentration at which self-assembly into tapes occurs in bulk solution. This was explained by a suppression of the twist in the tapes through electrostatic interactions between the surface and the amino acids in the peptide that are involved in the twist.

Deliberate modulation of the charge of a surface has been shown to control protein self-assembly at the interface.[38−41] Ban et al. imaged amyloid β (Aβ) self-assembly on nine different quartz-based surfaces that were chemically modified to be either uncharged or positively or negatively charged using total internal reflection fluorescence microscopy (TIRFM).[42] The surface-related self-assembly processes of Aβ observed on these surfaces were classified into three different scenarios that are illustrated in Figure 2. First, the tight electrostatic attraction between negatively charged peptides and a positively charged surface traps seed fibrils so that efficient fibril growth is

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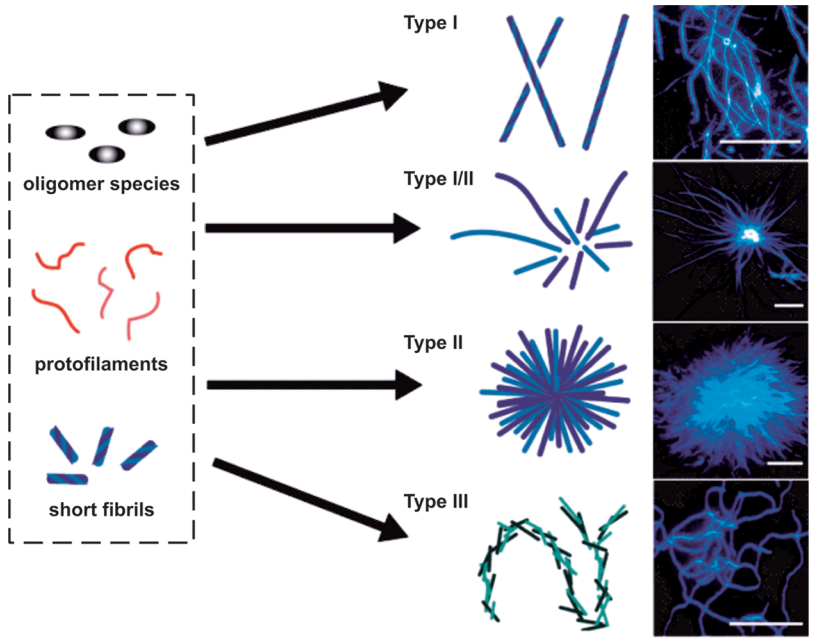

Figure 3. Schematic models of supramolecular fibrillar assemblies of amyloid β (1−40) on a quartz surface. The three types of assemblies observed were straight fibrils (type I), spherulitic assemblies (type II), and worm-like fibrils (type III). Scale bars represent 10 μm. Reprinted with permission from ref 43. Copyright 2007, American Chemical Society.

unfavorable. Moreover, adsorption of the molecules to the surface decreases the solution concentration of active monomers, thus inhibiting the growth. Second, when the surface charge is moderately negative, its interaction with negatively charged peptides is weaker. This causes the growth edge of seeds to be exposed, which leads to efficient fibril growth. Third, the modified polyethylenimine/polyvinylsulfonate (PEI/PVS) surface, a strongly negatively charged and hydrophilic surface, gives rise to the formation of large spherical objects from Aβ, which the authors hypothesized could be caused by the generation of seeds on the surface.

2.1.2. Control over Self-Assembled Structure in Solution. In addition to inducing the aggregation of molecules on the surface, different surface chemical modifications can also lead to differences in the aggregation of Aβ in solution. McMaster et al. prepared gold surfaces modified with alkanethiol monolayers with different end groups, including methyl, alcohol, carboxylic acid, fluoromethyl, sulfonic acid, and ethylene glycol, and brought them into contact with a solution containing Aβ to study the peptide aggregation on the surface and in solution.[38] They found that solution aggregation is affected by the different degrees of protein adsorption on the modified surfaces as the surface adsorption of proteins decreases the concentration of protein in solution and can provide seeds that detach and initiate aggregation in solution.

2.1.3. Control over Self-Assembly Kinetics. The early stage peptide/surface interaction is thought to be critical in controlling how the surface affects the outcome of the self-assembly process. Yagi et al. studied the very early nucleation stage of self-assembly of Aβ on a quartz surface.[43] Three types of supramolecular fibrillar assemblies were observed: straight fibrils, spherulitic assemblies, and worm-like fibrils (Figure 3). It is intriguing that while the quartz surfaces could give rise to any of the three structure types, each quartz surface promoted the formation of only one type. The distribution of structures observed over 60 samples was 58% spherulites (type II), 27% worm-like fibrils (type III), and 15% other structures (including failed samples) if the protein was left to self-assemble on its own. If the sample is seeded with fibrils obtained from bulk self-assembly, then the formation of straight fibrils (type I) is observed on the quartz surface. While the authors demonstrated the presence of different fibril morphologies on different surfaces, the exact nature in which the three different components involved in the self-assembly (oligomers, protofilaments, and short fibrils) interact with each other to form the observed structures remains unclear. The fact that surfaces that are at least nominally identical in their chemical composition (i.e., the same type of material was used in the experiments) produce different self-assembly structures indicates either that the self-assembly process is very sensitive to subtle differences in the surface properties that have not been identified or that other parameters that have not been controlled for in this system influence the self-assembly process. Nonetheless, the lack of formation of straight fibrils without seeding does perhaps indicate that nucleation at the surface is faster than in the bulk, causing more nucleation points and hence leading to the formation of more but shorter fibrils that subsequently from spherulitic or worm-like fiber structures.

Surface effects not only impact the final structure of the self-assembled peptide but also can alter the rate at which the self-assembly process proceeds. Zhu et al. found that fibril formation of the recombinant amyloidogenic light chain variable domain of smooth muscle actin (SMA) was accelerated significantly in the presence of mica surfaces compared to fibril formation in a Tris buffer solution. In the presence of the surface, the fibrils grew at faster rates and required lower concentrations of SMA.[44] Similar to the previous discussion above about Aβ in Figure 2, the authors propose that the small negative charge of the mica surface promotes SMA attachment while at the same time enables lateral mobility required for self-assembly. The formation of aggregates produces self-assembled building blocks, and the increased concentration of SMA on the surface due to surface

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adsorption of the protein causes rate acceleration of the self-assembly process. It is notable that in contrast to the negatively charged mica surface, positively charged and hydrophobic surfaces obtained by chemical modification of mica (silanization with 4-aminobutyl triethoxysilane and octadecyltricholorosilane, respectively) did not show any fibrils.

2.2. Screening of Surface Charge. *2.2.1. Control over Self-Assembled Structure at the Interface.* The above examples have focused on understanding the effect of the material surface charge on protein or peptide self-assembly and demonstrate some degree of control over the self-assembly process via surface modification. Instead of modifying the material surface directly, it is also possible to modulate the material−peptide/protein interaction via a change in pH[45,46] or the addition of charge-modifying species such as salts[46−52] in the bulk solution to screen the surface charges.

