Recent developments of nanotechnology in tissue adhesives

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Abstract. The high incidence of wounds coinciding with the current limitations of available treatments have established a high demand for novel and innovative approaches for wound healing. As a result, tissue adhesives, a promising substitute for traditional wound healing procedures, have lately gained great interest in clinical use. As most of the tissue adhesives are hydrogel-based, however, their behavior is severely weakened by the fragility of hydrogel. Recently, researchers have investigated the potential usages of nanoparticles (NPs) as promising candidates for addressing wound treatment and have managed to discover remarkable, enhanced nanotechnology-based adhesive hydrogels. In this review article, our chief focus is highlighting the latest advances in the usage of nanotechnology in tissue adhesives. In particular, we emphasize two fields in which nanotechnology is employed: the possibility to enhance the mechanical and biochemical properties of tissue adhesives as well as the new functions enabled by NPs, including regenerative ability and accelerated wound healing. We also explore unmet demands and potential future research directions of current technologies, while discussing promising strategies to promote wound-healing procedures.

Key words: wound healing; tissue adhesives; nanoparticles; nanotechnology; property enhancement; applications.

1. Introduction
With tens of millions of surgeries being carried out each year, developing safe and effective wound healing procedures has become an increasingly crucial research and clinical objective. Failure to provide a reliable and convenient wound healing method can lead to various complications that frequently cause morbidity and mortality, or add serious economic burdens to patients, especially for those who need to deal with chronic wounds, such as patients with diabetes [1,4]. The huge demand in improving wound-closing procedures highlights the need for rigorous investigation, and also encourages researchers to develop clinically feasible and novel approaches, such as tissue adhesives, in this field.

Tissue adhesives are liquid monomers that can transform into a polymer, usually hydrogel, that forms a strong tissue bond through an exothermic reaction when exposed to a moist surface (skin). Based on the type of material, tissue adhesives can be classified as natural/biological material-based, synthetic-based and semisynthetic-based (Fig. 1) [2,3]. Normally, natural biopolymers such as fibrin, collagen, gelatin, albumin, chitosan are used to produce biodegradable tissue adhesives with great biocompatibility [2]. In contrast, synthetic/semisynthetic-based adhesives usually have better adhesion
but suffer from lower bio-absorption, higher cytotoxicity, and increased chronic inflammation due to harmful degradation products [2,3]. Despite its promising future, however, tissue adhesives are not free of drawbacks. Their potential disadvantages are many, from cell toxicity and weak tissue-adhesive strength, as well as dehiscence and the possibility of inflammation [2]. In response to these deficiencies, nanotechnology sheds a new light on possible solutions.

Fig. 1 Applications and types of tissue adhesives for biomedical usages.

Nanotechnology is a rapidly developing branch of applied science that studies materials with diameters under 100nm (Fig.2) [7]. These materials possess unique properties — specifically their high specific surface area — as well as being available in sizes that allow the penetration of biological membranes and barriers [4,7]. Recent studies demonstrate the promising applications of nanotechnology in wound healing principally through two strategies: nanomaterials as drugs that assist wound healing with intrinsic therapeutic abilities, as well as nanomaterial-based delivery systems for therapeutic agents [4]. The first approach can be furthered divided into metallic/metal oxide/metalloid-based NPs and nonmetallic NPs. As findings emerge to demonstrate the potential of nanotechnology, the incorporation of nanotechnology into tissue adhesives is gaining more attention as a favorable approach to facilitating wound healing process.

Fig.2 Types of nanomaterials that could be utilized in wound treatment.

This review article highlights the latest progress and findings in the usage of nanotechnology in tissue adhesives. In particular, it will emphasize two fields in which nanotechnology is utilized: the possibility of nanoparticles to enhance the mechanical and biochemical properties of tissue adhesives, as well as the application of new functions to tissue adhesives, such as regenerative ability, anti-inflammatory ability and antimicrobial ability.
2. Property enhancement

Over the past few decades, conventional wound closing methods include sutures (stitches), staples, and adhesive tapes [7]. Although these traditional methods enable meticulous closure in most cases, they still possess unignorable disadvantages. Therefore, tissue adhesives have gained increasing popularity in various fields of clinical operations as an alternative to sutures and wound staples.

Ideally, tissue adhesives should possess several properties in order to comply with various medical and surgical requirements. Among other criteria, an ideal tissue adhesive should be biodegradable and biocompatible; be durable, elastic, and suitable for different tissues; adhere easily and firmly to wet surface (tissue); form a watertight seal and not interfere the wound healing process; express low cytotoxicity and minimal inflammatory response [2,7]. Presently, many tissue adhesives face the problem of balancing desired properties. Inspired by the special properties of nanoparticles, recent research has focused on utilizing nanotechnology to enhance both mechanical and biochemical properties of tissue adhesives by means of incorporating newly designed particles or utilizing their unique characteristics. In this section, we review the limitations of existing adhesive materials and describe how recent developed nanotechnology may overcome them.

