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Polydopamine Nanostructures as Biomaterials for Medical Applications

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Abstract

Polydopamine is a versatile and organic material that can be deposited as a conformal film with nanometer thickness on virtually any substrate. Much of the initial foundational work regarding polydopamine synthesis and processing was reported during the 2000s. Latter years have witnessed increasing interest and widespread adoptation of polydopamine as a material for many applications including medicine. Conformal polydopamine coatings confer unique chemical and physical properties to many substrate materials including metals, ceramics, polymers, and beyond. Polydopamine-modified surfaces permit facile bioconjugation of many biomedical materials for potential use as bioadhesives, contrast agents, drug delivery systems, and protein-adsorption resistant interfaces. Polydopamine-based materials and interfaces may improve the performance of biomedical devices used in neurotechnology, diagnostics, and cardiovascular applications. This highlight article reviews recent advances in polydopamine processing capabilities. The use of polydopamine as a material in various biomedical applications is also discussed. Finally, challenges and opportunites in translating polydopamine for future biomedical technologies are summarized.

1. Background and Introduction

Biological Inspiration for Polydopamine Coatings. The origins of bioinspired polydopamine (PDA) synthesis are linked to the composition of mussel foot proteins (mfps), biopolymers secreted by the blue mussel (*Mytilus edulis*) that exhibit unique mechanical properties and robust adhesion to diverse substrate materials in hydrated environments. Mfps contain high molar ratios of amino acid residues with primary amines and catechols, motifs that contribute to robust interfacial adhesion[1]. The richness and complexity of mfp structure, processing, and function continue to be studied and serve as an inspiration for the design of many new biomaterials. The processing challenges and intrinsic complexity of protein-based polymers motivate the synthesis and characterization of mfp-like materials such as catechol-bearing polymers including random copolymers[2], block copolymers[3], and telechelic network precursors[4]. The high concentrations of catechols and primary amines in mfp can also be recapitulated in dopamine, a precursor to hybrid organic-inorganic materials formed through successive steps of oxidative ring formation, polymerization, and condensation (Fig. 1). The resulting material, termed polydopamine (PDA), is composed of dense hyperbranched oligomers that coalesce into colloidal particles in the bulk solution and conformably coats interfaces including substrates immerged in the buffer[5]. PDA uses dopamine precursors and is one of the simplest catecholamine coatings, but other precursors can polymerize into coatings such as L-Dopa, for example.

Promise of Polydopamine as a Biomedical Material. PDA and its derivatives are attractive coatings for surface functionalization because PDA has facile and versatile processing conditions, exhibits ubiquitous and robust adhesion to many organic and inorganic substrates, and contains functional groups that can be used in post-modification. PDA and its derivatives

also exhibit unique potential as a material for functionalizing medical devices owing to robust adhesion to many commodity metals and polymers, naturally occurring precursors (e.g. dopamine, L-Dopa, norepinephrine), and the versatility of primary amines and hydroxyl groups in bioconjugation[6]. Many reports have advanced our understanding about structure-property-processing relationships in PDA, but many gaps in fundamental knowledge remain. This article highlights recent advances in PDA processing, further elucidating the nuanced relationships between structure, processing, and properties. In addition to materials composition, other facets of PDA properties will be summarized including electrochemistry, nanostructure, adhesion, and mechanics. Potential applications of PDA colloids and thin films will be discussed while focusing on using PDA as a biomedical material.

2. Advances in Polydopamine Synthesis and Processing

Summary of the State-of-the-Art of Polydopamine Synthesis. The canonical approach to synthesizing conformal PDA coatings with nanometer-scale thickness on surfaces uses auto-oxidative polymerization of soluble dopamine precursors in aqueous Tris buffers[7], though a variety of other amine-free or inorganic buffers can be used, too[8]. This method produces both colloidal PDA particles in the bulk solution and conformal PDA films at solid-liquid or liquid-vapor interfaces (**Fig. 2a**). This approach to PDA synthesis is advantageous because it uses benign aqueous solvents, requires mild polymerization conditions, and is compatible with many substrate materials including metals, oxides, and polymers. Furthermore, conformal PDA films can be uniformly deposited on substrates ranging from >1 m^2 in area down to colloidal dimensions. The robust interfacial adhesion of nascent conformal PDA films is critically attributed to chemical motifs (catechol & amine) also found in adhesive mfps. The combination

of catechols and primary amines in PDA can create a number of bonds for cohesive and adhesive interactions including coordination bonds, π- π stacking, hydrogen bonds, covalent bonds, hydrophobic interactions, and cation–π interactions[9–13]. Synergetic interactions between catechols and primary amines may further enhance the adhesion of PDA to materials in complex fluids by displacing salt ions at the interface[1]. Rich in various functional groups, PDA exhibits excellent chemical reactivity, allowing diverse functionalization schemes for various applications. Synthetic PDA is chemically and mechanically analogous to the natural pigment eumelanin[14], both of which exhibit in vitro and in vivo biocompatibility in various contexts[15–17].