The pH of the peptide solution alters the ionization state of the peptide, thereby affecting the electrostatic interactions between the peptide and surface.[53] Yang et al. found that by decreasing the pH, peptide EAK16-II becomes more positively charged, causing the affinity between the peptide and a negatively charged mica surface to increase.[45] This can lead to the adsorption of a nanofiber "seed" to mica, which can subsequently determine the density of growing nanofibers on the surface. Similar pH-dependent effects on the fibril formation of an amino acid-based biopolymer, composed of a central silk-like block and two collagen-like random coil end blocks on a negatively charged silica surface, have been reported by Charbonneau et al.[46]

Instead of pH changes, the addition of salts can also be used to control surface-mediated self-assembly. Hwang et al. found that an increased salt (NaCl) concentration can reduce the length of fibers formed by a silk−elastin-like protein on mica and ultimately lead to a change in morphology from a fiber network to spherical aggregates.[48] In addition, the surface density of the adsorbed polypeptide decreased significantly with increased NaCl concentration. It is further notable that the self-assembly of this system was observed only in the presence of mica but not in bulk solution nor on a highly ordered pyrolytic graphite (HOPG) surface. This suggests that high ionic strength weakens the attractive interaction between the protein and the mica surface and reduces the repulsive interactions between individual polymer strands, leading to a reduction of polypeptide adsorption on the mica surface and an increased number of polypeptide aggregates. In contrast, decreased salt concentration improved the affinity of the polypeptide for the mica surface and subsequently facilitated nanofiber growth.

Ions may not only influence the self-assembly process through their presence in solution but also can directly alter the surface properties and consequently modulate the interaction of the molecules with the surface. For example, Karsai et al. showed that the orientation of trigonally arranged fibrils formed by amyloid Aβ25−35 on mica depends on the cooperative interaction of a positively charged moiety on the Aβ25−35 peptide with the potassium binding pocket of the mica lattice.[50,51] K^+ can also neutralize the mica surface, reducing the binding affinity of collagen to mica, which leads to reduced collagen adsorption. However, the weaker binding forces also enhance the ability of collagen molecules to diffuse on the surface, thus affecting fiber alignment on the mica surface.[47]

By tuning the ionic strength of the reaction solution, the self-assembled structure of peptide GAV-9 on mica could be controlled. Dai et al. showed that peptide GAV-9 can self-assemble into highly ordered, multilayered nanofilaments with all-upright conformations on a mica surface under a high salt concentration.[49] Excess cations on the mica surface reduce the number of negatively charged surface cavities available for interaction with GAV-9, promoting the assembly of a second peptide layer on top of the first. It is noteworthy that different salt types can display different propensities to induce multilayer formation due to differences in their ion-exchange capacity with mica.

2.2.2. Control over Self-Assembly Kinetics. The effect of salts on the nucleation-and-growth mechanism has also been observed on biopolymers, where it can affect the kinetics of the self-assembly process.[46] The presence of salt can be used to screen the charge between histidine units inside the silk-like block of a block biopolymer (a silk-like block flanked by two collagen blocks) and weaken the protein attraction to a silicon surface. This results in a complex, pH-dependent effect on the formation and growth of fibers, ultimately leading to surfaces containing fibers of different lengths and at different densities. A higher pH decreases the repulsive interactions between the positively charged histidine units; this favors the elongation of fibers but limits nucleation. The addition of salt (NaCl) screens repulsive interactions between proteins at low pH, thereby increasing fiber growth. In contrast, the presence of salt at high pH screens attractive forces between the protein and the surface, leading to reduced nucleation. In addition to the salt effects, the concentration of self-assembling molecules required to obtain supramolecular structures was also reported to be lower in the presence of a surface. This is consistent with the observations discussed above that highlighted the role of increased local concentrations at the surface in the self-assembly process.

3. HYDROPHOBIC AND HYDROPHILIC INTERACTIONS

3.1. Impact of Surface Polarity on Self-Assembly at the Interface. *3.1.1. Control over Self-Assembled Structures at the Interface.* The hydrophilic and hydrophobic nature of a surface has been correlated with differences in the structures formed by self-assembling molecules on these surfaces. Surface hydrophilicity has been shown to prevent self-assembly in some instances. For example, graphite surfaces can promote the adsorption of proteins, facilitate amyloid fibrillation,[54] and support the formation of silk fibroin nanofibers due to hydrophobic interactions of graphene with nonpolar moieties of proteins.[55] In contrast, the oxidation of graphite into graphene oxide (GO) generates multiple hydrophilic functional groups on the surface that were shown to inhibit amyloid fibrillation.[56]

Accardo et al. investigated the self-assembly of Aβ fragments to a superhydrophobic Si_3N_4 membrane where they observed the strong presence of the fibrillar component accompanied by a quasi-crystalline structure.[57] This was attributed to the homogeneous evaporation rate of Aβ-containing aqueous droplets on superhydrophobic supports that provide sufficient time for the peptide to arrange in a gradual and ordered way.

Keller et al. recognized that the self-assembly of amyloid polypeptide IAPP depends largely on the surface hydrophobicity and incubation time. To probe these surface/IAPP interactions, they fabricated ultrathin hydrocarbon films grown

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on atomically flat ion-beam-modified mica surfaces for which the wettability could be tuned to take on water contact angles from 20 to 90° without significant changes in surface roughness and chemical composition.[58] More hydrophilic surfaces facilitated the formation of fibrils, whereas on more hydrophobic surfaces aggregation into large oligomers took place. Moreover, more hydrophilic surfaces displayed reduced lag times for the fibrillation process to start. These observations were attributed to different sizes of initial oligomer formation on the different surfaces. Hydrophilic surfaces promote the formation of smaller oligomers that are more mobile and can more readily assemble into fibrils, whereas hydrophobic surfaces promote the formation of larger, more stable oligomers that are less prone to self-assembly into other structures.

3.1.2. Control over the Orientation of Self-Assembled Structures. The above examples show that surface polarity may be a key factor that dictates if self-assembly occurs in a system. In cases where the surface hydrophobicity/hydrophilicity does not prevent self-assembly altogether, surface polarity can influence the orientation of the self-assembled structures. When adsorbing to substrates such as mica, graphite, graphene,[59] or gold,[60] a range of proteins including α-synuclein,[61] β-amyloid peptide,[62] dodecapeptide GrBP5 (IMVTESSDYSSY),[63] elastin peptide,[64] collagen,[65] insulin,[66] and prion protein[60] were shown to adapt a preferential alignment along two or three specific directions that reflect the crystallographic orientation of the substrate.[65]

Using atomic force microscopy (AFM), Kowalewski and Holtzman showed that Aβ fibrils adopt flattened globular shapes with high lateral mobility on mica surfaces, whereas on graphite surfaces, parallel sheets formed by elongated protein aggregates were observed.[62] These sheets followed three directions aligned at 120° to each other, following the crystallographic symmetry of the underlying graphite. In a similar study, Yang et al. also reported the preferential orientation of a peptide (elastin-like peptide, EP II) on a structured hydrophobic surface (HOPG).[64] On HOPG surfaces, EP II fibrils were oriented at a 60° angle to each other, while on mica, no orientation was evident. Brown et al.[67] showed that the interaction between the ordered structure of a HOPG surface and a de novo-designed β-sheet containing protein results in the formation of parallel fibers that adopt three preferred orientations at 120° to each other, imparted by the 3-fold symmetry of the graphite substrate (Figure 4). The structure of the protein assembled on the HOPG surface is an amphiphilic β-sheet with the polar side chains projecting away from the HOPG surface and the nonpolar side chains pointing down toward the HOPG surface. In all cases, the surface-induced imposition of structural orientation can be attributed to the anisotropy of the hydrophobic interactions between graphite and the hydrophobic parts of the peptide chain. It was suggested that the hydrophobic interactions between the peptide and the surface are maximized by the specific orientation adopted by the sheets of the self-assembled structure.

