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Mini-review

Peritendinous adhesion: Therapeutic targets and progress of drug therapy

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ABSTRACT

Peritendinous adhesion (PA) is one of the most common complications following hand surgery and characterized with abnormal hyperplasia of connective tissue and excessive deposition of extracellular matrix. Subsequently, various clinical symptoms such as chronic pain, limb dyskinesia and even joint stiffness occur and patients are always involved in the vicious cycle of "adhesion – release – re-adhesion", which seriously compromise the quality of life. Until present, the underlying mechanism remains controversial and lack of specific treatment, with symptomatic treatment being the only option to relieve symptoms, but not contributing no more to the fundamentally rehabilitation of basic structure and function. Recently, novel strategies have been proposed to inhibit the formation of adhesion tissues including implantation of anti-adhesion barriers, anti-inflammation, restraint of myofibroblast transformation and regulation of collagen overproduction. Furthermore, gene therapy has also been considered as a promising anti-adhesion treatment. In this review, we provide an overview of anti-adhesion targets and relevant drugs to summarize the potential pharmacological roles and present subsequent challenges and prospects of anti-adhesion drugs.

1. Introduction

Peritendinous adhesion (PA) after tendon repair surgery was considered as an intractable problem for hand surgeon[1–3]. As a part of extrinsic healing, adhesion is inevitably produced between the tendon and surrounding tissues during the biological process of tendon healing [4–6]. It was reported in the literature that the number of prevalent patients with tendon injury are over 320,000 per year in United States, adhesion formation was encountered following surgery in 30–40% of patients with tendon injury and even resulted in loss of function, which is the culprit behind gigantic socioeconomic burden and impaired quality of life [7–9]. Currently, tenolysis still remains standard clinical treatment of PA to remove adhesion tissue in spite of high rate of recurrence and postoperative complications [10–13]. More challenging and convoluted to prevent than primary adhesion, recurrent postoperative adhesion was reported to have a higher rate of 80% owing to the vicious circle of adhesiolysis surgery, which indicates an urgent demand for timely non-invasive intervention of PA based on biological and genetic innovation in modulating the healing response [14,15]. With in-depth research of the mechanism of PA formation, multiple drug treatments have been explored to reduce peritendinous adhesion without compromising tendon healing and thus achieve better gliding function of regenerated tendon [16–18]. Unfortunately, there remains a gap between drug discovery and clinical applications that numerous anti-adhesion drugs have only been curative in animal experiments but have not yet achieved satisfactory clinical results and even exerted adverse effects on tendon healing [19–21]. In this review, we summarize the mechanism of adhesion formation, advances in pharmaceutical treatments, and prospective biomarkers in preventing the occurrence and development of PA in a bid to provide guidance for designing more effective and targeted drugs (Fig. 1).

2. Overview of adhesion tissues formation

2.1. The pathologic process of PA

The natural process of PA is divided into three overlapping phases regulated by different cell types and cytokines: rapid inflammatory phase, complicated proliferative phase, and prolonged remodeling phase (Fig. 2) [22,23]. In inflammatory phage, inflammatory cells such as neutrophils and macrophages invade into the injured site through the bloodstream and release pro-inflammatory cytokines and chemokines to recruit fibroblasts [24]. Subsequently, myofibroblast (MFB) transformation, tenogenic differentiation of tendon stem cells (TSCs) and

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excessive collagen (Col) deposition were involved in proliferative phase [25]. The remodeling stage can be split into two sub-stages: in the consolidation stage, Col I begin to replace Col III with fibers arranged linearly along the direction of stress [26]; The mature stage is recognizable by increased cross-linking of collagen fibers, which mark the maturation of fibrous tissue though at the expense of decreased cell density and tensile strength [27].

Currently, PA is attributed to the imbalance between intrinsic and extrinsic healing [28,29]. In the microenvironment of regenerated tendon, intrinsic and extrinsic cell populations play different roles and result in distinct outcomes. Intrinsic healing is distinguished by the migration and differentiation of TSCs from endotenon [30], while extrinsic healing manifests that MFB penetrates into injury site from adjacent tissues and bloodstream [31]. Ideally, with the progress of tendon regeneration, the healing process will be gradually dominated by intrinsic healing, leading to regenerated tendon with favorable biomechanical properties and fewer complications. However, the reparative capacity of intrinsic healing is very limited as low cellularity and poor vascularity [32]. Therefore, the first two phases are dominated by extrinsic healing and characterized with fibrin clot deposition, MFB invasion and excessive synthesis of extracellular matrix (ECM) mainly composed of disorganized Col III, which eventually breeds adhesion tissues and is detrimental to the regeneration of the native tendon structure. Histologically, in contrast to healthy tendon, featuring parallel and slightly wavy collagen bundles, adhesion tissues are identifiable with loss of the longitudinal alignment of collagen fibers and unclear demarcation between adjacent collagen bundles[33–35].

2.2. The molecular mechanism of PA

Unfortunately, the molecular mechanism of PA is still inconclusive and several hypotheses had been proposed including inflammation, oxidative stress and excessive fibrogenesis[4,33,36,37]. The prevention and treatment of PA remains a persistently unsolved problem and can be principally attributed to the lack of suitable biomarkers to maintain the balance between tendon healing and PA [36]. Numerous intracellular and intercellular signaling pathways, including nuclear factor-κB (NF-κB), extracellular signal-regulated kinase (ERK) and transforming growth factor-β (TGF-β), have been shown to mediate the adaptive response towards tendon homeostasis [38–40].

2.2.1. Regulation of macrophage

The tendon injury, surgical trauma and implantation induce inflammatory response and oxidative stress with subsequent recruitment of macrophage into injury site. In the inflammatory phase, macrophage occupies the dominant position and is classified into two subpopulations (pro-inflammatory M1 and pro-healing M2 subtypes) based on biological function and cytokine profiles [41,42]. M1 subtype macrophage is most closely related to inflammation and secretes pro-inflammatory cytokines (interleukin 6: IL6 and tumor necrosis factor alpha: TNF-α) to accelerate myofibroblast activation. However, the specific targets for driving M1 polarization are poorly defined in PA. It was found that NF-κB phosphorylation contribute to macrophage M1 polarization and Col deposition to aggravate adhesion formation [38]. Inhibition of NF-κB can effectively reduce the activation of M1 subtype macrophage and release of IL6 and TNF-α to achieve anti-adhesion therapy [43,44]. As one of the inflammation subsides, M2 subtype macrophage secretes excessive pro-adhesion cytokine, such as TGF-β, contributing to adhesion and scar tissue formation. Mechano-growth factor (MGF) upregulated of histone acetylation and STAT6 phosphorylation to promote M2 polarization of macrophage [45]. In addition, Cui et al. also demonstrated that macrophage-derived exosome contributes to increase d proliferation, migration and fibrotic activity of fibroblast and tenocyte via directly miR-21–5p/Smad7 pathway [46].

