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Advances in studies on tracheal stent design addressing the related complications

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ABSTRACT

Tracheal stents can be used to quickly reconstruct the airway and relieve symptoms of dyspnea in patients with tracheal stenosis. However, existing tracheal stents lead to complications such as granulation tissue formation, difficulty in removal, persistent growth of malignant tumors, stent migration, and mucus plugging. In this article, we reviewed the main methods used to reduce complications associated with tracheal stent design. Drug-eluting stents can inhibit granulation tissue formation and prevent infection and local chemotherapy. The biodegradable stent can support the trachea for some time, maintain tracheal patency, and degrade gradually, which avoids removing or replacing the stent. Radioactive stents loaded with I^{125} have good potential for inhibiting the persistent growth of malignant tumors. Three-dimensional printing technology enables the manufacturing of patient-specific stents, which increases the degree of matching between the complex tracheal anatomy and the stent, thus providing a new solution for stent migration caused by structural mismatch. Minimizing the barrier of the stent to mucociliary clearance, providing an anti-fouling coating, and culturing respiratory epithelial cells on the surface of the stent are the main methods used to reduce mucus plugging. We also proposed future research directions for tracheal stents to guide the design and manufacture of ideal tracheal stents.

1. Introduction

The trachea plays a crucial role in the respiratory system. Various causes, such as infections, tumors, trauma, long-term intubation, tracheobronchomalacia, and tuberculosis, can result in tracheal stenosis, leading to symptoms such as dyspnea, post-obstructive infection, and coughing [1–5]. Surgical intervention, such as wedge resection [6], balloon bronchoplasty [7], bronchoscopic holmium laser ablation continuous cryoablation [8], stereotactic body radiation therapy [9], and photodynamic therapy [10], is the preferred form of treatment for tracheal stenosis. With the development of materials and the improvement in endoscopic intervention technology, tracheal stents have become an important method of treating tracheal stenosis and can be used to quickly reconstruct the airway and relieve symptoms of dyspnea. Following the introduction of tracheal stents, various types of tracheal stents have been developed [11–19] (Fig. 1).

Although the therapeutic effect of tracheal stents is remarkable, many complications are associated with their application, and the incidence and severity of the complications directly affect the therapeutic effect of stents. The complications associated with tracheal stents include stent migration, granulation tissue formation, mucus plugging, incoercible cough, stent fracture, and infection [20–24]. These complications may be caused by materials, continuous movement, infection, inhibition of mucociliary clearance, and the biomechanical properties of the stent [25]. Tracheal stents mainly include silicone stents, metal stents, and hybrid stents, based on the materials used. Commercially available silicone stents include Dumon silicone Y stents (Novatech SA, La Ciotat, France) and Dumon silicone stents (Novatech SA, La Ciotat, France); Metal stents include Microtech uncovered stents (Micro-Tech Co., Ltd., Nanjing, China), and Ultraflex uncovered stents (Boston Scientific Corporation, Natick, MA); Hybrid stents include Microtech covered stents (Micro-Tech Co., Ltd., Nanjing, China), Microtech covered Y stents (Micro-Tech Co., Ltd., Nanjing, China), Polyflex stents (Boston Scientific, Natick, MA, USA), Ultraflex partially covered metallic stents (Boston Scientific Corporation, Natick, MA), Aero covered stents (Alveolus, Inc., Charlotte, NC), and Dynamic stents (Freitag; Rüsch, Kernen, Germany). According to the clinicaltrials.gov website, the tracheal stents currently under evaluation in clinical trials

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include patient-specific silicone airway stents (NCT05050591), metal bare stent with I^{125} (NCT03944408), and covered metallic segmented airway stent modified by 3D printing (NCT03890523).

The silicone stent is the first choice for treating benign tracheal stenosis [26,27]. Silicone stents are elastic and biocompatible, can effectively reduce the formation of granulation tissue, and are easily removed [28]. However, silicone stents also have certain limitations, such as the need for rigid bronchoscopy during implantation, and its radial force is weaker than that of a metal stent, which is prone to migration and mucus plugging [29]. Metal stents are easier to implant than silicone stents and can be performed with only flexible bronchoscopy [30]. They have a strong radial force, with a low incidence of migration and mucus plugging. However, the greater radial force of metal stents increases the risk of granulation tissue formation and perforation, and these stents are difficult to remove [31]. Hybrid stents, also known as covered stents, consist of a metal stent and a polymer film; although they combine the advantages of a silicone stent and a metal stent, they hinder mucociliary clearance [32,33]. Regardless of the material, complications associated with tracheal stents are common [34].

Biomechanically, the complications are related to the structural and mechanical mismatch between the tracheal stent and the native trachea (Fig. 2). The main manifestations are as follows: (1) the silicone stent is usually cylindrical, whereas the cross-section of the trachea can be C-shaped, D-shaped, or U-shaped [35–37]; (2) the load-deformation curve of the trachea is typically J-shaped, whereas, the load-deformation curve of the silicone stent is usually R-shaped [38,39]; (3) the mechanical properties of the trachea are anisotropic, whereas, the mechanical properties of the silicone stent are isotropic [40–42]. Structural and mechanical mismatch can lead to stent migration; they can also irritate the trachea, causing inflammation and granulation formation. The tracheal stent should match the structure of the stenotic airway and exert different forces in the axial direction to maintain airway patency without further damaging tissues [43]. Therefore, researchers investigating tracheal stents are exploring ways to match the structure and mechanical properties of the tracheal stent and the native trachea through structural design.

Due to these complications, new stents need to be designed to address the flaws of existing stents. The strategies used in tracheal stents mainly include functional establishment, structural design, material selection, and modification (Fig. 3). The ideal tracheal stent should have the following characteristics [26,44,45]: (1) easy to implant and remove; (2) have an appropriate size; (3) have sufficient radial rigidity and longitudinal flexibility; (4) can simulate normal tracheal anatomy and physiology; (5) not hinder the function of mucociliary clearance. However, no tracheal stents are available in the clinical setting that can achieve the expected treatment effect. To achieve an ideal tracheal stent, researchers have developed tracheal stents, including drug-eluting stents [46,47], biodegradable stents [48,49], radioactive stents [18,50], 3D-printed stents [51–54], and stents with novel structural designs [55–58]. Each type of stent has several specific advantages, but they also have some complications.

To summarize, several complications are associated with tracheal stents that need to be addressed urgently, such as granulation tissue formation, difficulty in removal, persistent growth of malignant tumors, stent migration, and mucus plugging. Many studies have focused on a specific topic, while few comprehensive reviews have discussed the design of tracheal stents addressing related complications.

Therefore, in this article, we focused on how to reduce complications from the perspective of tracheal stent design and summarized the development and applications of various novel tracheal stents in recent years. We have also proposed future research directions for tracheal stents.

2. How can granulation tissue formation be reduced?

2.1. Causes of granulation tissue formation

Granulation tissue formation is a complication that often requires intervention. Granulation tissue consists of macrophages, fibroblasts, loose connective tissue, and newly developed capillaries. Mechanical stimulation and infection are the main causes of granulation tissue formation [59–63]. The factors associated with granulation tissue formation include tracheal wall thickening [64], structural airway obstruction [65], and the stent-to-vocal fold distance [66].

Mechanical stimulation is closely related to stent expansion. Large-scale stent expansion exerts excessive force on the tracheal wall, whereas small-scale stent expansion increases stent motion and increases friction between the stent and the tracheal wall [67]. A follow-up study reported that when the ratio of stent diameter to tracheal diameter was >100 %, 90–100 %, and <90 %, the granulation tissue formation rates were 42.86 %, 26.32 %, and 0 %, respectively [68]. The diameter of the metal stent is close to the diameter of the normal airway, the degree of inflammatory reaction is relatively reduced, and they have fewer complications than large-diameter tracheal stents [69]. During the respiratory cycle, the pressure at the proximal and distal ends of the stent changes significantly, whereas the pressure in the middle of the stent changes slightly. These findings are consistent with the location of granulation tissue formation in vivo [70].

Bacterial infection and proliferation may induce an inflammatory response, leading to granulation tissue formation. The bacteria colonized after stent implantation include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* spp., *Streptococcus pneumoniae*, *Streptococcus viridians*, nonhemolytic *Streptococcus*, *Haemophilus influenza*, *Neisseria* species, *Candida*, and *Rhizopus oryzae* [71–75]. *Staphylococcus aureus* and *P. aeruginosa* play important roles in the pathogenesis of infection during the application of Montgomery T-tubes [76]. There is a highly significant correlation between *S. aureus* and *P. aeruginosa* and granulation tissue formation, and *S. aureus* has a longer effect on granulation tissue [60]. The biofilm type and stent material are significantly correlated: the covered stent is the *Staphylococcus* type, the silicone stent is the *Corynebacterium*-dominated type, and the uncovered metal stent is the polymicrobial type [77].

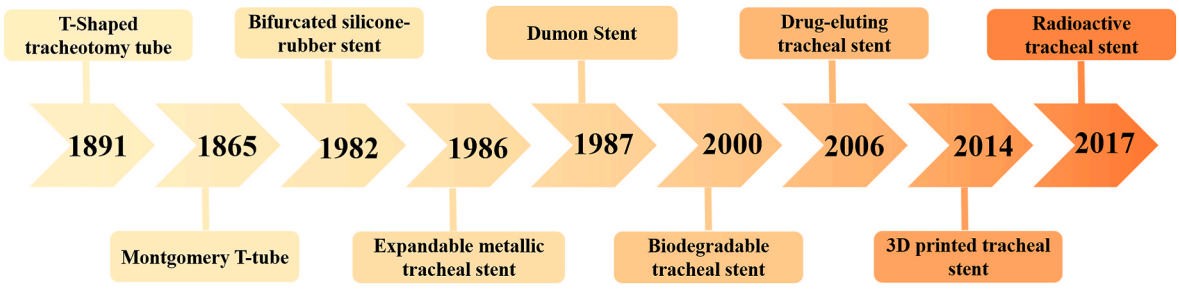

Fig. 1. A brief timeline for the development of tracheal stents.