The surface polarity has also been shown to control the orientation of self-assembled peptide fibrils out of the plane of the material surface. Amyloid peptide GAV-9 (NH_2-VGGAVVAGV-$CONH_2$) can "stand up" on mica surfaces and "lie down" on HOPG surfaces.[68,69] This has been explained by the propensity of the hydrophobic side chains to preferentially interact with the more hydrophobic HOPC

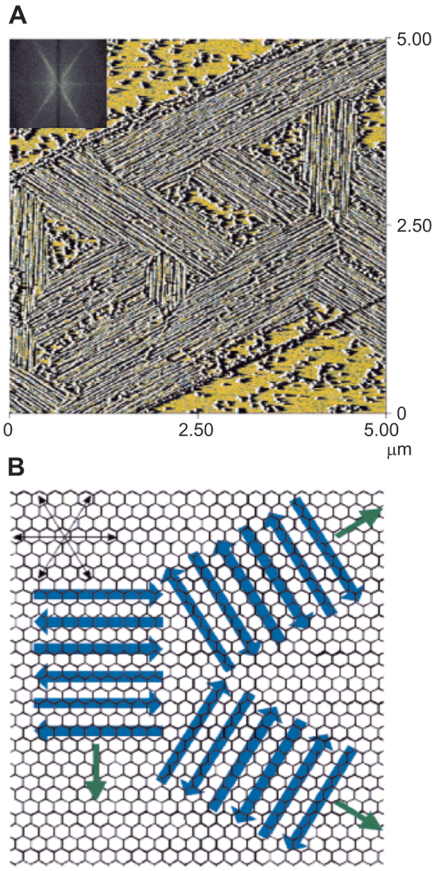

Figure 4. Preferential orientation of a de novo-designed protein deposited on highly ordered pyrolytic graphite (HOPG). (A) AFM image of the protein on HOPG. The orientation of aggregates along the three directions at 120° to one another is reflected in the characteristic 3-fold symmetry of the two-dimensional Fourier transform of the image (inset). (B) Schematic of the orientation of six-stranded β-sheet proteins (blue arrows) on a HOPG surface. Green arrows indicate the long axis of the fibers, which are perpendicular to the β-strands. Reproduced with permission from ref 67. Copyright 2002, American Chemical Society.

surface and hence adapt a lying-down orientation to maximize the hydrophobic interactions. In contrast, the presence of a hydrophilic water layer on the more hydrophilic mica would reduce the affinity of hydrophobic side groups for the surface and promote a standing-up orientation as described in Figure 5. MD simulations indicate that the higher hydrophobicity of the HOPG surface is a key factor in directing the adsorption of the first adsorbing peptide (EAK16-II), which subsequently is accompanied by additional electrostatic interactions that influence the deposition of the second adsorbing peptide.[70]

3.1.3. Control over Self-Assembly Kinetics. Hajiraissi et al. investigated an IAPP-derived peptide using time-resolved AFM.[71] Both the fibril growth rate and fibril density of human islet IAPP were lower on hydrocarbon films than on mica surfaces. Furthermore, the increased surface hydrophobicity of the hydrocarbon film leads to a delay in the onset of fibrillation and an increase in the number of oligomeric species and amorphous aggregates at the surface. Conceptually, these observations are in agreement with those made by Keller et al. with IAPP[58] that were discussed above, and the argument that more hydrophilic surfaces give rise to smaller, more

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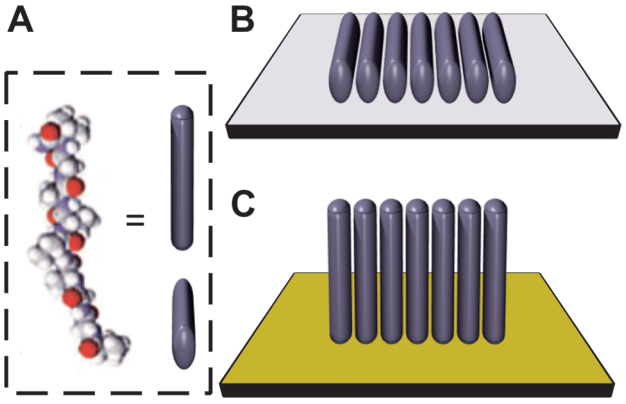

Figure 5. Schematic representation of self-assembled GAV-9 nanofilaments and their interfacial orientations at hydrophobic and hydrophilic surfaces. (A) GAV-9 nanotapes. (B) GAV-9 nanotapes lying horizontally on the HOPG surface. (C) GAV-9 fibrils oriented upright on mica. Adapted with permission from ref 69. Copyright 2006, John Wiley and Sons.

mobile aggregates that more readily promote further self-assembly could also be applied here.

3.1.4. Control over Mechanical Properties of Self-Assembled Structures. The influence of surfaces on the organization of self-assembled structures has also been shown to impact the overall mechanical properties of the resulting bulk self-assembled material. Using a cytidine-based hydrogelator,[72,73] Angelerou et al. recently demonstrated that thin gel films formed on hydrophilic glass surfaces and hydrophobic phenyl (Ph) surfaces display different physical (fiber diameter) and mechanical (gel stiffness) properties that are detectable by AFM on dry samples (Figure 6).[74]

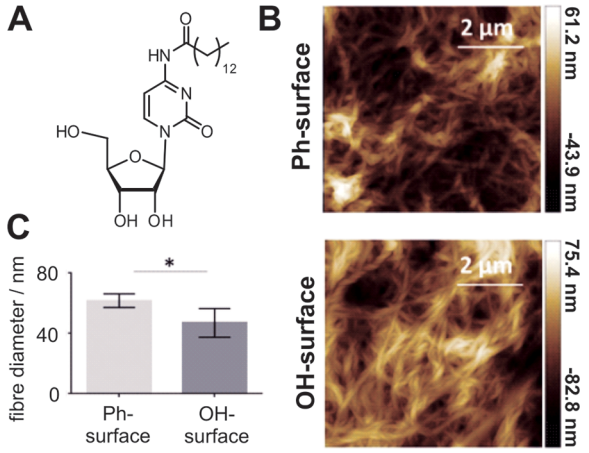

Figure 6. Films of fibers formed from a cytidine-based gel film on hydrophilic glass (OH) and hydrophobic phenyl (Ph) surfaces. (A) Structure of the gelator. (B) AFM images of the fibers formed on OH and Ph surfaces. (C) Average diameter of the fibers on the OH and Ph surfaces as measured by AFM. Reproduced with permission from ref 74. Copyright 2016, Royal Society of Chemistry.