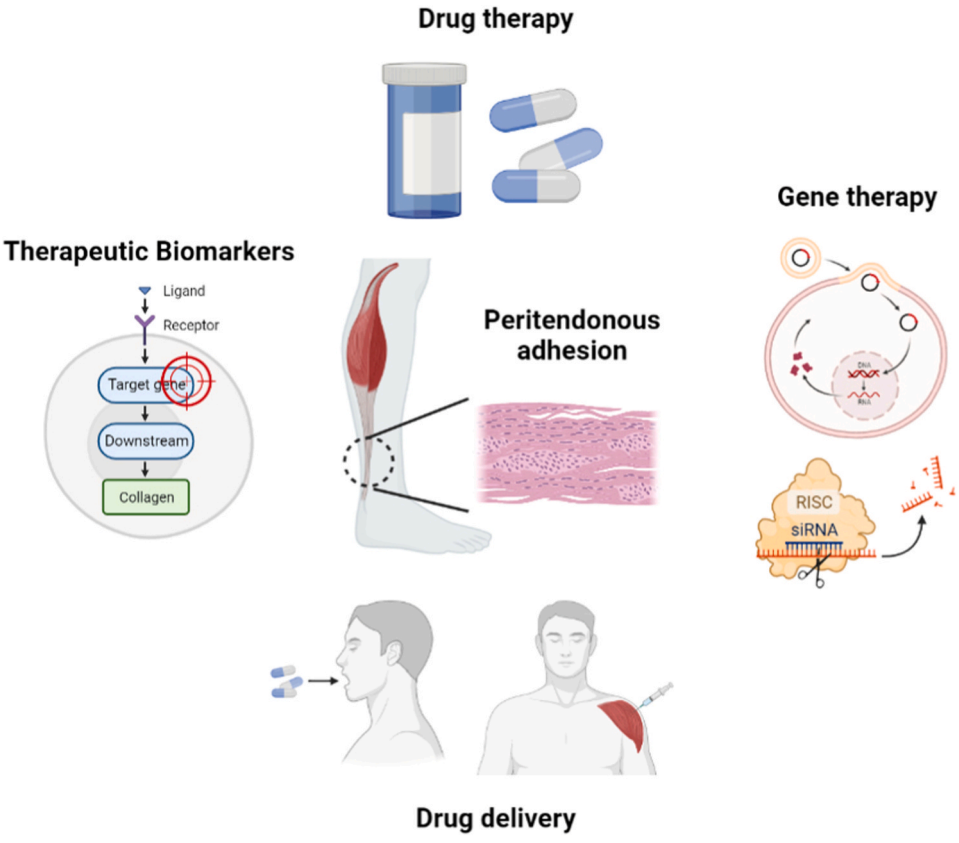


Fig. 1. Schematic diagram of therapeutic targets and drug therapy of PA. It exhibited the therapeutic biomarkers, drug therapy, gene therapy and drug delivery of PA.

2.2.2. Cyclooxygenase (Cox) pathway

Cox-2 is also regards as the vital regulator in inflammatory phase of PA and catalyzes the synthesis of prostaglandins (PEG) from arachidonic acid, which exerts pro-adhesion effect through binding to prostaglandin receptor E2 (EP4) [47]. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit Cox-2 can obviously relieve the collagen deposition in peritendinous tissues, but high dose of NSAIDs exacerbates the apoptosis of TSCs in regenerated sites and is detrimental to tendon healing [48]. Moreover, Ackerman et al. found that conditional knockout of EP4 in S100a4-lineage cells can ameliorate adhesion formation and contribute to tendon healing during early stage [49]. Unfortunately, systematically administration of EP4 inhibitor aggravates collagen synthesis and disorganized deposition instead [50]. Therefore, although Cox-2/PEG/EP4 pathway plays essential role in PA, there are still some nonnegligible questions to be solved.

2.2.3. Oxidative stress

Vascular system is damaged by intraoperative cutting and ligation, which results in local hypoxia, decrease of PH and metabolic byproducts accumulation, resulting in varying degrees of oxidative stress [51]. As essential mediators, reactive oxygen species (ROS) and the imbalance between glutathione (GSH) and oxidized glutathione (GSSG) can trigger fibrogenesis and reflect the level of oxidative stress in peritendinous tissues. Several studies indicated that the degree of adhesion was relieved through antioxidation strategies [52,53]. Nuclearfactor erythroidderived 2-like 2 (Nrf2) pathway was reported to balance the oxidation and antioxidation levels and regarded as crucial in the development of PA [53]. More importantly, the high concentrations of reactive oxidative suppressed TSCs viability and migration, leading to disorder of healing [54].