2.1 Advanced Synthesis Strategies for Polydopamine

Limitations on Established Methods for Polydopamine Synthesis. Expanding the synthetic toolbox could create new PDA-based materials with novel compositions, properties, and functions. The auto-oxidation of dopamine into PDA in bulk aqueous solutions typically relies upon dissolved O_2 (g) to initiate cyclization, polymerization, coalescence, and eventual deposition at interfaces. There are several important consequences of this widely adopted method. First, the polymerization kinetics of PDA is relatively slow and self-limiting. A typical process requires >10 h to deposit PDA films with thicknesses <100 nm. While this deposition rate is perfectly suitable for surface modification applications, this prohibits the rapid synthesis of PDA as a bulk material. Second, the auto-oxidation of PDA using the dissolved O_2 in bulk solutions produces films with granular morphologies and nanometer-scale roughness, properties that can negatively impact the properties of PDA interfaces such as texture-dependent adhesion, charge injection, and effective surface energy. Third, PDA polymerization from buffers creates PDA coatings at interfaces, but also creates colloidal PDA particles in the bulk solution that

adsorb to surfaces and contaminate interfaces. Recent and ongoing work aims to accelerate polymerization kinetics and improve the control of PDA texture.

Accelerating Polydopamine Synthesis Using Supplementary Oxidants. Introducing supplementary oxidants into precursor solutions can accelerate PDA deposition[22-23], but systematic structure-processing relationships as a function of oxidative potential have only recently been reported[18]. Dopamine buffers with sodium periodate (standard reduction potential of +1.55 V) achieve PDA deposition rates of ~100 nm hr^{-1}, which is significantly faster than observed deposition rates of 2-10 nm hr^{-1} achieved when using dissolved O_2 (g). Furthermore, PDA films synthesized in the presence of soluble oxidants exhibit root mean square (RMS) roughnesses of <20 nm. Dopamine buffers with $CuSO_4/H_2O_2$ deposit PDA at a constant rate of 43 nm hr^{-1} [19]. $FeCl_3/H_2O_2$ is another oxidant that accelerates PDA deposition[20]. The effect of pH and metal-ion-mediated oxidant on the initial phases of catecholamine oxidation can be described using a thermodynamic framework[21]. Transition-metal ions are intriguing choices for oxidants because they can accelerate PDA deposition and also incorporate into nascent PDA networks through coordination bonds. The full impact of "doping" PDA with transition metals has yet to be fully understood and is a compelling direction for future study.

Polydopamine Synthesis as an Output Signal. Natural proteins can also mediate PDA synthesis and deposition. Horseradish peroxidase (HRP) is an enzyme that rapidly oxidizes various small molecule substrates in the presence of H_2O_2. HRP is often conjugated on secondary antibodies and is used as a signal transducer in common immunoassays such as enzyme-linked-immunosorbent-assays (ELISA). HRP can also rapidly oxidize dopamine precursors to yield PDA, a process that is harnessed in a highly sensitive and generalizable technique for immunoassays termed enzyme-accelerated signal enhancement (EASE)[22]. EASE

combines bioconjugation capabilities with rapid and localized deposition of polydopamine at the target site. Together, these processes can increase the detection-sensitivity by up to 1000x. In one demonstration, combining EASE with ELISA can detect HIV antigens in blood down to <3 fg ml ml^{-1}. This intriguing demonstration can expand our preconceptions regarding how PDA can be used as a biomaterial. Although classically understood as a versatile coating process, the advantages of PDA polymerization help transduce biomolecule concentration into an optical signal to reduce the detection limit in immunoassays. The versatility and robustness of PDA polymerization can potentially increase the speed and sensitivity of many other diagnostic tests.

2.2 Advanced Processing Strategies for Polydopamine

Spray Coating Techniques for Polydopamine. Conformal deposition of PDA at interfaces is typically performed by submerging the substrate to be coated in a dopamine-containing buffer. This approach has obvious limitations for some substrates including those with components that are water-sensitive, those with large form factors, or water-soluble and hygroscopic materials. A spray coating method for PDA has been developed by Hong *et al.* that addresses some of these limitations[23]. The key innovation is careful control over the stoichiometry between dopamine and sodium periodate oxidant. A 2:1 ratio of [Dopa]:[$NaIO_4$] can achieve extrapolated deposition rates of 1800 nm hr^{-1}, orders of magnitude faster than immersion-based coating techniques. The rapid deposition rates permit spray coating of PDA thereby expanding the range of substrates that can be functionalized.

Microwave-Enhanced Polydopamine Deposition. Microwave radiation is another strategy to accelerate PDA deposition from bulk solutions[24]. Irradiating the solution with microwaves during PDA polymerization can increase the extrapolated deposition rate to 72 nm hr^{-1}, which is

18x faster than control experiments that exhibit extrapolated deposition rates of approximately 4 nm hr^{-1}. Furthermore, the rate of microwave-assisted PDA deposition is proportional to the source power up to 1000 W. A series of informative control experiments suggest that microwave irradiation increases the PDA deposition rate by generating free radicals in situ and by elevating the buffer temperature. Interestingly, the proportional relationship between temperature and PDA deposition rate was also observed when using dopamine precursor solutions supplemented with $NaIO_4$ [18].

Non-redox Active Chemical Additives. The chemistry and microstructure of poly(catecholamines) can also be controlled by doping precursor solutions with additives. PDA can be polymerized in the presence of other synthetic macromolecules such as polyethylene glycol (PEG), polyvinylalcohol (PVA), and polyvinylpyrrolidone (PVP)[25]. Co-deposition of PDA with either PEG or PVA enables non-covalent surface modification of films with the respective polymer while PVP suppresses efficient PDA formation. This method can produce protein adsorption-resistant materials in a one-step coating process without the need for covalent modification. PDA can also be co-deposited in the presence of charged macromolecules[26]. Both polycations and polyanions restrict the diameter of PDA particles to 10-100 nm. The diameter of spherical colloidal PDA particles can be limited to ~30 nm when polymerized in the presence of protein biopolymers such as albumin, lysozyme, and α-lactalbumine[27]. The precise mechanism(s) to describe PDA polymerization in the presence of macromolecules is still unclear. However, phenomenological trends suggest that polymers coat nascent PDA particles, which could retard particle growth and coarsening.

