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Catch bond-inspired hydrogels with repeatable and loading rate-sensitive specific adhesion

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ABSTRACT

Biological receptor-ligand adhesion governed by mammalian cells involves a series of mechanochemical processes that can realize reversible, loading rate-dependent specific interfacial bonding, and even exhibit a counterintuitive behavior called catch bonds that tend to have much longer lifetimes when larger pulling forces are applied. Inspired by these catch bonds, we designed a hydrogen bonding-meditated hydrogel made from acrylic acid-N-acryloyl glycinamide (AA-NAGA) copolymers and tannic acids (TA), which formed repeatable specific adhesion to polar surfaces in an ultra-fast and robust way, but hardly adhered to nonpolar materials. It demonstrated up to five-fold increase in shear adhesive strength and interfacial adhesive toughness with external loading rates varying from 5 to 500 mm min⁻¹. With a mechanochemical coupling model based on Monte Carlo simulations, we quantitatively revealed the nonlinear dependence of rate-sensitive interfacial adhesion on external loading, which was in good agreement with the experimental data. Likewise, the developed hydrogels were biocompatible, possessed antioxidant and antibacterial properties and promoted wound healing. This work not only reports a stimuli-responsive hydrogel adhesive suitable for multiple biomedical applications, but also offers an innovative strategy for bionic designs of smart hydrogels with loading rate-sensitive specific adhesion for various emerging areas including flexible electronics and soft robotics.

1. Introduction

Tissue-adhesive hydrogels have gained increasing popularity as an alternative to sutures, staples and bioglues for efficient wound healing [1–3]. A number of hydrogel adhesives (HAs) have been used *in vivo* or in preclinical tests, such as photocrosslinkable gelatin hydrogel-based adhesives [4,5], dry polymer crosslinking for wet adhesion [6,7], and mussel-inspired tissue adhesives [8,9]. Although many HAs have demonstrated potential clinical translation, there are still some major challenges in their clinical applications, including unsatisfying operability and complicated dressing change procedures.

So far, most of HAs extensively adhere to various solids (e.g., metals,

plastics, rubbers, minerals and tissues), whether they are polar or nonpolar [10–12]. Therefore, surgical instruments, including those made of nonpolar materials, *e.g.*, polypropylene (PP) and polystyrene (PS), can adhere to HAs, which causes surgeons to encounter great challenges. Recently, a ctenophore-inspired hydrogel that had specific underwater adhesion to biotic surfaces was developed because of its collaborative electrostatic interactions and dynamic catechol chemistry; moreover, it did not adhere to common abiotic surfaces in water [13]. However, it turns out that this hydrogel had the ability to adhere to both biotic and abiotic surfaces in air. On the other hand, the adhesive strengths of current HAs are usually not adjustable, and the detaching process is not efficient although dressing changes are an essential part of

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the wound healing process [14]. To swiftly detach HAs without secondary damage, thermal- and/or photo-responsive hydrogels have been developed with photodegradation- and/or temperature-induced sol-gel transformation properties [15–17]. Nevertheless, the liquefied dressing can hardly be completely removed from the wound. In the latest work, an injectable mussel-inspired adhesive hydrogel was reported, which could more easily detach from the wound by spraying with a Zn^{2+} solution for 10 min [18]. Similarly, a bioadhesive was developed, which could achieve triggerable benign detachment via treatment with a biocompatible triggering solution (0.5 M sodium bicarbonate and 50 mM glutathione) [19]. Such detaching methods rely on the diffusion of specific ions and/or other triggering solutions into the hydrogels, which requires a duration of at least 5 min. Although the biocompatibility of these triggering solutions has been demonstrated in vitro or in animal experiments, more clinical tests should be performed to confirm their biosafety.

In contrast to synthetic adhesive hydrogels, mammalian cells can only adhere to extracellular substrates/matrices via dynamic receptorligand binding mediated by multiple specific adhesion molecules (*e.g.*,

integrin family and cadherin family). For some bioinert substrates such as polyethylene glycol (PEG) hydrogels [20] and polydimethylsiloxane (PDMS) elastomers [21] without further modification, however, it is very difficult for the cells to form adhesion because of the absence of specific ligand molecules like RGD (Arginylglycylaspartic acid) peptides in such extracellular microenvironments (Fig. 1A). More strikingly, accumulating evidence has already indicated that the mammalian cell-governed adhesion is usually rate-dependent and even takes on a counterintuitive catch-bond behavior in response to external tensile forces, as quantified by some well-established mechanochemical coupling models (Fig. 1B) [22,23]. In essence, the so-called catch bonds, e.g., integrin-RGD bonds, are a class of protein-ligand bonds that are easily broken under relatively small tensile forces but tend to have much longer lifetimes when larger tensile forces are applied [24–27], which is seemingly counterintuitive and hard to reproduce in most man-made systems [28].

