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Marine-Inspired Polymers in Medical Adhesion

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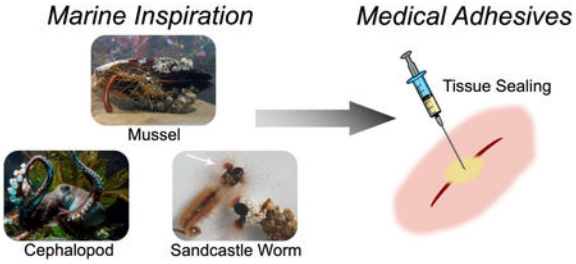
Abstract

Medical adhesives that are strong, easy to apply and biocompatible are promising alternatives to sutures and staples in a large variety of surgical and clinical procedures. Despite progress in the development and regulatory approval of adhesives for use in the clinic, adhesion to wet tissue remains challenging. Marine organisms have evolved a diverse set of highly effective wet adhesive approaches that have inspired the design of new medical adhesives. Here we provide an overview of selected marine animals and their chemical and physical adhesion strategies, the state of clinical translation of adhesives inspired by these organisms, and target applications where marine-inspired adhesives can have a significant impact. We will focus on medical adhesive polymers inspired by mussels, sandcastle worms, and cephalopods, emphasize the history of bioinspired medical adhesives from the peer reviewed and patent literature, and explore future directions including overlooked sources of bioinspiration and materials that exploit multiple bioinspired strategies.

Graphical abstract



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Keywords

Bioinspired material; tissue adhesion; medical adhesive; mussel; sandcastle worm; cephalopod; polymer biomaterials

Introduction

Medical adhesives that are easy to apply to seal wet tissues during surgery have enormous potential to replace invasive mechanical fixations such as sutures and staples, or to provide fluid-impenetrable sealing of a suture line.[1] Most engineering and consumer adhesives exploit non-specific interactions (e.g. van der Waals), but these adhesive interactions are dramatically weakened in the presence of the high dielectric and ionic strength of physiological fluids.[2, 3] Despite these challenges, a myriad of biological and synthetic adhesives have been developed and approved for specific surgical procedures.[4] Clinically used tissue adhesives include fibrin, gelatin resorcinol, and cyanoacrylates, all of which are considered to have shortcomings with respect to toxicity or mechanical performance.[4] They suffer from poor adhesion or biocompatibility and fail to meet the requirements of many surgical procedures including sealing leaks in the lungs and gastrointestinal system, fetal surgery, and most musculoskeletal repairs. This unmet clinical need has motivated the development of synthetic and bioderived adhesives, including polysaccharide and polyethylene glycol (PEG) based materials with improved adhesive strength and biocompatibility relative to clinically available formulations.

Here, our focus is on marine animals that firmly attach to biological or mineral surfaces underwater and the medical adhesive materials they have inspired. For a more general treatment of bioinspiration and bioinspired materials development, the reader is referred to several excellent reviews.[3–10] Well-studied underwater adhesion specialists include the mussel, sandcastle worm, and octopus (Fig. 1).[11–14] Basic science research has elucidated these animals' highly-evolved wet adhesion mechanisms, and researchers have since incorporated these chemical and physical wet adhesion strategies into medical adhesives. Much of the work in mussel-inspired adhesion has focused on understanding and mimicking the unusual adhesive proteins found in the terminal plaque of the mussel byssus.[15] Sandcastle worms employ coacervate-forming protein adhesives to construct their sand grain dwellings.[12] Cephalopods, on the other hand, rely on anatomical features, in the form of suction cups, to adhere robustly onto wet surfaces.[14] Moving forward, promising strategies in bioinspired adhesives will likely involve incorporating multiple bioinspired elements, for example mussel-inspired motifs together with a cephalopod-inspired suction cup microstructure or other combinations of chemical and physical adhesive strategies. Animals have evolved many strategies for adhering underwater, and incorporating these strategies into medical adhesives offers a tremendous opportunity to address unmet clinical challenges.

Mussel-inspired adhesion

Biology of mussel adhesion

Mussels secrete protein-based byssal threads to tether themselves to diverse underwater surfaces, including rocks, ships, and other organisms. At the distal end of these threads, adhesive proteins form an adhesive plaque that securely anchors the thread (and thus the mussel) to the surface, allowing the mussel to withstand the high shear forces of waves.[15–22] The mussel's adhesive plaque is arguably the most well-studied marine bioadhesive (Fig. 2). A landmark 1981 paper from the Waite lab identified a mussel adhesive protein in the byssus that had repetitive decapeptide sequences with a high concentration of 3,4-dihydroxypheny-l-alanine (DOPA), a post-translational modification of tyrosine. DOPA was hypothesized to mediate the high adhesion strength of these proteins.[23] Waite and colleagues went on to identify numerous other byssal proteins, each with a specific sequence, biodistribution and function.[22]

In particular, mussel foot proteins (mfps) found at the adhesive interface have high DOPA content. Surface force apparatus measurements of extracted and recombinant mfps clearly demonstrated the contribution of DOPA to bioadhesion.[21, 24] In another fundamental study, single molecule force spectroscopy experiments demonstrated the high adhesion strength of an isolated DOPA amino acid, furthering the hypothesis that DOPA, specifically its catechol side chain, mediates robust adhesion.[25] In the interfacial proteins with the highest DOPA content, DOPA was often flanked by the positively-charged, nitrogen-containing amino acids lysine and arginine.[26] Experiments with model siderophores (proteins that chelate iron) confirmed that catechol and amino functional groups contribute synergistically to wet adhesion in a spatially-dependent manner.[26] In addition to amino acid composition and protein sequence, recent research has shown that other chemical and physical phenomena including iron crosslinking, phase inversion and temporospatial control during byssal thread fabrication are essential to overall mussel adhesion.[11, 27, 28] A fundamental understanding of mussel adhesion has inspired many scientists to improve the performance of medical adhesives.[29]

Mussel-inspired tissue adhesives

DOPA oxidation, crosslinking and interactions with tissue surfaces—In theory, a robust medical adhesive would form covalent interfacial interactions with the tissue surface. Thus, many clinically approved synthetic adhesives rely on reactive motifs (e.g. aldehyde, N-hydroxysuccinimide (NHS) esters) that target lysine and cysteine residues that are omnipresent at the surface of most targeted tissues.[30] In the mussel and in mussel-inspired medical adhesives, DOPA facilitates wet adhesion to the substrate. As an amino acid, DOPA has thus far only been identified in the proteins of marine adhesives, likely due to its versatile reactivity which could interfere with organisms' biochemical processes.[11]

In alkaline seawater or after the addition of a strong oxidant (e.g., $NaIO_4$), catechols convert to reactive *o*-quinone species and can covalently conjugate with tissue surfaces via many possible reaction pathways (Fig. 3). A similar pathway in the bulk of the plaque leads to protein crosslinking, thereby contributing to elastic properties of the mussel byssus.[11]

Importantly for tissue adhesion and perhaps also for mussel adhesion, *o*-quinone is highly reactive towards tissue bound lysine and cysteine residues via nucleophilic addition or imine formation (Fig. 3). [31] Although the exact reaction pathways are still under investigation, it is clear that DOPA can form covalent bonds with nucleophilic substrates.