2.3 Controlling Texture of Polydopamine Interfaces

PDA films with reduced RMS roughnesses can be synthesized through several processing modifications including: reducing the concentration of dopamine precursor; limiting deposition time; enhancing convective mass transport; and orienting substrates to reduce fall-on particles from the bulk solution. Additionally, post-processing strategies such as sonication can also reduce the surface roughness. Cho *et al.* describes a PDA post-processing technique in which films are exposed to ultrasound in mildly basic solution to polish the interface[28]. PDA deposition times of 1 h followed by sonication in 10 mM Tris-HCl (pH = 8.5) produce films that are 3 nm thick with an RMS roughness <1 nm. PDA films are functionalized using polymers bearing glycidyl groups that covalently couple to primary amines or the hydroxyl groups from catechols. This intermediary layer than permits the patterning of block copolymers (BCP) into lamellar architectures. Taken together, smooth PDA films permit processing of BCP on diverse substrate materials including those that are flexible.

The texture of PDA can also be controlled easily by other processing conditions such as temperature[29]. As previously mentioned, the rate of PDA deposition is accelerated proportionally as the temperature of the buffer is increased to intermediate temperatures of 70 ^{o}C. These processing conditions create PDA particles with diameters of ~100 nm decorated with nuclei of ~10 nm. The hierarchical texture of PDA particles uniquely confers extreme hydrophobicity to these surfaces, which have a range of potentially compelling biomedical applications.

2.4 Synthesizing Polydopamine into Non-Conventional Form Factors

Strategies for Processing Polydopamine into Freestanding Nanomembranes. PDA synthesis in bulk solutions often produces both suspended colloidal particles, often in the form of

nanoparticles, or conformal coatings with thicknesses <100 nm. One often reported property of PDA is the robust interfacial adhesion between conformal PDA films and substrates composed of many different types of materials. However, processing PDA into freestanding PDA nanomembranes could enable new directions for materials characterization and technological translation. Klosterman *et al.* report a facile method to prepare freestanding PDA nanomembranes based on careful control of the buffer composition (**Fig. 3a**)[30]. The key innovation in this process is the composition of the post-processing buffer for delamination of the nanomembranes. Using alkaline buffers with monovalent cations disrupts catechol-substrate interactions thereby enabling transfer to other target substrates from liquid-vapor interfaces.

Techniques for Templated and Patterned Polydopamine Synthesis. Controlling the micro- and nanostructures of PDA affords many advantages for creating application-specific materials. There have been several important demonstrations that use various features of PDA polymerization and deposition to create custom geometries. Tokura *et al.* describe a bottom-up strategy to process PDA into arbitrary anisotropic nanostructures using DNA-origami templated polymerization with G4/hemin based DNA nanotiles as templates[31]. DNA origami controls PDA polymerization to create structures with nanoscale precision. This technique was then leveraged to create a supramolecular glue to control the conformations of DNA origami. Controlling PDA nanostructures can also be accomplished by using template-guided synthesis, microemulsion templating, or solvent combinations that shape colloidal PDA into hollow rods or capsules, for example[32,33]. Nador *et al.* describe an approach where sacrificial templates for PDA deposition can be removed using mild post-processing conditions[34]. Sheng *et al.* describe the preparation of PDA-based Janus particles using liquid marbles as microreactors. In this synthesis scheme, silica particles are trapped at the water/air interface wherein only one side of the particle is selectively

exposed to PDA polymerization. The adhesive capability of PDA is leveraged to create inorganic particles that are selectively modified with PDA to create Janus particles. UV irradiation can accelerate PDA deposition by creating reactive oxygen species in solution[35]. UV-trigger PDA polymerization not only increase the deposition rate, but affords opportunities for spatial control in a process that is analogous to a negative photoresist. The ability to start or stop UV-triggered PDA deposition requires neutral to acidic buffers. UV-triggered PDA polymerization could create functionalized surfaces with unique micropatterns for applications in controlling cell adhesion or creating sensor arrays. UV-triggered acceleration of PDA can be mediated by including a natural reduction agent in the buffer. Du *et al.* added sodium ascorbate (vitamin c) to inhibit PDA polymerization by reducing dopaminequinones back into dopamine[36]. Adding sodium ascorbate in conjunction with UV irradiation has several advantages including allowing PDA polymerization in basic buffers, tighter control over deposition rate, and more uniform PDA coatings. There are many other strategies to control PDA nano- and micro-structure that leverage the redox activity and UV absorption in PDA precursors, chemical stability of PDA, and robust adhesion from pendant catechols in PDA.

3. Polydopamine as a Medical Material

3.1 Antifouling Coatings Based on Polydopamine.

The unique combination of benign and facile processing, ubiquitous adhesion to many commodity materials, and diverse functional groups motivate the use of PDA as a coating for medical devices. The diverse chemical motifs present in PDA can be used as a dual-functional antimicrobial surface[37]. PDA is first co-polymerized with Cu^{2+} ions resulting in a copper-doped film that can be deposited on commodity materials used in medical devices including titanium

oxide, silicon oxide, gold, Nitinol, and silicone. PDA films 20-50 nm in thickness can be covalently coupled to zwitterionic sulfobetaine acrylamides through aza-Michael addition reactions between R_1-NH-R_2 groups in PDA and pendant acrylates in the small molecule. The resulting anti-microbial coating can be deposited on virtually any surface, reduces *E. coli* adhesion, and secretes potent anti-microbial Cu^{2+} ions to reduce bacteria growth as assessed by fluorescent microscopy and colony-forming unit. This demonstration of an antimicrobial coating summarizes many of the intrinsic advantages of PDA coatings: nanometer-scale thicknesses; deposition on various materials including organic and inorganic substrates; reversible metal ion chelation; diverse chemical motifs that are suitable for secondary surface functionalization.