Very recently, several HAs have demonstrated loading rate-sensitive adhesion behaviors to some extent [29–31]. However, most of them are essentially non-reversible because the adhesion interfaces are essentially



Fig. 1. Design rationale for the loading rate-responsive PNT hydrogel with specific adhesion properties. (A) The specific adhesion and (B) rate-dependent adhesion properties of mammalian cells. (C) Scheme of the application of the PNT hydrogels. (D) Synthesis of the PNT hydrogels.

governed by covalent bonds. In such situations, the rate-sensitive adhesion mainly stems from intrinsic viscoelasticity of HAs involved, rather than reversible interfacial physical interactions (e.g., hydrogen bonds which also play a pivotal role in regulating cell adhesion complexes [22]). Here, inspired by the catch bonds, we develop a hydrogen bonding-mediated hydrogel based on acrylic acid (AA), N-acryloyl glycinamide (NAGA) and tannic acid (TA), hereafter referred to as PNT hydrogel, to achieve repeatable, loading rate-sensitive specific interfacial adhesion. This ensures not only the stability of the adhered hydrogel but also the relatively easy detachment when deliberately and slowly peeled off, thus greatly facilitating clinical operation (Fig. 1C). In combination with its excellent biocompatibility, antioxidant and antibacterial properties, and wound healing promotion, it is particularly suitable for multiple biomedical applications. Likewise, we present a mechanochemical coupling model on the basis of the classical Bell-Evans theoretical framework [32] to dissect the nonlinear dynamic response of interfacial adhesion governed by reversible hydrogen bonds to externally applied loads and hence quantitatively reveal the inherent mechanochemical mechanism of loading rate-sensitive interfacial bonding. This provides perspectives and design strategies for the development of biomimetic adhesive hydrogels, which are also indispensable for many emerging fields concerning smart interfacial adhesion.

2. Results

2.1. Design and formation of the PNT hydrogels

The PNT hydrogels were synthesized by the free-radical copolymerization of AA monomers and NAGA monomers, and the subsequent physical entrapment of TA molecules (Fig. 1D). The derived NAGA monomers had a diamide structure on its side chain, which offers abundant H-bond acceptors and donors simultaneously [33]. High NAGA monomer concentrations (above 10 wt%) can form strong and stable physical crosslinks alone via diamide H-bond crosslinking, and the introduction of other specific comonomers (such as 1-vinyl-1,2,4-triazole (VTZ) and AA in this work) can disturb the formation of these diamide hydrogen bonds [34,35]. We synthesized a series of PAA-NAGA copolymers with decreasing densities of NAGA from 10 wt% (PAA5--NAGA5) to 8 wt% (PAA6-NAGA4) and 6 wt% (PAA7-NAGA3) with a fixed total monomer content at 20 wt%. We found that at 10 wt% NAGA, PAA5-NAGA5 was not reshapable under mild conditions, making it difficult to add the designed amount of TA (Fig. S1A). In contrast, PAA7-NAGA3 failed to reach fine gelation even when entrapping 15 wt % TA (Fig. S1B). Hence, the PAA6-NAGA4 precursor was selected for further evaluation.

The catechol groups of TA are well-known inhibitors of free-radical polymerization (Fig. S1C). Thus, the amount of TA in hydrogels is often limited [9,36]. However, these PNT hydrogels incorporated high TA concentrations (5 wt% in PNT-5, 10 wt% in PNT-10 and 15 wt% in PNT-15) by a simple mixing method after polymerization. As expected, all the PNT hydrogels were soluble in urea solution (hydrogen bond dissociator, 0.1 mol L^{-1} , 10 min of immersion), which confirmed that these hydrogels were fully crosslinked by hydrogen bonds (Fig. S2A). In addition to the H-bonding crosslinks formed by the adjacent PNAGA fragments, H-bonds also existed between the polymer chains and the pyrogallol/catechol groups of the TA molecules (Fig. 1D). Moreover, TA facilitated the formation of PNAGA-PNAGA hydrogen bonds and the conjugation of PNAGA blocks (Fig. S2B). According to scanning electron microscopy (Fig. S3), PNT-10 with 10 wt% TA had the smallest pores among the studied materials, which indicated the highest amount of crosslinking. Due to the dissociation of the hydrogen bonding, ~95% of the initial weight of the PNT-10 hydrogels disappeared after 96 h. It should be noticed that the PNT-10 hydrogels were more stable than the PNT-5 and PNT-15 hydrogels, which was also attributed to their higher cross-linking densities of hydrogen bonds (Fig. S4).

2.2. Mechanical properties

As shown in Fig. 2A & S5, the mechanical properties of the PNT hydrogels were highly dependent on the H-bond crosslinking density. Comparing PNT-5 with PNT-10, one could find that the latter showed a higher tensile strength because of its enhanced crosslinking density. However, with a further increase in the TA content, the tensile strength of PNT-15 (70 kPa) decreased compared to that of PNT-10 (140 kPa). This phenomenon confirmed that a large number of TA molecules disrupted the formation of the diamide hydrogen bonds in PNAGA, making the derived PNT-15 hydrogel increasingly weaker.