3.2. Impact of Solvent and Self-Assembling Molecule Polarity on Self-Assembly at the Interface. *3.2.1. Polarity of Self-Assembling Molecules.* Surface hydrophobicity has been reported to have different effects on gelators with slightly different compositions. Designed gemini-like amphiphilic peptides (GAPs) containing a short peptide sequence ($A_4G_3CK_2$) with different alkyl chain lengths (from 12 to 18) exhibit different self-assembly behavior when placed on silica surfaces. GAP-12 and GAP-14 form vertically aligned arrays of peptide nanofibers, while horizontal alignments of parallel nanofibers were observed for GAP-16 and GAP-18.[75] This was explained by the inability of GAP-16 and GAP-18 to maintain an extended conformation in which the molecule protrudes from the surface due to inceased alkyl chain length. Similar to the observations by Zhang et al. on GAV-9[69] that was discussed above, GAP-12 also displayed a surface-dependent orientation. Compared to more hydrophilic mica, more hydrophobic HOPG surfaces caused the protruding structure to collapse, most likely due to increased hydrophobic interactions between the surface and the molecule.

In addition to influencing the molecular structure of the GAP peptide building blocks, surface hydrophilicity/hydrophobicity also influences the fiber orientation of the self-assembled GAP peptide structures.[75] An increase in the hydrophobicity of the surface leads to more horizontally oriented fibers due to a change in the balance between evaporation-initiated forces and surface-tension-related forces on the peptide-containing droplet. The increased surface tension on hydrophobic surfaces provides a driving force for fiber growth parallel to the surface. In contrast, on a hydrophilic surface, the surface tension is considerably lower, leading to a stronger driving force through evaporation-related processes that act perpendicular to the surface and accelerate fiber growth away from the surface.

3.2.2. Polarity of the Near-Surface Solvent Environment. The near-surface solvent layer can also direct peptide self-assembled nanostructures. In an atmosphere containing water vapor only, peptide GAV-9a (CH_3CONH-VGGAVVAGV-$CONH_2$) tends to form flat nanofilaments on a mica surface.[76] An increase in the ethanol content of the vapor leads to the formation of bent fibers. In a pure ethanol atmosphere, the fiber orientation was observed to be close to perpendicular to the mica surface. The authors explained these observations with a compression of the surface area on which the peptides were self-assembled and a consequent reduction in the interaction with the lattice of the underlying mica if ethanol is present at the interface.

4. PHYSICAL SURFACE PROPERTIES

4.1. Surface Roughness. Surface roughness has been recognized as a factor that affects peptide fibrillation. Shezad et al. studied the role of surface roughness on surface-mediated Aβ fibrillation using surfaces displaying either polymer coatings of varying roughness (RMS roughnesses of 0.26, 0.67, and 1.81 nm) or polystyrene microparticles with three different surface topographies (described as smooth, slightly rough, and highly textured).[77] They showed that a rough surface decelerates the two-dimensional diffusion of peptides on the surface and increases the quantity of irreversibly adsorbed peptides. Thus, individual peptide molecules do not have enough space or time to achieve sufficient reorganization for interpeptide association, which causes a retardation of the kinetic pathway for the formation of new nuclei and fibrils.

4.2. Surface Topology. Huang et al. used flat glass surfaces and porous cellulose surfaces to study the interfacial self-assembly of the dipeptide FF.[78] They showed that FF can self-assembly into small aggregates in aqueous solution which hierarchically assemble into nanofibers on glass surfaces and micrometer-sized vesicles on porous cellulose surface. The

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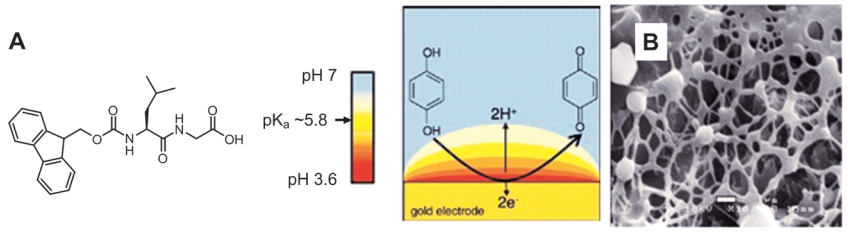

Figure 7. Electrochemically grown Fmoc-LG gel film. (A) Molecular structure of Fmoc-LG and electrochemical oxidation of hydroquinone to trigger near-surface gelation. (B) Cryo-SEM image of the top surface of the gel film. Reproduced with permission from ref 80. Copyright 2010, American Chemical Society.

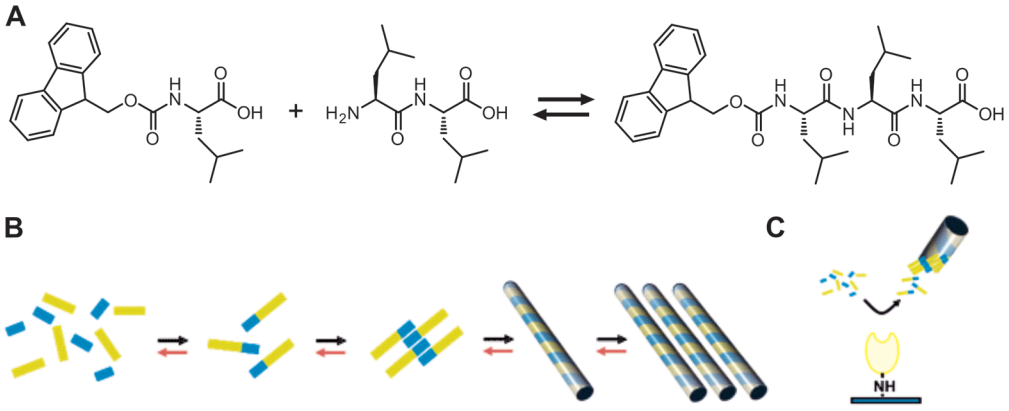

Figure 8. Biocatalyzed peptide self-assembly instructed by a surface-immobilized enzyme. (A) Fmoc-amino acid (Fmoc-L) reacts with a dipeptide (LL) in the presence of the enzyme, yielding the Fmoc-tripeptide (Fmoc-L_3) hydrogelator. (B) Schematic for the formation of the Fmoc-L_3 building block, which interacts through hydrophobic and hydrogen bonding interactions, yielding a nanoscale tubular structure. These align longitudinally, yielding a matrix which induces a gel/sol transition. (C) In the case of catalytica activity physically separating the assembled Fmoc-L_3, preventing further reactions. Reproduced with permission from ref 89. Copyright 2011, Elsevier.

authors proposed that low surface tension could promote the self-assembled organization into nanofibers while high surface tension may lead to random aggregation. It should be noted that in this example the potential contribution of the chemical composition of the different materials used was not directly accounted for.

