Review Article

Delivery System for Targeted Drug Therapy in Chronic Diseases

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Abstract

Chronic diseases affect many people and have become the leading cause of death and loss of health worldwide. The etiology of chronic diseases is complex. They are usually incurable and require continual medical management. Many chronic diseases deteriorate with time, resulting in an enormous burden on society and patients' families. During the past years, targeted agents have made improved the management of various chronic diseases. An optimal drug delivery system can improve the therapeutic efficacy of these targeted drugs and reduce systemic adverse effects, bringing benefits to patients with chronic diseases. Here, we highlight recent research progress in the development of targeted therapeutic drugs for chronic diseases and improved delivery systems.

Introduction

Chronic diseases, also known as chronic non-communicable diseases, have complex causes. They are usually incurable, require continual medical management, and often deteriorate with time.[1] In recent years, chronic diseases have contributed to 73.4% of all deaths globally, and thus form a substantial medical and economic burden to society. According to data released by the *Chinese Resident Nutrition and Chronic Disease Report* in December 2020, chronic diseases caused 88.5% of total deaths in China in 2019.[2] These data demonstrate that chronic diseases have become the primary threat to human health.

Targeted drug delivery systems can concentrate the active ingredient of a medicine at the site of a lesion or anatomical target, and keep the drug at an effective concentration in the targeted organ for a longer duration of time enabling patients to be prescribed medicines at a lower dose.[3] Targeted therapy is a treatment approach that aims to deliver the therapeutic drug to pathogenic organs or sites of required action at a cellular or molecular level. Targeted therapy can help eliminate and reduce drug-related adverse effects, thus improving safety and helping patients to continue taking their prescribed medicines at the prescribed dose and intended dosing frequency without being dissuaded or impeded from doing so by adverse effects. For these reasons, targeted agents are being widely applied in the field of pharmacy. In the past decade, ground-breaking progress has been made in developing targeted therapies for the treatment of chronic diseases. Here, we review

research advances in the development of targeted drugs for chronic diseases and their delivery systems.

The role of targeted therapies in metabolic system diseases

Targeted treatment of type 2 diabetes mellitus

Diabetes is mainly divided into four categories: type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and other specific types of diabetes. Type 2 diabetes is characterized by low degrees of inflammation, insulin resistance, glucose intolerance and an inadequate compensatory insulin secretory response.[4] Glucagon-like peptide 1 (GLP-1) is an insulin stimulating hormone that is secreted by intestinal L-cells in the postprandial period. It promotes insulin release, delays gastric emptying, reduces food intake, and thereby helps maintain blood glucose homeostasis.[5] However, GLP-1 is easily degraded by diptopeptidase IV (DPP-IV) *in vivo*, and has a short half-life of about two minutes.[6] At present, two types of anti-diabetes drugs targeting GLP-1 receptor (GLP-1R) signaling have been developed, namely, GLP-1R agonists and DPP-IV inhibitors. GLP-1R agonists bind to GLP-1R, acting in a similar manner to GLP-1. Exenatide was the first GLP-1R agonist approved for the treatment of type 2 diabetes, and has been widely used in the clinic. Other GLP-1R agonists includelixisenatide, a short half-life GLP-1R agonist, and the long half-life GLP-1R agonists liraglutide, albiglutide, dulaglutide, and semaglutide. DPP-IV inhibitors increase plasma GLP-1 levels, enhancing insulin secretion. There are currently five approved DPP-IV inhibitors: sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.[7] Targeted therapies based on GLP-1R agonists and DPP-4 inhibitors offer many advantages, including that they:

1. Promote insulin secretion and are associated with reduced risks of hypoglycemia than alternative anti-diabetes medicines such as sulphonylureas.
2. Relieve islet β-cell degradation and delay the deterioration of diabetes.
3. Provide cardiorenal protection.