Similar to certain hydrogels based on dynamic (*i.e.*, ionic, host/guest or H-bonding) crosslinking [37–39], the PNT hydrogels displayed loading rate-dependent tensile behaviors (Fig. 2B & S6). When the test velocity varied from 5 to 500 mm min⁻¹, the tensile strength of PNT-10 increased from 70 to 210 kPa, whereas the fracture strain decreased from 2000% to 750%. We next evaluated the anti-fatigue properties of PNT-10. After 12 cycles of tensile testing with a test velocity of 100 mm min⁻¹, the tensile strength of PNT-10 remained great than 100 kPa (Fig. S7), demonstrating acceptable elasticity. Moreover, due to the highly reversible PNAGA-TA hydrogen bonds, PNT-10 could self-heal within 5 s at ambient temperature (Fig. S8). The self-healing hydrogel samples could recover 86% of the tensile strength and 76% of the strain at break (Fig. 2C).

2.3. Specific and loading-rate-sensitive adhesiveness

Various repeatable interfacial interactions donated by the pyrogallol groups of the TA molecules brought adhesion to multiple substrates, which included hydrogen bonding, metal coordination, $\pi - \pi/\text{cation} - \pi$ interactions, thiol reduction and hydrophobic interactions [40]. As previously reported, TA molecules form hydrogen or electrostatic bonds with the polymeric network, leaving abundant free catechol/pyrogallol groups for extensive adhesiveness to various solid materials in air [41]. However, in the case of PNT-10, the conjugated PNAGA blocks, rather than the TA molecules, dominated the facial affinity (Fig. 2D). As the hydrogel-substrate adhesion was highly dependent on the interfacial affinity, due to the intrinsic high polarity of the PNAGA blocks, the interfacial interactions and adhesion between PNT-10 and nonpolar substrates, such as PE, PP, PS and PTFE, were significantly suppressed (Fig. 2E). In contrast, for polar abiotic materials (e.g., nitrile butadiene gloves, stone, metal and glass) and biotic materials (e.g., muscle (22.7 kPa), kidney (27.3 kPa), heart (27.0 kPa), and intestine (11.4 kPa)), PNT-10 displayed preferable adhesiveness (Fig. 2E & S9). Inspiringly, during clinical operation, PNT-10 offered great convenience to the application of nonpolar equipment like PE gloves, PP tubes, or PS tweezers/bistouries (Video S1).

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As shown in Fig. S10, PNT-10 could firmly bond to the surface of porcine skin and even be subjected to bending, distortion, stretching, or water soaking. The skins adhered by the PNT-10 hydrogels exhibited a relatively small decrease (less than 23%) in the measured lap shear stress after 48 h (Fig. S11). In order to investigate the relationship between the loading-rate and adhesion performance, the testing velocity was raised from 5 mm min^{-1} to 500 mm min^{-1} . For PNT-10, the interfacial toughness increased from 116 J m^{-2} to 560 J m^{-2} (Fig. 2F), and the adhesion strength increased from 12 kPa to 70 kPa (Fig. 2G). The PNT-5 and PNT-15 hydrogels also exhibited the loading-rate-sensitive behavior but had inferior adhesive properties (Fig. S12). To the best of our knowledge, hydrogels with permanent chemical crosslinking mostly have high tensile and adhesive strengths, but might be unfavorable for self-healing and repeatable adhesion [42]. By contrast, adhesive gels with fully reversible crosslinks are usually mechanically weak [13]. Accordingly, the developed PNT-10 exhibited high mechanical properties, high adhesiveness and loading-rate sensitive behavior, which was



Fig. 2. Mechanical properties, specific adhesion properties and loading rate-sensitive properties and self-healing abilities of the PNT hydrogels. (A) Tensile curves of PNT hydrogels with different TA contents. (B) Tensile strength versus testing velocity of the PNT-10 hydrogel. (C) Mechanism and tensile curves of the self-healing abilities of the PNT-10 hydrogels. (D) Mechanism and (E) images of the specific adhesiveness of the PNT-10 hydrogels to polar materials. (F) Interfacial toughness and (G) shear strength versus testing velocity for fresh porcine skins adhered using the PNT-10 hydrogels.

unique among the existing adhesive gels.

2.4. Catch bond-inspired mechanochemical coupling model describing hydrogel-substrate interfacial adhesion

Inspired by biological receptor-ligand interaction, *e.g.*, widespread catch bonds in mammalian cells, we put forward a mechanochemical coupling model based on the classical Bell-Evans theoretical framework [32,43] to quantitatively investigate the nonlinear dynamics of hydrogen bond-governed interfacial adhesion between the developed hydrogels and the corresponding substrates with the aid of the well-established Monte Carlo simulations. As shown in the inset in Fig. 3A & S13A, 100 × 100 lattices were selected as a representative small region on the hydrogel-substrate adhesion interface, where the black solid squares represented the receptor-ligand bonds whereas the white solid squares denoted the unattached receptor-ligand pairs. Under the action of the external force f, the interface force f_0 between the

hydrogel and the substrate was the superposition of the tensile force f_b on the N_b receptor-ligand bonds at this moment

$$f = f_0 = f_b \times N_b \tag{1}$$

Analogous to the cell adhesion model [23], the hydrogel, substrate and single receptor-ligand bond were viewed as a series four-component equivalent model (Fig. 3A), where the spring k_g and the dashpot η_g were used to describe the viscoelastic behavior of the hydrogel. The spring with an equivalent spring constant k_b represented the receptor-ligand bond, and the equivalent spring of the substrate had a stiffness of k_s , which was approximately estimated as $k_s = \frac{2Ea}{1-\nu^2}$, where E and ν were the Young's modulus and Poisson's ratio of the elastic substrate, respectively, and a was the equivalent radius of a single receptor-ligand bond [44]. For the series model, we had