4.3. Combined Physical and Chemical Effects. To explore the combined effect of surface roughness and chemical composition more systematically, Nayak et al. studied the fibrillation of insulin on different polymer surfaces (poly(tetrafluoroethylene), polyethylene, poly(vinylidine difluoride), poly(ethersulfone), and regenerated cellulose) with different roughnesses (RMS roughnesses of 54, 45, 195, 36, and 87 nm, respectively). They observed that with increasing surface hydrophobicity and decreasing surface roughness the lag time for fibril formation is decreased.[79] It is therefore possible that a high degree of surface roughness can present an obstacle to peptide diffusion, inhibiting the fibrillation process.

5. SPATIAL CONFINEMENT OF SELF-ASSEMBLY INDUCTION AT SURFACES

5.1. Seeding Layers. *5.1.1. Electrochemical Generation of Seeding Layers.* Localized self-assembly at a solid interface can be accomplished by confining self-assembly triggering events to the vicinity of the surface. Cameron and co-workers developed a method to locally trigger the growth of thin self-assembled Fmoc-LG (Fmoc = fluorenylmethyloxycarbonyl) hydrogel films by electrochemically inducing the oxidation of hydroquinone that leads to a local change in pH near a surface (Figure 7).[80] Liu et al. used this approach to drive Fmoc-F gelation via self-assembly at an electrode interface[81,82] and were able to co-deposit agarose on the surface.[81] This method has also been applied to simultaneously achieve a spatially and temporally resolved multicomponent gel from several naphthalene-containing dipeptide gelators.[83] The composition of the gels can be controlled by the judicious choice of the applied current and the selection of the low-molecular-weight gelator.

5.1.2. Immobilization of Self-Assembly-Triggering Molecules into Seeding Layers. The modification of a material surface with molecules that influence self-assembly has been used to create custom interactions between the self-assembling molecules and the surface. Mica surfaces were modified with oligonucleotides that act as capture motifs for DNA double-crossover (DX) motifs to direct the self-assembly of DNA (DX-A1B1) into quasi two-dimensional lattices.[84] Ku et al. developed a surface-based system inducing prion amyloid fibrillation in vitro by immobilizing prion peptides onto an NHS-activated glass surface.[85] Johnson et al. reported that by preparing a film from the Fmoc-LG dipeptide as a seeding layer, the surface-initiated growth of a thicker hydrogel film layer was achieved.[86] It has been suggested that a local decrease in pH due to protons trapped within the seeding layer as well as a modification of the apparent pK_a of Fmoc-LG near the surface could be responsible for triggering the nucleated growth from the surface. In a different study, Fmoc-FF was chemically immobilized on the surface of a silica wafer as an initial seeding layer; when immersing this peptide-modified silica wafer into an aqueous solution containing the same

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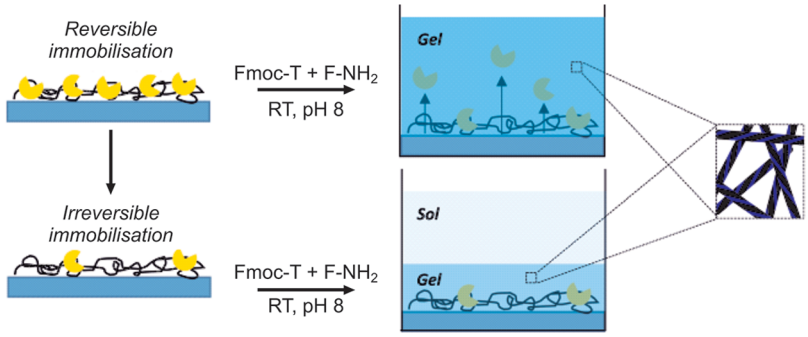

Figure 9. Reversible and irreversible enzyme immobilization on modified surfaces for biocatalytic self-assembly. Irreversible enzyme immobilization confines gel formation to the vicinity of the surface while reversible enzyme immobilization leads to gelation of the bulk material. Reproduced with permission from ref 91. Copyright 2017, American Chemical Society.

dipeptide, the immobilized peptide triggered the formation of nanorods on the surface.[87]

5.2. Immobilization of Catalysts. *5.2.1. Enzymatic Formation of Self-Assembling Molecules at the Surface.* Similar to catalysts that affect the solution pH, enzymes have been widely used to trigger self-assembly via the conversion of a precursor molecule into a self-assembling gelator.[88] By immobilizing enzymes to a surface, the formation of self-assembling molecules can be spatially confined (Figure 8).[89,90] Williams et al. immobilized thermolysin to an amine-[90] and polydopamine-functionalized[89] glass slide; the enzyme acts via reverse hydrolysis to produce Fmoc-tripeptide building blocks that are able to self-assembly into nanofibrils of 12 nm in diameter and several micrometers in length. These fibers then interact to form large fibrillar bundles, forming a network that leads to macroscopic hydrogelation. In a later study, the effect of reversible and irreversible enzyme immobilization on the spatial confinement of biocatalytic self-assembly was explored.[91] Polyphenol-modified surfaces were used to immobilize thermolysin on a glass surface. The immobilized enzyme catalyzes the coupling of Fmoc-T and F into a hydrogel-forming peptide, Fmoc-TF. Reversible enzyme immobilization caused bulk gelation of the solutions, whereas the irreversible binding of thermolysin confined gel formation to the vicinity of the surface (Figure 9).

Vigier-Carriere et al. employed alkaline phosphatase non-covalently immobilized in a polyelectrolyte multilayer to trigger the self-assembly and gelation of an Fmoc-protected tripeptide (Fmoc-FFY(PO_4^{2-})).[92] More recently, this group reported localized enzyme-driven self-assembly by surface-immobilized α-chymotrypsin in a poly(ethylene imine) film.[93] This enzyme catalyzes the production of $(KL)_n$OEt oligopeptides from a KLOEt (OEt: ethyl ester) solution; when a critical concentration of the formed oligopeptides is reached near the surface, the peptides self-assemble into β-sheets, resulting in a fibrillar network localized at the interface.

Enzyme-mediated self-assembly has not only been localized at the surfaces of functionalized inorganic materials but Xu and co-workers have also accomplished enzyme-catalyzed triggering of self-assembly at the surface of a cell. They reported the formation of a net-like hydrogel structure in the vicinity of the surface of cancer cells (MES-SA/Dx5) from Nap-FFY.[94] The precursor of this gelator, tripeptide Nap-FFpY which is phosphorylated on the tyrosine residue, is converted to Nap-FFY via dephosphorylation through surface and secretory phosphatases.

6. MECHANISMS OF SURFACE-MEDIATED SELF-ASSEMBLY

The mechanisms that underlie the governance of the interplay among surfaces, self-assembling molecules, and the intermediate and final structures of the self-assembly process are diverse and cross the borders of the descriptive classifications we have outlined above. While we have discussed mechanistic considerations when introducing the various surface-mediated self-assembly systems above, it is useful to review them here in a dedicated section to highlight key strategies that can be employed to design the interaction of surfaces with self-assembly processes. An overview of these mechanistic processes is presented in Table 1.