In addition to GLP-1R agonists and DPP-IV inhibitors, Traditional Chinese Medicine is considered to be effective in the treatment of type 2 diabetes. Some researchers have shown that puerarin, astragalus polysaccharides, and berberine can ameliorate type 2 diabetes, highlighting the potential value of traditional Chinese medicines as anti-diabetic agents.[8–10]

Targeted treatment of chronic kidney disease

Chronic kidney disease (CKD) is defined as an abnormality of kidney function or structure that lasts for more than three months. It is associated with type 2 diabetes, hypertension, obesity, and age-related degeneration.[11] CKD may lead to irreversible renal failure, end-stage renal disease and premature death, and is associated with high rates of incidence and mortality coupled with low rates of awareness.[12] In addition, there is currently inadequate implementation of strategies to prevent the development or deterioration of CKD.[12] Current therapies for CKD can only delay disease progression, and the cost of treatment can be a substantial economic burden for patients. Therefore, developing new therapies for the treatment of CKD is an area of intense research. Glomerular cells, endothelium cells, podocytes, macrophages, and tubular epithelial cells (TECs) are all involved in the course of CKD, with glomerular cells being particularly affected.[13] Gary *et al*. recently demon-

strated that nanoparticles modified with carboxymethyl-terminated poly (20~200 nm), can deliver drugs to the kidney for treatment of glomerular kidney disease more efficiently, enabling a greater concentration of drug to accumulate in diseased glomeruli.[14] Bruni *et al*. used four-arm star-shaped polymers as raw materials to obtain new drug-loaded ultra-small colloidal nanocarriers with a tunable size of 5–30 nm.[15] These drug-loaded ultra-small colloidal nanocarriers can repair podocyte damage and reduce albumin permeability *in vitro* drug models.[15] Tripathy *et al*. report that kidney-targeted nanoparticle-based transdermal microneedles can target folate receptors on renal epithelial cells *in vitro*.[16]

CKD is usually accompanied by renal fibrosis. Celastrol (CEL), a triterpene derived from traditional Chinese medicine, has potent anti-fibrotic activity. However, when administered by common drug delivery mechanisms its use is associated with severe systemic toxicity.[17] Li *et al*. generated a system to deliver CEL specifically to interstitial myofibroblasts that consisted of the pentapeptide Cys-Arg-Glu-Lys-Ala (CREKA) conjugated to PEGylated liposomes (CREKA-Lip), which can specifically bind to fibronectin.[18] Systemic administration of CREKA-Lip in mice with unilateral ureteral obstruction led to the accumulation of CREKA-Lip in fibrotic kidneys, effectively alleviating renal fibrosis, injury, and inflammation, with lower toxicity to other major organs than free CEL.[18]

The role of targeted therapies in chronic respiratory diseases

Targeted treatment of chronic obstructive pulmonary disease (COPD)

COPD is a common severe chronic pulmonary disease that affects over 250 million people around the world, and is the third-leading cause of death in the world.[19] COPD, like other respiratory diseases such as acute respiratory distress syndrome, chronic pulmonary fibrosis, and lung cancer is associated with long-term oxidative stress.[20] Currently, therapeutic strategies for COPD can only ameliorate symptoms. Targeted therapies could provide new treatment options for patients with COPD, and could form important adjuvant treatments for COPD. New targeted drugs based on the pathogenesis of COPD have been developed, including cytokine inhibitors, chemokine receptor antagonists, phosphodiesterase 4 inhibitors, nuclear factor κB (NF-κB) inhibitors and protease inhibitors.[21] Compared with oral administration, lung administration of targeted therapies offers a number of advantages, including a faster absorption rate, a concentrated distribution of metabolic enzymes throughout the lung, and lower rates of degradation of the active ingredient. The manner in which drugs are deposited in the respiratory system is mainly influenced by the diameter of the particles used to deliver the drug (Fig. 1). Studies have found that drug delivery systems that produce a higher proportion of drug particles with a diameter between 1.0 to3.0 μm result in more drug settling in the alveoli and bronchioles, leading to better therapeutic effects.[22] New drug delivery systems that could enable this include liposomes, nanoparticles, solid lipid nanoparticles, microspheres and microemulsions (Table 1).[23–34]