$$f_b = k_s u_s = k_b u_b = k_g u_g^e = \eta_g \dot{u}_g^v \tag{2}$$

where u_s , u_b , u_g^e and u_g^v were the displacements corresponding to the



Fig. 3. Catch-bond inspired mechanochemical coupling model of adhesion at the hydrogel-substrate interface. (A) Infographic of the catch-bond inspired mechanochemical coupling model. (B) The number of receptor-ligand bonds changes with time. (C) Comparation of the experimental data with the external force-time curves obtained by the model.

components k_s, k_b, k_g and η_g , respectively. The displacement of each component satisfied

$$u = u_s + u_b + u_g^e + u_g^v = vt \tag{3}$$

where v and t were the loading rate and time, respectively. The tensile force acting on a single receptor-ligand bond could be expressed as (See the section of Materials and Methods for more details)

$$f_b = \eta_g v \left\{ 1 - \exp\left(-\frac{k_b k_g k_s}{\eta_g \left(k_g k_s + k_b k_s + k_b k_g\right)}t\right) \right\}$$
(4)

The two states of the receptor-ligand pair (*i.e.*, bound and unbound) are shown in Fig. S9A. The receptor-ligand pair continuously underwent random transitions between these two states. Assuming that the number of receptors and ligands at the hydrogel-substrate adhesion interface were equal and that neither of them would diffuse or slip on the interface, this transition of state could thus be described as a reversible chemical process [44]

unbound
$$R - L pairs \underset{K_{r}(f_{b})}{\rightleftharpoons}$$
 bound $R - L pairs$ (5)

On the one hand, the receptor-ligand pairs in the unattached state could bind randomly. In order to successfully form a receptor-ligand bond, the receptor monomer and its corresponding ligand should be close enough to ensure that the forward reaction occurred. Here, the influence of displacement on the forward reaction rate was simplified as [45]

$$K_f = K_{f0}H(\delta_b - u_b) \tag{6}$$

where *H* was the Heaviside function, which indicated that, when the displacement of a single receptor-ligand bond u_b was less than the characteristic length δ_b , the forward rate was the constant K_{f0} . The receptor-ligand bond could no longer be generated once u_b was greater than δ_b . On the other hand, the receptor-ligand bond broke by randomly

escaping from the potential well. Analogous to the two-pathway model describing cell adhesion [28,46], we used the potential well shown in Fig. 3A to describe the breaking of the receptor-ligand bond. The receptor-ligand bond x_1 could be broken through the catch barrier x_c or the slip barrier x_s . When the receptor-ligand bond was not subjected to tensile force, the catch barrier was lower than the slip barrier, and the receptor-ligand bond was more likely to be broken through the catch barrier [47,48]. As the tensile force acting on the receptor-ligand bond increased, the catch barrier increases gradually, and the slip barrier decreased. When the slip barrier was lower than the catch barrier, the receptor-ligand bond was more likely to be broken through the slip barrier, which showed the characteristics of the slip-bond. In this case, it was easier to break the bond when the tensile force increased [49]. Therefore, the reverse reaction rate took the following form [28]

$$K_r = K_{c0} \exp\left(-a_c \Delta E_b / k_B T\right) + K_{s0} \exp\left(a_s \Delta E_b / k_B T\right)$$
(7)

where K_{c0} and K_{s0} were the reverse reaction rate coefficients of the catch-bond and slip-bond, respectively; ΔE_b was the elastic strain energy of a single receptor-ligand bond, which could be expressed as $\Delta E_b = f_b^2/2k_b$; a_c and a_s were the characteristic coefficients of the catch-bond and slip-bond, representing the sensitivity of the energy barrier to the tensile force; k_B was the Boltzmann's constant; and T was the absolute temperature. The parameters and their values involved in the simulations are summarized in Table S2.

With advancement of the Monte Carlo simulation step, the number and position of the receptor-ligand bonds changed constantly (Video S2). Fig. 3B shows how the number of receptor-ligand bonds varied with time at different rates. In order to show the results more clearly, the distribution of receptor-ligand bonds in the simulation region corresponding to several representative time points in the case of $v = 20 \text{ mm} \text{ min}^{-1}$ is also displayed in Fig. 3B, and other cases are given in Fig. S13B. The Monte Carlo simulations showed good numerical stability (Fig. S14). The corresponding external force-time curves are presented in Fig. 3C. Low-speed stretching corresponded to a smaller external force, which was in good agreement with the experimental data. This further verified that the present material was easier to separate from the substrate when it was peeled off in a deliberate and slow way.