2.1. Improving physical properties

2.1.1. Reinforced mechanical strength. Hydrogels, considered as the ideal material for tissue engineering in vivo, are also widely used in tissue adhesives [9]. Their tunable structure and ability to absorb water provide a bioenvironment resembling the extracellular matrix (ECM) [9]. By controlling the crosslinking density and polymer chemistry, the physical properties of a hydrogel, such as water content, mechanical strength and elasticity can be controlled as to be applicable to particular tissues types [2]. However, poor mechanical properties, such as fragility, have limited their application.

Many approaches have been used to improve the mechanical properties of hydrogels, one of which is to incorporate nanostructures with defined shape and dimensions. Arno et. al indicated that NPs with 2D platelets significantly increase both the mechanical strength of hydrogel and the adhesion between hydrogel surfaces, compared to their 0D spherical or 1D cylindrical counterparts [10]. Since the results are obtained by using translationally relevant calcium-alginate hydrogels and NPs as an adhesive, such a manipulation of nanostructures can have critical clinical usages.

Nanocomposite hydrogels is another promising scheme to obtain mechanically enhanced products. These gels are crosslinked polymer networks swollen with nanostructures, which render them higher elasticity and strength compared to their counterparts [16]. The NPs can either crosslink the gels, be attached to polymer chains, or add new properties to the gel by physical entrapment [16]. Many types of NPs have been demonstrated with the potential to mechanically strengthen tissue adhesives. For example, chitin nano-whiskers (CtNWs) have been be employed in various medical applications, reinforcing polymer gels even at low loadings [13]. Recently, Pang et al. formulated a novel tissue adhesive through the incorporation of CtNWs with a Schiff base crosslinking hydrogel of carboxymethyl chitosan (CMCS) and dextran dialdehyde (DDA) (Fig. 3A), maintaining the rapid formation of Schiff base reaction but overcoming its poor structural integrity [13]. The complexed hydrogel exhibits 1.87 times higher compressive stress than non-complexed ones and 1.51 folds higher adhesive strength on porcine skin [13]. The processability, as well as biocompatible and biodegradable properties, highlight the potential of CtNWs complexed CD hydrogel to enable rapid hemostasis and wound repair.

Mesoporous bioactive glass (MBG) particles is another type of NP that have attracted significant attention in recent years [15]. It is a silica-based synthetic material characterized by a highly ordered mesopore channel structure with pores varying from 5 to 20 nm [14,15]. Other materials, such as carbon-based nanomaterials (carbon nanotubes, graphene, etc.), inorganic nanoparticles (hydroxyapatite (HA), silica, etc.), and metal/metal-oxide nanoparticles, have also been combined with polymeric networks to acquire tough nanocomposite hydrogels for medical applications [16].

Another approach is to produce hydrogels with different chemistries. For more than a decade, studies have aimed at preparing hydrogels with increased adhesiveness and toughness using mussel-inspired
catechol chemistry [11,30]. Mussels demonstrate a strong adhesion to wet surfaces through mussel adhesive proteins, primarily L-3,4-dihydroxy-L-phenylalanine (DOPA) (Fig. 3B, Left) [12]. DOPA provides strong adhesion through an ortho-dihydroxyphenyl (catechol) functional group, and can be oxidized into o-quinone to form irreversible covalent crosslinks with amino groups on biological surfaces as well [11,12]. Inspired by the DOPA chemistry, researchers have developed several polymer systems by chemically introducing catechol moieties onto polymer backbones. Chitosan-catechol is one of the promising adhesive polymers for clinical usages due to their high biocompatibility [11]. The conjugation of catechol to chitosan significantly increases its solubility in aqueous solutions and provides enhanced mechanical properties due to catecholamine crosslinking (Fig. 3C) [11]. It exhibits a high tensile strength (9.6 ± 1.7 MPa) that is three times tougher than that of commercial paper and a hardness similar to that of human fingernails [11]. Moreover, catechol groups can also be functionalized with proteins, such as silk nanofiber. Research shows that PEG-silk fibroin conjugates can achieve mechanical reinforcement and reduce swelling through physical cross-linking by formation of β-sheets between silk chains [42].

Nanotechnology is also frequently employed in preparing catechol-based tissue adhesives with mechanical enforcement. Pandey et al. developed a nanocomposite-based, biodegradable tissue adhesive by blending poly(lactic-co-glycolic acid) (PLGA) or N-hydroxysuccinimide modified PLGA nanoparticles (PLGA-NHS) with alginate-dopamine polymer (Alg-Dopa) (Fig. 3D) [22]. Measurements reveal that the incorporation of PLGA/PLGA-NHS in Alg-Dopa significantly enhances the adhesive strength, as well as lap shear strength (33 ± 3 kPa) compared to that of Alg-Dopa gel (14 ± 2 kPa) [22].