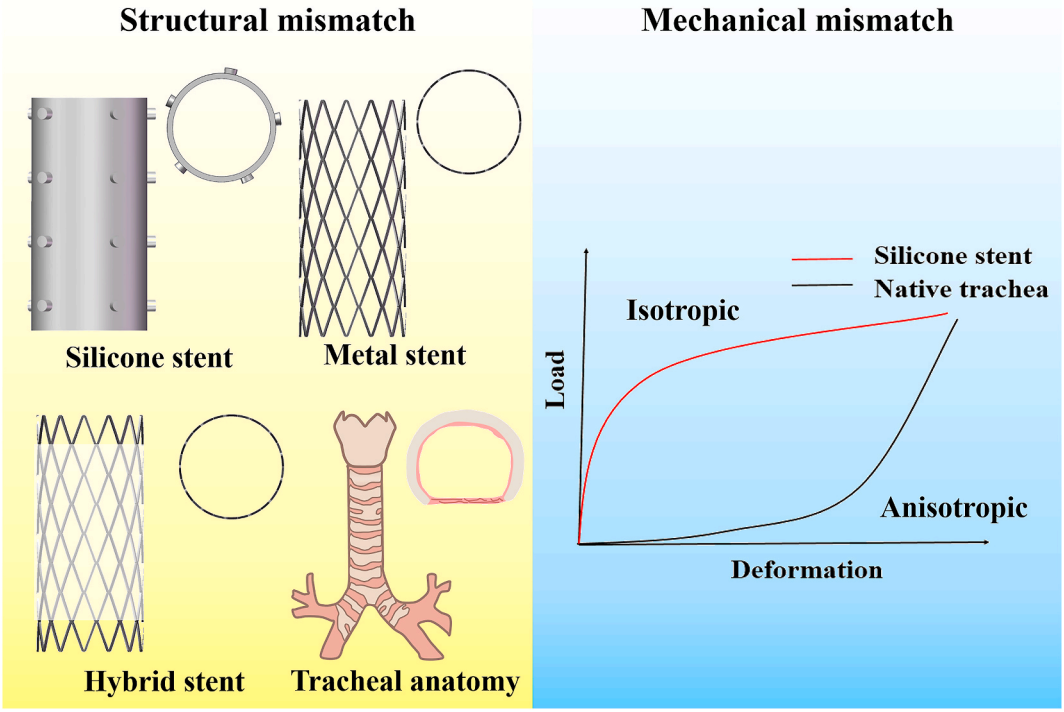

Fig. 2. Comparison of structure and mechanical properties between silicone stent and native trachea.

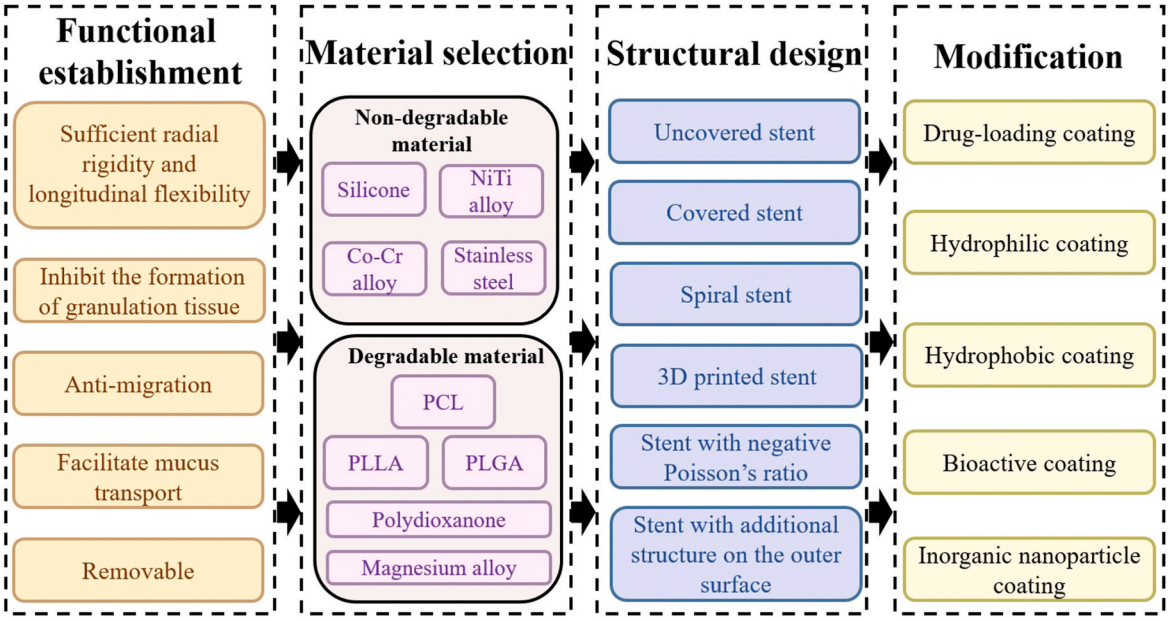

Fig. 3. The strategies employed in tracheal stents research.

2.2. *The mechanism of granulation tissue formation*

Mechanical stimulation can damage local tissues to some extent. After injury, protein adsorption, acute inflammation, chronic inflammation, foreign body giant cell formation, and fibrotic encapsulation occur sequentially (Fig. 4) [78].

2.2.1. *Protein adsorption*

Within seconds after injury, blood plasma proteins adsorb onto the stent surface and form a blood-based provisional matrix on and around the stent surface (Fig. 4 B) [79]. The provisional matrix contains various chemoattractants, cytokines, and growth factors, which affect the inflammatory response by regulating the activity of macrophages and other immune cells. The provisional matrix eventually develops into a fibrin-dominated thrombus. Acute and chronic inflammation occur sequentially. The strength of the inflammatory response depends on the degree of injury during implantation and the extent of the transient provisional matrix, and the factors mainly include surface topography, surface charge, surface wettability, stent size and shape, and stent stiffness [80,81].

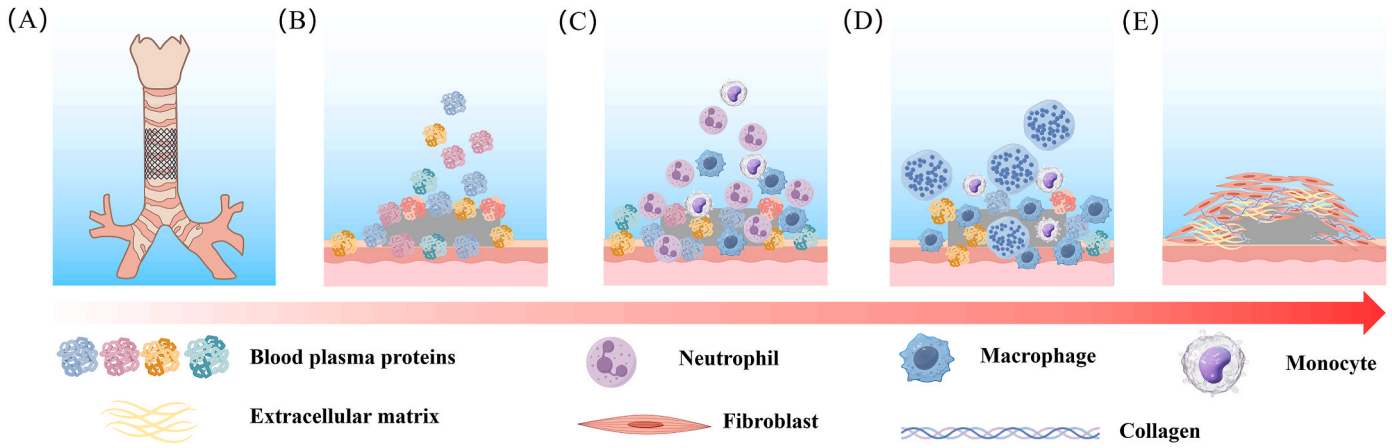

Fig. 4. The process of granulation tissue formation after stent implantation (A), including protein adsorption (B), acute inflammation (C), chronic inflammation and foreign body giant cell formation (D), and fibrotic encapsulation (E).

2.2.2. *Acute inflammation*

Neutrophil infiltration marks the beginning of an acute inflammatory response (Fig. 4C) [82,83]. Neutrophils and M1 macrophages disinfect wounds by phagocytosing bacteria and other microbes introduced by stents. However, extended neutrophil activity is harmful and may lead to prolonged inflammation or chronic injury. M1 macrophages secrete various proinflammatory cytokines and chemokines, further amplifying the inflammatory response. The acute inflammatory response usually resolves within a week, depending on the degree of injury.

2.2.3. *Chronic inflammation and foreign body giant cell formation*

Monocyte and lymphocyte infiltration and macrophage activation indicate the start of chronic inflammation (Fig. 4 D). M1 macrophage activation is characterized by the synthesis of interleukin-1 (IL-1), IL-6, and IL-8. Early use of an IL-1 receptor antagonist may decrease the efficacy of IL-1 in the inflammatory cascade [84]. Stent-induced tracheal stenosis is closely related to the increase in IL-8 expression in the blood one day after tracheal stent implantation: an increase of 1.19-fold compared to that at baseline [85]. Macrophages adhere to the stent for multiple days and release ROS, to phagocytose the stent [86]. In this context, macrophages often fuse to form foreign body giant cells, which depends on the activation of mast cells and lymphocytes that secrete IL-4 and IL-13. Macrophages are polarized into selectively activated or M2 macrophages that reduce the inflammatory response and promote wound healing by producing profibrotic factors to recruit and stimulate fibroblasts [87]. The resolution of acute and chronic inflammatory responses usually lasts for a maximum of two weeks, and infection is indicated if it lasts for more than three weeks.

2.2.4. *Fibrotic encapsulation*

Fibroblasts deposit collagen and other components of the extracellular matrix on the stent surface (Fig. 4 E) [88]. The deposited collagen contracts and forms a dense fibrous capsule, isolating the stent from the surrounding tracheal tissue [89]. The formation of fibrous capsules is influenced by various profibrotic and proangiogenic growth factors, such as VEGF and TGF-β1. After the expression of TGF-β1 increases in granulation tissue, TGF-β1 stimulates fibroblasts to produce VEGF at the mRNA and protein levels, after which the expression of VEGF increases. VEGF siRNA treatment, the selective Smad3 inhibitors SIS3 and UO126, low concentrations of erythromycin, and thalidomide can inhibit TGF-β1-induced VEGF production [90,91]. The granulation tissue consists of collagen fibers, proliferating capillary sprouts, collagen-secreting fibroblasts, and phagocytic macrophages [92].

The formation of granulation tissue can be inhibited by changing the physical properties of the stent, delivering drugs and biomolecules, and modifying bioactive elements on the surface of the stent [93]. The simplest way to change the physical properties of the stent is to add a film on the outer surface of the stent. The covered stent can block the granulation tissue from passing through the stent mesh [94–96]. Coating the tracheal stent with bioactive elements, such as hyaluronic acid, can reduce the degree of tracheal mucosal fibrosis and prevent tracheal stenosis [97]. Hydrophilic coatings and superhydrophobic coatings also effectively reduce protein adsorption [98,99], thus inhibiting the initial stage of granulation tissue formation. In most studies, the main approach used to inhibit granulation tissue formation is drug-eluting tracheal stents.