2.2.4. TGF-β signaling

As inflammation subsides, macrophage exhibits obvious subtype

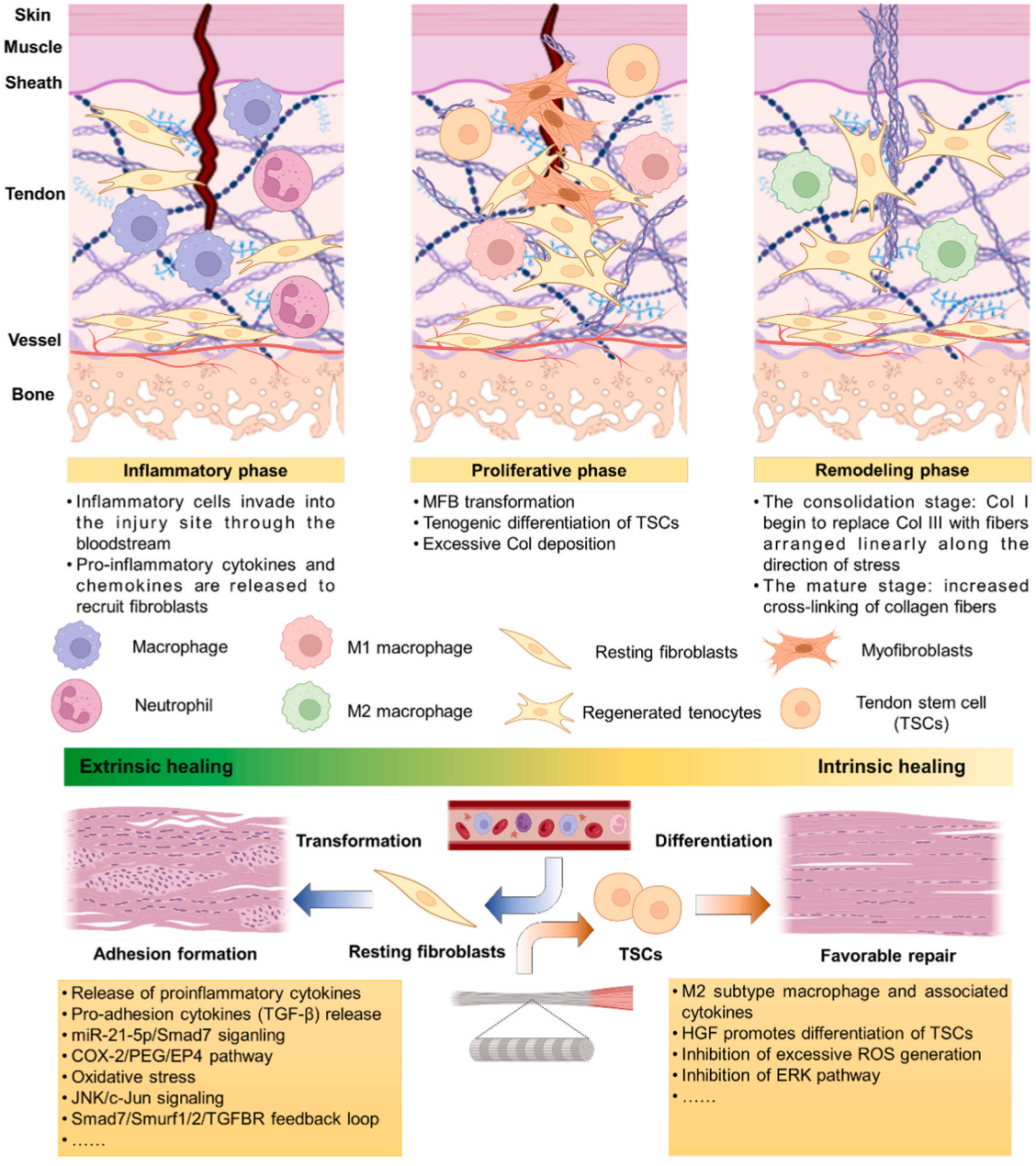


Fig. 2. Schematic diagram showing the pathologic process of PA and molecular mechanism of intrinsic and extrinsic healing of tendon.

reprogramming, from pro-inflammatory to pro-healing, and secretes excessive pro-healing cytokine including transforming growth factor-β (TGF-β) and IL10, resulting in promoting adhesion and scar tissue formation [40]. As the core regulator of PA, TGF-β has three main isoforms (TGF-β1, TGF-β2 and TGF-β3) with 70–82% amino acid homology but have different biological functions (Fig. 3) [55]. Among them, TGF-β1 was demonstrated to be mainly secreted from macrophage and strongly associated with PA and accelerate the progress of PA through Smad-dependent (canonical) and Smad-independent (non-canonical) signaling [56]. Extracellar TGF-β1 binds to surface TGF-β receptor 2 (TGFBR2) to recruit TGFBR1 and initials downstream signaling to regulate adhesion-related protein expression. For Smad-dependent signaling, Smad2/3 phosphorylation is activated by TGF-β1 and translocate to the nucleus to enhance transcriptional activity, leading to the transformation of fibroblast into myofibroblast and collagen deposition [57]. As an essential negative regulator, Smad7 acts as scaffold to recruit the E3 ligase Smurf1/2 and accelerate the degradation of TGFBR complex through negative feedback loops [58]. For Smad-independent signaling, TGFBR complex can trigger PI3K/AKT, extracellular signal-regulated kinase (ERK), p38 and TRAF6 pathway to participate in various biological effect including ECM organization, cellular proliferation, metabolism, tissues repair and organ fibrosis [59–61]. It was reported that specific knockout of TGF-β1 in macrophage obviously relieved PA through reducing myofibroblast infiltration [40]. Additionally, as the negative regulator of TGF-β family, treatment with TGF-β3 adenovirus vector during proliferation and remodeling phase exerts anti-adhesion and anti-inflammatory effect through inhibiting JNK/c-Jun signaling pathway [62]. Therefore, efficient monovalent inhibitors for different TGF-β isoforms should be developed to intervene adhesion formation [63,64].

Overall, although PA is a complex process involving multiple biological events and biomarkers, in-depth investigation of underlying mechanism is urgent to be explore to improve PA diagnosis and treatment.

3. Therapeutic intervention of PA

The ideal drugs for anti-adhesion treatment are expected to promote intrinsic healing while inhibit extrinsic healing and shows no adverse reaction to the human body. Since inflammation response, oxidative stress and excessive fibrogenesis are the troika in PA, corresponding agents have been investigated through clinical drug trials including PXL01 [65], collagenase clostridium histolyticum [66], carboxymethyl chitosan, ropivacaine and heparin [67], and reported to be effective (Table 1). With the revelation of therapeutic targets of PA, drugs for the inhibition of endogenous molecules like STAT6, NF-κB and ERK2, are also widely investigated [38,39,45].