In all, the universal fragility of hydrogels can be effectively overcome by the incorporation of NPs. By controlling the contents of NPs in a given tissue adhesive, mechanical strength can be further tuned according to specific requirements. However, due to the possible toxicity of NPs, balancing potential property enhancements against possible negative effects still remains as a challenge for further research.

![Fig. 3](image_url)

**Fig. 3** Schematic illustration of: (A) CtNWs complexed CMCS/DDA hydrogel formed by extrusion via double-tube syringe; (B) the structure of L-3,4-dihydroxy-L-phenylalanine (DOPA, left) and the structure of dopamine (right); (C) crosslinking chemistry of chitosan-catechol, forming coordination bonds by transition metal ions, e.g. Fe^{3+}; (D) the structure and fabrication of mussel-inspired nanocomposites based on NHS modified PLGA nanoparticles.
2.1.2. Increased durability and self-healing property of tissue adhesives. In order to provide reliable adhesion until wounds are completely healed, tissue adhesives should possess proper durability and stability for a given period of time. However, many adhesive hydrogels are fragile and fail to maintain their functions under high pressure or fatigue. For example, the production of effective long-lasting adhesive hydrogels containing catechol moieties is still challenging since the catechol groups would be oxidized to quinone groups, thus losing adhesion to tissue surfaces [17,18].

To solve this problem, Xiao et al. first described a novel way to fabricate durable adhesive hydrogels based on quercetin-assisted photo-radical chemistry (Fig. 4A) [18]. They demonstrated that in the presence of light, quercetin can generate quinone/semiquinone radicals, which further interact with ammonium persulfate (APS) to produce abundant free radicals and initiate polymerization of the hydrogel [18]. As-prepared gels show an adhesive strength of ~110 J/m² and a fracture energy around 400 J/m² [18]. In terms of long-term adhesive properties, these gels maintain adhesive strength after a 15-day storage period or after 50 peeling/adhering cycles [18].

With similar ideas, Gan et al. developed an Ag-Lignin NP to trigger the dynamic redox chemistry, which can maintain the quantity of catechol groups to make catechol-containing hydrogels tough and durable (Fig. 4B) [17]. The phenol/methoxy groups in plant-originated lignin can reduce silver ions (Ag⁺) to metallic Ag NPs while being oxidized to the corresponding quinone/hydroquinone [19]. At the same time, the Ag NPs can produce photogenerated electrons from surface plasmon resonance and convert quinone/hydroquinone groups into catechol groups [20]. According to this mechanism, Ag-Lignin NPs construct a dynamic catechol redox system, which continuously generate catechol groups to ensure long-lasting adhesiveness. Experience indicates that this hydrogel maintains good adhesion even after 30 repeated peeling/adhering cycles or after 28 days when applied [17]. Therefore, this plant-inspired hydrogel exhibiting durability, repeatable high adhesiveness, and cell affinity illustrates a strategy for developing tissue adhesives based on dynamic redox catechol chemistry.

Another way to achieve durability is by rendering the hydrogel with self-healing property. Self-healing property, the ability to recover original structures and properties without external forces, is an important characteristic of hydrogels that can withstand cyclic loading and repair tissue damage. Self-healable hydrogels are usually designed by introducing dynamic covalent bonds or reversible noncovalent bonds, including imines, hydrogen bonds, disulfide bonds, host-guest interactions, hydrophobic interactions, etc. [21]. They can provide significant advantages in wound closure: for example, using self-healing tissue adhesives as coatings can reduce the risk of bare implant surfaces’ contact with body fluids, for the damages generated on implants coating can be spontaneously repaired [23]. They can also be employed as injectable dynamic scaffolds to facilitate wound healing. Gantar et al. suggested a dynamic hydrogel nanocomposite with osteo-inductive properties and self-healing abilities to promote bone self-repair (Fig. 4C) [24]. This nanocomposite [Au-(PEGSH)₄-BAG] is fabricated by combining a self-healable Au-based 4-arms thiol terminated poly(ethylene glycol) [Au-(PEGSH)₄] gel with bioactive glass (BAG) NPs [24]. The combination efficiently overcomes the major drawbacks of each individual material, i.e. BAG NPs’ brittleness and Au-(PEGSH)₄’s weak consistency, resulting in a material composite with high stress resistance and deformation ability, thus injectability [24]. As a result, the Au-(PEGSH)₄-BAG hydrogel nanocomposite are considered as a potential biomaterial for bone regeneration and self-repair.
Fig. 4 Schematic illustration of: (A) the preparation of quercetin-assisted radical-chemistry triggered hydrogel upon light irradiation; (B) design strategy for the hydrogel based on Ag-Lignin NPs-triggered dynamic redox catechol-chemistry; (C) the preparation processes of the injectable and self-healing hydrogel based on bioactive glass NPs.

