POLYMERS

Mechanoresponsive self-growing hydrogels inspired by muscle training

Takahiro Matsuda¹, Runa Kawakami¹, Ryo Namba¹, Tasuku Nakajima^{2,3,4*}, Jian Ping Gong^{2,3,4*}

Living tissues, such as muscle, autonomously grow and remodel themselves to adapt to their surrounding mechanical environment through metabolic processes. By contrast, typical synthetic materials cannot grow and reconstruct their structures once formed. We propose a strategy for developing "self-growing" polymeric materials that respond to repetitive mechanical stress through an effective mechanochemical transduction. Robust double-network hydrogels provided with a sustained monomer supply undergo self-growth, and the materials are substantially strengthened under repetitive loading through a structural destruction-reconstruction process. This strategy also endows the hydrogels with tailored functions at desired positions by mechanical stamping. This work may pave the way for the development of self-growing gel materials for applications such as soft robots and intelligent devices.

iological load-bearing tissues are dynamic, open systems in which structural transformations to adapt to the surrounding mechanical environment are constantly occurring through metabolic processes (1, 2). Specifically, skeletal muscles hypertrophy and strengthen due to repeated exercise (Fig. 1, A and B). The destruction of the fibril structure is caused by exertion, whereas the supply of building blocks such as amino acids and constructive chemical reactions grows new muscle (2-4). By contrast, typical synthetic materials are usually considered part of static, closed systems, with no structural reconstruction after damage or substance exchange with surroundings. Therefore, repetitive mechanical loading typically leads to damage and even failure of these materials (5).

Many self-healing materials that can fully or partially recover have been developed (*6*, 7). Materials that self-stiffen during their mechanical use have been developed using composites (*8*, *9*) or liquid crystal elastomers (*10*). Several attempts to remodel polymer architectures by mechanical stimuli have also been reported that rely on mechanochemical cross-linking reactions (*11–15*), but remodeling bulk solid-state materials to improve their mechanical properties using these molecular mechanisms is still challenging.

We propose a biological metabolism-inspired strategy to develop the self-growing materials. Using double-network (DN) hydrogels (*16*), we succeeded in developing hydrogels that gain strength and mass under repetitive mechanical loading through coupling of mechanical stimuli and substance supply from environment. We also demonstrate that specific functions can be imparted selectively at desired positions in a DN hydrogel through spatially programmed loading.

The strategy and system

Our strategy is shown in Fig. IC. To build an artificial system that possesses the features of natural muscle, we have adopted a chemically cross-linked hydrogel that enables permeability to small molecules and efficient chemical reactions in the material (*17*, *18*). Force-induced polymer strand scission is the destructive trigger that initiates reconstruction. Rupture of a polymer chain by mechanical force typically generates mechanoradicals that can trigger chemical reactions (*11*, *19–22*). For the reconstructive reaction, we use polymerization induced by the mechanoradicals (*19*, *20*). As one radical can polymerize thousands of monomers, this is an efficient method for the reconstruction.

The key challenge is to generate a sufficient amount of mechanoradicals without causing bulk failure of the gels. Conventional single-network (SN) hydrogels are weak, purely elastic materials, and the rupture of a few polymer strands triggers catastrophic crack propagation that causes material failure (23). Thus, the concentration of mechanoradicals generated inside an SN gel may be too low to induce effective network reconstruction. In contrast, DN hydrogels, consisting of 80 to 90 weight % (wt %) water and two interpenetrating polymer networks of contrasting mechanical properties, are mechanically strong and tough. The first network, with short and prestretched polymer strands, is rigid and brittle, whereas the second network, with long and coiled strands, is soft and stretchable (24). With this contrasting network structure, mechanical loading of a DN gel causes scission of a substantial number of the brittle network strands, whereas the stretchable network remains intact, preserving the integrity of the bulk gel (24-29).

We used a series of DN gels consisting of poly(2-acrylamido-2-methylpropanesulfonic acid)

sodium salt (PNaAMPS) as the brittle network and poly(acrylamide) (PAAm) as the stretchable network (table S1). Each network is covalently cross-linked (fig. S1). As controls, PNaAMPS and PAAm SN gels were also used.