Zwitterionic PDA-like coatings can also be synthesized from random copolymers of [2-(methacryloyloxy)-ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide (SBMA) and dopamine-MA (DMA; **Fig. 4a**)[38]. Microgels composed of SBMA-DMA copolymers with 5 mol% DMA are then deposited on diverse substrates through drop casting. Pendant catechols function as an adhesion motif and a precursor for film formation through coalescence and crosslinking. The resulting zwitterionic SBMA-PDA films exhibit numerous compelling properties such as anti-fogging, anti-frosting, and protein-adsorption resistance. In situ formation of PDA after adsorption of macromolecular precursors is a compelling strategy to expand conditions to deposit PDA and enhance the mechanical stability of the resulting PDA films. PDA can be deposited as a nanometer-scale adhesion layer for post-modification with zwitterionic moieties or it can be formed in situ to ensure robust adhesion of zwitterionic polymer precursors. These two strategies to create zwitterionic surfaces illustrate many of the advantages of PDA as a motif to functionalize surfaces including adhesion to diverse substrate materials, versatile functional groups, and flexible processing.

3.2 Polydopamine as a Biomedical Adhesive

The Impact of Texture and Mechanics on Polydopamine Adhesion. The high molar concentration of adhesive catechols in PDA has motivated the use of this material as an underwater adhesive for use in biomedical applications. However, materials that produce strong intermolecular bonds are not enough to ensure robust adhesion of macroscopic bodies in complex fluids. Other properties such as texture and mechanics play important roles that govern the overall adhesion of PDA. By extension, controlling the texture of PDA at interfaces has important implications in the performance of catechol-bearing interfaces as adhesives. Kwon *et al.* demonstrated that the adhesive strength of PDA is strongly texture-dependent in both air and condensed phases such as water[39]. The nanometer-scale roughness can be controlled through processing parameters such as deposition time and post-processing such as sonication. Adhesion in PDA coatings is roughness-dependent since the experimental and theoretical predictions of the elastic modulus of PDA can approach E_{PDA} ~2 GPa [40,30], thereby exceeding Dahlquist's criterion for quick tack[41]. Furthermore, adhesion is dramatically attenuated with increases in both the RMS roughness and the roughness gradient of PDA interfaces. These experimental observations suggest that despite the high density of adhesive catechol motifs in PDA, the practical application of PDA as a broadly deployable adhesive is limited by the intrinsic mechanical properties and texture at the interface.

Colloidal Polydopamine as an Adhesion Layer. Colloidal PDA has also been studied as an adhesive to resist shear loading. Tran *et al.* deposited spherical aggregates of PDA as an intermediary layer between two metal-metal interfaces. Composites with colloidal PDA at the interface exhibited no statistical improvement in lap shear strength compared to various control

conditions. However, metal interfaces covalently functionalized with 3-aminopropyltriethoxysilane (APTES) prior to PDA deposition did exhibit a marked improvement in interfacial bonding under shear. Although this particular system is complex and the results largely empirical, it is clear that covalent conjugation across the metal-organic-metal interface in an important consideration while designing high performance adhesives. PDA therefore exhibits exceptional utility as a potential intermediary layer to functionalize surfaces and promote adhesion across inorganic-organic intefaces[42].

Prospects for Polydopamine-based Adhesives. More broadly, these findings are cautionary in the sense that depositing catechol-bearing PDA is not a panacea for improving the adhesion between materials. Rather, PDA must be deployed carefully with great attention to the chemical composition and microstructure at the interface. The intrinsic surface roughness and high Young's modulus are critical barriers to widespread use of PDA as an adhesive in many applications. Freestanding PDA can potentially be used as a biomedical adhesive for soft tissue because the target substrate will have a characteristic elastic modulus <100 kPa thus satisfying Dahlquist's criterion[41]. Robust adhesion requires conformal contact to ensure intermolecular bonding across interfaces, which is challenging. PDA could potentially be polymerized in situ across interfaces using a process that is analogous to curing an epoxy. The adhesion of in situ polymerization of norepinephrine-based poly(catecholamines) between two mica surfaces was studied[43]. These model environments may serve as useful models to study the fundamentals of intermolecular adhesion in PDA and PDA analogues. For example, the referenced study found that including amines in poly(catecholamines) increases the intermolecular adhesion in by 30x compared to polycatechol analogues without amines. However, there are obvious technical

challenges that must be addressed before in situ polymerization of PDA can be used in practical applications.