In synthetic materials, DOPA or catechol is often used for both adhesion (binding to substrates) and cohesion (crosslinking of the adhesive material), and there are several common strategies for oxidizing or crosslinking DOPA. The formation of coordination bonds between DOPA and Fe^{3+} has been extensively studied as a crosslinking and toughening mechanism in the mussel byssus and in mussel-inspired materials.[32, 33] However, for medical applications, iron should be used with caution, since soluble iron salts may increase bacterial growth and result in localized or systemic infection.[34–36] Swelling is an additional concern in iron-coordinated catechol gels; due to the dynamic nature of metal coordination bonds, hydrogels that are only crosslinked via metal-DOPA coordination may swell, causing the gel to dissipate.[37] Oxidizing agents such as $NaIO_4$ are regularly used to crosslink DOPA. However, when using such oxidizers with DOPA-functionalized polysaccharides, aldehyde formation via oxidative carbohydrate ring opening is important but often overlooked as a side reaction in these studies. Indeed, relying only on oxidative aldehyde formation in polysaccharides is enough to establish good tissue adhesion. This was exemplified by a study from the Elisseeff group in which methacrylated chondroitin sulphate was treated with $NaIO_4$ and resulted in the carbohydrate ring opening to yield aldehyde motifs.[38] Upon UV irradiation, the methacrylate motifs form a covalent network and the aldehydes form interfacial bonds resulting in a horizontal shear adhesive strength of 46 kPa to cartilage. $NaIO_4$ oxidation and Fe^{+3} coordination are ubiquitous in the mussel-inspired adhesives literature, but the benefits and drawbacks of each approach should be carefully considered in the context of the intended application.

Materials with mussel-inspired proteins and peptides—As Waite and colleagues discovered and characterized the proteins responsible for mussel adhesion, research teams have been striving to develop synthetic versions of mussel glue. Early efforts involved extracted mussel adhesive proteins intended for a range of applications including ligament reconstruction, skin grafts and dental restoration.[39] Extracting adhesive proteins from mussels proved to be impractical and expensive; thousands of mussels are needed to obtain even 1g of pure adhesive protein.[10] Therefore, a polymer with grafted DOPA-containing decapeptides was synthesized in an effort to mimic the high molecular weight of mussel adhesive proteins.[40] Tissue adhesive experiments on bovine corneal tissue revealed a shear adhesive strength of up to 32 kPa; however, unintended DOPA reactivity resulted in a short shelf life and large variation in observed adhesion strengths.[40] Despite this early research effort, neither material progressed to clinical use. Later, Biopolymer Products of Sweden disclosed in a patent the use of small, bioderived mussel adhesive decapeptides that were combined with charged polysaccharides (e.g. heparin, chitosan) and tested these as corneal adhesives.[41, 42]. For this particular application, the use of strong oxidizers or aldehyde compounds could be avoided, thus greatly increasing the biocompatibility. The only remaining commercial outcome of this early appears to be Cell-Tak™, an extract of adhesive

proteins from the mussel byssus that is available for non-medical applications including attaching non-adherent cells to surfaces for microscopy.[43]

In subsequent efforts, the Yamamoto group synthesized numerous polypeptides as mussel-inspired tissue adhesives.[44–47] For example, the addition of tyrosinase $(X\text{-}Tyr\text{-}Lys)_n$, (X = Gly, Ala, Pro, Ser, Leu, Ile, or Phe) resulted in the post translational modification of tyrosine into DOPA and subsequent oxidative crosslinking.[48] Tissue adhesion experiments on dry pig skin with concentrated solutions of the polytripeptides showed a shear tissue adhesion strength of 11 kPa. In an elegant approach, Deming and colleagues copolymerized lysine- and DOPA-functionalized α-amino acid N-carboxyanhydride (NCA) monomers into high molecular weight random polypeptides (>100 kg mol^{-1}).[49–51] This material was used to prepare moisture resistant bonds to aluminum, steel, glass, and plastics. In a related patent, Deming and coworkers hinted at the potential biomedical adhesive applications.[52] Taken together, early bioinspired research efforts focused on precise mimicry of the polypeptides of the mussel foot proteins and, while they informed future investigations, they were later replaced with efforts to develop materials with simplified designs.

Catechol-PEG materials—After Deming's influential work, the focus of the field of mussel-inspired materials shifted towards designs in which only one or a few bioadhesive elements are used to enhance wet adhesion. These approaches facilitate clinical translation but admittedly suffer from isolating one or more components (e.g. DOPA) from a complex protein adhesive. In an effort to obtain adhesive hydrogels, Lee *et al.* reported a 4-arm PEG macromer that was end-functionalized with DOPA motifs (cPEG, Fig. 4a).[53] The addition of an oxidizing agent ($NaIO_4$) to a solution of this polymer led to rapid gelation and adhesion to tissue. cPEG was tested as a tissue adhesive and showed a shear adhesion strength of 35.1 kPa towards porcine dermal tissue, a five-fold improvement over fibrin glue (Fig. 4b).[54] In the first *in vivo* use of cPEG, Brubaker, et al., secured transplanted islets to the liver or epididymal fat pad of diabetic mice with cPEG.[55] The material secured the islets in place *in vivo* for up to a year, with little evidence of inflammatory response or fibrotic capsule formation. Islet transplantation with cPEG and in sutured controls led to normoglycemia, reversal of the diabetic phenotype, in the mice.