Targeted treatment of bronchial asthma

Bronchial asthma (or asthma for short) is a chronic respiratory inflammatory disease. The main symptoms associated with it are shortness of breath, chest tightness and coughing, often accompa-
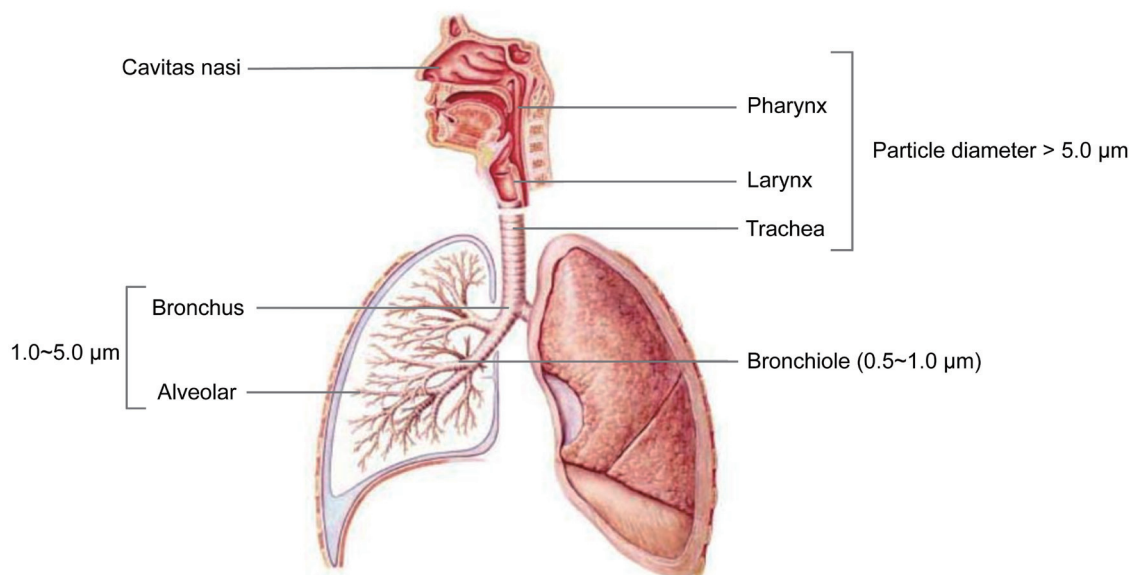
Fig. 1. A schematic diagram of particulate deposition in human respiratory system.

nied by hyperventilation. Asthma is also associated with airway remodeling due to smooth muscle cell proliferation. The symptoms of asthma often worsen over time and may lead to respiratory failure during an acute attack.[35] In recent years the prevalence of asthma has been increasing, and it is estimated that asthma may affect 400 million people by 2025.[36] Asthma may in fact be a collection of different phenotypes rather than a single disease, and can be clinically divided into four broad categories: refractory asthma, environmentally triggered allergic/non-allergic asthma, exercise/

aspirin-induced asthma and inflammatory asthma.[37] Each of these categories features airway inflammation as a common characteristic, which can be treated with glucocorticoids. Severe asthma is often accompanied by airway mucosal inflammation with neutrophil infiltration, resulting in a poor response to glucocorticoids. Therefore, developing a neutrophil-targeted drug delivery system has become a priority for the treatment of asthma.[38] T cells and eosinophils are also important targets for asthma treatment. In recent years, monoclonal antibodies and small molecule chemosynthetic

Table 1. The potential drugs targeting COPD and their mechanisms

Drug name	Method of preparation	Size	Ref
Liposomal dry powders of N-acetylcysteine (SD-NAC-Lip)	Reverse phase evaporation	100 nm	23
Budesonide and Colchicine liposomes	Thin layer film hydration method	100 nm	24
Chitosan or hyaluronan-coated liposomes of curcumin	Sonication and stirring	90~130 nm	25
Small Unilamellar Liposomes, Pluronic F127surface modified liposomes and PEG 2000PE-surface modified liposomes of beclomethasone dipropionate	Micelle-to-vesicle transition method	40~65 nm	26
Codelivery system using core-shell type lipid-polymer nanoparticles (LPNs)	Solvent displacement method	123 ± 31 nm	27
PEGylated dextran-coated superparamagnetic iron oxide nanoparticles	–	82.7~133.7 nm	28
Chitosan nanoparticles of budesonide	Ionotropic gelation technique	363~543 nm	29
Polymeric Nanoparticles of miRNA	Oil-in-water single emulsion solvent evaporation method	244.80 ± 4.4 nm	30
atRA formulated into solid lipid nanoparticles	Emulsification-ultrasonication method	177.3nm ± 29.23 nm	31
Mucoadhesive solid lipid microparticles	Ethanolic precipitation technique and ultraturrax homogenization	3.5~4.0 µm	32
Chitosan-genipin nanohydrogel	Reverse microemulsion method	30~100 nm	33
siRNA-loaded, lipidoid-modified PLGA hybrid nanoparticles	Double emulsion solvent evaporation method	200~260 nm	34