Although self-healing tissue adhesives shed light on developing more durable and stable wound treatments, many concerns and challenges remain. Major concerns include designing self-healing hydrogels with good biocompatibility and mechanical properties and being controllable in vivo biodegradability and the fate of NPs released from the composite materials [21].

2.2. Improving biochemical properties

2.2.1. Reduced toxicity and improved biocompatibility. Although tissue adhesives provide a painless and effective wound closure method, their potential toxicity remains as a problem that cannot be ignored. For example, the most common component of synthetic based tissue, cyanoacrylate (CA), has been shown to cause inflammation and tissue necrosis in vivo, which might further lead to thrombotic events [25]. In other research, toxicity of CA adhesive was considered as a major cause of post-operative arterial occlusive lesions [25]. At the same time, nanotechnology in wound healing also faces the limiting factor of high toxicity for living organisms that hinders its in vivo applications. Currently, researchers often face the problem of balancing the positive therapeutic effect of NPs and their negative toxic side effects [5,26].

The toxicity of NPs is largely determined by their physical and chemical characteristics, including size, shape, surface charge, and the active groups on the surface [26]. Specifically, the small size of NPs allows them to penetrate through epithelial and endothelial barriers and further into the lymph and blood of various organs and tissues [26]. The oxidation of leaked free metal ions from NPs’ cores, such as cadmium, lead, and arsenic, may also be a related cause of toxicity [26]. Therefore, it is hoped that safe and biocompatible NPs can be developed and used for the diagnosis and treatment of human diseases. Currently there are two main strategies to control the toxicity of NP-based adhesives: first, by reducing required doses to limit dissolution of NPs; second, by developing new types of NPs with different structures. Recent studies show that some types of NPs possess relatively low toxicity while maintaining the desired properties of tissue adhesives. For example, the biocompatibility of several representative types of nanomaterials has been thoroughly examined, including gold NPs, Ag NPs, and silica particles.

Gold NPs have long been used in various biomedical applications, including drug delivery, anticancer, angiogenesis, and biosensing applications by being functionalized with organic probe molecules.
(antibodies, enzymes, nucleotides, etc.) [4,5]. As early as in 2010, Brandenberger et al. devised an epithelial-airway model to mimic the respiratory tract after the inhalation of gold NPs [28]. Once exposed to 15 nm gold NPs using an air-liquid interface exposure system, neither inflammatory responses nor suppressive effect was noted, which suggested that gold NPs do not elicit immune reactions [28]. Owing to their inherent antioxidant properties with a high level of biocompatibility, gold NPs have emerged as promising candidates for wound healing applications to facilitate the wound healing process [4,5].

Researchers have developed nanocrystalline silver/silver NPs that are effective at lower concentrations, resulting in lower toxicity compared with conventional silver [4]. Silver NP-embedded dressings, such as Acticoat, have demonstrated controllable sustained release of silver ions that help overcome potential toxicity and inactivation of protein in wound tissues [4]. Although Ag NPs might decrease the temporary mitochondrial function, they do not cause cell cytotoxicity. An in vivo clinical study on human patients showed no toxicity, as observed by the absence of necrosis or apoptosis in the healed area [4].

Silica-coated/silica-NPs also demonstrate good biocompatibility, being able to enter the cell without affecting cell functions and survival [29]. These insights push research toward the development of silica-NPs-based tissue adhesives with reduced toxicity and multifunctionality [29]. In 2017, Shin et al. developed biocompatible tantalum oxide/silica core/shell nanoparticles (TSNs) with strong adhesive and real-time imaging properties [27]. Compared to imageable tissue adhesive for clinical use, i.e., the mixture of cyanoacrylate and Lipiodol (CA-Lp), TSNs exhibit a similar adhesive property while causing much less cellular toxicity and inflammation due to the inertness of the tantalum oxide [27]. Histological analysis demonstrates a significant decrease in the level of tissue inflammation when TSNs are applied, whereas CA-Lp results in severe toxicity caused by by-products such as formaldehyde.

All in all, the potential toxicity of NPs is still one of the main limitations of wider medical applications. It can be positively noted, however, that a number of effective approaches are already available to reduce the toxicity of NPs, such as surface modification and artificial control of NPs’ size and shape [26]. With more and more data becoming available regarding NPs toxicity, it is promising to design tissue adhesives with reduced toxicity while taking advantage of NPs’ special properties.