4. Applications that Leverage Optoelectronic Properties of Polydopamine

4.1 Polydopamine Coatings as Charge Injection Layers for Implantable Electrodes

PDA exhibits several properties that suggest it could serve as a charge injection layer for implantable electrodes including conformal geometry, robust adhesion, and high concentrations of redox active catechols (**Fig. 4b**). Redox active catechols in PDA coatings deposited on inorganic electrodes could enable charge injection through Faradaic reactions, thereby overcoming some of the limitations associated with capacitive charge injection. This hypothesis was tested by measuring the charge injection capacity of (CIC) indium tin oxide (ITO) electrodes modified with PDA[44]. The CIC of ITO+PDA electrodes approached 100 μC /cm^2, which is approximately 6x larger than the CIC of uncoated ITO electrodes (15 μC/cm^2) and comparable to the CIC of bare Pt electrodes, but significantly lower than the CIC of other electrode materials with Faradaic charge injection mechanisms such as activated iridum oxide. Interestingly, the maximum CIC for PDA-modified electrodes was achieved by holding the potential at +0.7V (vs. SHE), which is roughly the reduction potential of catechols. The CIC dropped tremendously if the pre-bias deviated from this critical value, which suggests that catechol groups are largely responsible for increasing the charge injection capabilities of PDA-modified electrodes.

4.2 Leveraging the Photothermal Properties of Polydopamine in Smart Materials

PDA is typically used as a surface modification strategy, but the bulk properties of PDA also have utility in many applications of biomedical materials. Melanin and melanin analogues

such as PDA exhibit broadband adsorption of light including UV wavelengths. Like melanins, PDA also exhibits highly efficient photon-phonon conversion, which makes it potentially useful as a photothermal sensitizer. In one demonstration, PLGA-PEG-PLGA block copolymers were processed into thermogels loaded with PDA-like melanin nanoparticles. Irradiation of concentrated solutions of PLGA-PEG-PLGA using UV light at intensities of 10.8 mW m^{-2} raises the temperature by +20 ^{o}C within 20 min, which is sufficient to induce thermal phase transitions in polymers with lower critical solution temperatures. As the solution temperature increasing with irradiation time, block copolymers undergo sol-gel transitions to create hydrogel networks. Subsequent heating induces precipitate formation as temperatures exceed >40 ^{o}C. The photothermal properties of PDA-like materials could have applications for other types of thermally responsive networks such as collagen or synthetic polymers with upper critical solution temperatures such as poly(*N*-isopropylacrylamide).

The efficient photothermal conversion of PDA has also been used in artificial muscles[45], self-healing materials[46], and shape-memory polymers[47](**Fig. 4c, d**). Shape-memory liquid crystalline elastomers (LCE) based on copolymers of diglycidyl ether of 4,4′-dihydroxybiphenyl and sebacic acid can be post-functionalized with PDA[48]. The temperature of LCE+PDA networks could be heated to >160 ^{o}C within 20 s of exposure to infrared light at 1.4 W-cm^{-2}, which is sufficient to induce LC-isotropic phase transitions. Patterning PDA also enables spatial control of thermal phase transitions, which in turn can be harnessed for applications in shape-memory applications and smart actuators. One potential limitation in using PDA as a photosensitizer for biomedical applications is the rapid attenuation of visible and near-IR light in tissue. Therefore, it's likely that smart materials that harness the photothermal properties of PDA will be constrained to external applications such as epidermal devices.

5. Challenges and Opportunities in Polydopamine Material Technologies

Knowledge Gaps in Polydopamine Synthesis and Processing. There have been extraordinary advances in the fundamental and applied knowledge related to PDA structure, processing, and properties, yet many knowledge gaps remain. The precursors to PDA are ostensibly simple and the underlying reactions to yield PDA, albeit complex, are largely understood individually. However, multiple precursor molecules, divergent synthetic pathways, and complex intra- and inter-molecular interactions lead to exponential chemical and structural complexity as the eventual bulk material is formed. Furthermore, there are many open questions regarding the self-assembly, nucleation, and coalescence of soluble precursors into pigment-like PDA nanomaterials. Additionally, catechols can chelate many transition metal ions thereby presenting additional opportunities to control PDA composition and properties. Understanding materials chemistry and mesoscale processes such as metal ion-doping, self-assembly, and particle formation is essential to understanding the various facets of emergent properties of PDA and its analogues. We posit that the intrinsic complexity of PDA produces knowledge gaps structure-property-processing relationships that have limited, to some extent, the technological translation of PDA-based materials for some biomedical applications.

Emergent Properties and Complexity in Polydopamine. The intrinsic chemical and structural complexity of PDA is challenging, but also creates unique interdisciplinary research opportunities. Advances in computing power and computational methods could help unravel the chemical heterogeneity, topological complexity, and amorphous structure that are associated with PDA. Simulating the macroscopic properties of PDA across composition, mesoscale structure, and metal-ion doping, could generate profound insight into structure-property

relationships. Furthermore, it may be possible to identify non-natural compositions or structures that can yield emergent properties including robust mechanical properties, unique optoelectronic behavior, or catalytic function. Consider the scenario of understanding the mechanical properties of PDA and its analogues. There are many fundamental questions that remain. What intermolecular interactions govern intrinsic mechanical properties? What are the fundamental limits of elasticity, strength, hardness, and ductility? How do "grain size" and "grain boundaries" contribute to macroscopic mechanical properties? Molecular dynamics and density functional theory can certainly predict many of these properties from simple molecular precursors that are organized into structure with short-range order. However, theoretical predictions must be reconciled with experimental data generated from scalable synthesis and characterization techniques. For example, measuring the thin film buckling phenomena of PDA nanomembranes on elastomers can rapidly determine the Young's modulus of coatings, a technique that can be rapidly scaled to measure mechanical properties as a function of composition. Other creative processing capabilities are needed to measure relevant macroscopic properties across various compositions in an efficient manner.