atRA, all-trans retinoic acid; COPD, chronic obstructive pulmonary disease; PLGA, poly lactic-co-glycolic acid.

drugs for controlling inflammatory mediators have been the subject of extensive research as targeted therapies for asthma.

Omalizumab is the first targeted agent for the treatment of asthma.[39] It is an anti-IgE monoclonal antibody which has typically been used for the treatment of severe allergic asthma. IgE binds to high-affinity receptors and releases a variety of pro-inflammatory mediators, including leukotrienes and interleukins (IL) such as IL-3, IL-4, and IL-5, which promote the aggregation of eosinophils and other inflammatory cells.[40] IL-5 plays a crucial role in the development of type 2 hyperreactivity-dominated asthma. Monoclonal antibodies against IL-5 that are utilized as treatments for asthma include mepolizumab, reslizumab and benralizumab. These can significantly reduce the number of eosinophils in the blood, relieve asthma exacerbations and improve lung function.[41] Dupilumab, which targets IL-4 and IL-13, is approved by the US Food and Drug Administration (FDA) for use in patients aged 12 years and over as an adjunct therapy for moderate to severe asthma with a corticosteroid-dependent refractory eosinophils (EOS) phenotype.[42] Thymic stromal lymphopoietin (TSLP), a member of the IL-2 cytokine family, acts on dendritic cells, mast cells, type 2 innate lymphocytes (ILC2) and eosinophils, promoting the differentiation of Th2 cells and the secretion of Th2 cytokines, such as IL-4, IL-5, and IL-13.[43] Prostaglandin D2 receptor 2 (CRTH2) is expressed on TH2 cells, eosinophils, basophils, epithelial cells and ILC2. CRTH2 expression in patients with severe asthma is higher than that in patients with mild to moderate disease or in healthy subjects without asthma, and is associated with the severity of asthma.[44] Chen *et al*.[45] have shown that CRTH2 may be involved in the occurrence and development of bronchial asthma by regulating the function of dendritic cells.[45] This suggests that CRTH2 could be a potential target for new therapies for bronchial asthma. Other therapeutic targets for bronchial asthma of interest include IL-17A, KIT, GATA-3, IL-33, IL-25, and significant progress has been made in developing drugs aimed at these targets and other inflammatory cytokines.[46]

Targeted therapies for cardiovascular diseases

Targeted therapies for pulmonary arterial hypertension (PAH)