2.2.2. Controlled biodegradability. In addition to biocompatibility, degradability is another important property that must be considered when designing an appropriate tissue adhesive. First, the degradation time of the tissue adhesive should coincide with the regeneration and/or healing process of the wound to ensure proper remodeling of the tissue. Second, the degraded product of the adhesive should be biocompatible and easily excreted from the body. Finally, mechanical property change caused by degradation should preserve compatibility with the healing or regeneration process [95]. More ideally, the degradation rate of the tissue adhesive should be controllable or tunable in order to fit various usages. Biodegradable biomaterials can be roughly divided into two categories: natural and synthetic. Natural biodegradable polymeric biomaterials include proteins (collagen, fibrin, silk, etc.) and polysaccharides (starch, chitin/chitosan, hyaluronic acid derivatives, etc.) [31]. More recently, sundew adhesives (natural polysaccharide-based hydrogels) and ivy nanoparticles (macromolecular compositions of nanospherical arabinogalactan proteins) have gained attention for their ability to create effective nanocomposite adhesives and usage as nano-carriers in drug delivery, respectively [32]. Synthetic biodegradable biomaterials include saturated aliphatic polyesters (poly(glycolic acid) (PGA), PLA, PLGA, etc.), polyglycols, polyurethane (PUR), and polylactides [31]. Compared to natural ones, synthetic biomaterials have mechanical properties and degradation rates that can be easily controlled [31].

NPs based on biodegradable and biocompatible polymers have recently shown potential as sustained drug-delivery vehicles and have been applied in wound-healing applications to deliver bioactive agents [31]. However, regarding tissue adhesives, current knowledge on NP’s ability to tune or control their degradation is still limited, and more focus have been given to develop new crosslinking types to
facilitate degradation. Therefore, more comprehensive and thorough research is still required in this direction.

3. Introducing new functions

Nanotechnology not only helps enhance the characteristics of current tissue adhesives, it also brings new functions, such as regenerative properties, accelerated wound healing, and antimicrobial properties, to conventional tissue adhesives. It also increases the accumulation of drugs in the target site, thus lowering the required dose and helps balance the discrepancy between concentration levels of drug dosage and its therapeutic/toxic effects [6]. This section will review the new functions of tissue adhesives that have been achieved through the utilization of nanotechnology.

3.1. Regenerative property

To Restore tissue integrity and function efficiently while minimizing post-injury aesthetic impact has long been the central concern of clinical care. Recently, nanostructured biomaterials such as nanoparticles, nanofibers, and nanocomposites that can actively regulate cellular responses for the regeneration process, as well as deliver drugs to wound sites have gained increasing attention in regenerative medicine. These biomaterials demonstrate several advantages over traditional treatments and growth factors in terms of prolonged half-life, enhanced tissue retention, improved stability and easily achieved immobilization for scaffolds, which make them promising candidates in tissue repair and regeneration [34].

One major barrier of promoting regenerative wound healing is the elevated reactive oxygen species (ROS) production in the injured site [33]. It is stated that ROS would trigger a set of deleterious effects, including cellular senescence, fibrotic scarring, and inflammation [33]. Therefore, recent studies have focused on alleviating oxidative stress in the microenvironment of injured site and leverage intrinsic regenerative capacity of the host for active wound regeneration [33]. A study of Wu et al. demonstrates a highly versatile ROS-scavenging tissue adhesive nanocomposite based on ceria nanocrystals decorated mesoporous silica nanoparticles (MSNs-Ceria) (Fig. 5A) [33]. MSNs-Ceria has several advantages: it has strong tissue adhesion strength; it enables a regenerative healing characteristic at the wound area characterized by limited scar formation; it also helps achieve a rapid closure of deep wounds owing to the nanobridging effect between nanoparticle and tissue matrix. Ceria nanocrystals are believed to possess a capacity for ROS reduction comparable to that of biological antioxidants due to the former’s multi-antioxidant enzyme-like activities and self-regenerative capacity [33]. The quick switch of the oxidation state in the surface of ceria nanocrystals between Ce⁴⁺ and Ce³⁺ enables MSN-Ceria nanocomposites to efficiently reduce ROS level [35]. Therefore, the ROS-scavenging effect triggered by MSN-Ceria nanocomposites results in a reduced inflammatory response and cellular senescence, creating a friendly microenvironment that enables the restoration of tissue integrity and tissue function simultaneously.

Hydrogel adhesives are also promising materials for the regeneration of cartilage lesions. The material, which mainly consist of collagen and glycosaminoglycan, are characterized by a high-water content which distributes stress on all articular areas [37]. In order to create cartilage-like hydrogels that can bear the high stress, nanofillers have often been used as in the case of the hybrid hydrogel to produce mechanically stable systems [37]. In recent years, composite hydrogels containing magnetic NPs demonstrate to a high degree the possibility of being used in cartilage tissue engineering as well. Zhang et al. reported a hybrid hydrogel composed of collagen II, hyaluronic acid, and PEG incorporating iron-based magnetic NPs that can be used to accurately place the scaffold in damaged areas using external magnets [36]. More recently, Chen et al. first demonstrated a multifunctional self-healing magnesium ions-quaternized chitosan/Pluronic® F127 (Mg-QCS/PF) hydrogel to achieve in situ and customized release of Mg⁡²⁺, which facilitate the fibrocartilaginous enthesis regeneration after rotator repair [38].
3.2. Accelerated wound healing