6.1. Strength of Adsorption of Molecules to Surfaces. Surfaces can play a key role in initiating self-assembly under conditions in which solution self-assembly would not take place. This could mean that self-assembly takes place either at concentrations below those required for self-assembly in solution[46] or that the onset or rate of self-assembly is considerably faster in the presence of the surface.[77,79] These phenomena are typically related to the degree of attraction between the surface and the self-assembling molecules and are generally not specific in nature. By enhancing the ability of molecules to adsorb to the surface, a local increase in the concentration of the self-assembling molecules in the vicinity of the surface can lead to the initiation of self-assembly and promote the recruitment of additional molecules to accelerate self-assembly.

The strength of the surface−molecule interaction can be tuned nonspecifically by changing the chemistry (hydrophobicity or charge) of the surface,[44,79] screening electrostatic interactions between the molecules and the surface,[45,46,48,49] or adsorbing solvents[68,69,76] or other molecules[56,84] to the surface. Increasing the roughness of the surface has also been shown to increase irreversibly the adsorption of molecules.[77,79] More specific control over the interaction could be accomplished by selectively occupying binding sites on the surface.[47,50,51] Among these parameters, the tuning of electrostatic interactions between molecules and surfaces has been shown to provide control over the density of the fibers formed on the surface.[45,46,48,49]

Typically, moderate interaction strengths between the surface and the self-assembling molecules are desirable for promoting self-assembly. If the surface−molecule interactions are too weak, molecule−molecule interactions are more favorable and self-assembly may not take place or it may proceed in solution. Strong adsorption may prevent further

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Table 1. Mechanisms and Underlying Concepts by Which Surface-Mediated Self-Assembly Can Be Controlled

mechanism	underlying concept	effect on self-assembly	surface	self-assembling molecules	category	ref
Adsorption Strength of Molecules to Surfaces						
modulate surface chemistry	increase/decrease in molecule−surface attraction	modulation of lag time and nucleation rate at lower concentrations	polymer films; immobilized polystyrene microparticles; chemically modified mica	protein (insulin, SMA)	hydrophilic/hydrophobic; electrostatic	44, 79
modulate charges on molecules	pH-induced change in charge on molecule	modulate fiber density on surface	mica	peptide (EAK16-II)	electrostatic	45
screen charges between molecules and surfaces	change in the ionic strength of the solution	initiation of self-assembly at lower concentrations; modulation of self-assembly structure and density	mica; silicon; HOPG	silk−elastin-like proteins; peptide (GAV-9)	electrostatic	46, 48, 49
occupation of ion binding pockets in surfaces	presence of K^+ ions modulates the charge of the surface and the availability of binding pockets	alignment of fibers	mica	amyloid Aβ 25−35; collagen	electrostatic	47, 50, 51
presence of solvent films on the surface	reduction of molecule−surface interactions and compression of surface area for self-assembly	modulation of structure and orientation of fibers	mica; HOPG	peptide (GAV-9; GAV-9a)	hydrophilic/hydrophobic	68, 69, 76
modulate surface roughness	increased roughness promotes irreversible adsorption of molecules	modulation of nucleation rate and lag time	polymer films; immobilized polystyrene microparticles	amyloid β; insulin	physical properties; hydrophilic/hydrophobic	77, 79
reduction or enhancement of surface−molecule attraction through the surface adsorption of molecules	layers of molecules can act either as barriers for surface recognition or as specific binding sites	initiation or inhibition of self-assembly	graphene oxide; modified mica	amyloid β; DNA (DX-A1B1)	hydrophilic/hydrophobic; spatial confinement	56, 84
Nucleation Site Generation at the Surface						
seed formation on the surface and subsequent release of seed into solution	protein adsorption and rearrangement on the surface	initiation of solution aggregation	self-assembled monolayers	amyloid β	electrostatic	38
modulate surface chemistry to control generation of nucleation sites	balance between molecule adhesion and mobility on the surface	initiation of self-assembly; modulation of fiber length and density	chemically modified mica and silica	biopolymer; proteins (SMA, amyloid β)	electrostatic	42, 44, 46, 79
modulate surface roughness or topography to control molecular diffusion on surfaces	increasing surface roughness retards surface diffusion of molecules	modulation of nucleation rate and lag time	polymer films; immobilized polystyrene microparticles	amyloid β; insulin	physical properties	77
modulate size of nucleation sites	surface hydrophilicity affects the size of oligomers formed on the surface	modulation of self-assembled structure and lag time	ultrathin hydrocarbon films on mica	protein (IAPP)	hydrophilic/hydrophobic	58
Formation of Self-Assembling Molecules at the Surface						
local change in pH triggers self-assembly near the surface	electrochemical oxidation near electrode surface	spatial control over self-assembly initiation	hydroquinone-modified electrode	Fmoc-LG; Fmoc-F; naphthalene dipeptides	spatial confinement	80−83
local change of ph and the apparent pK_A triggers self-assembly near surface	protons trapped in seeding layer	spatial control over self-assembly initiation	immobilized gelator	Fmoc-LG	spatial confinement	86
conversion of precursors into gelators at the surface	enzymatic catalysis	spatial control over self-assembly initiation	immobilized enzymes; cancer cells (MES-SA/Dx5)	Fmoc-L_3; Fmoc-TF; Fmoc-FFY(PO_4^{2-}); $(KL)_n$OEt; Nap-FFY	spatial confinement	89−94
Other Factors						
intramolecular bond interference	suppression of secondary structure formation	self-assembly at lower concentrations	mica	peptide (CH_3CO-QQRFQWQFEQQ-$CONH_2$)	electrostatic	37
templating of structures present on the surface	maximizing the interaction of hydrophobic parts of the molecule and hydrophobic parts of the structured surface	ordered alignment of self-assembled structures	graphite; HOPG	amyloid β; elastin-like peptide (EP II); de novo designed β-sheet containing protein	hydrophilic/hydrophobic	62, 64, 67
forces exerted by solvent evaporation and surface tension	varying surface hydrophilicity changes the surface tension and affects the balance between evaporative forces and surface tension	modulation of alignment and orientation of fibers	silica; superhydrophobic Si_3N_4 membrane	amyloid β fragments; alkyl-chain-modified peptides (GAP-12, GAP-14, GAP-16, GAP-18)	hydrophilic/hydrophobic	57, 75

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molecule−molecule interactions of molecules at the surface and impede self-assembly. Intermediate or weak surface−molecule interactions attract self-assembling molecules, increasing their local concentration, without restricting their ability to rearrange or interact with each other.

6.2. Nucleation Site Generation at the Surface. Mobility at the surface is important for individual molecules, and a certain degree of mobility is also essential for the growing supramolecular structure on the surface in which the growth edge of the structure has to remain accessible to interact with other molecules.[44] The formation and availability of such nucleation sites for self-assembly can be influenced by surface parameters.