Mechanoradical generation

First, we showed that DN gels, relative to SN gels, generate mechanoradicals in high concentrations by deformation. The mechanoradicals formed by covalent bond scission are known to react with water to generate hydrogen peroxide, which in turn oxidizes ferrous ions (Fe²⁺) into ferric ions (Fe^{3+}) in the Fenton reaction (Fig. 2A) (21). We introduced ferrous ions and xylenol orange (XO), an indicator of ferric ions (Fe^{3+}) (30), into a DN gel and then stretched the gel. Figure 2B shows the Fenton color reaction, from yellow to brown, in a DN gel stretched to a strain (ϵ) of 3.5 (350%) strain). The gel exhibited a mechanical "necking" phenomenon during tensile deformation (Fig. 2B, ii) that was due to the extensive fracturing of the brittle network strands (26, 27, 29). A color change characteristic of the presence of Fe³⁺ was seen in the necked region (Fig. 2B, iii), indicating the generation of a large number of mechanoradicals. Through ultraviolet (UV)-visible light absorption spectroscopic analysis, the Fe^{3+} concentration in the completely necked DN gel ($\varepsilon = 4.7$) was determined to be 26 $\mu M.$ By comparison, the Fe^{3+} concentrations were lower in unstretched ($\varepsilon = 0$) and unnecked ($\varepsilon = 1.6$) DN gels and in stretched SN gels (Fig. 2C and fig. S2). The control experiments using conventional radical generators showed that the concentration of Fe³⁺ was proportional to and on the same order as that of generated radical (fig. S3). Consequently, the mechanoradical concentration in the completely necked DN gel was estimated to be on the order of 10^{-5} M, which is higher than that in the SN gels (on the order of 10^{-6} M or less) and that reported in other SN gels ($\sim 10^{-7}$ M) (31).

The concentration of the mechanoradicals directly correlates with the degree of covalent bond scission inside the DN gel. Internal chain scission results in the softening of a DN gel, as seen from the mechanical hysteresis in cyclic tensile tests (25-28). Our DN gel showed large hysteresis loops due to substantial bond scission (Fig. 2D). In contrast, the SN gels did not exhibit distinct hysteresis (Fig. 2D and fig. S4), indicating negligible bond scission in the SN gels. Given the purely elastic nature of covalently cross-linked hydrogels, the area of the hysteresis loop, $U_{\rm hys}$ (reported in Joules per cubic meter), corresponds to the dissipated energy used for the scission of the polymer strands during mechanical loading (25, 27, 28). A linear correlation between the hysteresis area and the Fe³⁺ concentration was observed for the DN gel subjected to various strains (Fig. 2E). The same linear correlation holds true for DN gels with various compositions, as well as the SN gels. The inverse of the slope indicated that $\sim 10^8 \text{ J mol}^{-1}$ of mechanical energy was dissipated for the breakage of the network strands, which is in good agreement with the value predicted by the classical theory of fracture-induced energy release from

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a polymer strand (32). This result verified the mechanoradical concentration estimated from the level of ferrous ion oxidation.

Self-strengthening

D

For a DN gel fed 2 M monomer, for which 2acrylamido-2-methylpropanesulfonic acid (AMPS)

was used as an example, the monomer conversion was as high as 90% (1.8 M) for the gel stretched to the completion of necking in an argon atmosphere (fig. S5). Such mechanoradical polymerization of a high concentration of monomer leads to stressinduced formation of new network in a DN gel fed cross-linker along with monomer to exhibit



concentration (µM) 10 Unstretching Stretching Fe³⁺ Necking region 5 (ii) 0 0.0 ε = 0.0 16 4.7 0.0 0.2 5.0 Ε O DN₁ gel (various strains) Applied strain ω DN_i gels (various compositions) PNaAMPS SN gel Ò Time A PAAm SN gel 1.2 Stress (MPa) DN₁ gel 40 0.9 0.6 Fe³⁺ concentration (µM) 30 0.3 0 0 1 2 3 4 5 6 7 8 20 Strain ɛ (-) 0.15 Stress (MPa) PAAm SN gel 10 0.1 n 0.05 0.0 0.3 0 0 0 2 3 4 5 6 0 1 2 3 1 Mechanical hysteresis area U_{hys} (10⁶ J m⁻³) Strain ɛ (-)

self-strengthening behavior. To demonstrate such an effect, we fed the DN gels with monofunctional monomer 2-acrylamido-2-methylpropanesulfonic acid sodium salt (NaAMPS; 0.3 M) and trifunctional monomer N,N',N"-triacryloyl diethylenetriamine (TADETA; 0.3 M) as cross-linker (Fig. 3A). The stress-strain curves of the virgin and

Fig. 1. Conceptual scheme of the self-growth of materials induced by mechanical training.