Supplementary video related to this article can be found at https:// doi.org/10.1016/j.bioactmat.2022.09.002

2.5 Cytocompatibility, antioxidant capability and antibacterial properties

We examined the cytocompatibility of PNT-10. Live/dead staining and CCK-8 assays were performed with L929 cells on days 1 and 3 postseeding. As shown in Fig. S15, only a few dead cells (marked by red fluorescence) were detected in the PNT-10 group, and the green fluorescence from the living cells was comparable to that of the tissue culture plates (TCPs) group. The OD values from the CCK-8 assays further demonstrated that PNT-10-conditioned medium did not apparently decrease in the *in vitro* viability of L929 cells (Fig. 4A). However, for the PNT-5 and PNT-15 hydrogels, many dead cells were detected, and the cell viability dropped to \sim 50% that of the TCPs, confirming the poorer crosslinking and greater diffusion of TA molecules than that of PNT-10.

Many studies have pointed out that excessive reactive oxygen species (ROS) result in a sustained inflammatory response, which is adverse to wound healing, especially for chronic wounds [50,51]. Hence, wound dressings with antioxidant functions are vital for accelerating wound repair [16,52]. Plant-extracted polyphenols, such as TA in this work, have excellent antioxidant properties [41,53]. The scavenging efficiency of PNT-10 against overexpressed ROS reached as high as 88% (DPPH), which was attributed to the absence of the oxidant APS initiator during the subsequent addition of TA (Fig. 4B). This excellent antioxidant capability of PNT-10 played a vital role in wound healing, as discussed in the later section. Bacterial infection is another obstacle that prevents wound healing during a surgical procedure [54,55]. In this work, the high amount of TA (10 wt%) endowed PNT-10 with excellent



Fig. 4. Cytocompatibility, antioxidant and antibacterial properties of the PNT hydrogels, and wound healing after treatment with different wound closure methods. (A) CCK-8 assay of various PNT hydrogels. (B) DPPH scavenging rate of PNT-10 hydrogels. (C) Bacterial-killing efficiency of the PNT-10 hydrogels against *E. coli* and *S. aureus*. (D) Schematic, groupings and timeline of the method for the wound healing experiment. (E) Wound healing after different treatments at various time intervals. (F) Hematoxylin-eosin (H&E) staining of the wound sections after 7 days. The yellow two-way arrows on the right demonstrate the length of the dermis defect. (G) Statistical wound lengths of the epidermis and dermis. * denotes the significant difference. *(p < 0.05); **(p < 0.01); ***(p < 0.001).

antibacterial activity against both *E. coli* and *S. aureus*. The bacteria-killing efficiencies of PNT-10 against *E. coli* and *S. aureus* were 82% and 95%, and the corresponding minimal inhibitory concentrations (MIC) were 38.08 mg/mL and 10.85 mg/mL, respectively (Fig. 4C). In comparison, both untreated agar plates and plates treated with TA-free samples showed almost no antibacterial activity.

2.6 Clinically simulated biomedical applications

The above results demonstrated the potential applications of PNT-10 as a stimuli-responsive adhesive tape. On the one hand, the strengthening and stiffening effects of PNT-10 at high deformation rates hold great importance for protecting adhesion in emergencies (e.g., the adhered wound site confronted with sudden friction or collision). On the other hand, the adhered PNT hydrogel tape can be easily changed without any secondary damage by slowly tearing it off (Video S3).

Supplementary video related to this article can be found at https:// doi.org/10.1016/j.bioactmat.2022.09.002

In order to evaluate the practical effects of PNT-10 on wound healing, we applied PNT-10 as a band-aid in rat skin incision models. As positive controls, the defects were sutured or treated with the commercial 3 M Tegaderm films (Minnesota Mining and Manufacturing Corporation). For the negative control, the injured area was merely washed with sterile PBS. To mimic dressing change in the clinic, the Tegaderm films and PNT-10 hydrogels were gently torn off and replaced with new dressings on day 1 and day 3 post-operation (Fig. 4D). From day 1 to day 7, the wound defects gradually disappeared in the PNT-10 hydrogel-treated, sutured and 3 M film-treated groups. In contrast, the PBS-treated group displayed obvious blood crusts and scars (Fig. 4E). The final wound closure percentage of these four groups experiencing 7day post-operation was 59.2 \pm 7.2% for Blank group, 73.6 \pm 5.9% for Suture group, 71.8 \pm 9.1% for Tegaderm group, and 92.9 \pm 4.0% for PNT-10 group, respectively (Fig. S16). The details of tissue regeneration in the wound defects were visualized by H&E staining. As shown in Fig. 4F, an intact layer of epidermis was observed after 7 days in the PNT-10-treated and 3 M film-treated groups. However, the PBS-treated group failed to achieve complete epidermal regeneration, and scars were found on the top (red star). In the sutured group, despite the seemingly intact epidermis, we found a secondary wound (red triangle) caused by the suture needle and a nondegradable suture line. The lengths of the premature tissues in both the epidermis and dermis were measured and summarized (Fig. 4G). The PNT-10-treated group showed the shortest length in both the epidermis (no significant difference from the positive groups) and dermis (significant difference from the positive groups, p < p0.05). In particular, in the PNT-10 hydrogel-treated group, no obvious inflammation was observed around the wound site, and the gap between the dermis incision edges was indistinct, with abundant collagen deposition and hair regeneration, indicating better tissue regeneration than that observed in the other positive groups; this result is closely related to the antioxidant functions of TA. Furthermore, the systemic toxicity of the PNT-10 hydrogel was evaluated in vivo (Fig. S17). H&E staining of the tissues of the heart, liver, spleen, lung, and kidney showed that the application of the PNT-10 hydrogel did not cause any damage to the main organs, indicating the good biocompatibility and biosafety of this hydrogel with specific and peeling speed-related adhesion properties for promising clinical translation.