2.3. *How to design a drug-eluting tracheal stent?*

The design of drug-eluting tracheal stents often relies on the experience of drug-eluting coronary artery stents. This procedure includes drug selection, drug carrier material selection, drug carrier preparation, the use of a stent platform, drug release evaluation, and biosafety evaluation.

2.3.1. *What drugs can inhibit granulation tissue formation?*

Various antimicrobial drugs and immunosuppressive and anticancer agents can inhibit granulation tissue formation (Table 1). Among them, sirolimus (also known as rapamycin) [100–102] and paclitaxel are widely used [103–106] (Fig. 5). Other drugs, such as ciprofloxacin

Table 1
Drugs that can inhibit granulation tissue formation.

Drugs used in tracheal stent to inhibit granulation tissue formation			Drugs with the potential to inhibit granulation tissue formation
Single use		Mix use	Single use
Sirolimus	Gifitinib	Ciprofloxacin and dexamethasone	β-elemene
Paclitaxel	Kenalog	Cisplatin and AgNPs	Tenoxicam
Allicin	Curcumin	Poly(ciprofloxacin fumaric acid) and poly(gadodiamide ciprofloxacin fumaric acid)	Isoniazid
Doxycycline	Mitomycin C		Erythromycin
Vancomycin	Dexamethasone		Penicillin
Ciprofloxacin	Methylprednisolone sodium succinate		Budesonide
Arsenic trioxide	Indomethacin		

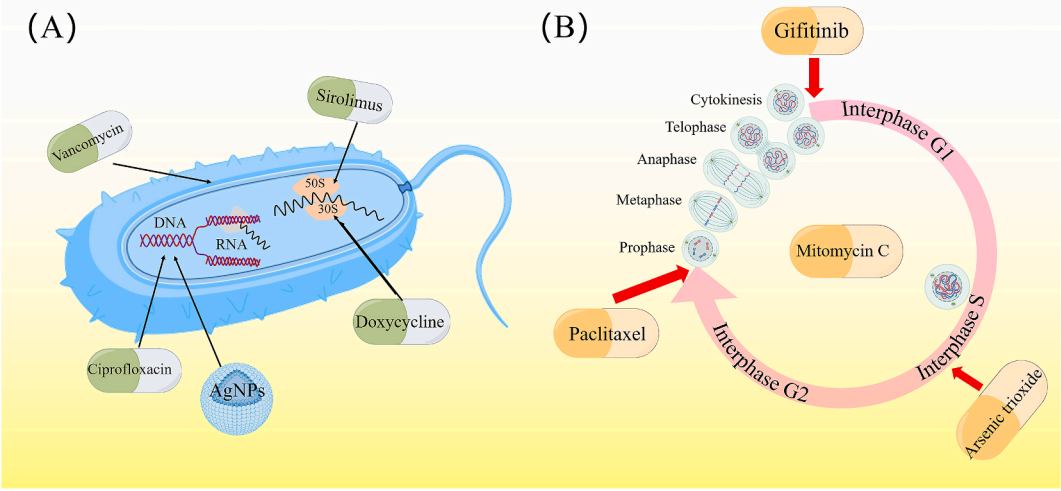

Fig. 5. Antibacterial drugs (A) and anti-hyperplasia drugs (B) loaded on tracheal stent.

[107], doxycycline [108], and vancomycin [109], are also commonly used for drug-eluting tracheal stents.

2.3.1.1. Sirolimus(rapamycin). Sirolimus inhibits mTOR, which in turn decreases inflammation and associated downstream fibrosis. It has the weakest effect on human tracheal epithelial cells [110,111]. In vitro cell experiments revealed that sirolimus can significantly decrease the proliferation, metabolism, and collagen deposition of human laryngotracheal fibroblasts (Fig. 6 A) [112]. The mechanism underlying the inhibitory effects of sirolimus involves the reduction of oxidative phosphorylation in human laryngotracheal fibroblasts. The in vitro drug release pharmacokinetics of a sirolimus-coated stent revealed that it has good surface morphology and sustained effective drug release characteristics for 42 days [100]. The sirolimus-loaded poly-L-lactide and polycaprolactone blend (PLLA-PCL) stent can perform sustained drug release and has adequate mechanical stability in vitro and in vivo [101]. In vitro, it reduces scar and normal fibroblast proliferation, as well as, collagen gene expression. In vivo, it effectively decreases fibrosis and generates a mild inflammatory response (Fig. 6 B). The PLLA-PCL stent loaded with sirolimus exhibits reliable release of sirolimus, satisfactory mechanical stability under physiological conditions, biocompatibility, almost no inflammatory response in the trachea, and reduced scar formation [102].

2.3.1.2. Paclitaxel. Paclitaxel has significant anti-proliferative effects on fibroblasts, vascular smooth muscle cells, and endothelial cells. In vitro experiments on paclitaxel-loaded poly(lactic-coglycolic acid) (PLGA)-coated tracheal stents revealed favorable surface morphology and sustained effective drug release behavior for more than 40 days [103]. A tracheal stent containing paclitaxel was prepared by coating a bilayered film on the surface of the stent [104]. Paclitaxel was released mainly through a diffusion mechanism. This stent can cause a local inflammatory response that is temporary and self-alleviated (Fig. 6C). The self-expanding C-shaped tracheal stent loaded with paclitaxel can release paclitaxel using a temperature-responsive mechanism under an alternating magnetic field [46]. It has satisfactory biosafety in the rabbit trachea and maintains airway patency without mucus plugging within one month after implantation (Fig. 6 D). The results of in vivo animal experiments revealed that the granulation tissue of the paclitaxel-loaded tracheal stent was significantly reduced compared to that of the bare metal stent (Fig. 6 E) [105]. No high concentrations of drugs were detected in the trachea or lung tissues, and no side effects were found in the blood. However, one study compared the response of stainless steel stents, nitinol alloy stents, and paclitaxel-loaded drug-eluting stents in the rabbit trachea [113]. The results showed that the stainless steel stent group presented granulation tissue and stenosis, whereas the drug-eluting stent group presented significant lesions, which were not superior to those of the nitinol alloy stent group, possibly because of the dose of paclitaxel used. Generally, paclitaxel-loaded stents show positive effects in basic and animal experiments, but in real-world applications, they cannot prevent tracheal restenosis due to granulation tissue formation [106]. This difference might occur because of the following reasons: the trachea is normal in animal experiments but stenosed in clinical experiments; the stent becomes longer when the patient coughs, which can cause friction between the end of the stent and the tracheal wall. Electric knife, cryotherapy, or balloon dilation is performed before stent implantation in clinical experiments. Paclitaxel can inhibit fibroblasts and mucosal epithelial cells.

2.3.1.3. Other drugs. **Ciprofloxacin**: The shape memory tracheal stent prepared using digital light processing technology has a smaller insertion profile and greater flexibility [107]. The porous structure can prevent mucus plugging, and the loaded ciprofloxacin also imparts antibacterial activity to the stent (Fig. 7 A). Poly(ciprofloxacin fumaric acid) and poly(gadodiamide ciprofloxacin fumaric acid) can inhibit the growth of four common airway pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, and *P. aeruginosa*, and are expected to act as candidates for tracheal stent coating (Fig. 7 B) [114]. Combining ciprofloxacin and dexamethasone can achieve anti-infection and anti-inflammatory effects; ciprofloxacin can be released in a controlled manner for one week, and dexamethasone can be released for three months [115].

Doxycycline: Matrix metalloproteinase-2 and matrix metalloproteinase-9 are expressed mainly in inflammatory tissues and can be inhibited by doxycycline, a broad-spectrum antibiotic. Doxycycline-eluting core-shell nanofiber tracheal stents can prevent restenosis (Fig. 7C and D) [108,116].

Vancomycin: Vancomycin is a universal antimicrobial agent with no cross-resistance to other antibiotics [117]. It interferes with the synthesis of bacterial cell wall peptidoglycans and inhibits the production of cell wall phospholipids and peptides, thus inhibiting bacterial growth and reproduction, eventually leading to their death [118]. The tracheal stent loaded with vancomycin has good antibacterial activity against *S. pneumoniae* and methicillin-resistant *S. aureus* [109]. It not only reduces the thickness of granulation tissue and collagen density (Fig. 7 E) but also downregulates the expression of α-SMA and CD68.

Allicin: A polydopamine-mediated coating method was used to prepare a silicone tracheal stent coated with allicin, which had no cytotoxic or significant anti-inflammatory or antibacterial effects in vitro. The rabbit model showed favorable mucosal healing, a significant