The chemistry (charge or hydrophilicity)[42,44,46,79] and roughness or topography[77] of a surface can (nonspecifically) influence the mobility of molecules on surfaces and thereby control if nucleation sites form and are accessible on a surface. As discussed above, intermediate surface adhesion, i.e., intermediate or weak surface charges, are most beneficial for the effective growth of a supramolecular structure from the surface. If the surface attraction is sufficiently weak, then nucleation sites that have been formed on the surface may detach again and initiate self-assembly in the bulk solution.[38]

The strength of interaction between the surface and the self-assembling molecules can lead to the formation of different sizes of nucleation sites.[58] Smaller and more mobile nucleation sites are formed on surfaces with weaker interactions with the molecules, leading to fiber formation, whereas stronger molecule−surface interactions can lead to larger nucleation sites that form aggregates.

6.3. Formation of Self-Assembling Molecules at the Surface. In contrast to modulating a molecule's adsorption strength and the formation of nucleation sites via tuning the surface properties, the formation of self-assembling molecules in the vicinity of the surfaces is not dependent on physicochemical surface properties but on the ability of the surface to perform a catalytic function. Consequently, any catalytic mechanism that is able to generate self-assembling molecules and can be spatially confined to a surface is in principle suitable for this approach.

To date, catalytic effects involving surface-immobilized enzymes and local changes in pH of the near-surface environment have been described. Enzymes such as thermolysin, α-chymotrypsin, and alkaline phosphatase have been immobilized on surfaces to convert precursors of amphiphilic peptides into gelators.[89−94] Depending on the enzyme used, these reactions can be selective to specific molecules and thereby provide more specific surface−molecule interactions. In contrast, a local change in pH represents a less specific approach to modulating the surface−molecule interaction. A pH change can be accomplished either via electrochemical reactions such as the oxidation of hydroquinone[80−83] or by forming a proton-rich seeding layer where the lower pH triggers self-assembly at the surface.[86]

6.4. Other Factors. A number of other factors that do not fall into the above categories have also been reported as useful tools for controlling self-assembly at surfaces. These include the interference of the surface with intramolecular bonds, the use of structured surfaces as templates, and the influence of thermodynamic forces on a water droplet in which self-assembly takes place.

Intermolecular bond interference can take place if the interaction of the self-assembling molecule with the surfaces leads to the adaptation of different conformational states of the molecule. For example, the interaction of peptide CH_3CO-QQRFQWQFEQQ-$CONH_2$ with mica surfaces was reported to suppress secondary structure formation, leading to the promotion of self-assembly.[37]

The ordered structures on graphite or HOPG enable molecules to specifically interact with more hydrophobic parts of the surface, thereby following the structure of the surface pattern and giving rise to the preferential orientations of fibrils that align with the surface structure.[62,64,67] Among the three parameters discussed in this section, the surface templating approach is the only one that could be considered to present a certain level of specificity for the surface−molecule interaction as the geometric structure of the surface chemistry may require a certain degree of overlap with the chemical geometry of the molecules.

Finally, it was shown that in water droplets containing the self-assembling molecules that are placed on a surface, two separate forces influence the orientation of the fibers formed. Evaporation forces act perpendicular to the surface while surface tension acts parallel to the surface. By changing the surface chemistry, the surface tension can be altered and the balance between the two forces shifts, thereby increasing or decreasing the relative contribution of the parallel and perpendicular forces, which ultimately leads to the preferential orientation of fibers in the direction of the overall force vector.[57,75]

7. APPLICATIONS

An increasing number of publications describe the application of self-assembled materials in controlling stem cell fate,[94−97] bacterial signaling,[98] drug delivery,[99,100] and templating inorganic nanostructure to form hybrid materials[101−104] and nanosensors.[105−108] Applications related to supramolecular materials obtained by surface-mediated self-assembly are also beginning to emerge and encompass biomedical applications where cell surfaces are exploited as self-assembly-mediating surfaces to influence cell fate, templating mechanisms to create other structures and as analytical sensing devices.

7.1. Biomedical Applications. In section 5.2.1, we discussed the ability of surface-immobilized enzymes to trigger the self-assembly of peptide amphiphiles and the possibility to implement the same strategy using enzymes immobilized on the surface of cells. Fibrils and networks of supramolecular materials formed by enzymatic triggering of the self-assembly via cell-surface-bound enzymes (phosphatases) provide localized barriers around cancer cells, leading to cell death. Xu and co-workers[94,96] showed that pericellular D-peptide hydrogels formed by an enzyme (alkaline phosphatase) instructed the self-assembly of innocuous monomers at the cell membrane, which can block cellular mass exchange to induce the apoptosis of cancer cells. This work illustrates a new way to control the fate of different types of cells according to the expression and location of enzymes that regulate the spatiotemporal profiles of molecular nanofibrils. Subsequently, this led to the development of a phosphorylated and 4-nitro-2,1,3-benzoxadiazole (NBD) conjugated D-peptide as an image probe of alkaline phosphatases.[97] This enzymatically triggered peptide fibrillization combined with an anticancer drug, cisplatin, was also shown to dramatically enhance drug toxicity against drug-resistant cells.[100]

Other examples of biomedical applications are also available. A recent study demonstrated that human α-defensin 6 (HD6)

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self-assembles in contact with bacterial surface protein to form nanonets that entrap the bacteria and block their translocation.[95] Zheng et al.[109] demonstrated that Nap-FFG can self-assemble and gel around the surface of platelets through an unknown ligand−receptor interaction. This surface-induced hydrogelation around the platelet surface can inhibit human platelet aggregations. Liu et al. used electrochemical reactions to lower the pH of the near-surface (electrode) environment.[82,98] This stimulates the formation of an Fmoc-F gel that can serve as a temporary fabrication aid to allow the codeposition of a gelatin gel matrix and the entrapment of reporter cells (CT104) able to detect quorum sensing signaling molecules.[98] Kundu et al. studied the directed assembly of natural silk proteins on an aminated silica surface into organized, dendritic structures. They demonstrated that these structures can function as topographical cues for PC12 cells which showed enhanced surface recognition and cytoskeletal guidance on surfaces displaying the structured silk protein features.[110]

7.2. Templating Inorganic Nanostructures to Form Hybrid Materials. Surface-directed self-assembled soft materials have been used to organize inorganic phases at the nanoscale. One such example is the ordering of quantum dots that is directed by the self-organization of the M13 virus into herringbone patterns.[101] These patterns display long-range (micrometer-scale) order in which the ZnS nanocrystals were located at the junction between lamellar layers of the structure. Such mechanisms have inspired engineers to develop hybrid materials where both nanoscale features and complexity are realized through a nonequilibrium assembly process. Leon et al. found that interfacially confined peptides can be used to form atomically smooth single-crystal triangular gold nanoplatelets without the use of additional reducing agents or high temperatures.[102] The rational design of this peptide includes a tryptophan residue responsible for the reduction of Au^{3+} to Au^0 and histidine residues that inhibit the growth of the (111) facet of gold. The Mezzenga group reported the production of single crystal gold platelets using self-assembled β-lactoglobulin fibrils, which not only provide the required amino acids necessary for the salt reduction but also sustain the crystal growth due to their structural anisotropic features.[103] Subsequently, the same group reported free-standing films of an amyloid fibrils−graphene composite in which amyloid fibrils from β-lactoglobulin and graphene form organized, alternate layers. This material was shown to possess shape memory properties and is biodegradable via enzymatic proteolysis of the fibrils.[104]