Concluding Thoughts. PDA is a promising biomaterial for many prospective applications in medicine. In recent years, there has been significant progress to expand PDA processing capabilities and invent new techniques for post-functionalization of PDA. There are obvious applications in creating protein-adsorption resistant coatings for applications in sensors or non-fouling biomaterials. Surface coatings will continue to be a fertile and productive area of research as the boundaries of these capabilities continue to be pushed in interesting new directions. However, there are any other applications that could potentially leverage the unique properties of PDA. Leveraging oxidative PDA polymerization to enhance immunoassays is one

such example, but there are likely dozens of other potential use cases that will be identified through interdisciplinary collaborations. We also predict that bulk PDA could eventually be leveraged as a material for many applications including tissue adhesives or non-toxic electrodes for safe and implantable power supplies. These efforts in technology translation will be collectively empowered by research collaborations that coordinate progress in PDA processing, characterization of PDA, and computational tools.

Conflicts of interest

The authors declare no conflicts of interest.

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Table of Contents Graphic

Recent advances in polydopamine synthesis are described with a particular focus on biomedical applications. Prospects and future challenges for the application of polydopamine as a biomaterial are also described.

Figures and Figure Captions

Fig. 1

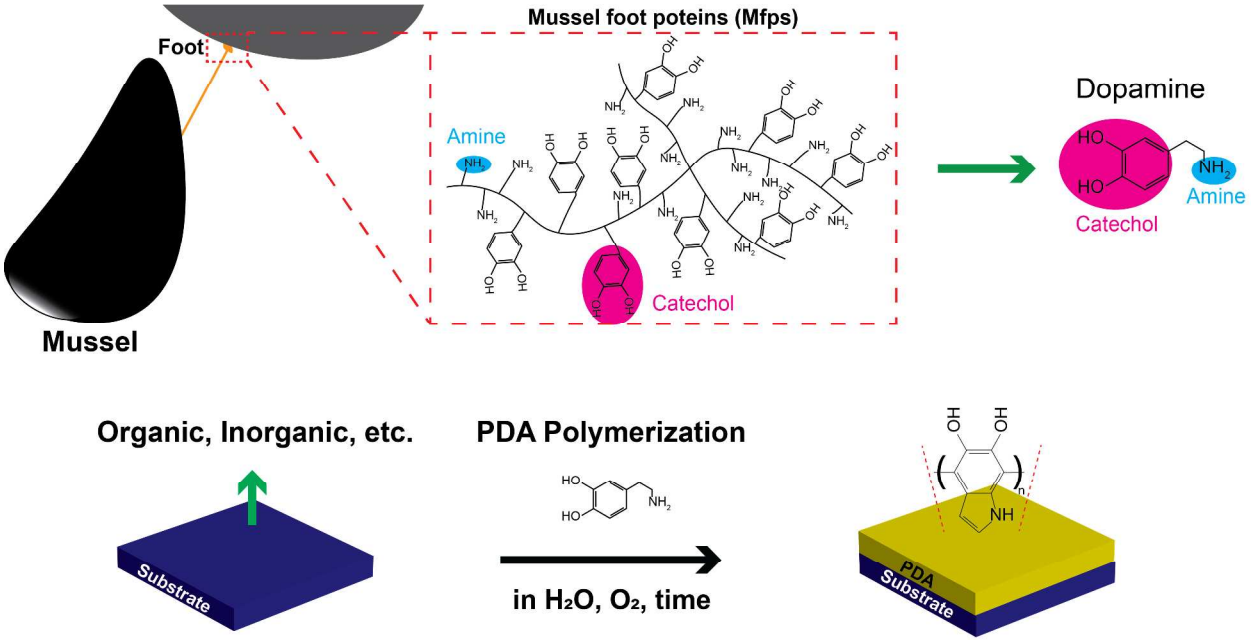

Fig. 1 Top) Schematic illustrating the mussel-inspired chemistry of dopamine that is used as a precursor material for the synthesis and deposition of conformal polydopamine (PDA) films. Auto-oxidative cyclization of catecholamines through the intramolecular aza-Michael addition of the primary amine with the oxidized *o*-quinone. This nascent reactive intermediate can then polymerize into polydopamine, a branched oligomer that can coalesce from solutions to form colloidal particles or conformal films that deposit at interfaces such as substrates (shown here).