3 Discussion

Bioinspired hydrogel adhesives (Bio-HAs) have broad applications from drug carriers and wearable devices to tissue repair and wound dressing. Traditionally, these Bio-HAs mimic specific organisms (*e.g.*, octopi [56], mussels [57], and ctenophores [13]) with special chemical components and/or micro/nanostructures. As the basic unit that makes up an organism, mammalian cells which exhibit specific, repeatable, and rate-dependent adhesion properties *via* protein–ligand complexes with catch bonds, have often been inconspicuous. Catch bonds have been found in several proteins including integrin [58], catenin [59], cadherin [26] and actin [27], and proved to play pivotal roles in regulating cellular behaviors represented by cell adhesion, cell migration, and T cell receptor antigen recognition [25].

In recent years, attracted by the counterintuitive phenomenon concerning force-enhanced lifetimes of catch bonds, researchers have developed several theoretical models to describe some catch-bond-like behaviors presented by polymer-grafted nanoparticle networks [48], self-strengthening biphasic nanoparticle [47], molecular switches [28], or other active materials [49]. These models provide meaningful guidelines for the reproduction of catch bonds in man-made systems. Nevertheless, there is still no report on catch bond-inspired synthetic materials with adaptive mechanical responses. As a matter of fact, the biological receptor-ligand interactions generally involve reversable hydrogen bonding, which is somewhat similar in nature to reversible physical adhesion dominated by hydrogen bonds [22]. Further, the external force-regulated protein conformational changes in the receptor-ligand-modulated bioadhesion are also analogous to the rearrangements of hydrogen-mediated hydrogel networks at adhesive interfaces [26,58,59]. These facts inspired us to design the hydrogen bonding meditated PNT-10 hydrogel, which exhibited some unique interfacial bonding properties, as mentioned above. Interestingly, it turned out that the proposed mechanochemical coupling model on the basis of the classical Bell-Evans theoretical framework [60,61] which was originally employed to dissect the physical nature of the biological receptor-ligand interactions, could quantitatively describe the nonlinear dependence of the reversible interfacial adhesion between the developed hydrogel and the underlying substrates (e.g., porcine skin in this work) on the rates of applied loads. The mechanochemical model not only deepens our understanding of interfacial adhesion presented by the derived hydrogel, but also provides a new bionic design paradigm for the development of smart adhesion hydrogels.

HAs with on-demand removability have attracted considerable attention in advanced dressing designs [62]. For example, Liang et al. developed a hydrogel consisting of protocatechualdehyde (PA) containing catechol, ferric iron (Fe), and guaternized chitosan (QCS) [63]. The hydrogels governed by the dual-dynamic-bond cross-linking (i.e., catechol-Fe bonds and Schiff base bonds) can be dissolved and removed in an on-demand manner. So far, however, the reports of loading rate-induced removal are still very rare. It is worth pointing out that the intrinsic viscoelasticity of the hydrogel and substrates has already been included in the model because it is very likely to play an import role in regulating the loading-rate sensitive adhesion behaviors as well. For example, a tough alginate-polyacrylamide (Alg-PAAm) hydrogel, which was adhered to porcine skin using bridging polymers and covalent coupling reagents, showed a 2-fold increase in adhesion energy approximately when the applied loading rate varied by two orders of magnitude [31]. By contrast, the derived PNT-10 hydrogel exhibited an at least 5-fold increase in shear adhesive strength and interfacial adhesive toughness, as confirmed by our experimental data and theoretical model.

With the cytocompatibility, antioxidant capability, antibacterial properties, and the unique catch-bond inspired specific, repeatable, and loading rate-sensitive adhesion, the developed PNT-10 hydrogel is expected to serve as a bioadhesive with high operability. In the future, catch bonds can further inspire the design and synthesis of more active materials that can realize programmable mechanical properties and adhesive performance, and bear large mechanical stress. We believe that these predictable materials with catch-bond-like phenomenon will be ideal candidates for multiple applications, such as wound healing, forceresponsive drug delivery, flexible electronics, and soft robotics.

4 Materials and Methods

4.1 Materials

Acrylic acid (AA) with a purity of 99.0% was purchased from Shanghai Macklin Biochemical Co., Ltd. (China). N-acryloyl glycinamide (NAGA) with a purity of 98.0% was purchased from Shanghai Yuanye Bio-Technology Co., Ltd. (China). Ammonium persulfate (APS) with the purity of 98% was provided by Shanghai Titan Scientific (China). Tannic acid (TA) with a purity level of PT was purchased from Alfa Aesar (Thermo Fisher Scientific, United States). All other reagents and solvents used were of analytical grade and supplied by Beijing Chemical Reagent Co., Ltd. (China), unless specifically noted.