(A) A skeletal muscle becomes bigger and stronger under the application of repetitive mechanical stress and a continuous nutrient supply through metabolic cycles. (B) As a result, such a tissue is initially weakened (purple arrows) but then recovers or even shows enhanced performance (red arrows) due to mechanical stimuli. The green outline indicates one mechanochemical cycle. (C) Our strategy to develop self-growing materials based on mechanical training of DN gels. Mechanical stress leads to breakage of the brittle network (blue), whereas the highly stretchable network (pink) maintains the integrity of the gel. The mechanoradicals generated at the broken ends of the brittle network strands trigger polymerization of monomers supplied from the external environment to form a new network (orange). The chemistry of the newly formed network can be the same or differ from that of the original brittle network, as required.

Fig. 2. Quantification of Fe²⁺ oxidation in stretched gels based on the Fenton reaction.

(A) Fenton color reaction induced by mechanoradicals (21). (B) Optical images of a DN_1 gel fed Fe^{2+} , XO, and H_2SO_4 (i) before, (ii) during, and (iii) 30 min after the stretching (strain ε = 3.5). (**C**) Estimated Fe³⁺ concentrations in the unstretched and stretched gels. (D) Cyclic tensile loading curves of the gels. (E) Correlation between the mechanical hysteresis areas and the Fe³⁺ concentrations in the stretched gels: DN₁ gels stretched to various strain levels $(\varepsilon = 0, 1.0, 1.6, 4.7, 6.0);$ DN_i gels of various compositions (i = 2, 3, 4, 5, 6) stretched until the completion of necking; the PNaAMPS SN gel $(\varepsilon = 0, 0.2)$; the PAAm SN₁ gel ($\varepsilon = 0, 5.0$). The dashed line is a guide for the eye. The error bars in (C) and (E) represent standard deviations among three measurements. For the gel codes, see table S1.

0.6

prestretched samples are shown in Fig. 3B. In contrast to the monomer-free DN gel, which showed softening due to the breaking of the brittle network, the sample fed both monomers exhibited substantial enhancement in its mechanical properties. The polymer fraction of the strengthened DN gel was increased about twofold in comparison with the virgin sample, from 14 to 26 wt % (Fig. 3C). By contrast, the DN gel fed only monofunctional monomer NaAMPS (1.2 M) and without cross-linker showed softening similar to the monomer-free sample, even though its polymer fraction was increased from 13 to 36 wt %. These results showed that the newly formed network strengthens the DN gel, whereas the newly formed un-cross-linked graft chains have no effect on strengthening of the DN gel. Neither the strength nor the polymer weight fraction increased in a prestretched PAAm SN gel fed both monomers, indicating that the mechanoradical concentration generated in an SN gel is too low to induce distinct polymerization (Fig. 3C and fig. S6).

The extent of self-strengthening depends on the number of polymer strands in a unit volume ("number density") of the newly formed network, which depends on the concentration of the fed monomers. For the sample fed a constant concentration of NaAMPS (0.3 M) and varied concentration of TADETA as cross-linker, the modulus of the stretched sample increased monotonically with the TADETA concentration when the concentration was higher than 0.01 M (Fig. 3D), indicating that the newly formed polymer formed a percolated network above this concentration threshold. The modulus at high concentration (>0.3 M) was higher than that of virgin DN gel, suggesting that the number density of newly formed network strands surpasses that of the

Fig. 3. Deformation-triggered strengthening of DN gels by mechanoradical polymerization.

(A) Monomers fed in the gels. (B) Stress-strain curves of virgin and prestretched DN₇ gels fed or not fed monomer(s). The curves were normalized based on results for residual strains induced by prestretching (32). (C) Polymer fraction in the virgin and prestretched DN7 and PAAm SN₂ gels by mechanoradical polymerization. In (B) and (C), 1 denotes a gel fed 1.2 M NaAMPS without cross-linker and 1 + 2 denotes a gel fed 0.3 M NaAMPS and 0.3 M TADETA. (D) Elongation-triggered elastic modulus changes of DN gels fed NaAMPS (0.3 M) and various concentrations of TADETA. The modulus was measured with an indentation test. The moduli of the virgin DN and stretched DN gels with no feeding of monomers are shown by blue (0.37 MPa) and red (0.07 MPa) dashed lines, respectively. The error bars in (C) and (D) represent standard deviations for three measurements. In the experiment depicted in this figure, the prestretch strains were $\varepsilon \approx 6$ for the DN gel and $\varepsilon \approx 4$ for the PAAm SN gel. The volumes of the samples after stretching were the same as the virgin sample volumes.