Sealing of the amniotic sac after fetal surgery has been an important strategic focus for marine-inspired adhesives. Fetal surgery can correct some severe congenital abnormalities like spina bifida and twin-twin transfusion syndrome *in utero*, but to access the fetus, surgeons must puncture the amniotic sac (fetal membranes).[57] This fragile membrane does not heal or withstand suturing, and can rupture, leading to high risk of preterm birth (Fig. 4c).[57] Common commercial tissue adhesives were unsuccessful in this application;[58] however, marine-inspired adhesives excel at sealing in wet environments and are well-poised to address this unmet clinical need. With collaborators at the University Hospital Zurich, our group reported cPEG based hydrogels as a promising material to seal induced amniotic sac defects (Fig. 4d).[56, 59, 60] *Ex vivo* evaluation of the sealant showed a comparable acute tissue toxicity response to fibrin sealants.[56]

Nerites Corporation explored PEG-catechols as synthetic mussel-inspired tissue adhesives for medical applications. In a comparative study, the authors compared 4-arm PEG based

adhesives functionalized with a single DOPA motif, tetra DOPA sequences and short DOPA-lysine sequences, respectively.[61] Surprisingly, they did not observe a significant difference in tissue shear adhesion strength between adhesives carrying a single DOPA versus tetra DOPA sequences. However, upon addition of short DOPA-lysine sequences, a marked increase in lap shear tissue adhesion strength was found, confirming the synergy between DOPA and lysine. Lee and colleagues also developed a library of linear copolymers of polycaprolactone (PCL) and 4-arm PEG macromers in which two PEG-arms are functionalized with DOPA.[62, 63] With hernia repair as a target application, these functionalized PEGs were coated onto surgical meshes and biological scaffolds to form materials with high adhesive strengths.[62] The authors showed that adding an oxidant is necessary to form a strong adhesive interface. In another approach from the same team, unreacted $NaIO_4$ was incorporated into the polymer coating via a solvent casting process, rendering the patches immediately adhesive upon contact with tissue.[62] While strong oxidants such as $NaIO_4$ are perceived as potential biotoxins, biocompatibility studies showed acceptable cell viability (> 70% cell survival per ISO standard 10993–1).[62] On a cautionary note, cytotoxicity of mussel-inspired hydrogels was mainly attributed to the generation of H_2O_2 during oxidation of aromatic diols.[64, 65] This effect could be reversed with the addition of catalase to suppress oxidative stress.

To introduce degradability into PEG-catechol hydrogels, one can exploit linkers that are photo- or hydrolytically labile or that are susceptible to enzymatic cleavage. Our group introduced di-alanine (Ala-Ala) as spacer in DOPA functionalized 4-arm PEG macromers in order to exploit peptide cleavage by tissue elastase *in vivo*.[66] In another attempt to obtain degradable 4-arm PEG hydrogels, Zahid and coworkers functionalized 4-arm PEG polymers with photocleavable ortho-nitro substituted catechol groups.[67] After oxidative formation of the hydrogel, irradiation with UV light resulted in photocleavage of the crosslinks and hence debonding of the adhesive.

One drawback of PEG-based hydrogels is significant swelling which has the potential for postoperative complications such as blocked nerves. To address swelling, Barrett *et al.* reported the synthesis of 4-arm polypropylene-PEG (Tetronic) functionalized with DOPA (cT).[68] Subsequent oxidative crosslinking ($NaIO_4$) yielded a hydrogel that displayed a shear adhesion strength of 49 kPa and an absence of swelling due to a thermally induced hydrophobic transition of the PPO domains. Interestingly, a comparative investigation between cPEG and cT as amniotic sealant did not reveal a significant difference in critical burst pressure when sealants were used to seal a membrane that was inflated until rupture.[58]

Polysaccharide materials—Polysaccharides are strong candidates for mussel-inspired modification because they have a range of modifiable substitutions such as primary amines (e.g. chitosan) and carboxylic acids (e.g. alginate, hyaluronic acid) to derivatize with phenolic motifs.[4, 69] In one example with hyaluronic acid, Cho and Haeshin Lee formed hydrogels of dopamine-conjugated hyaluronic acid oxidized with $NaIO_4$.[70] Although these hydrogels could also be formed by photo crosslinking of methacrylated hyaluronic acid, the authors showed that catechol was essential for the formation of an adhesive interface. While such DOPA containing hydrogels did not show appreciable pull-off

adhesion to liver tissue (1.4 kPa), the authors observed an adhesive strength of 48 kPa to heart tissue. In a similar fashion, the Cho group formed hydrogels of hyaluronic acid functionalized with aromatic triols in alkaline conditions or after addition of $NaIO_4$.[71] Interestingly, rheological tack tests were used to qualitatively show that alkaline conditions lead to higher adhesion strengths. This observation may indicate that adhesion of DOPA-containing materials is sensitive to the oxidation method and suggests different oxidation method-dependent kinetics or reaction pathways. Additionally, hyaluronic acid conjugated with dopamine was combined with thermo-responsive PEO-PPO-PEO (Pluronic) to prepare a lightly crosslinked injectable hydrogel.[72] Upon increasing the temperature to 37 °C, adhesive hydrogels were formed. Tissue adhesion experiments on mouse skin revealed a pull-off adhesion strength of 7 kPa.

Another polysaccharide of high interest for medical applications is chitosan, a (partly) deacylated chitin that is commercially derived from crustaceans. One important commercial medical application of chitosan films is hemostatic wound dressings (e.g. HemCon®).[73] Taking advantage of the hemostatic ability of chitosan, Lee, Park, and colleagues prepared hydrogels by reacting catechol functionalized chitosan (Chi-C) with thiol endcapped Pluronic.[74] These hydrogels had a pull-off adhesive strength of 15 kPa, and reduced blood loss when applied as a hemostat. InnoTherapy is currently pursuing these materials commercially.[75, 76] To improve the mechanical properties of bioinspired chitosan hydrogels, Hwang and colleagues synthesized pyrogallol-functionalized chitin fibers that formed adhesive hydrogels after oxidation with $NaIO_4$ or chelation with Fe^{3+}.[77] In another innovation from Lee and coworkers, oxidatively crosslinked Chi-C was drop casted onto needle shafts to form hemostatic needles. [76, 78] Intravenous and intramuscular injection into mice using these coated needles revealed a complete prevention of blood loss due to self-sealing of Chi-C. Likewise, the same authors also coated cotton swabs with Chi-C.[79] Simply swiping coated swabs onto a bleeding wound reduced blood loss in both normal and coagulopathic (diabetic) mice.