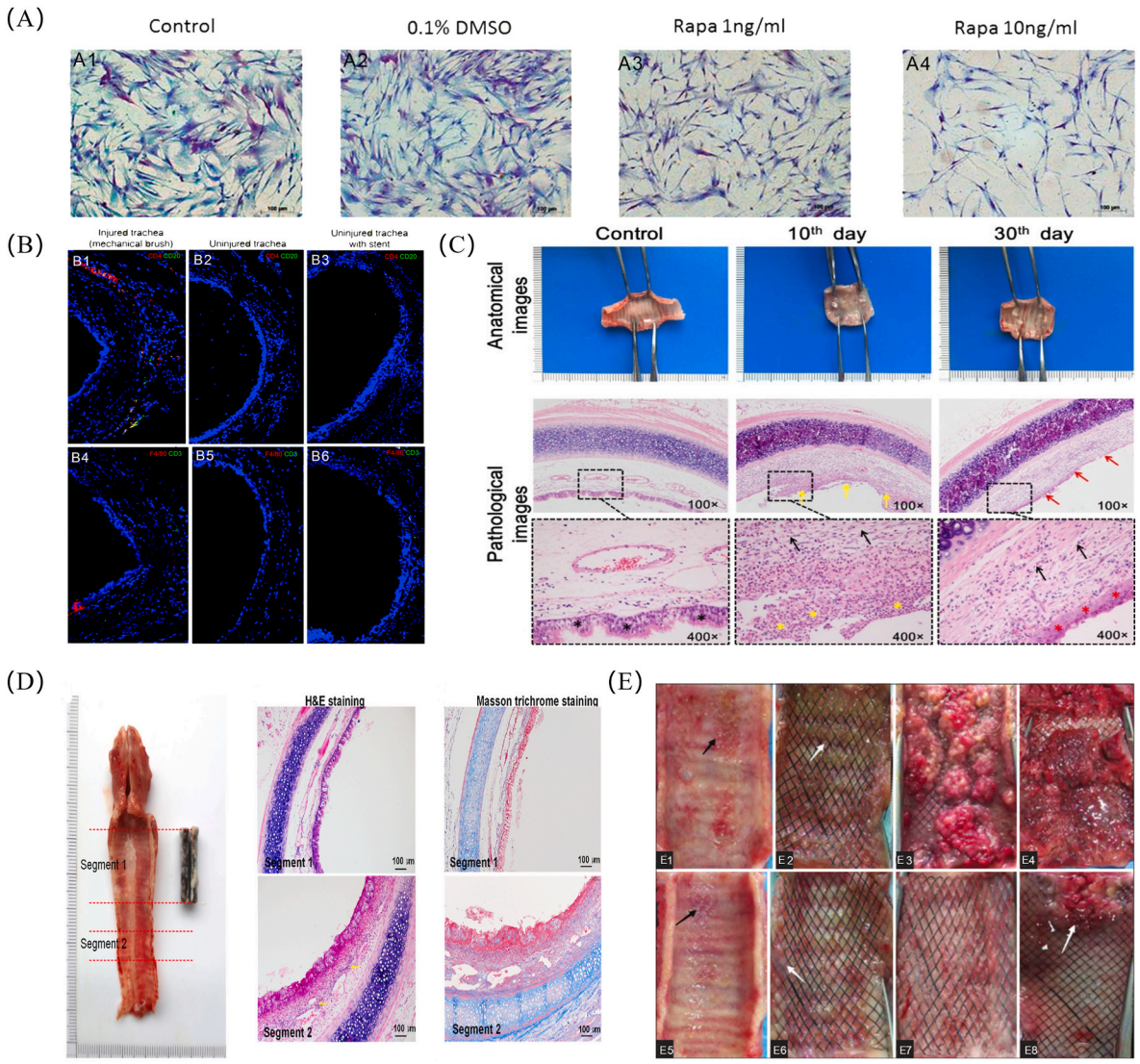

Fig. 6. (A) Fibroblast morphology of normal (A1) and after treatment with DMSO (A2), lowdose rapamycin (A3) and highdose rapamycin (A4) [112].(B) CD4 (red), CD20 (green) of injured trachea (B1), F4/80 (red) and CD3 (green) of injured trachea (B4). CD4 (red), CD20 (green) of uninjured trachea (B2), F4/80 (red) and CD3 (green) of uninjured trachea (B5). CD4 (red), CD20 (green) of injured trachea with stent (B3), F4/80 (red) and CD3 (green) of injured trachea with stent (B6) [101]. (C) General observation and H&E staining of the healthy trachea (control) and the trachea in contact with the PTX30/TSs at 10th and 30th day [104]. (D) Appearances of the trachea and the C-shaped tracheal stent. H&E and Masson's staining of the tracheal tissue [46].(E) 1 and 3 months after stent implantation in control group (E1, E2); 5 months after stent implantation in control group (E3, E4); 1 and 3 months after stent implantation in experimental group (E5, E6); 5 months after stent implantation in experimental group(E7, E8) [105].

reduction in proinflammatory cytokines, a significant reduction in the number of attached cocci-shaped bacteria, and faster regeneration of normal respiratory epithelial structures (Fig. 8A and B) [47].

Arsenic trioxide: Arsenic trioxide exhibits antitumor and anti-inflammatory effects, mainly by directly inducing cell apoptosis and inhibiting cell proliferation, cell differentiation, and angiogenesis [122]. Therefore, tracheal stents loaded with arsenic trioxide can effectively inhibit granulation tissue formation (Fig. 8C) [119].

Mitomycin C: Mitomycin C is a potent inhibitor of human fibroblasts [123]. When injected into granulation tissue, mitomycin C was found to inhibit the proliferation of granulation tissue and reduce the degree of tracheal stenosis [124–127]. The bioabsorbable tubular stent loaded with mitomycin C resulted in the least mucus plugging and airway obstruction caused by tracheal stenosis after implantation into the rabbit trachea [128]. After 12 weeks, the degree of tracheal stenosis was only half that of the silicone stent.

Gifitinib: Gifitinib can compete with ATP to bind to the intracellular tyrosine kinase domain of epidermal growth factor receptor, thus inhibiting receptor autophosphorylation and blocking downstream signal transduction. The sandwich structure of gifitinib-loaded poly (lactic-coglycolic acid) microspheres in polyurethane coatings is suitable for tracheal stents that release anticancer drugs over a long period [129,130].

Additionally, tracheal stents loaded with cisplatin, Kenalog, methylprednisolone sodium succinate, dexamethasone, curcumin, and indomethacin can also achieve effective granulation tissue suppression [131–136]. Some in vitro cell experiments and drug experiments have shown that β-elemene, tenoxicam, isoniazid, erythromycin, penicillin, and budesonide can reduce the proliferation of tracheal fibroblasts, thus reducing granulation tissue and preventing recurrent stenosis [137–140]. However, they are currently not used in manufacturing drug-eluting tracheal stents.

2.3.1.4. Inorganic nanoparticles. **Silver nanoparticles (AgNPs)**: AgNPs have antibacterial and anti-inflammatory activities. A novel tracheal stent coated with polylactic acid (PLA) and silver nanoparticles was

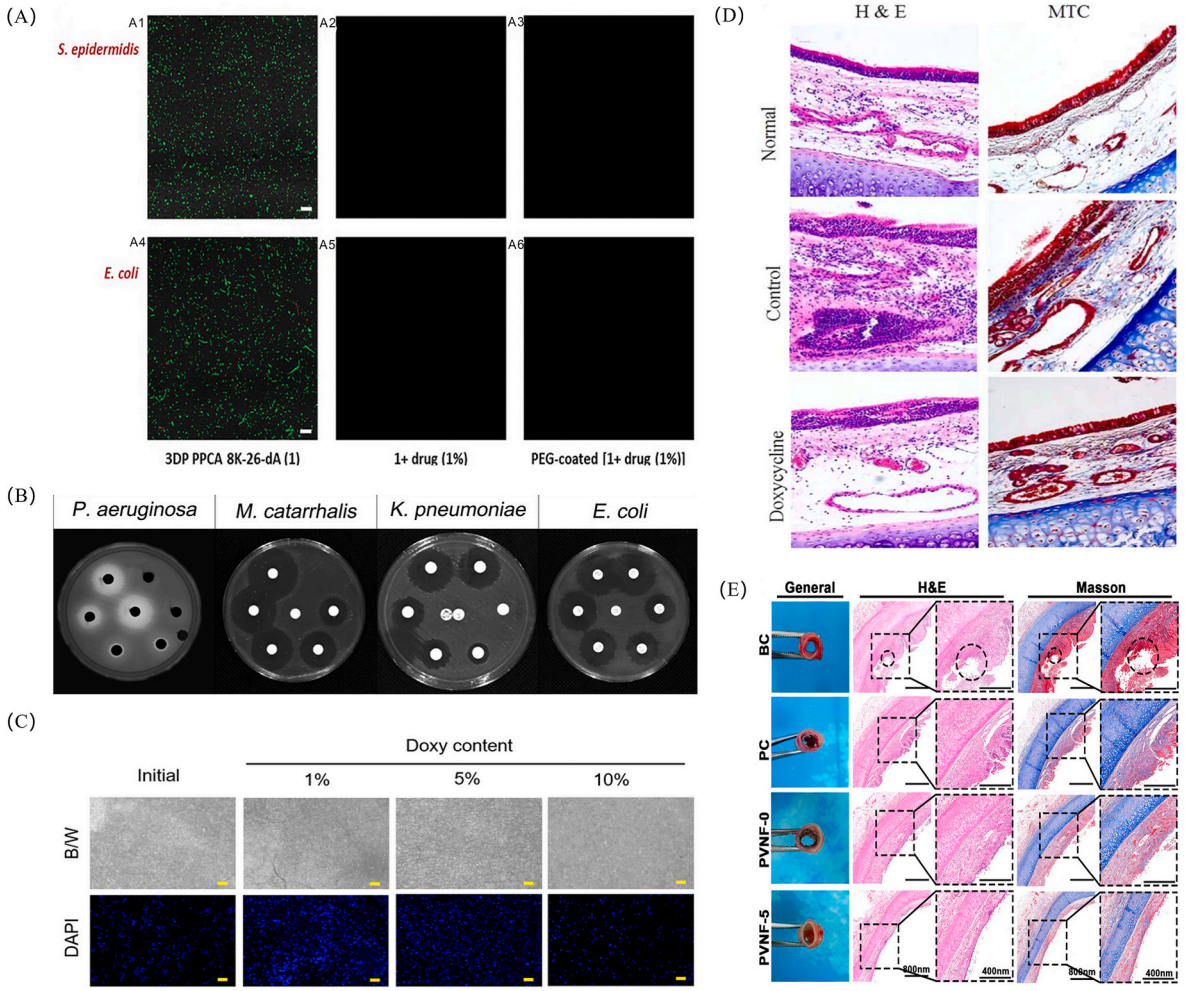

Fig. 7. (A) Confocal images of S. epidermidis and E. coli. The green and red regions represent live and dead bacteria, respectively [107].(B) Images of typical incubated standard plate of the four airway bacteria strains [114]. (C) Fibrosarcoma cells were incubated under different doxy concentration, and stained with DAPI [108].(D) H&E and Masson's staining of tracheal mucosa [116].(E) General observation, H&E staining and Masson's staining of blank control (BC), pellosil matrix-covered stent (PC), PVNF-0-covered metallic stent, and PVNF-5-covered metallic stent [109].

fabricated by electrospinning [120]. The in vivo experimental results indicated that the tracheal stent inhibited granulation tissue formation by reducing bacterial content, inflammation, and collagen deposition (Fig. 8D and E). The synergistic effect of cisplatin and AgNPs leads to bacterial death and reduces the content of inflammatory factors, α-SMA, and collagen deposition, thus inhibiting granulation tissue formation (Fig. 8F and G) [121,141,142]. Besides AgNPs, other antimicrobial inorganic nanomaterials, such as copper nanoparticles [143], Al_2O_3 nanoparticles [144], TiO_2 nanoparticles [145], ZnO nanoparticles [146], gold nanoparticles [147], and CuO nanoparticles [148], are also widely used in biomedical applications. These methods may help expand the stent design.

2.3.2. *How to choose the appropriate drug carrier?*

Drug carriers should have the following characteristics: (1) good biocompatibility and no serious immune response; (2) sufficient strength and flexibility to adapt to the deformation of the tracheal stent; (3) long-term, stable, and controlled drug release; (4) ability to maintain the physicochemical properties of the drug without affecting its pharmacological effects.