PAH is defined as a pulmonary arterial pressure (M PAP) $\geq$25 mmHg when measuring right cardiac catheterization at rest. PAH is attributed to a variety of factors, particularly an increase in pulmonary vascular resistance that leads to pulmonary arterial remodeling. It is mainly characterized by pulmonary artery smooth muscle cell dysfunction, resulting in right ventricular overload, hypertrophy and dilation, eventually leading to right ventricular failure and even death.[47] PAH is associated with a poor prognosis due to the progressive development of these changes or the onset of other complications or syndromes.[48] In recent years, the study of PAH therapeutic targets and potential therapeutic strategies has brought new hope for the treatment of PAH. Most therapeutic drugs currently being tested are focused on reducing pulmonary arterial pressure and dilating the pulmonary artery. Three strategies that can regulate pulmonary vasoconstriction or vasodilation and are the target of new therapies for PAH include: nitric oxide-cyclic guanosine monophosphate (NO-cGMP), endothelin receptors and prostacyclin.[49] Nitric oxide (NO) is produced by endothelial cells and has a strong vasodilatory effect. Enhancement of NO production can effectively reduce pulmonary artery pressure. Phosphodiesterase 5 (PDE5) is an enzyme that degrades cyclic guanosine, and PDE5 inhibitors or other soluble guanosine cyclase (SGC) activators can enhance the nitric oxide-cyclic guanosine pathway, resulting in blood vessel dilation. The main drugs currently targeting this pathway are tadalafil, vardenafil, sildenafil, and riociguat. Prostacyclin can not only dilate blood vessels, but also inhibit platelet aggregation and have antithrombotic effects. Prostacyclin analogs commonly used in the clinic currently include epoprostenol, iloprost, and prostacyclin receptor agonists such as selexipag.[50] Endothelin-1 (ET-1) binds to its receptors A and B, causing vasoconstriction and vascular smooth muscle cell proliferation. Aberrant activation of the endothelin system can lead to continuous vasoconstriction and abnormal vascular smooth muscle cell proliferation. Hence, endothelin receptor antagonists are useful treatments for PAH. Commonly used endothelin receptor antagonists currently in clinical use include bosentan, macitentan, ambrisentan, and ligustrazine, among others.[51]

In recent years, additional therapeutic targets for PAH have been discovered and tested in animal models. These may lead to a future breakthrough in the treatment of PAH. Endosialin (CD248) is a transmembrane protein and is highly expressed by pericyte cells and fibroblasts. A number of research findings suggest that CD248 could be a useful new target for PAH therapy, including that abnormal levels of CD248 expression have been detected in PAH patients, the degree of CD248 activation in pulmonary smooth muscle cells correlates with the severity of PAH, and that deletion of the CD248 gene in rats can reduce pulmonary vascular remodeling in rat models of PAH.[52] The autonomic nervous system is also involved in the pathogenesis of PAH, suggesting that this neurohormonal system can be regulated to treat PAH.[53] Besides CD248, there are other potential therapeutic targets for PAH such as miRNAs and spermidine. MiRNAs are non-coding single-stranded RNAs of approximately 22 nucleotides in length. For example, inhibition of the miRNA miR-140-5p promotes pulmonary artery smooth muscle cell (PASMC) proliferation and migration *in vitro*. In a rat model of PAH, aerosol delivery of miR-140-5p mimics effectively prevents the development of PAH and attenuates the progression of established PAH.[54] Using targeted metabolomics, He *et al*. have found that spermidine can significantly promote the proliferation and migration of human PASMCs induced by platelet-derived growth factor-BB and aggravate arterial remodeling in animal models of PAH.[55] Therefore, inhibition of spermine synthesis may be a potential treatment for PAH. Studies have also shown that periosteum protein, hypoxia-inducible factor (HIF), protease-activated receptor 1, and silencing regulatory protein 1 may be therapeutic targets of PAH.[56–59]

Targeted treatment of coronary atherosclerotic heart disease

The primary pathogenesis of coronary atherosclerotic heart disease (CAHD) is characterized by atherosclerotic lesions in coronary arteries that cause stenosis or obstruction of the vascular lumen, resulting in myocardial ischemia, hypoxia, or necrosis and inducing heart disease.[60] The clinical classification of coronary heart disease can be divided into acute coronary syndromes or chronic myocardial ischemia syndromes.[61] The incidence and fatality rates of coronary heart disease around the world are increasing yearly, bringing with them substantial economic burdens. The development of coronary atherosclerosis is mainly driven by lipid deposition and macrophage infiltration in the arterial wall, leading to chronic inflammation. Therefore, inflammation is one of the most critical targets for treatment of coronary heart disease. However, at present, drug therapy for the treatment of CAHD is mainly limited to controlling risk factors and providing antithrombotic therapy, and there are currently no specific anti-inflammatory