Alginate, a polysaccharide found in certain bacterial biofilms and brown seaweed, is also a promising material for medical adhesives. Upon addition of Ca^{2+}, alginate will form weak hydrogels due to the formation of ionic bonds. Inspired by the tanning of brown algae, Bianco-Peled and colleagues oxidized a solution containing phloroglucinol, alginate and Ca^{2+} to form adhesive hydrogels.[80] Depending on the concentration of each component, the authors observed tissue shear adhesive strengths from 17 to 25 kPa. In a subsequent report, the same authors investigated the influence of alginate concentration in combination with various phenolic compounds as a sealant using a burst device.[81] In such a device, a hole in a fluid-filled chamber is covered with cellulose and the sealant. Then, the chamber is inflated and the pressure at which the sealant bursts is recorded. Contrary to their previous results, no significant difference in burst pressure was detected in the presence or absence of phenolic compounds. In addition, two of the polyphenolic compounds (epicatechin and morin) appeared to reduce the adhesive performance.

To increase the tissue adhesive strength of alginate gels, Mooney and coworkers prepared a family of double network hydrogels that contain alginate, Ca^{2+} and a second covalently crosslinked polymer such as poly(acrylamide) or NHS-crosslinked chitosan. These materials

adhered to diverse tissues.[82] In a control experiment using chitosan labeled with fluorescein, the authors observed significant tissue penetration (30 μm), suggesting that mechanical interlocking of cationic polymers into tissue surfaces is at least partly responsible for the adhesive interfacial strength of these chitosan adhesives.

Gelatin-based materials—The use of DOPA or catechol to mediate adhesion in wet environments is usually considered to be mussel-inspired, but, to the best of our knowledge, the first reported example of a marine-inspired medical adhesive was actually inspired by the strong underwater adhesion of barnacles. Barnacle adhesive plaques had been found to contain tyrosine and polyphenol oxidase enzymes that were hypothesized to be responsible for the strong interfacial adhesion. [83, 84] Based on the assumption that catechol-lysine crosslinks serve an essential role in barnacle adhesion, the Erhan group reported the first marine-inspired medical adhesive – gelatin functionalized with aromatic diols.[84, 85] Adding polyphenol oxidase to a solution of functionalized gelatin resulted in a material that adhered to bone slices. However, protein analysis of barnacle adhesives subsequently showed an absence of DOPA,[86] and Rittschof and Wahl reported that tyrosine and polyphenol oxidase enzymes are connected to surface priming: eliminating marine biofilms before the establishment of permanent adhesion.[13, 86–88] Since the early barnacle-inspired work, Wang and coworkers crosslinked DOPA-functionalized gelatin using Fe^{3+} or genipin, resulting in an adhesive hydrogel.[89] Shear adhesion studies on moist porcine dermal tissue and cartilage showed an adhesion strength up to 25 and 194 kPa respectively.

Polymethacrylate materials—There is a large research effort to incorporate DOPA into polymethacrylates to develop wet adhesives for engineering and tissue sealing applications. The Grubbs group prepared adhesive hydrogels by reacting poly(dopamine methacrylamide (DMA) - NHS ester acrylate - acrylic acid) with thiol end-functionalized three-arm PEG, revealing a shear adhesive strength of approximately 12 kPa towards porcine dermal tissue. [90] In a report from Kuroda and coworkers, poly(DMA-methoxyethyl acrylate (MEA)) was tested as dental adhesive with and without the addition of Fe^{3+} salts.[91] The authors observed especially strong adhesive bonds to dentin in the presence of Fe^{3+}, and the presence of saliva during adhesive application did not significantly reduce the bonding strength. In an elegant approach to render methacrylate based polymers biodegradable, Agarwal and coworkers copolymerized a mixture of 2-methylene-1,3-dioxepane, DMA and PEG methacrylate monomers, resulting in randomly distributed degradable ester bonds in the polymer backbone.[92] Tissue adhesion experiments on fresh porcine skin revealed a shear adhesive strength of 6 kPa, with a further increase to 8 kPa and 13 kPa after the addition of H_2O_2 or Fe^{3+} salts, respectively.

Polymethacrylates containing catechol were also used in a combined mussel- and gecko-inspired adhesive material in which the wet adhesive capabilities of the catechol were combined with the dry, structural adhesive strategies used by many organisms including geckos.[93–95] Geckos' impressive climbing abilities are due in large part to nanofibers on their foot pads that provide a large surface area for non-specific interactions like van der Waals forces. However, gecko feet, as well as many synthetic gecko-inspired materials, have limited adhesive abilities in wet environments as water disrupts these non-specific

interactions. [93, 96, 97] It is likely for this reason that geckos are less active during rainy weather.[98] To overcome the reduced wet adhesion of synthetic nanofibrillar-patterned materials, our lab reported the first gecko- and mussel- inspired wet adhesive: nanopatterned PDMS coated with a DOPA-containing poly(DMA-co-MEA).[99, 100] In dry conditions, adhesion was doubled compared to uncoated nanostructures, and in wet conditions, the coated samples could maintain the adhesive strength during 1000 contact cycles. The combination (nanofibers and polymer coating) material exerted stronger adhesion forces in wet conditions than the gecko-inspired (nanofibers only) material. This is one example of researchers combining multiple bioinspired strategies to create materials to address challenging problems.

Materials for mucoadhesion—Mfps extracted from the threads and plaques of mussel byssal threads were found to have mucoadhesive properties, but, at first, the exact contribution of DOPA to this adhesion was unclear.[39, 101] Experiments with cPEG revealed significant mucoadhesion that could be attributed more definitively to catechol, since PEG alone is not mucoadhesive; this demonstrated DOPA's ability to form effective interfacial bonds with mucosa.[102] Several other DOPA-containing materials have been tested for mucoadhesive properties. Cerruti and colleagues infiltrated or conjugated chitosan with DOPA, hydrocaffeic acid or dopamine. These materials were mucoadhesive, and oxidation was initiated upon contact with mucosa.[103, 104] Likewise, Haeshin Lee and coworkers observed increased gastrointestinal (GI) tract retention due to mucoadhesive properties of Chi-C.[105] In addition to DOPA-functionalized materials, oxidative coatings of polydopamine have also been evaluated. Sunoqrot and coworkers tested the mucoadhesive properties of polydopamine coated mPEG-PCL nanoparticles, targeting gastric mucosa for controlled drug release. Compared to uncoated particles, the authors observed an increase in mucosal retention and a similar drug release profile.[106] Mussel-inspired chemistries and materials are promising mucoadhesives and poised to address many clinical mucosal adhesion challenges.

