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Building mechanochemistry into soft biomaterials

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When soft tissue is mechanically deformed, new material properties and functionalities can emerge. Through rational design of dynamic covalent chemistry and network architecture, new force-catalysed activities in hydrogels can be achieved, forming the basis of a 'mechanochemical toolbox' to expand the functionality of soft synthetic biomaterials.

State-of-the-art synthetic hydrogel biomaterials are impressive — emulating many of the biochemical, biophysical and structural aspects of native matrices — yet fail to match nature's toolbox with respect to dynamic stimuli-responsive functionalities. In this Comment I propose bioinspired mechanochemistry as a new strategy to instil complex properties and autonomous behaviour into next-generation synthetic hydrogels.

Force-mediated signalling in extracellular matrices

The biopolymer matrix that resides throughout our body is comprised of a large assortment of proteins, proteoglycans, polysaccharides and other molecules. Nature has evolved these assemblies to accomplish numerous tasks, from regulating transport of molecules and cells to orchestrating cellular assembly that dictates the myriad of forms underlying function[1]. A key signalling modality has emerged, in which the forces exerted by the environment, resident cells and tissues will elicit changes in the chemistry, organization and properties of the matrix. For example, cell-generated forces can unfold secondary structures and expose binding sites, thereby facilitating immobilization of molecular cargo such as proteins, polysaccharides and metabolites, a process known as 'sequestration'. Similarly, the reverse process occurs, whereby applied force will lead to the release of molecules to direct cellular behaviour. These are just two examples of many, demonstrating how nature has evolved tissue matrices to coordinate signal propagation in response to force.

Polymer mechanochemistry inspired by nature

Chemical reactions that are mediated through force have been an active area of research and technology for decades. The field of 'mechanochemistry' has seen great success in polymer science and engineering, harnessing force to catalyse chemical reactions, with nature serving as a motivator in many polymer systems[2]. For instance, constrained ring systems have been designed to respond to force through intramolecular rearrangement, yielding changes in physical and optical properties. A classic example is the spiropyran–merocyanine conversion, in which force leads to a visual colour change that serves as a strain indicator, bearing a superficial resemblance to natural colour changes that occur in response to force, such as bruising[3]. The key element to most polymer mechanochemistry systems is the 'mechanophore' linkage that is force-responsive and can be integrated into the polymer backbone in diverse ways. In addition to intramolecular rearrangements, mechanophores have been designed wherein force mediates controlled degradation, growth, release of pendant molecules and new functionalities that could be amenable to further reactions[2,4] (Fig. 1a). Whereas polymer mechanochemistry continues to see rapid advances in molecular design, with demonstrations of new properties and functionalities, the integration of mechanophores into hydrogel biomaterials has received less attention.

Challenges to hydrogel mechanochemistry

Mechanophores are often hydrophobic, making their integration into water-swollen polymer networks challenging. To solve this problem, gels have been formed in organic solvents to ensure mechanophore miscibility and uniform integration, followed by solvent exchange to yield the mechanoresponsive hydrogel[5]. A drawback of this approach is the incompatibility with living cells. Alternatively, solubility issues have been addressed using micelle-forming molecules as carriers, wherein the hydrophobic mechanophore can be evenly dispersed in advance of polymerization[6]. However, this approach suffers from the potential of polymerization handles being buried within the micelle interior, which could hamper even network distribution. In addition to aqueous solubility, another limitation is the brittle nature of most synthetic hydrogel systems, with mechanical failure preceding the force required for mechanochemical activation. To improve mechanical durability, a second, more flexible network can be integrated within a brittle hydrogel, so-called double network hydrogels, to help manage stress dissipation and discourage failure, such as crack propagation[4]. Structural aspects of both the first and the second network influence the mechanical performance of the hydrogels, providing design criteria to guide network selection as a function of mechanochemical activation parameters[7]. Other toughening strategies have recently emerged — such as engineering entanglements within networks or designing force-induced reactions to extend polymer chains[8] — that provide scope for enabling a wide array of mechanochemical transformations to be achievable. The latter approach is interesting because it points to an emerging paradigm of dynamic activity and autonomous behaviour, whereby cyclic loading can catalyse evolving properties (Fig. 1b).

Outlook

Adapting polymer mechanochemical concepts to the field of soft biomaterials science and engineering promises to achieve previously unrecognized properties and functionalities. To prove successful, advances in mechanophore design will need parallel progress in network chemistry. For example, molecular design can be coupled with the toughness afforded by polymer double networks to facilitate molecular release from an oxanorbornadiene linkage with high activation (up to 20%)