4.2 Preparation of the PNT hydrogels

The designed amounts of AA (0.5 g, 0.6 g or 0.7 g) and NAGA (0.5 g, 0.4 g or 0.3 g) were added and dispersed into deionized water under constant stirring. Next, 0.02 g of APS was dissolved in distilled water and then added dropwise into the mixture under stirring. The obtained solution was treated by ultrasonication to remove the bubbles, and polymerization was conducted in a water bath at 60 °C for 2 h. The obtained PAA-NAGA pregel solution was dialyzed (Spectrum, 4000 Mw cutoff) against water for 48 h. To ensure such polymer concentration after dialysis, the dry PAA-NAGA copolymer was collected by lyophilization and then re-dissolved in DI water to prepare a certain concentration of polymer solution. Afterwards, the designed amounts of TA were dissolved in water and then added to PAA-NAGA pregel solution at 60 °C. Finally, the mixed solution was homogenized at 5000 rpm for 3 min with the aid of a homogenizer (IKA Germany). The formed PNT hydrogels were washed with deionized water. The detailed compositions and abbreviations of the samples prepared in this study are listed in Table S1.

4.3 Characterization

Fourier transform infrared (FTIR) spectroscopy was carried out on a PerkinElmer Spectrum 100 spectrophotometer from 4000 cm⁻¹ to 600 cm⁻¹ (resolution: 1 cm⁻¹). Hydrogel samples were dehydrated in an oven at 60 °C overnight. Each sample was scanned 16 times. The PNT hydrogels were observed by SEM (JEOL JSM-7500F, Japan) after freezedrying, cross-sectioning and gold sputtering (Cressington 108, England) to examine their morphology.

4.4 Tensile tests

The tensile tests were carried out with an STS10 N tensometer (Xiamen East Instrument Co. Ltd.) equipped with a 10 N load cell at a crosshead speed of $5-500 \text{ mm min}^{-1}$. The tested cylindrical samples were 15 mm long and had a gauge length of 5 mm. For the cyclic tensile tests, a maximum strain of 5 was chosen. We prepared 10 samples of the self-healed PNT-10 hydrogels to perform the tensile tests. The tensile curves of 5 random samples were test directly, while the other 5 samples were cut into two, and the separate PNT-10 hydrogels were tightly connected to each other. After 1 min at room temperature, the tensile tests of the self-healed PNT-10 hydrogel samples were carried out.

4.5 Adhesion tests

The adhesive tests were conducted on the same tensometer mentioned above. The shear strength was determined by lap-shear tests (ASTM F2255) of PNT hydrogels-bonding two fresh porcine skin pieces with a bonding area of $10 \times 10 \text{ mm}^2$ under a pressure for 10 s in air at ambient temperature, and then the external pressure was removed immediately at a crosshead speed of 5–500 mm min⁻¹. The maximum stress during the shear adhesive tests was recorded as the adhesive strength, which was calculated by the maximum force divided by the

initial bonding area. The interfacial toughness was determined according to testing standard ASTM F2256 for 180-degree peel tests. Poly (methyl methacrylate) films (with a thickness of 50 μ m) were applied using cyanoacrylate glue as a stiff backing for the tissues and hydrogels. For each mechanical test, at least 8 samples were tested to obtain statistical data.

4.6 Mechanochemical model describing tensile force acting on a single bond

Denoting the tensile forces acting on the spring components k_s , k_b , k_g and the dashpot component η_g as f_s , f_b , f_g^e , f_g^γ , respectively, we had

$$f_{s} = k_{s}u_{s}, f_{b} = k_{b}u_{b}, f_{g}^{e} = k_{g}u_{g}^{e}, f_{g}^{v} = \eta_{g}\dot{u}_{g}^{v}$$
(8)

Since the components were connected in series, i.e.,

$$f_s = f_b = f_g^e = f_g^v \tag{9}$$

$$\dot{u}_s + \dot{u}_b + \dot{u}_g^e + \dot{u}_g^v = v \tag{10}$$

we could therefore deduce the first-order linear differential equation

$$\frac{d}{dt}\left(u_s+u_b+u_g^e\right)+\frac{k_bk_gk_s}{\eta_g\left(k_gk_s+k_bk_s+k_bk_g\right)}\left(u_s+u_b+u_g^e\right)=v$$
(11)

Noting that $u_s = u_b = u_g^e = 0$ in the case of t = 0, we found

 $u_s + u_b + u_g^e =$

_

$$\eta_g v \frac{k_g k_s + k_b k_s + k_b k_g}{k_b k_g k_s} \left\{ 1 - \exp\left(-\frac{k_b k_g k_s}{\eta_g (k_g k_s + k_b k_s + k_b k_g)}t\right) \right\}$$
(12)

So, the tensile force acting on a single bond was solved as

$$f_{s} = f_{b} = f_{g}^{e} = f_{g}^{v}$$

$$= \frac{k_{b}k_{g}k_{s}}{\left(k_{g}k_{s} + k_{b}k_{s} + k_{b}k_{g}\right)} \left(u_{s} + u_{b} + u_{g}^{e}\right)$$

$$= \eta_{g}v \left\{1 - \exp\left(-\frac{k_{b}k_{g}k_{s}}{\eta_{g}\left(k_{g}k_{s} + k_{b}k_{s} + k_{b}k_{g}\right)}t\right)\right\}$$
(13)