Sandcastle worm inspired medical adhesives

Chemistry of sandcastle worm adhesion

Sandcastle worms, *Phragmatopoma californica*, are small marine worms that build their own underwater dwellings out of sand particles that they cement together with protein coacervate glue that they excrete (Fig. 1b). [7, 12, 27, 107] Coacervate formation is a thermodynamically driven liquid-liquid phase separation in which oppositely charged (amino acids in) proteins are triggered to phase separate by a change in temperature, pH or ionic strength. The exclusion of water during coacervation results in the formation of a concentrated macromolecular liquid that can solidify into a porous solid.[108] The rapid formation of solid coacervates by marine organisms has been hypothesized to be triggered by injection of proteins from acidic storage glands into seawater (pH ~ 8.1) while, simultaneously, Ca^{2+} and Mg^{2+} ions coordinate with phosphorylated serine residues.[109] As the sandcastle worm constructs its dwelling, after initial coacervate formation, the excreted adhesive is further slow-cured via oxidative DOPA crosslinking.[12] While the proteinaceous cement of the sandcastle worm contains DOPA residues (Fig. 1b), these

reactive amino acids are mainly indicated for cohesive protein crosslinking via polyphenol formation and DOPA-cysteine crosslinks. This suggests that the adhesive interface mostly relies on non-specific interactions.[12, 109] Inspiration from marine coacervate formation has led to the development of several medical adhesives.

Sandcastle worm-inspired materials

Inspired by the proteins involved in complex coacervate formation in sandcastle worms, Stewart and coworkers developed several complex coacervate tissue adhesives. As an analog to the phosphorylated anionic proteins of the sandcastle worm's coacervate, the authors synthesized poly(monoacryloxyethyl phosphate-co-DMA). To mimic the cationic protein, gelatin was functionalized with primary amines (Fig. 5b).[110] A fluid coacervate was observed upon addition of Ca^{2+} to an acidic solution that contained both polyelectrolytes at low pH (Fig. 5c). Mimicking sandcastle worms' adhesive secretion into basic seawater, a shift to basic pH led to solidification of the synthetic coacervate. The coacervated adhesive was well tolerated *in vivo* and adhered to bone in a rat model of craniofacial reconstruction. [111] To improve the adhesive strength, the same authors also prepared a double network hydrogel that combined a complex coacervate consisting of poly(monoacryloxyethyl phosphate-co-DMA) and poly(acrylamide-co-aminopropyl methacrylamide) with a PEG diacrylate hydrogel.[112]

While the presence of DOPA in sandcastle worm glue is hypothesized to primarily serve a cohesive role, synthetic sandcastle worm-inspired materials can become adhesive to tissue when oxidized with $NaIO_4$. In collaboration with TissueTech, the Stewart group tested these adhesive hydrogels to seal defects after fetal surgery.[56, 113] In an *ex vivo* experimental setup, they demonstrated that complex coacervate-coated fetal membrane patches outperformed uncoated patches in their ability to withstand pressure when inflated with fluid. In an *in vivo* model of fetal membrane sealing in Yucatan pics, the same authors were unable to detect a difference in efficacy between a bioinspired coacervate gel and a human amniotic membrane patch because the fetal membranes of Yucatan pigs healed spontaneously, a phenomenon not seen in human fetal membranes.[114] The complex coacervate glue was also tested for *in utero* spina bifida repair in a sheep model, but this study showed fetal neuronal degeneration or necrosis.[115] While the reasons for the negative response in this animal trial remain unclear, this body of work shows promise for the development of coacervate based injectable tissue adhesives.

Researchers have also taken inspiration from the mechanisms that sandcastle worms use to process their adhesive and its precursors. Before coacervate formation, the sandcastle worm stores the two oppositely charged proteins in separate secretory granules inside its glands. [12] Because proteins are stored in granules, the proteins are stable at the acidic pH of the glands but destabilize upon contact with seawater. This strategy is a practical approach to overcome high protein viscosity and prevents premature coacervate formation inside the glands. Inspired by this secretion approach, a collaboration between the groups of Langer, Lin and Karp coated particles of a highly viscous polymer, poly(glycerol sebacate acrylate) (PGSA), in alginate, resulting in a low viscosity, injectable aqueous dispersion.[116, 117] After injection of the nanoprecipitate dispersion, positively charged protamines were added,

and the material rapidly coalesced. Formation of a solid was achieved after rapid crosslinking of the viscous polymer using high intensity UV irradiation (10s, 380 mW cm $^{-2}$). Tissue adhesion studies onto epicardium tissue showed a pull-off adhesive strength of 14 kPa and cell viability studies indicated cytocompatibility. Commercial application of PGSA is currently pursued by Gecko Biomedical with a recent approval for clinical use in Europe.

Adhesives inspired by cephalopods

Anatomy of cephalopod adhesion

Mussels and sandcastle worms secrete proteinaceous adhesives that are intended to form a permanent holdfast. However, in nature, as in the clinic, adhering reversibly or temporarily can be quite useful. Cephalopods, a class of mollusks that includes octopus, squid, cuttlefish, and nautilus, adhere to underwater surfaces temporarily for numerous purposes including prey capture, mating, camouflage, and locomotion. [118] As in gecko and sea star adhesion, most cephalopod adhesion is the result of anatomical features, like muscular suction cups, or suckers, that adhere reversibly to surfaces [14]. However, some species in four cephalopod genera secrete adhesives from epithelial gland structures in different parts of the body to accomplish specially evolved functions including camouflage (*Euprymna*), attaching to underwater plants (*Idiosepius*), enhancing adhesion of the digital tentacles (*Nautilus*), and improving mechanical adhesion (*Sepia*) [118]. The biochemical makeup of these adhesives in each genus is still an active area of investigation, but early evidence suggests that they are composed of carbohydrates or protein. [118–120] As the biochemistry of these adhesives is elucidated, they may inspire synthetic mimics, but thus far, most cephalopod-inspired tissue adhesives have mimicked the suckers that serve as muscular hydrostats to allow cephalopods to grasp objects and attach reversibly to underwater surfaces, including living tissue (prey) and irregular surfaces.[14]

Materials inspired by octopus suckers

Octopus arms are covered with suckers that serve as muscular hydrostats. In *Octopus vulgaris*, there is an unusual small round protuberance inside each flexible suction cup. It is hypothesized that compression of this protuberance against a surface leads to a spatial separation between water at the top of the chamber and at the surface, effectively creating a vacuum that attaches the cup to the surface (Fig. 6a).[14, 121, 122] Importantly, this type of adhesion is only strong perpendicular to the surface. When a force in the plane of the surface is applied, water can easily re-enter and eliminate the pressure difference. Pang and coworkers reported patterned surfaces that are inspired by octopus suction cups.[14] The adhesive patches were prepared by reactive molding of a polyurethane acrylate-based polymer into an inverted silicon master. The authors compared various patterned geometries including perforated cylinders, cylindrical pillars, cylindrical holes and the *vulgaris* inspired sphere-in-cup architecture. In wet conditions, the octopus inspired architecture outperformed other geometries.