Fig. 2

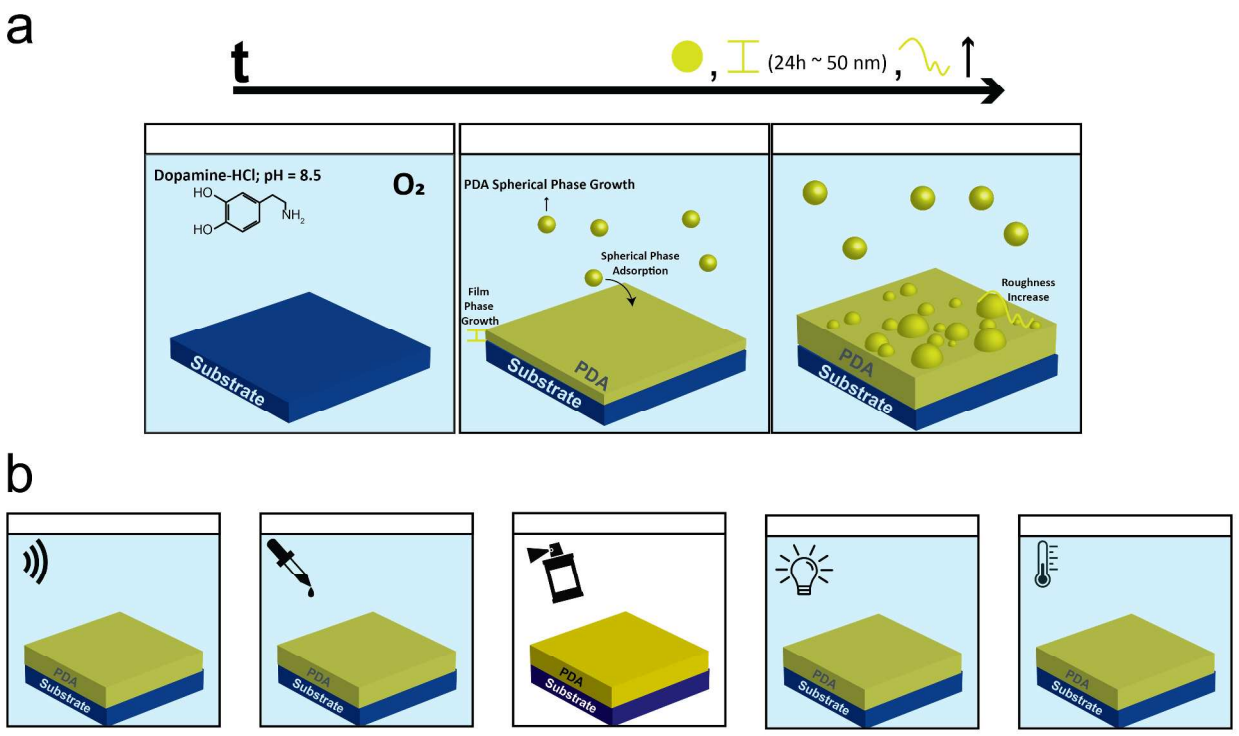

Fig 2. (a) Schematic illustrating dopamine polymerization as initially described by Lee *et al*. Incubating virtually any material in a weakly alkaline buffer (pH = 8.5) with soluble dopamine-HCl and ambient dissolved O_2 (g) produces conformal PDA films at interfaces with thicknesses that approach 50 nm after ~24 h. The initial stages of PDA film deposition are followed by the formation of colloidal particles that adsorb on the substrate. (b) There are many possible companion processes to mediate PDA deposition at interfaces including (L to R) sonication, addition of supplemental oxidants, spray coating of PDA, UV irradiation, and temperature. Deposition is done in air for spray coating as noted by the transparent background. These strategies expand processability and increase the range of possible properties for PDA. For example, post-deposition sonication can reduce surface roughness and supplemental oxidants can accelerate deposition while spray coating and UV irradiation can create well-defined microstructures on various substrate materials.