3.1. Anti-inflammatory drugs

Elimination of local inflammation is a vital strategy for prevention and treatment of PA. Inflammation is closely linked with coagulation, fibrin deposition and consequently, with adhesions. Therefore, a variety of anti-inflammatory drugs have been developed to reduce macrophage infiltration and inflammatory cytokines release (Table 2). Among them, NSAIDs are the most widely used drugs in clinical treatment. Ibuprofen was achieved to local sustained release from anti-adhesion barriers through covalent grafting or blending electrospun, which exhibited anti-inflammation property to decrease the expression of TNF-α Cox-1 and Cox-2 [68]. It was reported that proper concentration of ibuprofen applied with hyaluronic acid nanofibrous membranes could inhibit the aggregation of macrophages around the injured site [69]. As a natural compound, curcumin exhibits anti-bacteria property complied with the ability to suppress local inflammatiory reaction so as to inhibit adhesion formation [70]. In addition, a study revealed that curcumin and celecoxib co-loaded oxidative stress-sensitive EPM showed excellent tissue regeneration, bare adhesion, and minimal inflammatory infiltration and formation of granulation tissue and have synergistic anti-adhesion effect [71]. Furthermore, Wang et al. found that NF-κB activation could induce macrophage M1 polarization, and thus constructed JSH-23-loaded (a selective antagonist of NF-κB) barriers to decrease IL6 and TNF-α release at inflammatory stage [44]. Likewise, Lu et al. also established constructed novel anti-adhesion barriers of long-acting inhibition of NF-κB up to 21 days through blending electrospun with pyrrolidinedithiocarbamate (PDTC) [43]. In addition to small-molecule drugs, bioactive macromolecules also have great anti-inflammatory effects. As the splicing products of insulin-like growth factor 1 (IGF-1), MGF has been applied in various field including tendon injury repair and bone regeneration. It has been demonstrated that MGF has an immunomodulatory ability to accelerate macrophage reprogramming towards anti-inflammatory subtypes through upregulation of histone acetylation and STAT6 phosphorylation, resulting in achieving adhesion prevention [45].

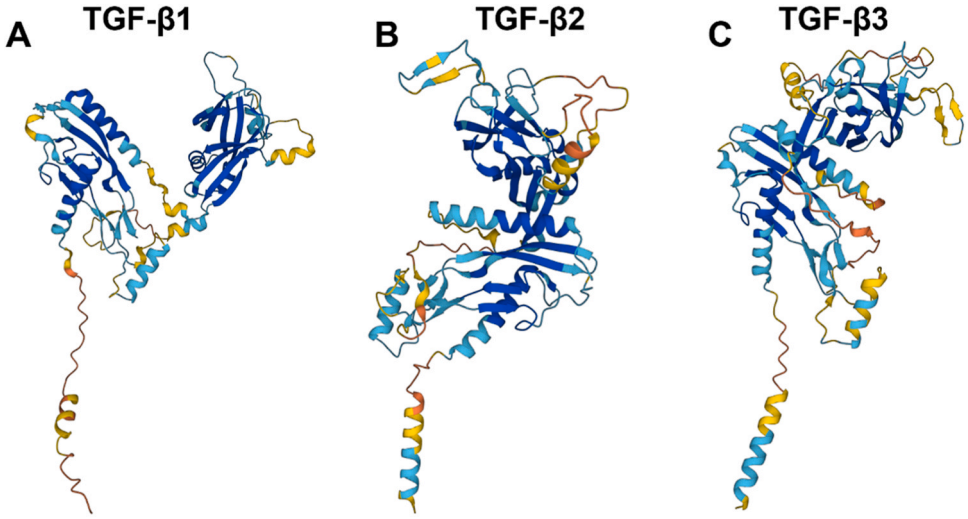


Fig. 3. The crystal structures of TGF-β1 (UniProt number: P01137), TGF-β2 (UniProt number: P61812) and TGF-β3 (UniProt number: P10600) were downloaded from Alphafold database.

Table 1
Clinical drug trials for the treatment of PA.

Drugs	Clinical Trial Name	Identifier	Dose	Primary Outcome	Conclusion
PXL01	Study of PXL01 Versus Placebo to Inhibit Adhesion Formation After Flexor Tendon Surgery (PHSU02)	NCT01022242	Local injection with 0.5 ml PXL01 of 20 mg/ml	Evaluate total active motion (TAM) of the injured finger, tip-to-crease distance, sensory function, tenolysis rate and grip strength, and safety parameters for 12 months post-surgery.	Treatment with PXL01 in sodium hyaluronate improves hand recovery after flexor tendon repair surgery.
Collagenase clostridium histolyticum	Collagenase in the Treatment of Zone II Flexor Tendon Adhesions in the Hand	NCT00261209	0.58 mg per injection	Measure restoration of proximal interphalangeal and distal interphalangeal joint motion. Assess hand grip strength	Collagenase clostridium histolyticum significantly reduced contractures and improved the range of motion in joints affected by advanced Dupuytren's disease
Carboxymethyl chitosan	A Prospective Randomized Controlled Study of Ultrasound-guided Delayed Injection of Carboxymethyl Chitosan in the Prevention and Treatment of Tendon Adhesion	ChiCTR2100042886	/	Measure visual analog score (VAS), TAM, postoperative infection rate, tendon rupture rate and Michigan hand outcome questionnaire (MHQ)	/
Ropivacaine	Effects of axillary brachial plexus block with low concentration and high volume ropivacaine on early recovery in patients undergoing forearm tendon adhesionolysis: a randomized controlled study	ChiCTR2100042886	0.5% ropivacaine 30 ml and 0.15% ropivacaine 100 ml single transaxillary brachial plexus block	Measure numerical rating scale (NRS), score of wrist joint for motor function and maintenance time of motion block	/
Heparin	Effect of Heparin on Post-Operative Adhesion in Flexor Tendon Surgery of the Hand	/	injection of 0.5 cc heparin (5000 IU/cc)	Measure TAM, extension and flexion gap	Heparin may improve the tendon function and reduce the postoperative adhesions in zone II of the hand; however there is a significant risk of tendon rupture.

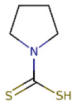
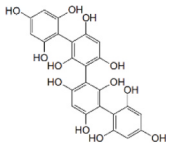
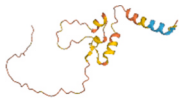
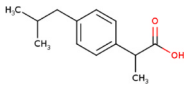
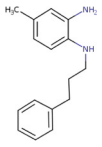
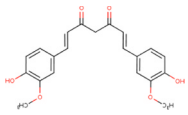
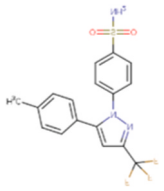
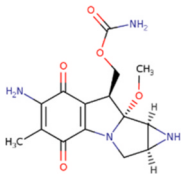
3.2. Anti-oxidative drugs