7.3. Sensors. Surface modification and surface interactions with biomolecules are key aspects for the development and characterization of sensors. Surface-mediated self-assembly processes such as the ones discussed here have been explored for applications as sensors. A commonly used self-assembling motif for sensor fabrication is the dipeptide FF. FF has been reported to organize into tubular nanostructures.[111] These nanostructures were immobilized on electrode surfaces either by direct modification of the structures with thiols to enable bonding to gold[107] or by allowing self-assembly of the tubes to take place during solvent evaporation directly on the electrode[106,108,112] to detect NADH,[106,107] H_2O_2,[107] oxygen,[108] or ammonia.[112] In these devices, the self-assembled peptide structures typically provide increased sensitivity and reproducibility as well as nonmediated electron transfer, short detection times, large current densities, and higher sensor stability.[108]

For the context of this review, where the focus is on the influence of surfaces on the self-assembly process, two examples will be highlighted in more detail. The first example is a composite surface composed of peptide (FF) nanowires and graphene (PNWs-G) fabricated on a silicon surface that was employed to generate an electrochemical sensor for the detection of NADH. The graphene sheets were used to support the orientation of FF-based fibers and obtain an ordered hybrid graphene/peptide structure. When measuring the presence of NADH by the detection of an oxidation current, it was shown that the ordered structure of the composite layer improved the electronic conductivity and enhanced the sensing performance (via a higher current sensitivity of the sensor) compared to the sensors composed of the individual components alone or a disordered composite surface.[106] The second notable example shows that FF nanotubes with different architectures can be formed on a 4-mercaptopyridine-modified gold electrode surface if the self-assembly process takes place in different solvent atmospheres. Under water vapor, a mixed population of small fibers and larger, flat tapes was obtained, while under aniline vapor, the formation of larger fibers but no tapes was observed. This further translated into different crystal structures being formed on the surface; an orthorhombic structure with a $P22_12_1$ space group was formed under aniline vapor, and a hexagonal $P6_1$ space group was attributed to the structures formed under water vapor. The most notable difference between the sensors prepared from these two structures is that the aniline-vapor-based orthorhombic structure was considerably more stable. The increased stability was attributed to the stronger interaction between the FF structures and the 4-mercaptopyridine molecules on the electrode surface caused by the increased ability of the FF molecules to engage in $\pi-\pi$ interactions and mixed hydrophilic/hydrophobic interactions with the surface.[112]

8. CONCLUSIONS

Self-assembly processes and supramolecular materials have been studied for several decades, but there is still the potential for new, useful developments. A more recent addition to the repertoire of tools at the disposal of research in self-assembly is the influence of solid surfaces on the self-assembly process. Virtually all self-assembly is conducted in the presence of a surface or interface. If this surface participates in the self-assembly process, then it may become a key contributor to the final properties of the self-assembled material.

In this review, we have discussed the surface-mediated self-assembly of protein-, peptide-, and nucleoside-based molecules by classifying the type of interaction between the surface and the self-assembling molecules into electrostatic, polar, and physical (topology or roughness) interactions as well as the confinement of self-assembly-initiating processes. The material surface can impact the location, organization, orientation, mechanical properties, and formation kinetics of the self-assembled materials. In spite of our attempt to classify these interaction, it is important to highlight that it is not always clear if the reported surface properties are indeed the only contributing surface parameters that impact interfacial self-assembly. This is also relevant when drawing parallels to systems where specific interactions between surfaces and molecules are exploited to control interfacial self-assembly

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because both specific and nonspecific components may contribute to the direction of the self-assembly process.

From a mechanistic point of view, the formation of self-assembling molecules at the surface and the ability to control the strength of the molecule−surface interaction (and hence the mobility of molecules or nucleation sites at the surface) play central roles in influencing the self-assembly process in many of the known examples. The routes by which this can be accomplished are diverse and may vary depending on the molecules and surfaces involved. Not all observations related to the surface-mediated influence on self-assembly are fully understood, and there is considerable scope to investigate these interactions in more detail to establish particular design rules for specific classes of surfaces and self-assembling proteins, peptides, and nucleosides. Similarly, the potential synergistic effect of multiple parameters on a particular self-assembly process is poorly understood and remains to be elucidated. A better understanding of the mechanisms of nonspecific surface-mediated self-assembly may even lead to the development of improved specific surface-directed self-assembly by highlighting key surface parameters that could be exploited in a focused manner, indicating the potential need for the screening of interfering nonspecific interactions or by providing the opportunity to generate systems that synergistically exploit both specific and nonspecific interactions.

An emerging concept in self-assembly is the use of multivalent binding sites to structure multiple ligands or increase the binding affinity.[113,114] With the potential exception of modulating the availability of charges of molecules adsorbed on a surface,[49] this approach has yet to be actively explored in the context of the surface-mediated self-assembly of complex architectures but would be a potentially exciting area for mimicking biological functions.

Most of the work in the surface-mediated self-assembly area has been carried out on planar surfaces because these are much more readily analyzed than more complex surface topologies. There is a potential benefit in expanding the surface-mediated control over gelation to more complex surface topologies and particles as this would open up further application potentials as biomaterials in drug delivery and regenerative medicine. The range of the surface-induced effect is also rather unexplored. Knowledge about the distance over which a surface effect persists before bulk gelation becomes predominant is still lacking but could prove essential to understanding how best to exploit the influence of the surface on the self-assembly process.

Surface-mediated self-assembly is in the early stages of its scientific development and its application potential is only just beginning to be exploited, but it may have an exciting role to play in the future in the self-assembly field.

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Maria Marlow is a pharmacist with a Ph.D. in drug delivery and subsequent postdoctoral research in tissue engineering at the Massachusetts Institute of Technology. She also has 18 years of industrial drug delivery experience, notably working on AstraZeneca's metered-dose inhaler Symbicort. Her industrial career includes scientific and line manager roles in 1996, leading multidisciplinary teams in early formulation and product development. In 2012, she was appointed as an associate professor in formulation science and pharmaceutical materials in the School of Pharmacy, University of Nottingham. Her research interests are novel drug delivery systems that address an unmet clinical need. Her current research projects use supramolecular hydrogels and include the self-assembly of prodrug gelators for localized delivery, improving the therapeutic outcomes of existing drugs and nucleoside-based hydrogels for the delivery of proteins and peptides.

Mischa Zelzer obtained his first degree in chemistry from the Technical University Graz and completed his Ph.D. in 2009 at the University of Nottingham. He then moved on to undertake postdoctoral research at the University of Newcastle and the University of Strathclyde before joining the Technical University Eindhoven under a Marie Curie Fellowship. He then came back to the U.K. in 2013 to take up his current position of assistant professor at the University of Nottingham. Mischa's research interests revolve around interfacial phenomena and responsive materials for applications in a biological context, including supramolecular self-assembly at interfaces, enzyme and light responsive materials, peptide-based biomaterials, and the modification and analysis of biomaterial surfaces.

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