Fig. 3

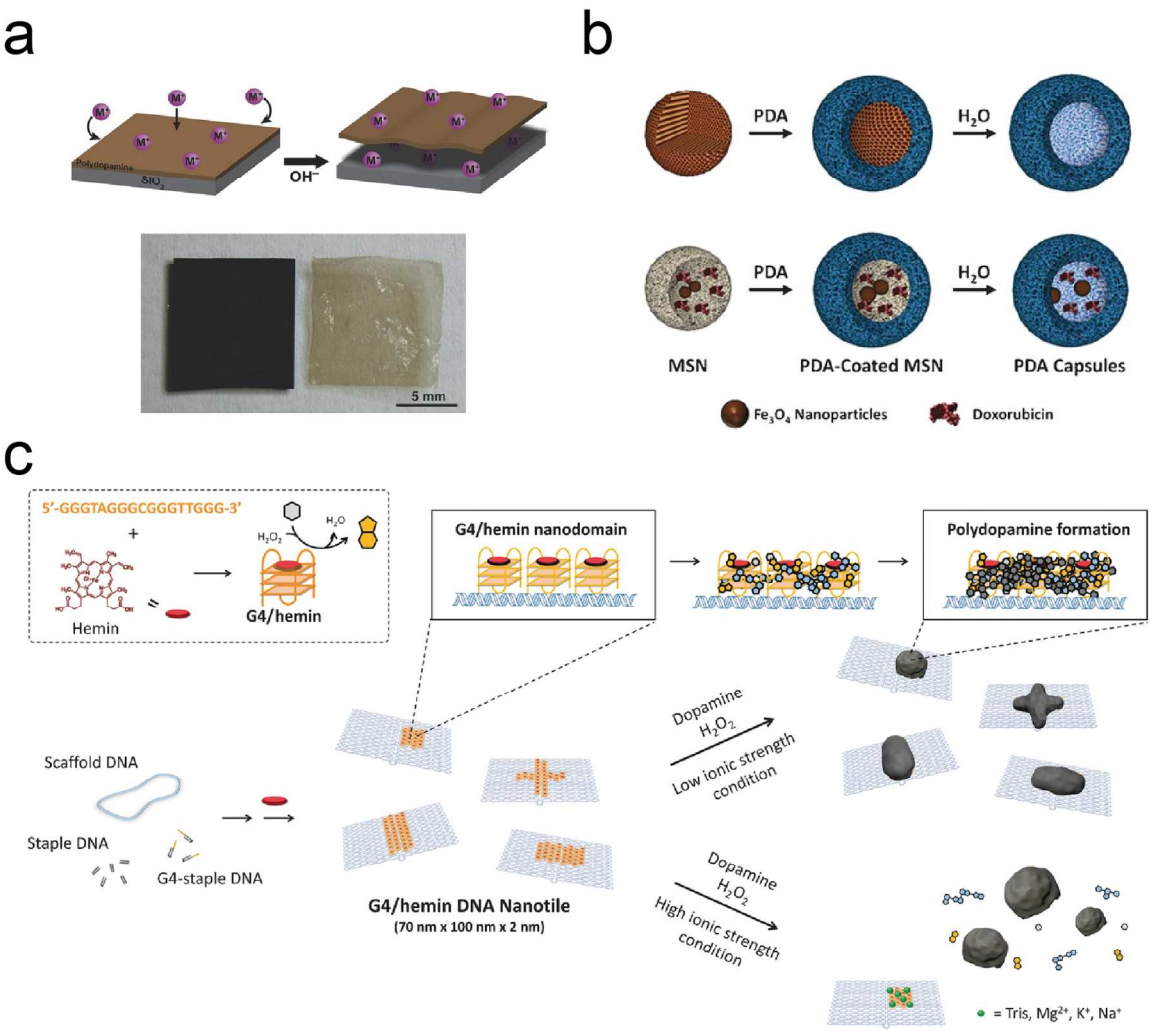

Fig. 3 Various synthetic routes can expand the range of form factors of PDA beyond conformal adherent nanoscale films and spherical colloidal particles. (a) Conformal PDA nanomembranes can be delaminated from the underlying substrates by dissociating catechol groups through incubation in alkaline buffers with monovalent salts. The result is a freestanding PDA nanomembrane <100 nm in thickness[30]. Reproduced with permission. Copyright 2017 Wiley-VCH. (b) Hollow PDA nanocapsules can be synthesized by first depositing conformal films on nanoparticle-based sacrificial inorganic templates composed of either Fe_3O_4 or mesoporous SiO_2[34]. Once the template is removed through selective dissolution, the hollow PDA

nanocapsules remain, which could have potential biomedical applications including theragnostics and drug delivery. Reproduced with permission. Copyright 2016 Wiley-VCH. (c) Schematic illustrating the fabrication process of PDA nanostructures with various defined geometries on the DNA nanotile (light blue) bearing G4/hemin DNAzyme nanodomains (orange and red, respectively)[31]. Reproduced with permission. Copyright 2018 Wiley-VCH.

Fig. 4

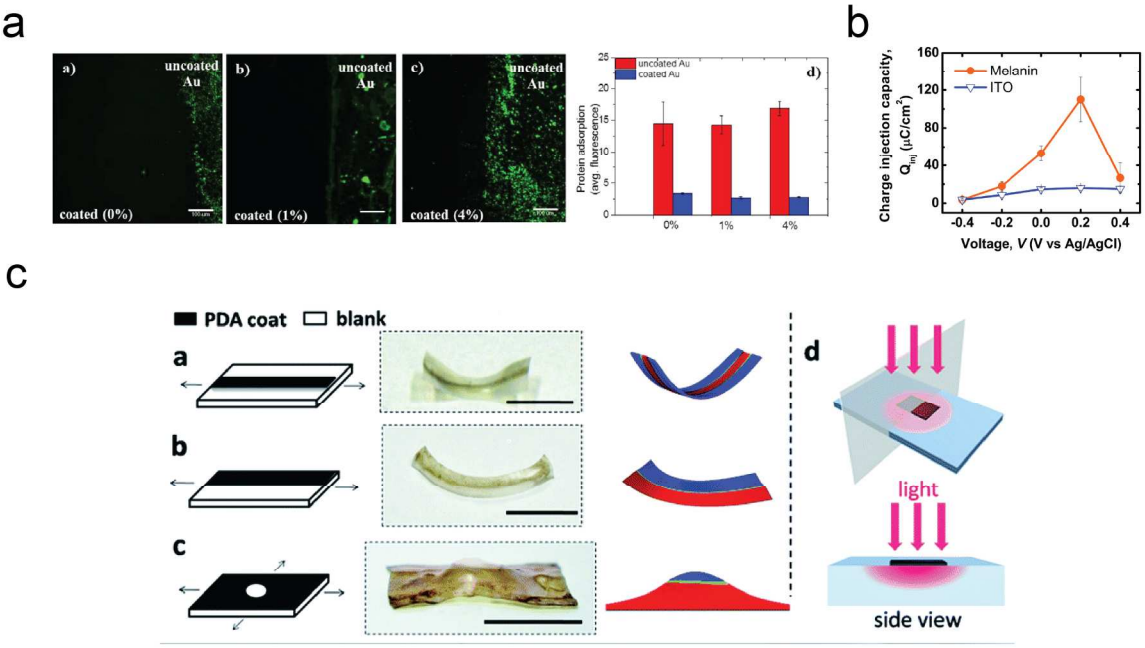

Fig 4. Recent developments in applying polydopamine-based coatings in various biomedical devices applications. (a) *Antifouling surfaces*. Fluorescent micrographs of labeled bovine serum albumin proteins adsorbed to Au substrates modified with zwitterionic PDA-like coatings (scale bar is 100 um). Quantified micrographs show that Au substrates modified with zwitterionic-PDA coatings are more resistant to protein adsorption compared to bare controls[38]. Reproduced with permission. Copyright 2018 American Chemical Society. (b) *Charge-injection materials for implantable electrodes*. Charge injection capacity of the PDA-coated indium tin oxide (ITO) electrode and bare ITO electrode, as a function of the dc bias versus Ag/AgCl[44]. Reproduced with permission. Copyright 2016 Royal Society of Chemistry. (c) *Photothermal dopants in shape-memory materials*. Schematic representation (left), optical micrograph (middle; scale bar = 1 cm), and finite element model simulation (right) of PDA coated shape memory polymers with different patterns[48]. Schematic representation of the photothermal effect of PDA pattern. Reproduced with permission. Copyright 2016 Royal Society of Chemistry.

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