Trauma induces increased level of ROS in local tissues, GSH/GSSH imbalance, and suppression of the antioxidant system, aggravating inflammation and resulting in adhesion tissue formation. Oxidative stress not only triggers excessive inflammation but also prevents tendon regeneration. Therefore, another therapeutic strategy is to reduce oxidative stress to prevent PA and associated drugs are also identified (Table 3). angiotensin II (Ang II) was demonstrated to play a pro-inflammatory role in oxidative stress in fibrotic diseases. Therefore, as Ang II inhibitors, telmisartan and enalapril were regarded as effective candidates for reversing oxidative stress markers including malonyl dialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT) and thiol. Significant alterations of collagen deposition, biomechanical properties and adhesion formation were observed through inhibiting Ang II pathway [72]. Furthermore, vitamin is an indispensable nutrient for maintaining health and also serves as natural antioxidant. Consequently, vitamin-C and trolox (a vitamin E analog) were reported to have anti-oxidative properties in preclinical studies. Local administration of vitamin-C enhanced the level of GSH and reduced fibrotic area and glide resistance [52]. Similarly, rats injected with Trolox displayed low level of lipid peroxidation and inflammatory cytokine. Compared with vitamin-C, the effect of Trolox to relieve PA is less dose-dependent and cannot contribute to collagen synthesis [73]. The selective anti-oxidation property of hydrogen is considered as the representative of therapeutic medical gas. Deservedly, hydrogen was also involved in therapy of PA and found that hydrogen activated Nrf2 pathway to decrease the level of MDA and 8-OHdG and increased the level of SOD and GSH [53].

3.3. Anti-fibrogenesis drugs

The underlying reason of PA formation is the excessive proliferation of fibroblast and disordered arrangement of collagen deposition. Hence, multiple drugs are chosen to effectively limit the fibroblast transformation and process of collagen synthesis to exhibit anti-fibrogenesis property (Table 4). Collagenolytic activity is strongly associated with collagen deposition. By stimulating collagenase production and increasing collagenolytic activity, the application of exogenous collagen has obviously prevented PA formation. Celecoxib could suppress fibroblast proliferation and excessive collagen synthesis by the down regulation of ERK 1/2 and Smad2/3 phosphorylation [74]. As a nonsteroidal agent, tamoxifen has been found to have antifibrotic potential by altering the TGF-β1/Smad signaling to decrease collagen production [75]. In rat PA model, the local administration of tamoxifen showed benefit in the reduction of peritendinous adhesion but the low-dose treated group showed better strength biomechanically [76]. The activation of mammalian target of rapamycin complex 1 (mTORC1) phosphorylates Atg 13 which can prevent the formation of ULK1 kinase complex and inhibit autophagy activation. Rapamycin has the effect to inhibit the activation of mTORC1 and induce autophagy. Zheng et al. reported that rapamycin can effectively suppress cell proliferation and decrease ECM production to alleviate peritendinous fibrosis by inducing autophagy [77]. Hydroxycamptothecin (HCPT), a kind of small

Table 2
Anti-inflammatory drugs for PA.

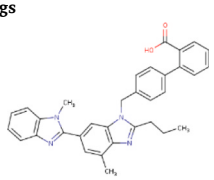
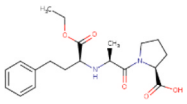
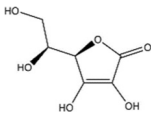
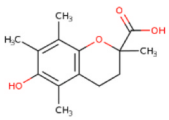
Drugs	Molecular structure	Pharmacological mechanism	Study model	Reference
Anti-inflammatory drugs				
PDTC		Inhibition of macrophage M1polarization through blocking NF-κB phosphorylation; Reduction of pro-inflammatory cytokines (IL6 and TNF-α)	LPS-induced Raw264.7; Sprague Dawley rat PA model with PDTC-loaded barriers (Observation at 21th day postoperatively)	[43]
Phlorotannins		Downregulating iNOS protein expression Relieving macrophage infiltration Suppressing inflammatory response on subcutaneous tissue	LPS-induced Raw264.7; Subcutaneous implantation in Sprague Dawley rat model with phlorotannins-loaded barriers (Observation at 1st, 3rd and 7th day postoperatively)	[101]
MGF		Contributing to STAT6 nuclear translocation Directing anti-inflammatory phenotype transition of macrophage	Raw264.7 treated with 0, 10 and 20 ng/ml MGF Subcutaneous implantation in Sprague Dawley rat model (Observation at 14th and 28th day postoperatively) Sprague Dawley rat PA model with MGF-loaded barriers (Observation at 7th, 14th and 21th day postoperatively)	[45]
Ibuprofen		Inhibition of macrophage proliferation, adhesion; Reducing TNF-α release; Suppressing macrophage infiltration; Inhibition of Cox-1 and Cox-2	Raw264.7 Sprague Dawley rat PA model with ibuprofen -loaded barriers (Observation at 21th day postoperatively);	[102]
JSH-23		InhibitingI NF-κB nuclear translocation; Suppressing macrophage M1 polarization; Preventing myofibroblast activation; Reducing IL6 and TNF-α expression	LPS-induced Raw264.7; Sprague Dawley rat PA model with JSH-23-loaded barriers (Observation at 3rd and 10th day postoperatively)	[44]
Curcumin		Reducing IL1β, IL6 and TNF-α expression; Lowering inflammation scores; Exhibiting anti-bacteria property	Sprague Dawley rat PA model with curcumin-loaded barriers (Observation at 21 day postoperatively);	[70]
Celecoxib		Lowering inflammation scores; Suppressing neovascularization; Reducing IL1β, IL6 and TNF-α expression; Exhibiting anti-bacteria property	flexor digitorum profundus chicken PA model (21 days postoperatively); Sprague Dawley rat PA model with celecoxib-loaded barriers (Observation at 21th day postoperatively)	[71]
Mitomycin-C		Inhibition of inflammatory reaction	Wistar albino rats PA model with injection of 0.2 ml with 0.08 mg mitomycin-C for 4 weeks (Observation at 30th day postoperatively)	[103]

molecule agent that has the potential to prevent tendon adhesion by suppressing cell proliferation and inducing fibroblasts apoptosis [78,79]. The rest of anti-fibrogenesis drugs and theirs pharmacological mechanism was involved in Table 4.