Few studies have investigated the use of nondegradable polymers as drug carriers, mainly because long-term implantation may cause an inflammatory response, and these materials need to be removed after drug release. The nondegradable polymer used for studying drug-eluting tracheal stents is mainly the ethylene-vinyl acetate copolymer [46]. To avoid the inflammatory response caused by polymer persistence, many studies have used biodegradable polymers as drug carriers. These biodegradable polymers include PLGA [100,103,105,129], PCL [109,121,132,142], PLA [120], PLLA-PCL [141], Poly-L-lactide-caprolactone [119,135], Poly (DL-lactide-co-glycolide) [101], polydopamine [47], and polyurethane [108,116]. Two main risk factors are associated with drug-loaded tracheal stents: rapid release of the drug at the implantation site and coating damage. Double-layer coatings [149,150], asymmetric coating [151], and micro-patterned diamond-like carbon coating [152] an effectively control the rapid release of drugs at the implantation site. For coating damage, polymer-free drug-eluting stents have been introduced for coronary artery stents [153–155]. However, this technology has not yet been applied to tracheal stents.

2.3.3. *What is the preparation process for drug carriers?*

Selecting the appropriate preparation process is the key to preparing drug-eluting stents. The common processes used to prepare drug-eluting tracheal stents include dip coating [100,103,105], spray coating [129,131], electrospinning [108,109,116,120,121,135]. Dip coating is simple and inexpensive but has the disadvantages of drug waste, non-uniform thickness, and inability to accurately control drug loading [156]. Spraying does not waste drugs, and it is a convenient technique to prepare multilayer structures with uniform and controllable thicknesses.

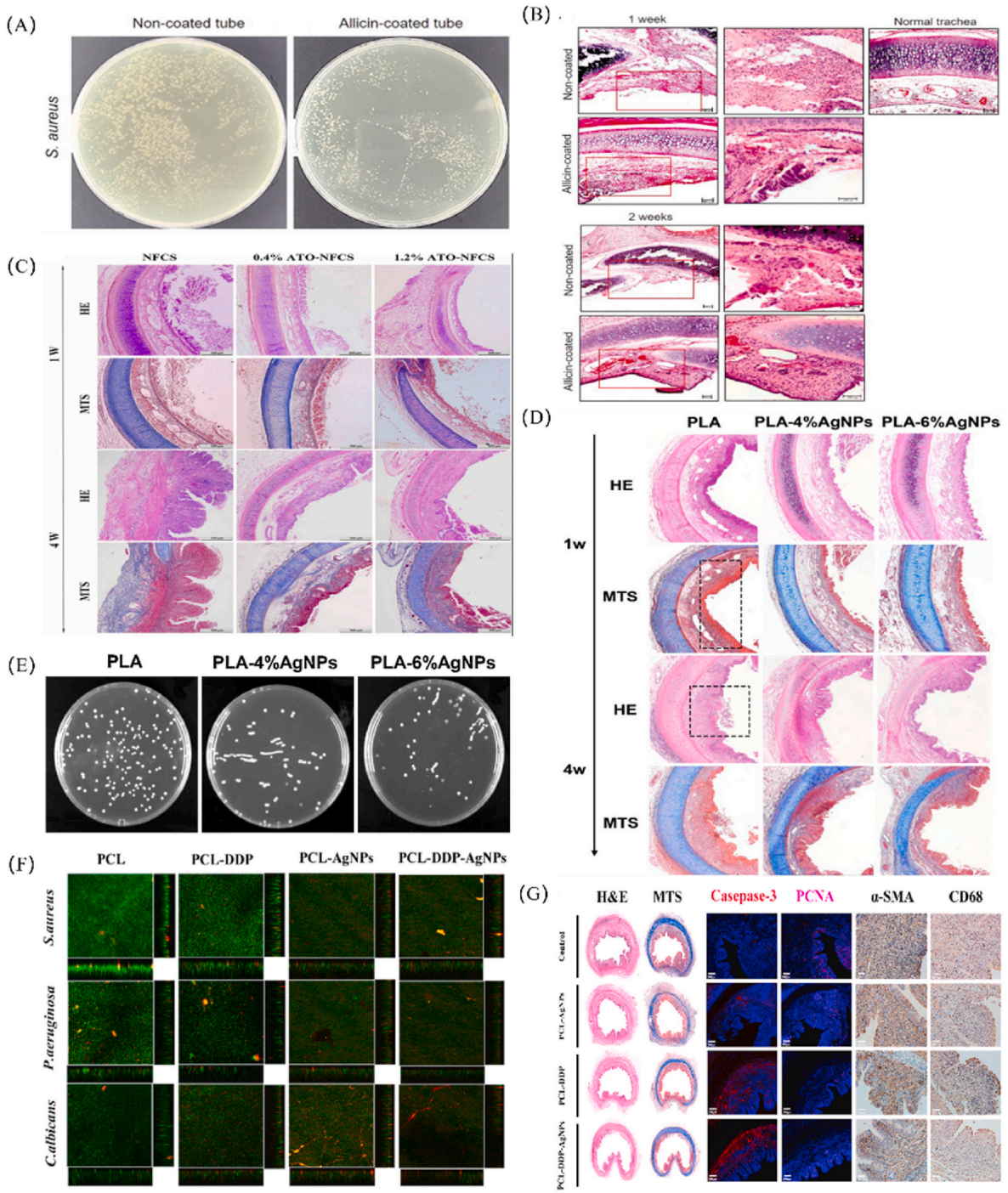

Fig. 8. (A) In vitro antibacterial effect of allicin [47].(B) H&E staining of trachea 1 and 2 weeks after implantation [47]. (C) H&E and Masson's staining of the trachea at 1 and 4 weeks in the NFCS, 0.4 % ATO-NFCS, and 1.2 % ATO-NFCS [119]. (D) H&E staining and Masson's staining of the trachea in the PLA, PLA-4 % AgNPs and PLA-6 %AgNPs [120]. (E) Plaques in PLA, PLA-4 %AgNPs and PLA-6 %AgNPs [120]. (F) CLSM images after staining with the Live/Dead BacLight Bacterial Viability Kit [121].(G) H&E staining, Masson's staining, Casepase-3, PCNA, α-SMA and CD68 of the trachea in the control, PCL-DDP, PCL-AgNPs and PCL-DDP-AgNPs fiber film-coated tracheal stent [121].

However, special spraying equipment needs to be customized according to different types of stents. Although electrospinning can produce drug-loaded nanofibers with high specific surface areas and porosities, the types of polymers available for electrospinning are limited. Some researchers added drugs directly to the stent material [107,128,132]. Additionally, films with arrays of microchambers to accommodate drugs are also used for drug-eluting tracheal stents [133].

2.3.4. *Stent platform and stent evaluation*

For the stent platform, most drug-eluting stents are made of permanent metals, mainly stainless steel, cobalt-chromium alloy, and nitinol alloy. The stent persists even after the drug is completely released, leading to complications. Therefore, in future studies on drug-eluting tracheal stents, the application of biodegradable stent platforms should be considered to further improve the therapeutic effect of these stents. No unified evaluation criteria are currently available for the in vitro drug release and biosafety of drug-eluting tracheal stents; thus, the

corresponding criteria need to be established urgently.

The above-mentioned drug-eluting stents were validated by in vitro drug release and animal experiments, and all of them were found to decrease the inflammatory response and inhibit granulation tissue formation. However, most of these studies were animal experiments, and only a few were human trials.

3. How can the difficulty of stent removal be avoided?

Due to severe complications such as stent migration, granulation tissue formation, mucus plugging, incoercible cough, and stent fracture, secondary surgery is usually required to remove the stent. Secondary surgery may be difficult to perform, and patients are exposed to additional risks. Therefore, a tracheal stent needs to be developed that is easy to remove or does not need to be removed. A tracheal stent that is easy to remove can be designed from the structure. Also, biodegradable materials can be used to prepare tracheal stents so that the tracheal stent can support the trachea for a period, maintain tracheal patency, and gradually degrade, thus avoiding stent removal.

3.1. How can the difficulty of removing the stent through structural design be reduced?

Covered stents can reduce the difficulty of stent removal. Compared to those of bare metal stents, the incidence of granulation tissue and stent fracture of covered stents is lower, and the success rate of stent removal is higher [157,158]. The uncovered self-expanding metal stent made of nitinol alloy through the knitting process is removable because the stent can be disentangled into a single thread from which it was made [159]. Additionally, the use of spiral stents can reduce the difficulty of removal [160–162].

3.2. How can the difficulty of stent removal be reduced by selecting the proper materials?

Biodegradable tracheal stents can maintain airway patency and degrade completely after the objectives are achieved. An ideal biodegradable tracheal stent must have good mechanical properties, an appropriate degradation rate, and high biocompatibility. The materials currently used for making biodegradable tracheal stents mainly include biodegradable polymers and biodegradable metals. The biodegradable polymers used for biodegradable tracheal stents include polydioxanone [163–165], silk fibroin-PCL [166], poly(lactic-co-glycolic acid) with polyisoprene [167], amino alcohol based poly(ester amide) [168], PCL [169,170], etc. The biodegradable metals used for making biodegradable tracheal stents are mainly magnesium alloys [48,49,171].

3.2.1. Mechanical properties

A stent needs favorable crimping properties, sufficient radial force, longitudinal flexibility, and a low recoil rate. A few studies have reported the data on mechanical properties provided by manufacturers; however, the stent sizes reported in such data do not match the stent sizes used in these studies [163,172]. Assessment of the mechanical properties of biodegradable tracheal stents and changes in the mechanical properties during the degradation process is lacking.

3.2.2. Degradation behavior

An appropriate degradation rate is crucial for the biodegradable stents to perform their support function. Retrospective studies on tracheal stent removal have shown that the interval between stent implantation and removal is about three months [157,173–176]. Therefore, the complete degradation period of biodegradable tracheal stents should match this.

The degradation of polydioxanone stents in normal rabbits starts at 10 weeks (Fig. 9 A), and the degradation rate increases in tracheomalacia model rabbits, starting at four weeks [177].In two other studies in a normal rabbit model, the stent completely degraded without remnants after 10 and 14 weeks of implantation [172,178]. In a rabbit model of tracheal stenosis, no degradation occurred within 30 days, 50 % degradation occurred at 60 days, and 100 % degradation occurred at 90 days [179].