Successful and expedient wound repair is always a major challenge in the healthcare industry. When wounds become chronic, the accompanied function loss and increasing pain is a burden on both the individual patient and the healthcare system [39]. Fortunately, nanotechnology provides a solution by enabling advanced healing therapy that can accelerate wound repair with minimal scarring [39]. Various approaches based on nanomaterials have been proposed to target specific phases during the wound healing process. For instance, silica NPs have received increasing attention in novel tissue adhesive design due to their intrinsic superiorities, especially mesoporous silica nanoparticles (MSNs) [33]. Having a porous structure and an active surface, MSNs are capable of fast degradation and strong adhesion to tissue [8]. Researchers took advantage of these properties to reduce the occurrence of delayed healing process caused by the slow elimination of exogenous adhesives [8]. Recently, Pan et al. demonstrated a tissue adhesive that can elicit acute inflammatory response and degrade after tissue reformation by exploiting the inherent properties of MSNs [8]. Such nanocomposites can subsequently recruit acute inflammation and support prominent infiltration of inflammatory cells as a bioactive scaffold, resulting in outstanding healing outcomes. Outstandingly, MSNs exhibit an accelerated healing process for approximate three days and 143% increase of wound breaking strength after 10 days, compared with the control group. These assessments explain the potential of MSNs as adhesives that could effectively accelerate the healing process, as well as serve as temporarily stimulate inflammatory response to promote wound repair [8].

Tissue adhesives with accelerated wound healing property are especially useful in treating chronic or long-term wounds, such as those of diabetes patients. Many factors, such as insufficient, cell proliferation, cell migration, and angiogenesis, can lead to the failure in healing chronic wounds [40]. To overcome these barriers, ceria is used in many biomedical applications because of their antioxidant and angiogenic properties, as well as cerium oxide NPs (nCeO$_2$) [40]. More recently, Augustine et al. reported a novel nCeO$_2$ containing electrospun poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) membrane for diabetic wound healing applications, where nCeO$_2$ with antioxidant property improves the healing process by inhibiting ROS generation (Fig. 4B) [40]. Histological analysis showed a considerable improvement in cell infiltration and capillary ingrowth after 30 days in diabetic wounds treated by PHBV/nCeO$_2$ membranes even with only 1% (w/w) NP loading. Based on these results, PHBV/nCeO$_2$ membranes can serve as a promising method to significantly enhance the diabetic wound healing process.

Fig. 5 Schematic illustration of: (A) the production for MSN-Ceria; (B) the structure and in vitro studies of nCeO2-containing PHBV membrane for wound healing applications; (C) the preparation processes of h-CuS NPs for NIR irradiation to yield CO$_2$. 

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Moreover, local hypoxia caused by insufficient microcirculatory blood flow is also a major cause of nonhealing [39]. Therefore, the improvement of microcirculation and oxygen supply in the wounded areas has been one of the keys to treatment. Li et al., taking advantage of CO2’s efficacy in improving both microcirculation and the rise of oxygenation level, designed the hollow CuS nanoshells (h-CuS) to yield CO2 for wound healing (Fig. 4C) [39,41]. These h-CuS NPs are water-dispersed and can be topically applied on wounded area in the form of colloidal solution. Upon exposure of near-infrared (NIR) lamp, the temperature of NPs will rise, leading to the generation of CO2. Furthermore, CO2 delivery creates a weak acidic microenvironment in blood, which promotes microcirculation to accelerate wound healing. Therefore, this NIR-driven CO2 release system provides a new idea in accelerated wound healing.

4. Conclusion and Outlook

Traditional methods for wound closure have certain disadvantages, especially for vulnerable and delicate tissues. Tissue adhesives provide a promising alternative for these purposes and have attracted extensive interests in recent years due to their outstanding performance and maneuverability. At the same time, nanotechnology can be efficiently employed in myriad medical applications, including wound therapy. This review summarizes the recent advances of nanotechnology’s application in tissue adhesives. Extra features such as antibacterial and hemostatic properties can also be introduced to tissue adhesives by the use of nanotechnology. For example, metal NPs such as silver, gold and zinc possess outstanding antibacterial activity; nano-compounds encapsulating growth factors, genes or stem cells are under development to offer new treatments in the near future [7].

However, there are still many challenges and barriers that remain. Their anticipated behavior and toxicity in the human body; the long-term safety of nanomaterials; the bulk scale preparation and purification of nanomaterials as per FDA standards; the reoccurrence of NP-resistant bacteria, and so on [4]. Therefore, comprehensive studies are indispensable to provide insights into the molecular mechanisms involved in wound healing and formulate effective strategies to translate nanotechnology-based therapies to the clinic, as well as fulfill the need for better synthetic tools and analytical methods.