3.4. Gene therapy

Gene therapy is a promising method to regulate the expression of specific gene [80]. The treatment methods include small interfering RNA (siRNA) interference, adeno-associated viral (AAV) gene therapy, nonviral plasmid transfection. As its name indicates, siRNA interference is design to block mRNA translation and facilitate mRNA degradation. The silence of ERK2 can not only inhibit fibroblast proliferation but also reduce the deposition of collagen type III. ERK2-siRNA was found to decrease cell proliferation and downregulate the expressions of ERK2 and its downstream SMAD3 [39,81]. TGF-β can induce fibroblast proliferation and improve collagen deposition. Cai et al. designed MMP-2 responsive unidirectional hydrogel-electrospun patch loading TGF-β1 siRNA polyplexes, and the results showed that this kind of polyplexes were able to silence the expression of TGF-β1 and suppress the proliferation of fibroblasts [82]. In addition, the application of AAV gene therapy becomes more and more extensive. Local administration of

Table 3
Anti-oxidative drugs for PA.

Drugs	Molecular structure	Pharmacological mechanism	Study Model	Reference
Anti-oxidative drugs				
Telmisartan		Relieving oxidative stress; Downregulating MDA expression; Upregulating thiol, SOD and CAT activity	Wistar albino rats PA model with injection intraperitoneally of 10 mg/kg/day telmisartan for 21 days (Observation at 21th day postoperatively)	[72]
Enalapril		Relieving oxidative stress; Downregulating MDA expression; Upregulating thiol, SOD and CAT activity	Wistar albino rats PA model with injection intraperitoneally of 10 mg/kg/day telmisartan for 21 days (Observation at 21th day postoperatively)	[72]
Hydrogen		Activation of Nrf2 pathway; Decreasing the level of 8-OHdG and MDA; Increasing the level GSH and SOD; Scavenging ROS in fibroblast	H_2O_2-induced skin fibroblasts Sprague Dawley rats PA model with intraperitoneal injection of 10 ml/kg/d hydrogen water (Observation at 1th, 3rd, and 6th week postoperatively)	[53]
Vitamin-C		Enhancing the concentration of GSH	Flexor digitorum profundus chicken PA model with injection of 0, 5, 50 mg/ml vitamin-C solution (Observation at 2nd and 6th week postoperatively)	[52]
Trolox		Suppressing inflammatory cytokines release	Flexor digitorum profundus chicken PA model with local injection of 0, 100, 200 mM trolox solution (Observation at 2nd and 6th week postoperatively)	[73]

TGF-β3 -overexpressed adenovirus vector to injury sites could be observed the improvement of TGF-β3, Smad7 and mechanical strength, and reduction of glide resistance, inflammatory cytokines release through inhibition of JNK/c-Jun pathway [62]. Furthermore, it was reported that bFGF has the ability to promote endogenous healing of tendon by stimulating collagen secretion and tenocyte proliferation. Tang et al. transferred bFGF plasmid to digital flexor model and found significant improvement in healing strength during the critical tendon-healing period without increased adhesion formation [83]. The application of nanoparticle loading bFGF and vascular endothelial growth factor (VEGFA) genes exhibited better tendon strength and enhanced tendon gliding function, which indicated that co-delivery of different anti-adhesion associated genes may lead to less adhesion [84].

3.5. Delivery of drug administration

Early administrations of anti-adhesion agents include medication-only treatment like subcutaneous injection of hyaluronic acid (HA) [85] and local injection of vitamin C [52], topical injection of heparin and infiltration of mannose-6-phosphate (M6P) [86]. In the case of HA, researchers initially used it as a lubricant to promote tendon gliding to relieve limb stiffness associated with adhesion. Subsequently, HA was demonstrated to be effective in inhibiting the proliferation of myofibroblasts and ameliorating inflammatory-associated reactions [87]. Moreover, Badalamente et al. adopted collagenase injection therapy in 3 subjects to evaluate it's ability to lyse flexor tendon adhesions in zone II of the hand. Clinical trial results found that the range of finger at the proximal interphalangeal and distal interphalangeal joint in patients had improved. Therefore, for patients with PA, collagenase debridement may achieve removal of adhesion tissues and avoid damage to normal peritendinous tissues by bluntly separating adherent tissue. However, such exclusive medication treatment can only regulate cell behaviors without physical barriers to separate tendon damaged site from the external synovial sheath. In addition to local injection, HA can also be used to fabricate composite patch for its outstanding lubrication capability and biodegradability. HA grafted with biocompatible and biodegradable polymers like poly caprolactone (PCL) has shown great efficacy in reducing PA [88]. Embedding HA in the core of a core-sheath nanofiber membrane ensures the controlled and consistent release of HA [89]. Hydrogels have been widely used in tendon repair for their excellent biocompatibility and structural porosity [90]. Incorporation of agents or genes into hydrogels has been proven to be efficient. Injectable hydrogels show more convenience and work as a minimally invasive way to alleviate patients suffering. What is noteworthy is that hydrogel-based scaffolds are not able to provide sufficient mechanical support for the lack of mechanical strength and stiffness. Fibrous membranes are mostly seen in tendon repair due to their adjustable fiber diameters to mimic the topographic features of native tendon sheath and provide enough mechanical support. More importantly, their tunable porous microstructure contributes to the prevention of fibroblast penetration without hampering nutrients and waste transportation [7,22]. However, although electrospun fibrous membranes with large aspect area to loaded with drugs, but they cannot achieve on-demand drug-release and cell targeting profiles, leading to mismatched release and drug wastage. Adopting delivery carriers, such as nanoparticle or lipidosome, can overcome these problems effectively. Researchers also made bold innovations and developed a variety of carriers with different properties. Sun et al. encapsulated Cox-siRNA nanoparticles inside the membrane of M2 subtype macrophages, which exhibited remarkable targeting properties to gather toward inflammatory sites and reduced

Table 4
Anti-fibrogenesis drugs for PA.