broken ones. Similarly, at a fixed molar ratio of NaAMPS and TADETA (NaAMPS:TADETA = 1:1 mol/mol), the modulus increased more than 10-fold when the concentration of each monomer was higher than 0.4 M and reached 23-fold for 0.8 M (fig. S7).

Self-growth in strength and size

With proper conditions, our DN gel exhibits persistent growth in strength and size under repetitive mechanical training. Two requirements must be satisfied: Enough monomers should be continuously externally supplied, and the newly formed network should serve the role of a brittle network that then breaks during the next deformation to trigger subsequent network formation. To satisfy the first requirement, we performed repetitive stretching of a DN gel in monomer solution so that the monomers could diffuse into the gel, as an open system (Fig. 4A). For the second requirement, we used monomer solution at a relatively low concentration but high cross-linker ratio. Specifically, we used a monomer solution containing 0.08 M NaAMPS and 0.08 M N.N-methylenebisacrylamide as cross-linker (100 mol %). For comparison, we also performed an experiment with a sample that was prefed the same monomer solution but was not immersed in the monomer solution during the stretching process (closed system).

The samples were stretched from an initial gauge length (15 mm) to a preset gauge length (90 mm) and then returned to the initial position. Such a loading-unloading process was repeated over four cycles, with a 1-hour incubation between two consecutive cycles (Fig. 4B). In the first cycle, the force-time curves of both the open and closed systems almost overlapped with that of a reference DN gel stretched in pure water. In the second cycle, both systems showed a distinct force increase com-

pared with the reference curve. In the third and fourth cycles, the open system showed a further force increase with each cycle, whereas the closed system showed a slight decrease in force. Even in the second cycle, the open system showed higher strengthening than the closed system, indicating that the polymerization after the first cycle shifted the equilibrium of the monomer distribution, inducing additional monomer diffusion into the gel from the surroundings and further polymerization. Under this condition, the DN gel eventually broke in the fifth or sixth loading. This is because the newly formed network had become too dense and the contrasting DN structure required for extensibility of the material was not held anymore (33).

The persistent self-strengthening of the open system with the sustained monomer supply from the external environment is a consequence of repetitive new network formation triggered not by the progressive rupture of the original brittle network but by the rupture of the network formed in the previous cycle. This is seen in the forcegauge length curves (Fig. 4C), which were replotted from the data in Fig. 4B. In contrast to the reference sample, which showed mechanical hysteresis only in the first cycle, both the closed and open systems showed hysteresis in the subsequent cycles. This hysteresis is evidence of the breakage of the newly formed network strands during the next stretching. The destruction of the new network strands in the open system induced further remodeling with the supply of monomers, as observed from the increase in hysteresis with an increasing number of cycles. By contrast, hysteresis in the closed system decreased with number of cycles, indicating that the destruction could not initiate subsequent polymerization due to monomer depletion.





Fig. 4. Repetitive stretching-triggered

mechanical growth of DN gels. (A) Illustration of stretching a DN gel with a continuous monomer supply from surrounding solution, acting as an open system. The applied force and the gauge length are denoted by F and L, respectively. (B) Time profiles of the repetitive stretching of DN7 gels (1-mm thick) in terms of L and the required force F. The red, green, and blue curves represent a DN₇ gel stretched in a monomer solution (open system), a DN_7 gel prefed monomer and stretched in an argon atmosphere (closed system), and a DN7 gel stretched in pure water (reference), respectively. (C) Force-length curves show the cyclic loading-unloading behavior. For the reference sample, all curves except the first loading curve overlap. (**D**) Optical images showing the growth in strength and length of a DN₇ gel caused by repetitive mechanical training. In a monomer solution, a DN gel connected to a weight was repeatedly lifted to a fixed height. An aqueous solution of 0.08 M NaAMPS and 0.08 M N,N'-methylenebisacrylamide (cross-linker) was used in the experiment depicted here.