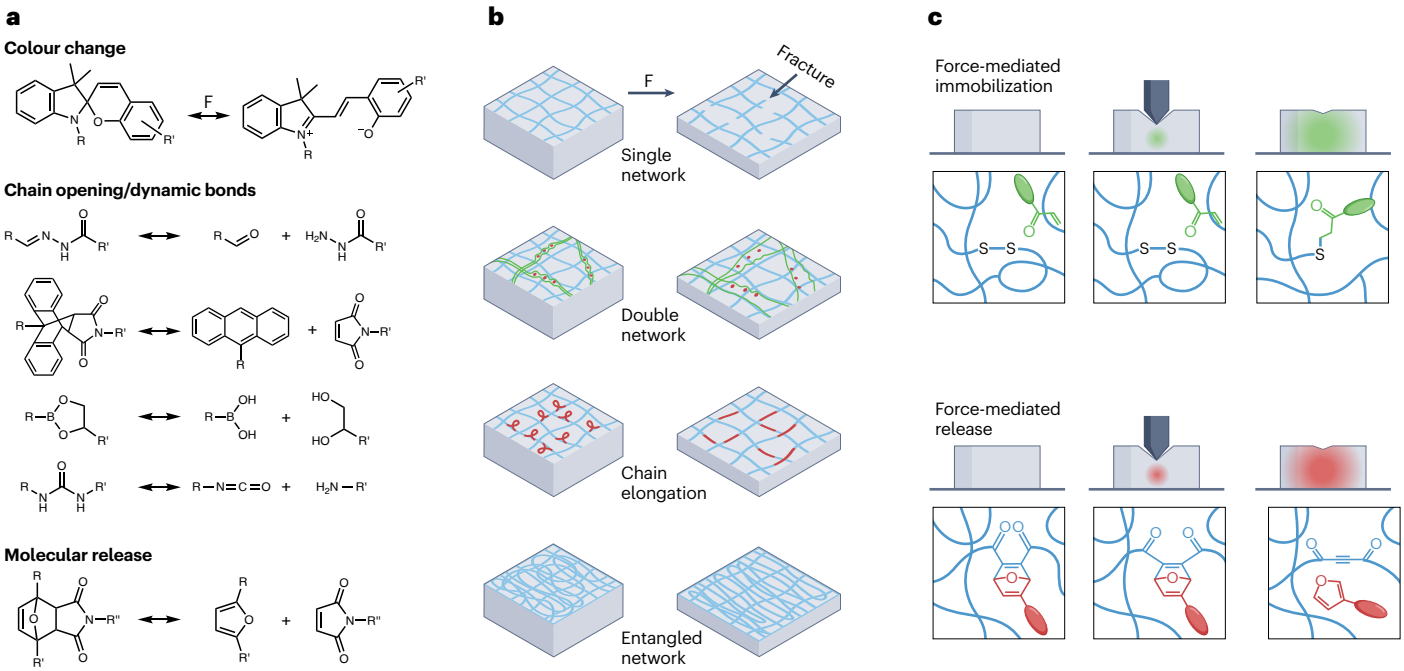

Fig. 1 | Approaches to build mechanochemistry into hydrogels. a, Highlights of common mechanochemical reactions in polymers. **b**, Schematic depictions of toughening approaches in hydrogels. **c**, Examples of force-mediated immobilization and release in hydrogels.

using physiologically relevant forces (kilopascals)[5]. Disulfide-linked polyethylene glycol and alginate double network hydrogels could control a mechanochemical reaction between thiol groups revealed under tension with solution phase maleimide-terminated molecules, thereby providing a means for force-mediated immobilization[9]. Similarly, the reverse reaction, in which force opens an anthracene–maleimide adduct, facilitates immobilization of solution phase thiol-terminated peptides to direct cell adhesion[10]. The versatility of the system was expanded by inclusion of a second disulfide-linked network, resulting in stepwise functionalization of hydrogels using force and light, with spatial patterning of multiple cell types. Importantly, aqueous environments will influence mechanochemical activation thresholds, which could lower the energy barrier compared to systems in bulk polymers, thereby bringing the required forces for activation substantially lower and more in line with biological force regimes. These examples serve as synthetic analogues to the mechanochemical release, sequestration and patterning of molecules observed in natural tissue (Fig. 1c). Integrating multiple responsive moieties, with distinct external triggering mechanisms, will improve the flexibility for temporal control of physical and chemical properties in hydrogel biomaterials.

Advances in hydrogel network chemistry have produced new materials and methods, and the majority of mechanophore activation energies are now readily accessible in soft systems. Nevertheless, most hydrogel biomaterials reported in recent literature remain static, with few reports of 'smart' stimuli-responsive behavior[11]. Recent examples have demonstrated the utility of linking mechanophores within widely used hydrogel systems, demonstrating how bioinspired activities such as mechanical toughening, molecule immobilization and release, and tissue patterning can be built into virtually any platform[5,9,10]. However, hydrogel mechanochemistry as a field remains in its infancy, with a host of opportunities for new discoveries and applications. There is scope for new mechanophores with advanced functions, such as pH and gas regulation, pairing multiple mechanophores with tuneable activation thresholds, introducing complementary activities and built-in reaction networks, and autonomous behaviour such as self-healing, strengthening and growth. The time is ripe for mechanochemistry in hydrogel biomaterials.

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Competing interests

The author declares no competing interests.