The tracheal stents made of Mg-Nd-Zn-Zr alloy or Mg-Ca-Zn alloy remained intact two months after implantation into the trachea of New Zealand rabbits [49]. Compared to tracheal stents made of pure magnesium and AZ31 alloy, those made of the Mg-3Y alloy experienced the slowest corrosion loss after 24 weeks in the rat tracheal bypass model (Fig. 9 B) [171]. The biodegradable ultrahigh ductility Mg-Li-Zn alloy tracheal stent was found to fully degrade in vivo after eight weeks of implantation (Fig. 9C) [180].

Polydioxanone stents implanted in children were found to degrade 4–6 weeks after surgery [181], whereas the periods of complete degradation were different (eight weeks, 10 weeks, 3–4 months, 17 weeks, 18

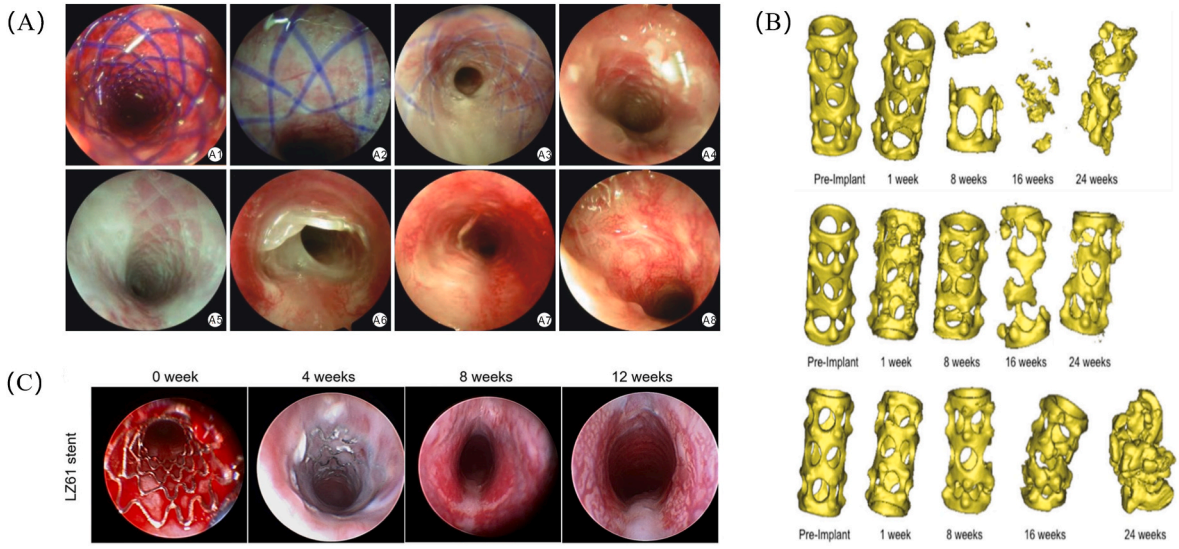

Fig. 9. (A) Bronchoscopy images taken immediately after stenting (A1) and 1(A2), 2(A3), 4(A4), 6(A5), 8(A6), 10(A7), and 12 weeks(A8) after stenting [177]. (B) Images of 3D micro-CT volumes for pure Mg stent, AZ31 alloy stent, Mg-3Y alloy stent prior to implantation and at the 1, 8, 16, and 24 weeks after implantation [171]. (C) Endoscopic images of the stented airway right after implantation, and 4, 8, and 12 weeks after implantation [180].

weeks, six months, and nine months) [182–184]. Six polydioxanone stents were implanted in four adult patients with benign stenosis; three months after implantation, small pieces of fiber were detected in their cough [164].

Few studies have investigated the effect of the airway environment on stent degradation. One study showed that the increase in bicarbonate ions in Gamble's solution accelerated the degradation of AZ31 magnesium alloy, whereas adding mucin retarded degradation [185]. In vitro immersion experiments of high-purity magnesium, high-purity zinc, and pure iron revealed that high-purity magnesium and zinc have appropriate corrosion rates and good biocompatibility [186]. Therefore, high-purity magnesium and zinc may be good candidates for tracheal stent materials.

3.2.3. Biocompatibility

A rabbit model revealed that the use of a polydioxanone tracheal stent can prolong survival [163,177]. However, there are also inflammatory responses [178]. The most pronounced inflammatory response was observed five weeks after implantation [172]. The inflammatory response decreased from week 5 to week 15. After 15 weeks of implantation, the trachea had completely healed. The implantation of polydioxanone stents does not increase the tracheal wall collagen area or change the cartilage structure [165,178].

Significant histological inflammatory damage was recorded after poly(lactic-co-glycolic acid) was implanted with a polyisoprene stent in the rabbit trachea; the damage was probably caused by excessive stent wall thickness (Fig. 10 A) [167]. The mechanical properties of tracheal stents printed based on blends of poly(DLLA-co-CL) methacrylate are comparable to those of state-of-the-art silicone stents; these stents have good biocompatibility in healthy rabbits and degrade after seven weeks in situ (Fig. 10 B) [187].

David et al. first demonstrated the feasibility of the use of biodegradable polydioxanone tracheal stents for treating tracheal stenosis in children. Initially, all patients experienced relief from stenosis, and no bleeding or perforation occurred after stent implantation, but a size mismatch was detected [182]. No major stent-related complications occurred, and only mild or moderate granulation tissue was observed during follow-up [184]. Symptoms were relieved in all adult patients, but they still experienced cough, mild mucosal irritation, mucosal hyperplasia, and mucus plugging (Fig. 10C) [164]. All patients experienced mild and easily treatable adverse events, and they were relieved from tracheal stent at the end of follow-up (Fig. 10 D) [188].

Tracheal stents made of Mg-Nd-Zn-Zr alloy and Mg-Ca-Zn alloy were implanted into the trachea of New Zealand rabbits [49]. No significant systemic inflammatory response was found, and no significant difference was found in liver and/or kidney function before and after stent implantation, which indicated that biodegradable magnesium alloy tracheal stents are feasible for treating patients with tracheal stenosis (Fig. 10 E). The prototype tracheal stent was prepared using Mg-Al-Zn-Ca-Mn (AZXM) alloy and implanted into the rabbit trachea [48]. he results showed that the airway tissue could tolerate the AZXM alloy and its degradation products and did not interfere with the epithelium (Fig. 10 F). These findings indicated that the AZXM alloy is a suitable material for making biodegradable tracheal stents. Tracheal stents made of pure magnesium, AZ31, or Mg-3Y alloy were implanted into a rat tracheal bypass model [171]. The trachea had good tolerance and acceptance of magnesium within six months, the foreign body reaction was minimal, and airway functions were not negatively affected. The tracheal tissue was tolerated by the Mg-Li-Zn alloy and degradation products without any significant local or systemic toxicity (Fig. 10 G) [180].

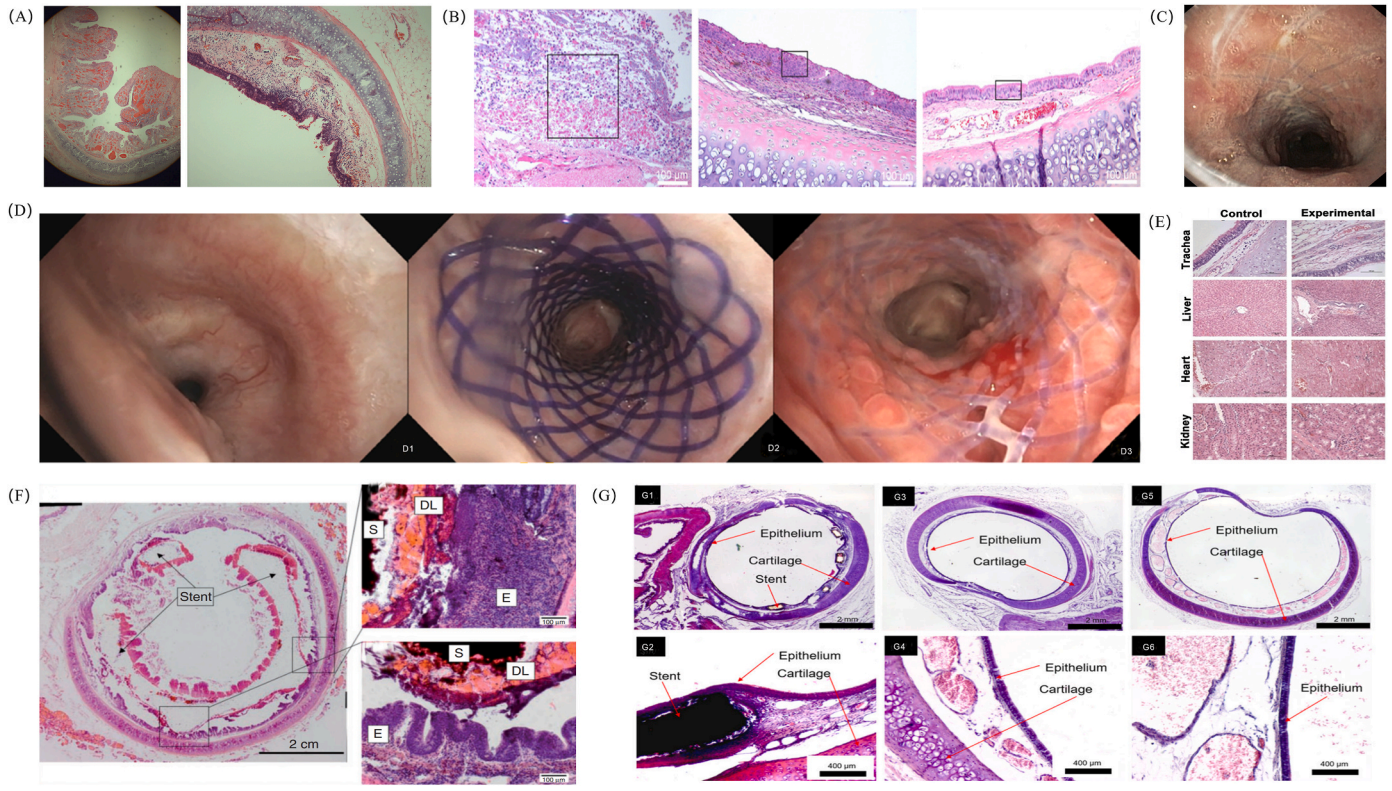

Fig. 10. (A) Histological images of stent group and fragment group [167]. (B) Tissue morphology changes in the rabbit's trachea 2, 6, and 10 weeks after the stent implantation [187].(C) Inflammation and hyperplasia of mucosa after stent implantation [164]. (D) Severe circular malacia of the left main bronchus (D1). Treatment with BDS (D2). Bronchoscopy images taken 7 weeks after implantation (D3) [188]. (E) H&E staining in the rabbit tracheal, liver, heart and kidney tissues of the control and experimental groups [49]. (F) H&E staining of stented tracheal 4 weeks after implantation (S: stent, E: epithelium and DL: degradation layer) [48]. (G) A LZ61-KBMS stent stented trachea at various magnifications 4 (G1, G2), 8 (G3, G4), 12 weeks (G5, G6) after implantation [180].