Yang and colleagues also created sucker-inspired tissue adhesives with a simplified cup architecture with no protuberance (Fig. 6b).[123] Silicon substrates were patterned with nanosucker geometries and tested on porcine epicardium tissue. Pull-off experiments

showed the patches had an adhesive strength of around 28 kPa on a wet glass substrate, and the patches maintained the initial adhesion strength for at least 80 min when submerged. Due to plastic deformation of PDMS, the authors found that the suction cups showed a significant loss of adhesion after 30 contact cycles. Patterned arrays of nanosuckers were also used to develop a multilayer skin adhesive patch that could serve as a wearable temperature sensor.[124] Similar to observations of Pang, et al., the authors found that a cylindrical hole pattern only results in appreciable dry adhesion.[14, 124] Taken together, octopus inspired patterned surfaces are an exciting new avenue of exploration for reversible tissue adhesive materials.

Inspiration from squid sucker ring teeth

Like octopus, squid also use suction cups on their tentacles to capture prey, but some squid species have a set of tough sucker ring teeth inside each sucker that they use to grip escaping prey. These sucker ring teeth attracted attention from materials engineers after Miserez and coworkers discovered that sucker ring teeth (SRT) were mainly composed of proteins, not chitin as previously suspected.[125–127] The authors showed that SRT proteins contain randomly oriented β-sheet nanocrystals dispersed in an amorphous matrix. This protein structure gives SRT their relatively high elastic modulus.[125] In the absence of covalent crosslinks, SRT proteins are readily soluble and melt processable, which is distinctive for natural load bearing materials. Pena-Francesch and colleagues demonstrated that SRT protein (suckerin) extracted from squid SRT have promising tensile and lap shear adhesive strengths to various underwater surfaces.[128] The potential of suckerin and suckerin-inspired materials as bioadhesives was furthered when Ding and colleagues produced recombinant suckerin that could be crosslinked into gels and films across a range of stiffnesses. When human primary fibroblasts, mesenchymal stem cells, or embryonic kidney cells were cultured on these suckerin materials, cells attached, were viable, and proliferated.[129] Together, this preliminary work represents promising first steps towards for biomedical applications by demonstrating that suckerin materials are adhesive and cell compatible.[128]

Outlook

Future research to develop bioinspired adhesives for clinical use may take inspiration from other sources, for example animals' materials processing strategies, or may combine multiple adhesive strategies. Future research efforts should address the mechanical mismatch often found between tissue adhesives and target tissues. To achieve high tissue adhesive strengths, it is essential to avoid a mechanical mismatch between the tissue and adhesive. This mismatch exists in most commercial tissue adhesives because the focus of development is usually on the formation of an adhesive interface rather than on the cohesive properties of the adhesive itself. In nature, adhesive interfaces feature sophisticated mechanical gradients to eliminate mechanical mismatch, for example as found in the squid beak where the gradient of hardness and toughness from the tip of the beak to the underlying soft tissue spans two orders of magnitude.[130] Squid beak gradients have inspired synthetic mimics,[131, 132] and squid beak-inspired materials could address the unmet challenge in tissue engineering of adhering tissues with different mechanical properties together, for example

attaching ligament to bone or tendon to muscle.[133, 134] Developing adhesives whose mechanical properties closely match those of the target tissue may necessitate development of different glue formulations for different applications, but the improved adhesive performance would likely be appreciable.

Another focus of future work should be to better understand processing methods used by marine creatures to store, process, and deliver the adhesive to the interface. Indeed, biomimicry of sandcastle worm complex coacervate formation described above is an early example of this. However, further research into coacervate formation is necessary to relate phase behavior to mechanical properties as a function of pH, concentration, temperature and ionic strength. For most surgical procedures it is desirable to prepare injectable formulations, which require a combination of low viscosity and rapid setting kinetics to form a load bearing adhesive. An often-used strategy is injection of two solutions through a mixing chamber, one containing an adhesive polymer and the other a (macromolecular) crosslinker. Notably, oxidative curing of DOPA-containing proteins (e.g. mussel plaque, marine egg cases) is slow in nature. Slow oxidation combined with tissue penetrating polymers may significantly increase (long term) interfacial adhesion via mechanical interlocking and anchoring. Therefore, it may be desirable to combine rapid initial gelation with slow curing.

Besides injectable formulations, tissue-adhesive patches are also valuable for medical applications. Gecko-inspired adhesive patches cannot adhere in wet environments unless an adhesive coating is applied or swellable amphiphilic blockcopolymers are used.[135] On the other hand, octopus-inspired patches do not require such a coating.[124] Like the gecko inspired wet adhesive patches, adding a wet-adhesive coating to octopus sucker-inspired patches may further improve their adhesion. Unlike in cephalopod adhesion, reversibility is not desired for most internal surgical applications, though it may be desirable in treatment of skin wounds. One advantage of patch-based adhesives is that the adhesive properties of patterned adhesive patches are largely substrate independent. Thus, adhesiveness can, for the most part, be decoupled from the bulk mechanical properties of the patch, improving material tunability.

Stimuli-responsive properties, including the ability to bond or de-bond on demand, may also be desirable in medical adhesives. Nitro-catechols have been incorporated into mussel inspired materials, and these adhesives de-bond upon exposure to UV irradiation. [67, 136] Another promising strategy to achieve de-bonding on demand in catecholic materials is to incorporate catechol-boronate chemistry, which features a pH-dependent boronate ester bond. Thus, changes in pH can be used to cycle a material between adhesive and non-adhesive states.[137] Other examples include the skin of many cephalopod species which can respond to physical and chemical stimuli with a rapid change in color or texture.[138] Researchers have developed cephalopod skin-inspired materials for applications including films that change color when stretched, innovations towards the development of wearable electronics, dynamic patterning, and materials that can change shape and texture.[138–140] Phan, et al., expertly reviewed dynamic materials inspired by cephalopod skin.[140] Many such technologies have the potential for eventual clinical translation to enhance tissue adhesives, especially those on the skin. Dynamic adhesives may be able to report strain or respond to skin temperature, and materials that can de-bond on demand (e.g. after exposure

to specific wavelengths of light) may be valuable as, for example, adhesives to attach monitor leads to neonates, the elderly, or other patients with compromised skin.