Table 2. Studies on targeted delivery nanomedicine for coronary heart disease

Drug name	Method of preparation	Therapeutic effect	Ref
Polymer nanosystems composed of core-shell nanoparticles of polyethyleneglycol-based block copolymers	–	Drug were selectively released to the balloon-injured artery	73
A novel "nanopolypill"	Emulsion- diffusion-evaporation method	Has a potential of decreasing pill burden.	74
TPCD/TA nanoparticles	Polyphenol-assisted nanoprecipitation/self-assembly	Effectively protected cells from hypoxic-ischemic injury, by internalization into cardiomyocytes	75
Au nanospheres with VCAM-1-binding peptide	–	Inhibiting the formation of atherosclerotic plaques.	76
Rapamycin/Ac-bCD180-derived nanotherapy	Oil-in-water (o/w) emulsion solvent evaporation technique	Stabilized atherosclerotic plaques compared with free rapamycin, and sustain RAP release in a well-controlled manner both *in vitro* and *in vivo*	77

treatments for patients with coronary heart disease. Inflammatory factors involved in the pathogenesis of coronary atherosclerosis include: (1) high sensitivity c-reactive protein (hs-CRP); (2) IL-6, IL-8, IL-18, and other pro-inflammatory interleukins; (3) tumor necrosis factor-α (TNF-α); (4) plasminogen activator inhibitor-1 (PAI-1); and (5) transforming growth factor-β (TGF-β) and others.[62] Specific cell types involved in these inflammatory processes or in the release and response to these factors include monocytes, macrophages, lymphocytes, vascular endothelial cells, vascular smooth muscle cells, platelets, and others.[62] IL-1β mediates the expression of genes during the process of immune response and inflammation, promoting the adhesion of monocytes and leukocytes to vascular endothelial cells, and inducing the proliferation of vascular smooth muscle cells, the main targets of anti-inflammatory therapy.[63] Canakinumab is a monoclonal antibody against IL-1β which can inhibit IL-1-mediated inflammatory responses. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial has demonstrated that inflammation plays a crucial role in atherosclerotic disease.[64] In addition, IL-1β can activate downstream IL-6 receptor transduction pathways, resulting in endogenous platelet-derived growth factor (PDGF) production and smooth muscle cell proliferation.[65] The IL-6 inhibitor tocilizumab can block this inflammatory cascade and delay the progression of atherosclerosis.

Tozizumab can reduce IL-6 activity and significantly improve endothelial function in high-risk rheumatoid arthritis, even with elevated levels of total cholesterol and low-density lipoprotein.[66] Akitake reported a case of a patient with rheumatoid arthritis that was complicated by three-vessel coronary artery disease and severe heart failure.[67] The patient received tocilizumab for five years with no adverse events, suggesting that tocilizumab may be a useful therapeutic option for coronary heart disease and rheumatoid arthritis in the future.

In recent years, research has demonstrated that intestinal flora plays a crucial role in human health and that changes in intestinal flora are closely related to coronary heart disease. The diversity and composition of intestinal flora are different between patients with coronary heart disease and healthy controls, with a decrease in the proportion of *Bacteroides* and an increase in the proportion of Firmicutes bacteria in patients with coronary heart disease.[68] Intestinal flora influence host metabolic pathways through the production of metabolites, one of which is trimethylamine oxide (TMAO). TMAO accelerates atherosclerosis, suggesting that it may be a potential target for predicting and treating coronary heart disease.[69,70] Takuo et al.[71] have demonstrated that intestinal flora and their metabolites can be used as diagnostic markers for coronary artery disease. The potential relationship between intestinal flora and coronary heart disease has been widely studied, but its application in the diagnosis, treatment, and prevention of coronary heart disease still needs further experimental examination. In the future, the treatment of coronary heart disease by targeting intestinal flora could revolve around the following interventions: adjusting the composition of the diet, regulating the metabolic pathway of intestinal flora, supplementing the diet with probiotics, altering intestinal flora through the transplantation of fecal bacteria, and targeted modification of microorganisms.