4. How can the persistent growth of malignant tumors be reduced?

Stent restenosis often occurs in some patients with malignant tumors because malignant cells can enter the lumen through the stent mesh or grow at the end of the stent [189–191]. Brachytherapy inserts radiation sources within or close to the target lesion, which provides high radiation doses within or close to the lesion [192–194]. I^{125} is a radionuclide with a half-life of 60 days. I^{125} seeds provide sustained gamma rays at low doses, killing tumor cells by synchronizing cancer cells to the radiation-sensitive G2-M phase but allowing normal tissue to repair sublethal tissue damage [195,196]. Additionally, iridium-192, palladium-103, and cobalt-60 can also be used as radiation sources for brachytherapy [197,198]. To overcome this complication, tracheal stents loaded with radionuclides have been developed to prevent restenosis associated with tumor regrowth.

The tracheal stent loaded with I^{125} was implanted in the trachea of healthy beagle dogs, the tracheal mucosal epithelium showed inflammatory reaction and mild injury [18]. The tracheal injury score increased with the increase of the dose of radioactive seeds. Even in the high-dose group, radioactive seeds did not increase complications. In vivo experiments on New Zealand white rabbits showed that the brachytherapy injury increased with the accumulation of radiation dose and I^{125} brachytherapy could inhibit the granulation formation within 8 weeks [199].

A stent loaded with radioactive I^{125} seeds was used to treat adenoid cystic carcinoma of the central airway [200]. The patient tolerated the operation and showed no signs of relapse three years after the stent was removed. Lin et al. showed that treating patients with malignant tracheal stenosis by using an I^{125} stent is feasible. This technique can immediately relieve dyspnea and significantly improve quality of life [201]. However, it has several complications such as bleeding, coughing, loss of I^{125}, and infection.

A comparison of the safety and efficacy of radioactive bare metal stents and traditional bare metal stents in patients with malignant tracheal stenosis showed that the stenosis grade of radioactive bare metal stents was significantly lower than that of traditional bare metal stents, and the median survival was significantly longer than that of traditional bare metal stents [50]. The incidence of complications was similar between these groups. The results of a meta-analysis indicated that implantation of radioactive stents can decrease the rate of restenosis and prolong overall survival in patients with malignant airway stenosis compared to implantation of normal stents [202].

Although radioactive tracheal stents can strongly inhibit the persistent growth of malignant tumors, the binding mode and quantity of radioactive seeds in the radioactive stent are different, and the dose distribution between multiple seeds on the surface of the stent has reciprocal effects. Therefore, injury persists in the dosimetry of radioactive stents. A standard dosimetry measurement model needs to be established for radioactive tracheal stents to determine the dose distribution characteristics, such as the prescription dose, tumor target areas, and dose to the surrounding normal tissue. The optimal timing of radioactive tracheal stent removal needs to be further investigated.

5. How can tracheal stent migration be reduced?

Stent migration occurs mainly due to inappropriate stent selection, inappropriate shape and size of the stent, and improper implantation. A tracheal stent requires good anchorage to reduce the risk of migration, but this should be achieved without exerting excessive stress on the surrounding tissue to reduce the risk of granulation formation.

5.1. How to improve structural matching?

Structural mismatch may lead to tracheal stent migration. Patient-specific tracheal stents can prevent migration by matching the size of the stent with the patient's trachea, resulting in a better fit. Such stents can be made by using 3D printing technology, which can be used to construct the stent layer-by-layer through a computer-aided design system. Fused deposition molding technology is used to print the stent molds, which are filled with medical-grade silicone to obtain a silicone tracheal stent (Fig. 11 A,B) [19,203]. This method facilitates quick and affordable manufacture of patient-specific tracheal stents. The drug-loaded PLGA stent printed by fused deposition modeling has low stent porosity, high mechanical strength, and sustained drug release function [204]. A medical-grade polyurethane tracheal stent manufactured by fused deposition molding was used for the first time in humans (Fig. 11C) [205]. The stent matched the airway size of each patient and achieved excellent stent fit. The 3D-printed stent showed very precise consistency in the trachea (Fig. 11D) [206]. Seven days after surgery, the patient experienced significant improvements in dyspnea, quality of life, and functional parameters without complications associated with the procedure. Three-dimensional-printed tracheal stents were implanted into 10 patients with complex anatomical tracheal stenosis, nine of whom showed great congruence, and eight showed significant improvement in dyspnea, quality of life, and respiratory function [207]. However, the incidence of complications, including mucus plugging, severe cough, and stent migration, at three months was 40 %.

Although 3D-printed tracheal stents allow excellent matching between the tracheal stent and trachea, they have certain limitations. For example, 3D-printed tracheal stents rely on patient-specific tracheal stenosis, and traditional 3D reconstruction methods are inefficient and cannot meet clinical requirements. Although 3D printing technology can use various materials, many materials are not biocompatible and cannot be used to manufacture tracheal stents. Moreover, 3D-printed tracheal stents usually require postproduction surface treatments to ensure that their surface is smooth and defect-free. Postproduction surface treatments also include drug coating. A C-type tracheal stent coated with curcumin can effectively prevent tracheal stenosis by reducing collagen deposition and inflammation [208]. These postproduction surface treatments increase the complexity and cost.

The design of 3D-printed stents requires a balance between shape and mechanical properties [209]. The 3D-printed tracheal stents allow a wider range of shapes and fit well with the trachea. However, the mechanical properties require more attention. The radial force and flexibility of the stent depend on the combination of the thickness, diameter, and hardness of the material.

5.2. Improving mechanical property matching

Mismatched mechanical properties promote tracheal stent migration. The deformation caused by the force applied to the tracheal stent must be consistent with the deformation of the trachea [210]. The stent designed by the tetrachiral and anti-tetrachiral hybrid structure can match the nonlinear mechanical response of the native trachea, and the effect of its negative Poisson's ratio plays a vital role in maintaining patency and reducing stent migration (Fig. 12 A) [211]. A ring-hollow alternating PCL stent was prepared using 3D printing technology, and then, the perfusion-lyophilization method was used to embed a collagen sponge into the hollow area of the stent and implant chondrocytes (Fig. 12 B) [212]. The biomimetic stent with a separated-ring structure has a similar anatomical structure, radial rigidity, and longitudinal flexibility to the native trachea. To mimic the natural rigidity and flexibility of the trachea, thermoplastic polyurethane tracheal stents with straight or wave patterns have been developed, and electrospun fibers have been used to improve the cell attachment performance (Fig. 12C) [213].

Along with mechanical matching, the radial force and fatigue of the tracheal stent also need attention. The addition of 1 wt% hydrophobic nanosilica was found to improve the radial force of the silicone stent and maintain the transparency and viscosity of the stent structure [215]. To

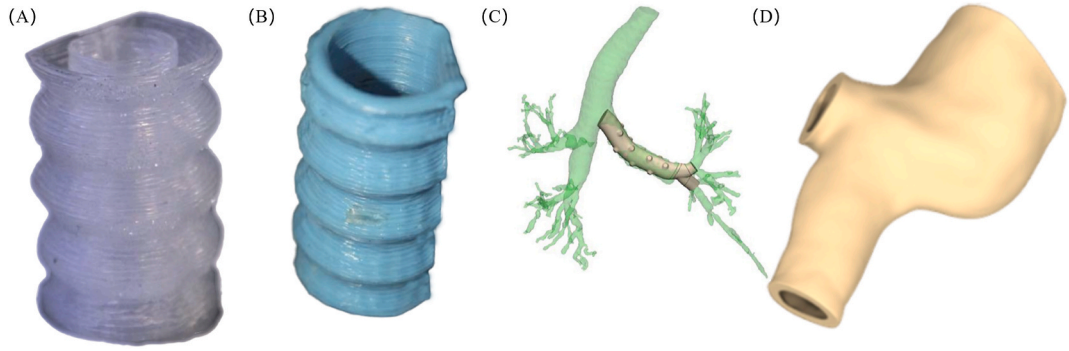

Fig. 11. (A) Silicone mold [19]. (B) Silicone stent [19].(C) 3D Stent designing [205].(D) Conception of the virtual stent [206].

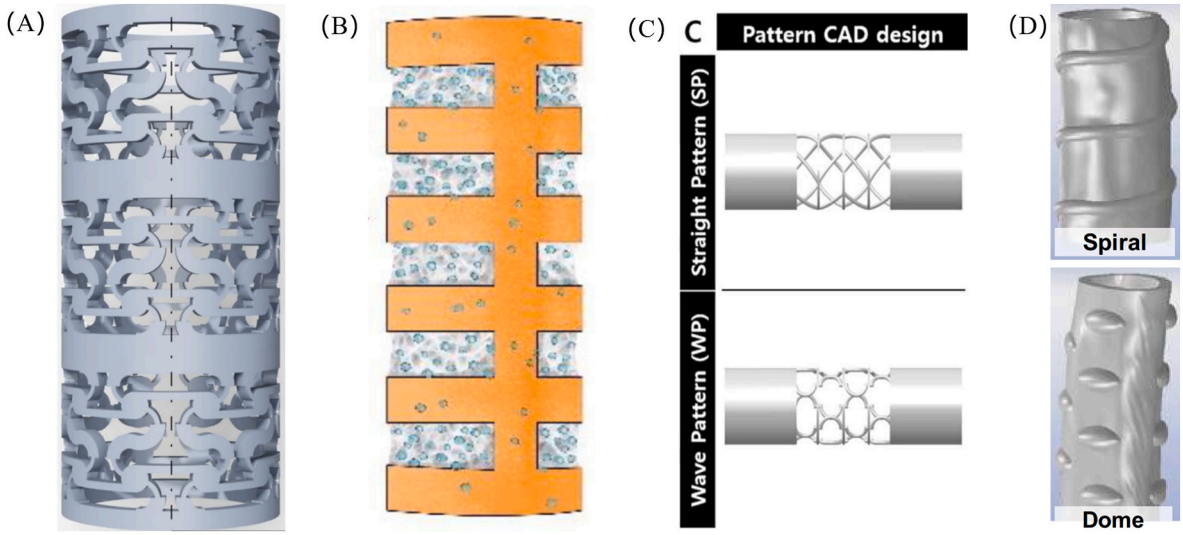

Fig. 12. (A) Geometric design parameters of the W-N-L chiral stent [211].(B) Biomimetic PCL stent as framework interspersed with collagen [212].(C) Flexible straight pattern or wave pattern tubular stent [213].(D) The helical profile and domes on the outer surface of the stent [214].

achieve the high flow rate required to drain secretions, dynamic compression is essential in the normal airway, and the stent can deform under these pressure swings [24]. However, repetitive deformation may lead to fatigue fracture. When the patient coughs, their tracheal smooth muscle contracts and relaxes violently, exerting great radial pressure on the tracheal stent. Additionally, the cough is not harmonious, and the intensity of the cough fluctuates randomly. A study reported that the nitinol alloy tracheal stent may experience stochastic resonance during cough, which may lead to stent fracture or loss [216].