It is expected that new nanotechnology platforms for developing tissue adhesives will arise soon. Overall, the expeditious advance in nanotechnology-based tissue adhesives has illustrated its huge potential in wound treatments, and will further promote the design in the next generation of wound-healing nanotechnologies.

References

[1] Han G, Ceilley R. Chronic Wound Healing: A Review of Current Management and Treatments[J]. Advances in Therapy, 2017, 34(3): 599-610.
[2] Taboada G, Yang K, Pereira M et al. Overcoming the translational barriers of tissue adhesives[J]. Nature Reviews Materials, 2020, 5(4): 310-329.
[3] Ge L, Chen S. Recent Advances in Tissue Adhesives for Clinical Medicine[J]. Polymers, 2020, 12(4): 939.
[4] Nethi S, Das S, Patra C et al. Recent advances in inorganic nanomaterials for wound-healing applications[J]. Biomaterials Science, 2019, 7(7): 2652-2674.
[5] Li X, Wang L, Fan Y et al. Biocompatibility and Toxicity of Nanoparticles and Nanotubes[J]. Journal of Nanomaterials, 2012, 2012: 1-19.
[6] Patra JK, Das G, Fraceto LF et al. Nano based drug delivery systems: recent developments and future prospects[J]. Journal of Nanobiotechnology, 2018, 16(1): 71.
[7] Dumville JC, Coulthard P, Worthington HV et al. Tissue adhesives for closure of surgical incisions[J]. Cochrane Database Syst Rev, 2014, (11): CD004287.
[8] Pan Z, Zhang K, Gao H et al. Activating proper inflammation for wound-healing acceleration via mesoporous silica nanoparticle tissue adhesive[J]. Nano Research, 2020, 13(2): 373-379.
[9] Hunt J, Chen R, Van Veen T et al. Hydrogels for tissue engineering and regenerative medicine[J]. J. Mater. Chem. B, 2014, 2(33): 5319-5338.
[10] Arno M, Inam M, Weems A et al. Exploiting the role of nanoparticle shape in enhancing hydrogel adhesive and mechanical properties[J]. Nature Communications, 2020, 11(1).
[11] Ryu J, Hong S, Lee H. Bio-inspired adhesive catechol-conjugated chitosan for biomedical applications: A mini review[J]. Acta Biomaterialia, 2015, 27: 101-115.
[12] Lee Y, Chung H, Yeo S et al. Thermo-sensitive, injectable, and tissue adhesive sol–gel transition hyaluronic acid/pluronic composite hydrogels prepared from bio-inspired catechol-thiol reaction[J]. Soft Matter, 2010, 6(5): 977.
[13] Pang J, Bi S, Kong T et al. Mechanically and functionally strengthened tissue adhesive of chitin whisker complexed chitosan/dextran derivatives based hydrogel[J]. Carbohydrate Polymers, 2020, 237: 116138.
[14] Wei S, Pei M, Pan W et al. Gelatin Hydrogels Reinforced by Absorbable Nanoparticles and Fibrils Cured in Situ by Visible Light for Tissue Adhesive Applications[J]. Polymers, 2020, 12(5): 1113.
[15] Yan X, Yu C, Zhou X et al. Highly ordered mesoporous bioactive glasses with superior in vitro bone-forming bioactivities[J]. Angew Chem Int Ed Engl, 2004, 43: 5980-5984.
[16] Fuchs S, Shariati K, Ma M. Specialty Tough Hydrogels and Their Biomedical Applications[J]. Advanced Healthcare Materials, 2019, 9(2): 1901396.
[17] Gan D, Xing W, Jiang L et al. Plant-inspired adhesive and tough hydrogel based on Ag-Lignin nanoparticles-triggered dynamic redox catechol chemistry[J]. Nature Communications, 2019, 10(1).
[18] Xiao D, Jiang M, Zhang X et al. Seeking Answers from Tradition: Facile Preparation of Durable Adhesive Hydrogel Using Natural Quercetin[J]. iScience, 2020, 23(8): 101342.
[19] Milczarek G, Rebis T, Fabianska J. One-step synthesis of lignosulfonate-stabilized silver nanoparticles[J]. Colloids and Surfaces B: Biointerfaces, 2013, 105: 335-341.
[20] Ke J, Niu C, Zhang J et al. Significantly enhanced visible light photocatalytic activity and surface plasmon resonance mechanism of Ag/AgCl/ZnWO4 composite[J]. Journal of Molecular Catalysis A: Chemical, 2014, 395: 276-282.
[21] Liu Y, Hsu S. Synthesis and Biomedical Applications of Self-healing Hydrogels[J]. Frontiers in Chemistry, 2018, 6.
[22] Pandey N, Hakamivala A, Xu C et al. Biodegradable Nanoparticles Enhanced Adhesiveness of Mussel-Like Hydrogels at Tissue Interface[J]. Advanced Healthcare Materials, 2017, 7(7): 1701069.
[23] Rahimnejad M, Zhong W. Mussel-inspired hydrogel tissue adhesives for wound closure[J]. RSC Adv., 2017, 7(75): 47380-47396.
[24] Gantar A, Drnovšek, N, Casuso P et al. Injectable and self-healing dynamic hydrogel containing bioactive glass nanoparticles as a potential biomaterial for bone regeneration[J]. RSC Advances, 2016, 6(73): 69156-69166.
[25] Leggate P, Smith D, Kedjarune U. Surgical Applications of Cyanoacrylate Adhesives: A Review of Toxicity[J]. ANZ Journal of Surgery, 2007, 77(4): 209-213.
[26] Sukhanova A, Bozrova S, Sokolov P et al. Dependence of Nanoparticle Toxicity on Their Physical and Chemical Properties[J]. Nanoscale Research Letters, 2018, 13(1).
[27] Shin K, Choi J, Ko G et al. Multifunctional nanoparticles as a tissue adhesive and an injectable marker for image-guided procedures[J]. Nature Communications, 2017, 8(1).
[28] Brandenberger C, Rothen-Rutishauser B, Muhlfeld C et al. Effects and uptake of gold nanoparticles deposited at the air–liquid interface of a human epithelial airway model[J]. Toxicology and Applied Pharmacology, 2010, 242(1): 56-65.
[29] Zhao Y, Trewyn B, Slowing I et al. Mesoporous Silica Nanoparticle-Based Double Drug Delivery System for Glucose-Responsive Controlled Release of Insulin and Cyclic AMP[J]. Journal of the American Chemical Society, 2009, 131(24): 8398-8400.
[30] Espinoza-Ramirez A, Fuentes-Rodriguez H, Hernandez-Herrera E et al. Nanobiodiversity and Biomimetic Adhesives Development: From Nature to Production and Application[J]. Journal
of Biomaterials and Nanobiotechnology, 2019, 10(02): 78-101.