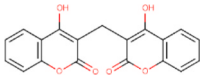
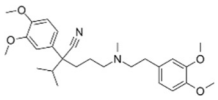
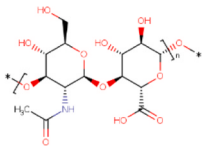
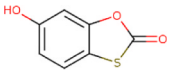
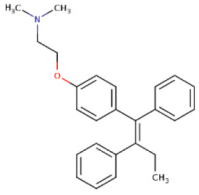
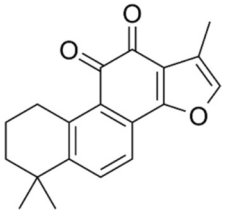
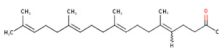
Drugs	Molecular structure	Pharmacological mechanism	Study Model	Reference
Anti-fibrogenesis drugs				
Dicumarol		Inhibition of connexin43 and TGF-β/Smad3 pathway; Reducing fibroblasts proliferation and adhesion; Ameliorating collagen deposition	NIH 3T3 fibroblast; Sprague Dawley rat PA model with dicumarol-loaded barriers (Observation at 3rd and 6th week postoperatively)	[104]
Verapamil		Inhibition of TGF-β expression; Suppressing myofibroblast transformation;	Sprague Dawley rat PA model with verapamil nanoparticle-loaded barriers (Observation at 3rd and 6th week postoperatively)	[105]
Hyaluronic acid		Inhibition of TGF-β1, TGF-β2 and PAI-1 expression; Ameliorating collagen deposition	Sprague Dawley rat PA model with local injection of 0.3 ml hyaluronic acid solution (Observation at 10th week postoperatively)	[85]
Tioxolone		Inhibition of JAK3/STAT3/CyclinD1 pathway; Reducing fibroblasts proliferation and adhesion; Ameliorating collagen deposition	NIH 3T3 fibroblast; Sprague Dawley rat PA model with tioxolone-loaded barriers (Observation at 3rd and 6th week postoperatively)	[92]
Tamoxifen		Improving stiffness of regenerated tendon; Reducing adhesion tenacity score; Local administration of tamoxifen is more effective compared with systemic administration;	Wistar albino rats PA model with systemic administration of 0, 1 and 40 mg/kg tamoxifen and local administration of 1 mg/kg tamoxifen for 4 weeks (Observation at 6th week postoperatively); New Zealand White rabbit PA model with oral and local routs of tamoxifen administration at 2.5 mg/kg/day (Observation at 3rd day postoperatively)	[75,76]
Tanshinone IIA		Downregulating TGF-β/Smad3 pathway; Inhibition of cyclin D1 expression; Ameliorating collagen deposition	Primary fibroblast from adhesion tissues; Sprague Dawley rat PA model with injection of 0.1 μM tanshinone IIA (Observation at 3rd week postoperatively)	[106]
Umbilical cord stem cell-derived exosomes	/	Suppressing myofibroblast transformation; Ameliorating collagen deposition; Inhibition of NF-κB phosphorylation	TGF-β-stimulated fibroblast; Sprague Dawley rat PA model with subcutaneous injection of 200 μg exosomes (Observation at 3rd week postoperatively)	[107]
Teprenone		Elevating HSP72 expression Suppressing myofibroblast transformation; Ameliorating collagen deposition	NIH 3T3 fibroblast; Sprague Dawley rat PA model with injection of 400 mg/kg teprenone (Observation at 4th and 8th week postoperatively)	[108]
Platelet rich plasma	/	Prompting tenocyte migration; Minimizing fibroblast proliferation and attachment; Ameliorating collagen deposition	Tenocytes and NIH 3T3 fibroblast; New Zealand White rabbit PA model with platelet rich plasma-loaded barriers (Observation at 3rd and 6th week postoperatively)	[109]

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Table 4 (*continued*)

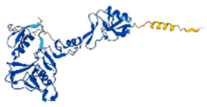
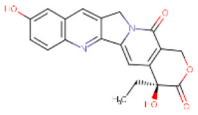
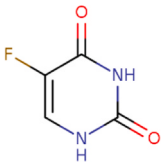
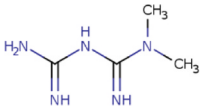
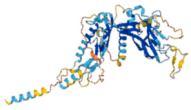
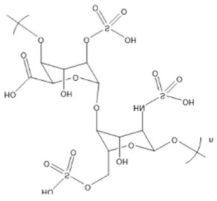
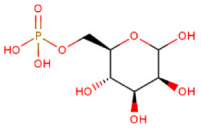
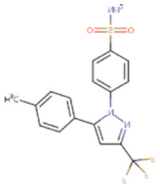
Drugs	Molecular structure	Pharmacological mechanism	Study Model	Reference
Follistatin		Inhibition of MMP1,MMP2, PAI-1 TRPV4, α-SMA, desmin, and PAX7 expression	Primary fibroblast from adhesion tissues transfected with adenovirus-follistatin vector;	[110]
Hydroxycamptothecin		Suppressing ERK, ATF6 and IRES pathway Activation of endoplasmic reticulum stress; Inhibition of fibroblast proliferation; Induction of apoptosis of fibroblast through Bax signaling; Reducing Col 3 and α-SMA expression.	Sprague Dawley rat PA model with treatment of 0.01, 0.05 and 0.1 mg/ml hydroxycamptothecin for 5 min (Observation at 3rd week postoperatively)	[78,79]
5-Fluorouracil		Inhibition of fibroblast proliferation; Ameliorating collagen deposition	New Zealand White rabbit PA model with treatment of 50 mg/ml 5-fluorouracil solution (Observation at 3rd week postoperatively)	[111]
Metformin		Inhibition of ERK and Smad2/3 pathway; blocking AMP-activated protein kinase signaling; Induction of fibroblast apoptosis; Ameliorating collagen deposition	NIH 3T3 fibroblast; Sprague Dawley rat PA model with treatment of 200 mg/kg/day metformin (Observation at 3rd week postoperatively)	[112]
TGF-β3		Inhibition of TGF-β/Smad3 pathway through activation of Smad7;	Tenocyte from tendon tissues treated with 10 ng/ml TGF-β3.	[62]
Heparin		Increasing extension gap, range of motion and flexion gap;	Randomized clinical trial	[67]
Mannose-6-phosphate		Activation of P38 pathway to inhibit cell viability and migration;	Primary fibroblast from adhesion tissues; New Zealand White rabbit PA model with treatment of 50 mM, 200 mM and 600 mM mannose-6-phosphate (Observation at 3rd week postoperatively)	[86,113]
Celecoxib		Inhibition of ERK1/2 and Smad2/3 pathway; Suppressing fibroblast proliferation	tenocytes and dermal fibroblasts from tendon tissues; New Zealand White rabbit PA model with celecoxib-loaded barriers (Observation at 21th day postoperatively)	[74]

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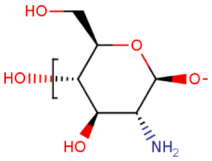
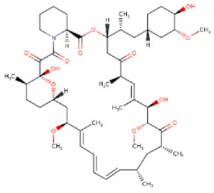
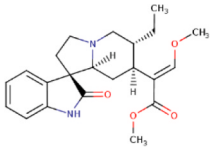
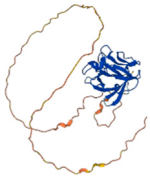
Table 4 (*continued*)