It is important to note that the mussel and the sandcastle worm evolved primarily to adhere to stiff surfaces. For the development of tissue adhesives, it would be relevant to investigate bioadhesive organisms that attach to soft and living surfaces. Potential sources of bioinspiration include several species of barnacles that can strongly attach to the skin of whales, reversible adhesion of sea star tube feet, and the pressure sensitive adhesive properties of squid sucker rings.[95, 128, 141] Analysis of the responsible protein sequences and subsequent biomimicry could lead to superior tissue adhesives. It was recently discovered that barnacle larvae secrete enzymes and lipids to clear omnipresent biofilms from marine surfaces before they establish permanent adhesion.[13] While the exact components that are responsible for this surface priming are not yet fully understood, the addition of a primer can be easily implemented to improve adhesion of bioinspired tissue adhesives.

Summary

Marine animals have evolved numerous methods for adhering underwater, and researchers have adapted many of these approaches into adhesive materials with promise for clinical tissue adhesion. Critical to the development of these and future materials is a deep understanding of the basic science underlying these natural adhesives and the marine organisms that create them. Early work in the field of mussel-inspired adhesives focused on direct replication of whole or fragmented mussel adhesive proteins. Over time, researchers have identified the chemical groups that most strongly contribute to mussels' wet adhesion (DOPA and, to a lesser extent, lysine) and created synthetic adhesive polymers using just these moieties to render natural and synthetic polymers adhesive towards wet tissue. Impressive progress in wet tissue adhesion has been achieved with this approach. Similarly, in the cases of sandcastle worm and cephalopod inspired materials, mimetic strategies that utilize only the most essential adhesive elements may surpass more thorough mimicry attempts. This strategy also allows for the incorporation of additional chemical functionality. In fact, taking inspiration from multiple biological sources, incorporating synergistic elements inspired by the mussel, sandcastle worm, octopus, or other animals as yet unexplored, may give ample opportunity for future advancement.

In mimicking and taking inspiration from the ocean's adhesives, researchers have developed materials with remarkable adhesion to wet mammalian tissues. Moving forward, engineers developing novel materials are buoyed by basic science researchers, who are discovering and characterizing the wet adhesives of the natural world. This biological understanding is paired with new breakthroughs from the lab bench, including new polymer synthesis strategies, nanofabrication techniques, and crosslinking chemistries. In developing adhesives for the clinic, tissue wetness is an enduring hurdle. Researchers and clinicians alike should continue to turn to the seas, where this challenging problem has been solved many times over.

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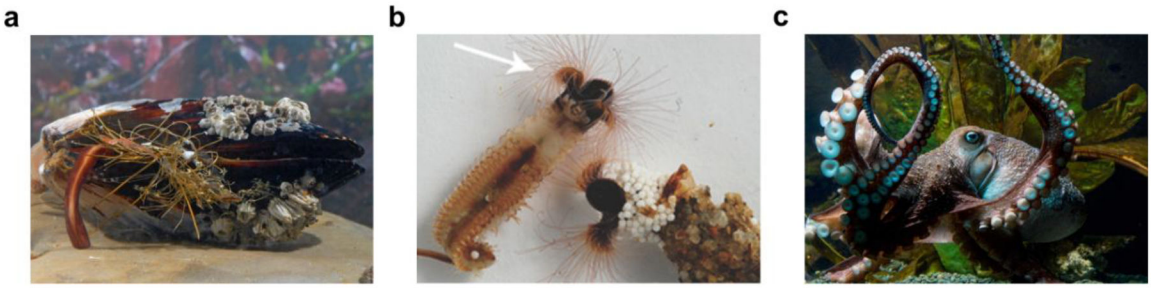

Fig. 1.

Underwater bioinspiration for medical adhesives. **(**a) Mussels strongly attach to underwater surfaces with a protein-based plaque and can withstand the strong forces of crashing waves. Image was generously provided by and reused with permission from Gary McDonald. (b) The sandcastle worm builds tubular dwellings of sand particles cemented together with adhesive proteins. Photo of a sandcastle worm (left, arrow) and a worm inside a tubular dwelling in construction. The (untanned) white granules contain the coacervated and uncured adhesive. Reproduced under the terms of the Creative Commons Attribution 4.0 International License [7] Copyright 2016, John Wiley & Sons, Inc. (c) A common New Zealand octopus uses suction cups to reversibly adhere to diverse surfaces and can use this attachment to move around its environment. Courtesy of the National Aquarium of New Zealand.

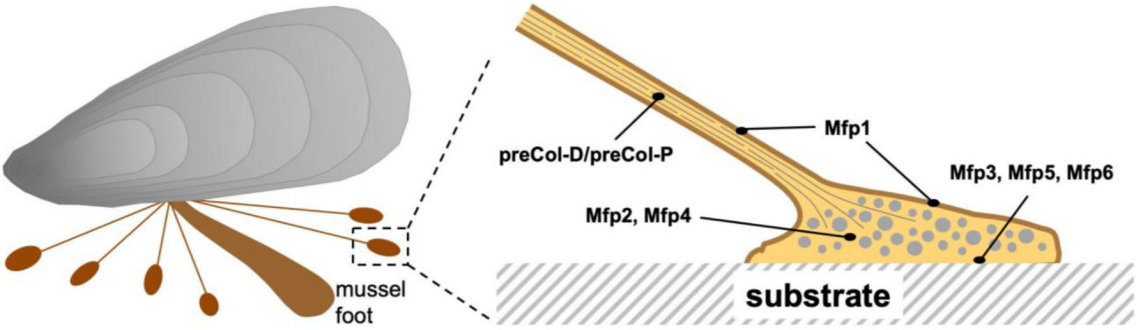

Fig. 2.

The mussel byssus. Mussels secrete many byssal threads to securely attach to underwater surfaces and withstand the high forces exerted by waves. During formation of a byssal thread, glands along the mussel foot secrete a mixture of byssal collagens and mfps that self-assemble and solidify into the thread shaft and the adhesive plaque. The core of the adhesive plaque consists of a porous complex coacervate with mfps with low DOPA concentrations (mpf 2, 4). Mfps at the adhesive interface (mfp 3, 5, 6) have high DOPA content.