With the repetitive loading-unloading in the monomer solution, the size of the DN gel also grew. As shown in Fig. 4C (open system), the gauge lengths at which the tensile force started to rise above zero in the second and later cycles were much larger than the initial length (15 mm), indicating the increase of the sample length after the mechanical cycles.

This persistent growth characterized by increases in strength and size is visually demonstrated in Fig. 4D and movie S1, which show repetitive lifting of a DN gel connecting to a weight in monomer solution. The weight could not be lifted in the first cycle owing to the relative softness of the DN gel, although it was lifted to higher levels with an increasing number of lifting cycles because the gel progressively stiffened. Whereas the width of the gel remained almost unchanged, the length of the sample in the load-free state, as seen from the beginning of the second and third cycles, was 1.9 and 2.2 times greater than that of the virgin sample, respectively.

Space-selective functionalization

Mechanoradical polymerization can also be used to endow a DN gel with a specific property(s) or functionality at a desired position by using the appropriate functional monomers and applying spatially programmed deformation. As the mechanoradicals generated at the ends of the broken chains are nondiffusive, new polymers are expected to be grafted to the network at the desired positions through mechanoradical polymerization. We performed a spatial mechanopolymerization of poly(N-isopropylacrylamide) (PNIPAAm), which is a thermoresponsive polymer that exhibits a lower critical solution temperature (LCST) in water (34). A DN gel fed N-isopropylacrylamide (NIPAAm) was compressed by a stamp embossed with the raised letters "LSW" (Fig. 5, A and B). Although the whole gel sample was transparent at 5°C, the letters LSW appeared when the gel was heated to 50°C, resulting from the LCST-type micro-phase separation of the PNIPAAm that was selectively polymerized in the compressed regions. Using the same NIPAAm monomer, we were also able to transform the surface properties of a DN gel by slicing a NIPAAm-fed DN gel with a razor blade (Fig. 5, C and D). The slicing induced mechanoradical generation on the surface that initiated the polymerization of the NIPAAm, resulting in an increase in the surface hydrophobicity at elevated temperature.

Conclusion

We demonstrated that robust DN gels respond to repetitive mechanical stimuli with an increase in their polymer amount and size and acquire further strength, similar to the growth of skeletal muscles that is induced by habitual physical exercise. Furthermore, as exemplified by the thermoresponsive property imparted by stress-induced NIPAAm polymerization, diverse functions can be imparted on demand by applying programmed mechanical stimuli to DN gels fed appropriate functional monomers.

The internal fracturing behavior exploited here is common to DN gels, regardless of the chemical species of the polymer or the solvent (28, 29, 35–37). Therefore, the concept of using DN gels to realize self-growing materials that undergo bond rupture–initiated mechanoradical reactions would be applicable to various DN gels and multiple-network gels supplied with monomers that undergo radical polymerization. In addition, fracture-triggered mechanochemical transduction with various polymer mechanochemistries (15, 38-41) may be also applied to DN gels for diverse force-initiated or -catalyzed reactions.

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Fig. 5. Deformation-triggered PNIPAAm functionalization of DN gels by mechanoradical

polymerization. (A) Illustration of space-selective mechanoradical polymerization in a DN gel fed NIPAAm monomer under compression with a stamp embossed with the raised letters LSW. (B) Optical images of the DN₁ gel after compression with the stamp. The letters LSW were reversibly displayed or erased by changing the temperature. (C) Illustration of mechanoradical polymerization on the surface of a DN gel fed NIPAAm monomer and sliced by a razor blade. (D) Optical images of a water droplet (0.8 μ l) on the sliced surface of the DN₈ gel. The contact angle of the water droplet on the surface is different at different temperatures (see fig. S8 for details).

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SUPPLEMENTARY MATERIALS

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Supplementary Text Figs. S1 to S10 Tables S1 and S2 Movie S1

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Mechanoresponsive self-growing hydrogels inspired by muscle training

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Working harder, getting stronger Self-healing polymers attempt to restore mechanical strength after deformation. Polymer gels tend to be too soft for this to occur. Matsuda et al. generated self-healing hydrogels composed of a double-network material (see the Perspective by Craig). A mechanical stress breaks the more brittle of the two networks, while the other retains stability. On breakage, the fractured chains create radical initiators that polymerize new network material. With repeated network breakage and a supply of monomers, the gel gets stronger. Science, this issue p. 504; see also p. 451

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