4.7 In vitro biocompatibility tests

Cytocompatibility in vitro was determined by culturing L929 fibroblast cells with complete RPMI medium 1640 (Gibco) containing 10% fetal bovine serum (Gibco) and 1% penicillin-streptomycin solution (Gibco) in a 5% CO₂ incubator at 37 °C. The tested hydrogels were immersed in complete medium to make extracts and sterilized with a 0.2 µm filter. The cells were treated with trypsin-EDTA (Gibco) and then resuspended in the extracts. Cells at a density of 1×10^3 were seeded into each well of a 96 -well plate and allowed to grow for 24 or 72 h. The cytocompatibility of the hydrogels was analyzed by a cell counting kit-8 (CCK-8) assay (Bimake) and a live/dead assay [64]. The CCK-8 assay was conducted as follows. After a specific period of incubation in a 96-well plate, CCK-8 solution was diluted 10-fold with the extracts. After the removal of the original medium, 100 µL of CCK-8 reagent was added to each well, which was cocultured with the cells in a 5% CO₂ incubator at 37 °C for 2 h before measurement of the absorbance with a microplate reader (BIO RAD) at a wavelength of 450 nm. The live/dead assay was conducted as follows. First, 2 μM calcein AM (in DPBS) and 4 μM EthD-1 (Invitrogen) working solutions were added to the wells. The 96-well plate was then incubated in a 5% CO_2 incubator at 37 °C for 20 min. A laser scanning confocal microscope (Nikon, Japan) was used to observe the morphologies of the cells. For each group, 6 parallel experiments were conducted.

4.8 In vitro antibacterial activity tests

Before performing anti-bacterial tests, all of the tested hydrogels were sterilized under UV irradiation for 30 min on a clean bench. To evaluate the inhibitory efficiency of the hydrogel to inhibit *S. aureus* and *E. coli* growth, the sterilized hydrogels were cocultured with 10⁸ CFU/mL *S. aureus* or *E. coli* in Mueller-Hinton broth medium for 24 h. After diluting the bacterial solution by a factor of 10⁴, coating on an LB agar plate and culturing at 37 °C for 24 h, the number of clones on the plate was counted by the ImageJ software. MIC was tested through the two-fold agar dilution method. For each group, 3 parallel experiments were conducted.

4.9 In vitro antioxidant activity tests

For the DPPH scavenging assay, hydrogel samples (1 g) were mixed with a DPPH (1 mg) solution in ethanol (20 mL). The system was kept for 5 min in a dark place at room temperature, and then the absorbance (AM) of the liquid was measured at 519 nm with a UV–vis spectrophotometer. A blank solution (without polymer) was prepared, and its absorbance (AB) was measured as a control. The DPPH scavenging efficiency (%) was calculated as $100 \times (AB - AM)/AB$.

4.10 In vivo wound healing tests

The care and operation of animals followed the international standards on animal welfare, and the protocol was approved by the Animal Care and Use Committee of Fifth Central Hospital of Tianjin (Tianjin, 300450, P. R. China). Experimental rats were purchased from Sibeifu (Beijing) Biotechnology Co., Ltd. They had ad libitum access to food and water under a controlled temperature (22-24 °C) and stable humidity (40-60%). Incisions (2 cm) were made on the backs of five male SD rats (200-250 g) to evaluate wound healing effects. After sterilization, four incisions were made on the back of each rat. In this assay, the incisions were treated with PBS (negative control group), suture closure, 3 M Tegaderm[™] film (positive control group), or PNT-10 hydrogel patches. To mimic the dressing changes in the clinic, the Tegaderm[™] films and PNT-10 hydrogels were gently torn off and replaced with new dressings on day 1 and day 3 postoperation. The wound healing effects were observed 1, 3, and 7 days postoperation. The rats were euthanized to harvest the skin tissue containing the wound area 7 days postoperation, and the heart, liver, spleen, lung, and kidney tissues were harvested as well. Paraffin sections (5 µm in thickness) were prepared for histological analysis and stained with hematoxylin and eosin (H&E). The mean wound lengths of the epidermis and dermis were calculated using the ImageJ software. All the measurements were performed by analysts blinded to the tested groups.

4.11 Statistical analysis

All quantitative data are shown as mean \pm standard deviation (SD). One-way analysis of variance (ANOVA) with Tukey's test was used for statistical analysis. Differences between groups with p<0.05 were regarded as statistically significant. Values of p<0.01 and p<0.001 were considered highly significant.

CRediT authorship contribution statement

Zuoying Yuan: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. Xiaocen Duan: Methodology, Software, Data curation, Formal analysis, Writing – original draft. Xing Su: Methodology, Investigation. Zhuoling Tian: Investigation, Visualization. Anqi Jiang: Investigation, Formal analysis. Zhuo Wan: Investigation, Validation. Hao Wang: Investigation. Pengfei Wei: Validation. Bo Zhao: Resources. Xiaozhi Liu: Resources, Writing – review & editing. Jianyong Huang: Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that there is no conflict of interest in this manuscript.

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Appendix A. Supplementary data

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