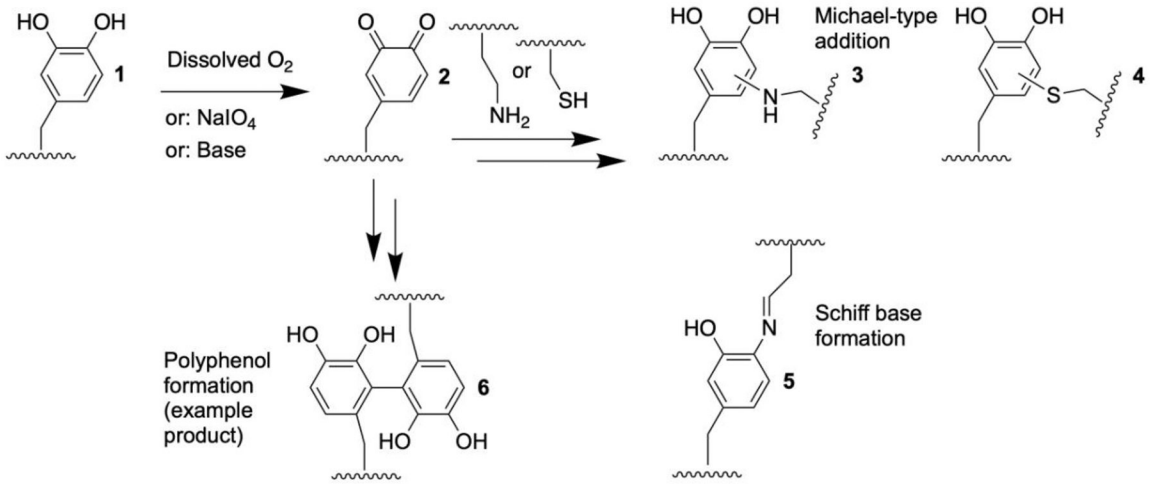

Fig. 3.

DOPA's reactivity leads to multiple chemical pathways relevant to wet tissue adhesion. DOPA's side chain, catechol (1), forms the highly reactive *o*-quinone (2) intermediate upon (auto)oxidation with dissolved oxygen, a strong oxidant (e.g. $NaIO_4$) or basic conditions. *o*-Quinone can then react with tissue pendent lysine or cysteine residues to form covalent interfacial bonds via Michael-type addition (3, 4) or Schiff base formation (5). Alternatively, tanning of *o*-quinone also results in polyphenol crosslinks (6), which contribute to the elastic properties of the byssus or synthetic wet adhesives.

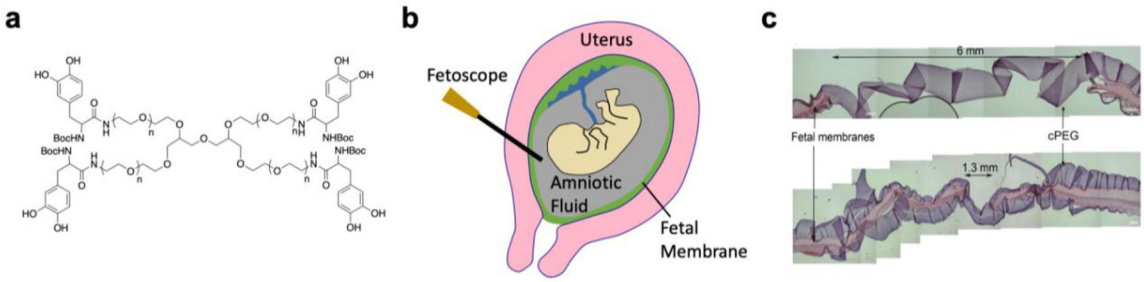

Fig. 4.

Mussel-inspired adhesives for fetal surgery. (a) Chemical structure of DOPA functionalized branched PEG polymer (cPEG). (b) Insertion of a fetoscopic instrument during fetal surgery. After removal of instrument, a small defect is left in the uterus and the amniotic sac (fetal membranes). The sac defect does not heal, leading to postoperative complications including membrane rupture and preterm birth. (c) Histology of the fetal membrane (pink) shows that the mussel inspired sealant (purple) successfully sealed a trocar-induced defect. Reprinted from [56], Copyright 2010, with permission from Elsevier.

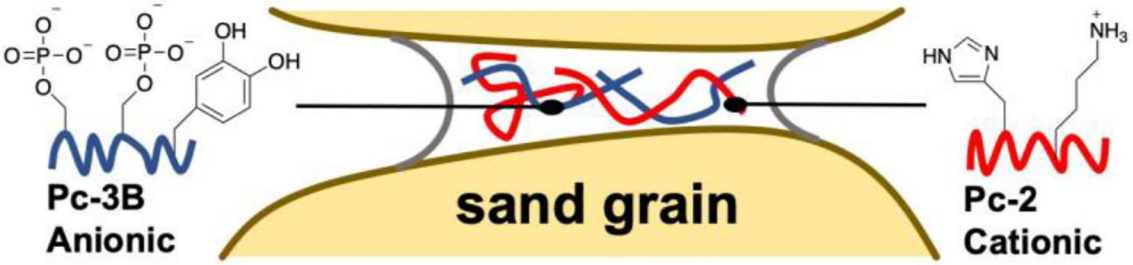

Fig. 5.

Inspiration from the sandcastle worm. The sandcastle worm connects sand grains to build tubular dwellings. The load bearing bioadhesive that connects sand particles consists of a complex coacervate of highly phosphorylated anionic proteins (Pc-3B) and cationic proteins (Pc-2).

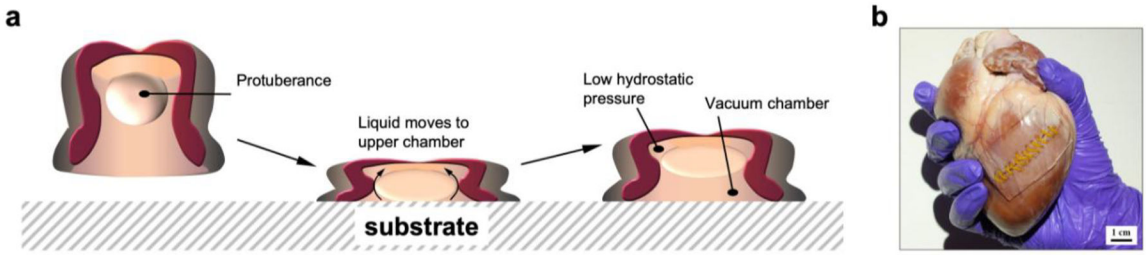

Fig. 6.

Octopus-inspired tissue adhesive patches. (a) It is hypothesized that *Octopus vulgaris* muscular hydrostats reversibly adhere to surfaces by compressing suction cups, causing liquid to flow to the upper chamber, above the protuberance resulting in a low hydrostatic pressure. A vacuum is created in the lower chamber. Adapted from [14]. (b) A simplified biomimetic suction cup patch showed wet tissue adhesion to a porcine heart. Reprinted with permission from [123] Copyright 2017 American Chemical Society.