Drugs	Molecular structure	Pharmacological mechanism	Study Model	Reference
Chitosan		Downregulating TGF-β/Smad3 pathway through enhancing miR-29b expression; Ameliorating collagen deposition	Primary fibroblast from adhesion tissues; Sprague Dawley rat PA model with treatment of 50 mg chitosan (Observation at 8th week postoperatively)	[114, 115]
Collagen prolyl 4-hydroxylase inhibitor	/	Ameliorating collagen deposition	Flexor digitorum profundus chicken PA model with oral gavage of 50 mg/kg collagen prolyl 4-hydroxylase inhibitor (Observation at 2nd and 6th week postoperatively)	[116]
1D11	/	TGF-β neutralizing antibody to inhibit TGF-β expression	C57BL mice PA model with intraperitoneal injection of 1D11 for 3 times per week for 1 week	[40]
Rapamycin		Contributing to fibroblast autophagy through promoting LC3B/P62 pathway; Inhibition of myofibroblast transformation; Suppressing fibroblast proliferation; Ameliorating collagen deposition	NIH 3T3 fibroblast; Sprague Dawley rat PA model with intraperitoneal injection of 2 mg/kg/d rapamycin (Observation at 3rd week postoperatively)	[77]
Rhynchophylline		Inhibition of Smad2/3 pathway; Promoting fibroblast apoptosis; Accelerating ECM degradation	Tendon and adhesion cells from flexor digitorum profundus tendon; Flexor digitorum profundus chicken PA model with rhynchophylline-loaded barriers (Observation at 3rd and 6th week postoperatively)	[117]
Basic fibroblast growth factor		Increasing biomechanical property of regenerated tendon; Promoting ordered arrangement of collage; Suppressing macrophages and lymphocytes infiltration;	New Zealand White rabbit PA model with injection subcutaneously of 1200 ng/kg (Observation at 28th and 84th day postoperatively)	[118]

the release of IL-6, IL-1β, and TNF-α and collagen deposition [91]. In addition, the presence of large amounts of lipase and MMP2 was demonstrated in peritendinous tissue during the proliferative and remodeling phases. To utilize this feature, Li et al. fabricated a polymerized tioxolone-loaded barriers, in which the ester bond of polymerized drug can be hydrolyzed by lipase to convert into monomer in responsive releasing profile for subsequent anti-adhesion in repair site [92]. Cai et al. also synthesized MMP2 responsive unidirectional hydrogel-electrospun patch to release TGF-β1 siRNA in MMP-2 overexpression microenvironment to achieve adhesion prevention [82].

Lasers have been used as a physical method to reduce adhesion formation. During the first 2 weeks after tenolysis, yttrium aluminum garnet (YAG) lasers have been found to be highly effective in improving tendon gliding compared to scalpel, possibly by reducing hemorrhage and postoperative swelling [93]. However, CO_2 laser application has significantly increased adhesion formation compared to conventional sharp dissection technique [94]. A retrospective longitudinal study suggests that high-intensity laser therapy, when combined with peritendinous HA injection, appears to be effective in lateral elbow tendinopathy for improving pain and muscle strength [95]. The reduction in pain results from the anti-inflammation effect of laser. Accordingly, high-intensity laser therapy may have promising prospects in PA research. Ultrasound therapy has been shown to be effective against PA in animals. Maiti et al. studied on goats and found that therapeutic ultrasound steadily improved the tendon gliding movement and that the ultrasound-treated group showed faster resolution of inflammation and early tendon injury healing [96]. Ultrasound therapy can also suppress granulation tissue formation, which may due to reduced formation of new extracellular matrix by inhibiting mononuclear phagocytosis and lymphocytes. However, the mechanism by which ultrasound acts on PA is still not fully understood [97]. Extracorporeal shock wave therapy (ESWT) is widely used in musculoskeletal disease, and low-dose ESWT can accelerate tendon healing [98]. Low doses of ESWT also have anti-inflammatory effects by modulating NO levels and macrophage activity [99]. When compared to ESWT alone, ESWT plus HA injection resulted in better symptomatic improvement in rotator cuff tendinopathy. And this may be due to the stimulation of neovascularization growth by ESWT and the inhibitory effect on the fibroblast activity of exogenous HA. However, the effect of ESWT on PA treatment has not been studied [100].

4. Summary

PA is characterized with poor therapeutic effect, easy relapse and high disability, which plagues hand surgeons and patients worldwide. Although several studies have been revealed the pathogenesis of PA, the concrete mechanism is still blurred and speculated to be linked with inflammation, oxidative stress and excessive fibrogenesis. Therefore, exploring the underlying mechanism of PA and improving prognosis efficacy needs to be solved urgently. In recent years, plenty of anti-

adhesion drugs and methods of drug delivery are reported to greatly improve greatly therapeutic effects. Drug therapy is of great significance in peritendinous adhesion, which is exceedingly dependent on the understanding of adhesion mechanisms. By inhibiting or promoting different signaling pathways and factors, agents can reduce the incidence of adhesion and improve prognosis of tendon injuries. Anti-adhesion treatment demand for persistent drug release and desired dosage in case of drug toxicity or insufficient efficacy. Therefore, it is essential that drug release maintain appropriate rate, which denotes that drug delivery methods play a decisive role in the effect of agents to some extent. However, there remains various deficiencies to achieve clinical application. Firstly, the absence of pharmacological and pharmacokinetic research may cause us incapacity to identify te suitable drug dosage and preferred way of drug administration, Worse still, the potential side effects are easy to be overlooked. Furthermore, clinical experiments on the pharmacological treatment of PA are currently underdeveloped, which leads to lack of clinical evidence to design clinical guidelines and standardize clinical treatment. Therefore, further studies should be performed around two main questions to early achieve approval of anti-adhesion drugs for clinical application.

CRediT authorship contribution statement

Conceptualization: Shuo Wang, Pan Sha and Shen Liu. Visualization: Pan Sha and Xuewen Zhao. Supervision: Shen Liu. Writing—original draft: Shuo Wang, Pan Sha, Xuewen Zhao and Shen Liu. Writing—review & editing: Shuo Wang, Pan Sha, Zaijin Tao and Shen Liu.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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