[31] Song R, Murphy M, Li C et al. Current development of biodegradable polymeric materials for biomedical applications[J]. Drug Design, Development and Therapy, 2018, Volume 12: 3117-3145.

[32] Huang Y, Wang YJ, Wang Y et al. Exploring naturally occurring ivy nanoparticles as an alternative biomaterial[J]. Acta Biomater, 2015, 25: 268-283.

[33] Wu H, Li F, Wang S et al. Ceria nanocrystals decorated mesoporous silica nanoparticle based ROS-scavenging tissue adhesive for highly efficient regenerative wound healing[J]. Biomaterials, 2018, 151: 66-77.

[34] Shin S, Bae H, Cha J et al. Carbon Nanotube Reinforced Hybrid Microgels as Scaffold Materials for Cell Encapsulation[J]. ACS Nano, 2011, 6(1): 362-372.

[35] Celardo I, Pedersen J, Traversa E et al. Pharmacological potential of cerium oxide nanoparticles[J]. Nanoscale, 2011, 3: 1411e1420.

[36] Zhang N, Lock J, Sallee A et al. Magnetic Nanocomposite Hydrogel for Potential Cartilage Tissue Engineering: Synthesis, Characterization, and Cytocompatibility with Bone Marrow Derived Mesenchymal Stem Cells[J]. ACS Applied Materials & Interfaces, 2015, 7(37): 20987-20998.

[37] Piantanida E, Alonci G, Bertucci A et al. Design of Nanocomposite Injectable Hydrogels for Minimally Invasive Surgery[J]. Accounts of Chemical Research, 2019, 52(8): 2101-2112.

[38] Chen B, Liang Y, Bai L et al. Sustained release of magnesium ions mediated by injectable self-healing adhesive hydrogel promotes fibrocartilaginous interface regeneration in the rabbit rotator cuff tear model[J]. Chemical Engineering Journal, 2020, 396: 125335.

[39] Li W, Su C, Wang S et al. CO2 Delivery to Accelerate Incisional Wound Healing Following Single Irradiation of Near-Infrared Lamp on the Coordinated Colloids[J]. ACS Nano, 2017, 11(6): 5826-5835.

[40] Augustine R, Hasan A, Patan N et al. Cerium Oxide nanoparticle incorporated electrospun Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) Membranes for Diabetic Wound Healing Applications[J]. ACS Biomaterials Science & Engineering, 2019, 6(1): 58-70.

[41] Jensen F. Red blood cell pH, the Bohr effect, and other oxygenation-linked phenomena in blood O2 and CO2 transport[J]. Acta Physiologica Scandinavica, 2004, 182(3): 215-227.

[42] Burke K, Roberts D, Kaplan D. Silk Fibroin Aqueous-Based Adhesives Inspired by Mussel Adhesive Proteins[J]. Biomacromolecules, 2015, 17(1): 237-245.