5.3. Other methods for increasing stent anchorage

The additional structure on the outer surface of the tracheal stent can also improve the anchorage of the stent. The helical profile on the outer surface of the stent and the addition of domes on the outer surface of the stent can improve the anchorage of the stent (Fig. 12 D) [214]. The right-angled triangular shape of the outer ring and the raised three-line arrangement of the GINA stent allow it to possess antimigratory ability [217].

6. How can mucus plugging be reduced?

The normal tracheal defense mechanisms of the trachea include the mucociliary transport system, cough reflex, and immunological mechanisms. Among these, the mucociliary transport system is the first line of defense of the trachea [218,219]. Foreign bodies and secretions entering the trachea can be expelled in the form of mucus due to the action of the cilia. However, the tracheal stent may hinder mucociliary clearance, leading to mucus plugging, which may lead to secondary infection. Therefore, tracheal stents that do not impair the function of mucociliary clearance are urgently needed in the clinical setting.

6.1. Minimizing the barrier to mucociliary clearance

To avoid mucus plugging, the barrier to mucociliary clearance of the tracheal stent should be minimized. The single-tube-braided tracheal stent has sufficient radial rigidity, can decrease the impediment to mucus flow, and is less likely to cause mucus plugging (Fig. 13 A) [220]. Porcine models can tolerate the helical Ni-Ti tracheal stent, allowing noninvasive implantation and removal and facilitating minimally impeding mucus clearance (Fig. 13 B) [161,162]. The low-profile airway stent is a thin, metal zig-zag wire that partially covers the cilia in the trachea, reducing mucus plugging [221].

6.2. Anti-fouling coating

Mucus plugging may be reduced by introducing an anti-fouling coating on the surface of the stent. Hydrophilic anti-fouling coatings effectively prevent mucin adhesion to silicone stents [224], Uncoated stents and hydrophilic polymer-coated stents have been implanted in the right and left mainstem bronchi of pigs. Compared to uncoated stents, coated stents are associated with reduced mucostasis, lower injury scores, lower airway injury scores, and lower goblet cell hyperplasia [225]. In another study, uncoated stents and hydrophilic

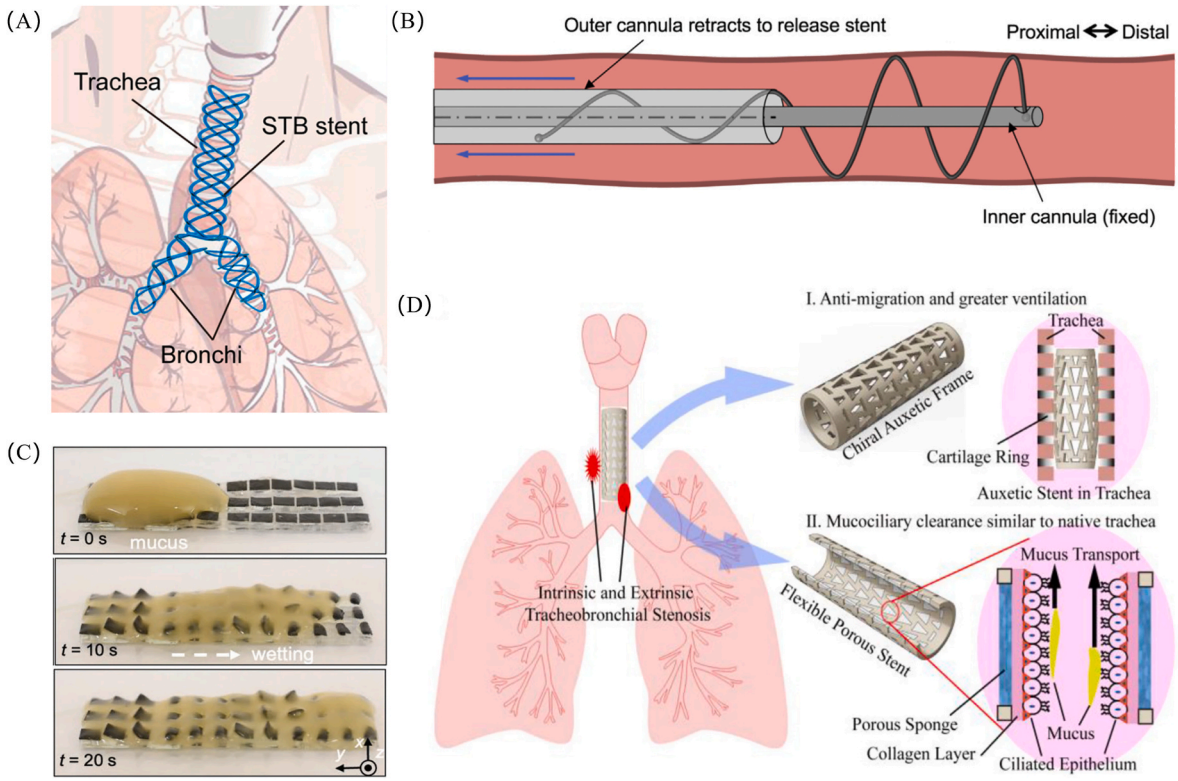

Fig. 13. (A) A schematic diagram of Y-type single-tube-braided (STB) stent [220].(B) A schematic diagram of the delivery of the stent [162].(C) The wetting-based transportation for artificial cilia arrays with hydrogel coating in mucus [222].(D) Ciliated epithelium was cultured on the inner surface of the stent [223].

polymer-coated stents were randomly implanted into the tracheas of three pigs [226]. Compared to the uncoated stents, the coated stents caused less injury, but the average total dry mucus weight of the coated stents was slightly greater. This occurred probably because the uncoated stents migrated out and were not included in the total dry mucus weight.

6.3. *Artificial cilia and culture of respiratory epithelial cells*

Integrating artificial cilia on tracheal stents may help address mucus plugging. The bioinspired nonreciprocal motion and metachronal waves control the movement of magnetic artificial cilia within the tracheal stent, facilitating excessive mucus transportation (Fig. 13C) [222]. A lubricating hydrogel coating was also applied on artificial cilia, which further enhanced excessive mucus transportation.

The hybrid structure of tetrachiral and anti-tetrachiral materials was used as the stent frame, the hollows were filled with a porous silicon sponge, and the ciliated epithelium was cultured on the inner surface of the stent (Fig. 13 D) [223]. The ciliated tracheal epithelium differentiated from the inner wall of the stent can reduce mucus plugging. In an animal study, respiratory epithelial cells were implanted on tracheal stents covered with a polycarbonate urethane nonwoven film by endoscopic spraying in situ, and no severe mucus plugging was recorded [96].

7. Conclusions and prospects

For bronchial-related diseases, most medical practitioners recommend surgical treatment, but not all patients can undergo surgery. In such cases, tracheal stent is often the best alternative for symptomatic management. Different stents have unique advantages and limitations. Appropriate stents (including the type, shape, tension, etc.) and implantation time should be selected based on the patient's location of stenosis, tolerance, disease progression, and economic conditions to alleviate the symptoms and improve outcomes. Complications associated with tracheal stents, such as granulation tissue formation, difficulty in removal, persistent growth of malignant tumors, stent migration, and mucus plugging, can be addressed by designing suitable tracheal stents. Drug-eluting stents can strongly inhibit granulation tissue formation and prevent infection, thus eliminating the need to administer local chemotherapy. The biodegradable stent can support the trachea for some time, maintain trachea patency, and degrade gradually; thus, removing or replacing the stent is not necessary. Radioactive stents loaded with I^{125} can strongly inhibit the persistent growth of malignant tumors. Three-dimensional printing technology can be used to manufacture patient-specific stents, which increases the degree of matching between the complex tracheal anatomy and the stent, thus providing a new solution for stent migration caused by structural mismatch. Minimizing the stent's hindrance to mucociliary clearance, providing an antifouling coating, and culturing respiratory epithelial cells on the surface of the stent are the main methods used to reduce mucus plugging.

However, further research is needed to achieve the ideal tracheal stent design. In future studies on tracheal stents, researchers need to do the following:

(1) Despite the promising prospects of drug-eluting stents, few clinical trials exist, and drug-eluting tracheal stents are still in the early stages. Thus, more clinical studies are needed to confirm the effectiveness of drug-eluting stents. The risks associated with damaging the coating or rapidly releasing the drug at the implantation site are not clear, and a comprehensive assessment is required.
(2) Although several studies have reported the application of biodegradable tracheal stents in humans, large-scale clinical studies are lacking. More research is needed to determine how to control the degradation time and strength of the stent. No study is available on tracheal stents made of biodegradable zinc alloys and iron alloys, which may be promising materials for manufacturing metal tracheal stents [186]. Additionally,

biodegradable metals can be combined with emerging fabrication techniques, such as 3D printing, to produce tracheal stents with complex, customized geometries and tailored mechanical properties. Using this strategy might allow researchers to better replicate the characteristics of the human trachea.

(3) Further research is needed on the radiation dose of radioactive tracheal stents to achieve satisfactory treatment effects and tolerance. Besides I^{125}, various radiation sources are used for brachytherapy, and the treatment effect of tracheal stents loaded with these sources needs to be studied.

(4) Although 3D-printed stents can closely match the tracheal anatomy, they are still foreign bodies, and complications might arise. Therefore, the mechanical properties of 3D-printed tracheal stents need to be given more attention to better match the structural and mechanical properties.

(5) Regarding mucus plugging, many studies have investigated anti-fouling coatings and anti-fouling structures in other fields, which may be applied to tracheal stents.

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CRediT authorship contribution statement

Shiliang Chen: Writing – original draft, Visualization, Investigation, Conceptualization. **Tianming Du:** Writing – review & editing, Supervision, Conceptualization. **Hanbing Zhang:** Writing – review & editing, Conceptualization. **Yanping Zhang:** Writing – review & editing, Conceptualization. **Aike Qiao:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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.

Data availability

No data was used for the research described in the article.

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