Another area of intense research interest is developing targeted treatments for coronary heart disease using new drug delivery systems. Due to their unique size, physical properties and chemical composition, nano agents can flow in blood and tissues without becoming deposited in the endothelial wall, which could enable them to deliver targeted drugs throughout the body while prolonging the length of time those drugs are present in the circulation, which could result in reduced systemic non-targeted cytotoxicity. Nanoparticles prepared by Zang et al. promote the expression of vascular endothelial growth factor (VEGF), dilate coronary arteries, improve cardiac function and reduce the recurrence of angina in patients with coronary heart disease.[72] As the development of nanotechnology has progressed, there have been more and more studies into nano-drug targeted treatment of coronary heart disease in recent years (Table 2).[73–77]

The role of targeted therapies in neurological diseases

Targeted treatment of Alzheimer's disease

Alzheimer's disease (AD) is a progressive and aggravating degenerative disease of the central nervous system (CNS), with a high incidence in the elderly. The main symptoms include memory loss, disordered thinking, loss of speech, behavioral changes and difficulty eating,[78] all of which seriously affect the patients' daily work, life and social interactions. The pathogenesis of AD is still unclear, although various hypotheses have been pursued, such as the cholinergic hypothesis, the amyloid cascade hypothesis, the excitotoxicity hypothesis, the mitochondrial cascade hypothesis, and the tau hypothesis.[79] Currently, there are few medicines avail-

able for the prevention and treatment of AD in the clinic and only three FDA-approved drugs for the treatment of AD are available: cholinesterase inhibitors (CHEI), n-methyl-D-aspartate receptor antagonists (NMDA), and both drugs in combination.[80] The delivery of drugs across the blood-brain barrier (BBB) to the CNS is a significant obstacle for the treatment of Alzheimer's disease. In addition, the development of Alzheimer's-related drugs has been hindered by rapid removal from the circulation and a low bioavailability of candidate treatments.[79] As such, the unique size and physicochemical properties of nano-formulations may make them suitable alternatives for the treatment of AD, offering safer treatments than traditional delivery methods.[81] Nanoparticles can penetrate the BBB, carry drugs into the brain, and have the advantages of better biocompatibility, easier degradation, and lower toxicity.[82] Poly lactic-co-glycolic acid (PLGA) has become one of the most commonly used polymer particles in nanomaterials due to the fact that it readily biodegrades. Yadav *et al*. have prepared long circulating nanoparticles of etoposide using PLGA, MPEG and PLGA pluronic block copolymers.[83] Nanoparticles of these drugs with a particle size of 100 nm can evade metabolism by the liver and improve the aggregation of drugs in the CNS, without the need for surface modification of drug particles to achieve these ends.[83] Nanoemulsion is a dispersive system that produces nanoscale oil droplets with a size between 20 and 200 nm. These contain surfactants and are suitable for the delivery of insoluble drugs to the brain. Phenylethanoid glycoside in Cistanche deserticola is the primary pharmacochemical basis for preventing and treating AD, and the traditional way of administration makes it difficult to cross the BBB to play the therapeutic role. Therefore, Hu *et al*. have prepared nanoemulsions of phenylethanol glycosides.[84] Through nasal administration, the absorption of phenethyl alcohol glycosides is significantly improved, helping them to cross the BBB and reach their desired target site and improve bioavailability *in vivo*.[84] Another alternative approach is to use liposomes, which have a diameter of 50 nm to 5 µm and a double-layer structure similar to cell membranes. They are composed of phospholipid and cholesterol molecules, and their hydrophilic and hydrophobic parts can encapsulate water- and fat-soluble drugs, thus improving the stability and biocompatibility of drugs.[85] Borneol-modified curcumin cationic liposomes can significantly improve curcumin stability in brain tissue and prolong curcumin circulation time *in vivo*.[86] Other potential nano-targeted drug delivery systems for AD include nanogels, nanosuspensions, dendrimers and micelles, among others.[81] Although there have been substantial advancements in the use of nanomedicines in preclinical studies, data from *in vivo* and clinical studies are limited and the toxicity of these approaches, or side effects associated with them, are not fully understood. Therefore, further research is still needed to validate the potential therapeutic efficacy of nanocarriers for Alzheimer's disease.

Targeted treatment of Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD.[87] PD predominant affects elderly people and seriously reduces their quality of life. The pathogenesis of PD is still unclear. Pathologically, PD is characterized by a loss of dopaminergic neurons in the substantia nigra of the brain. Risk factors for the development and occurrence of PD include aging, exposure to environmental toxins and family genetics. The clinical symptoms of PD are resting tremor, bradykinesia or weakness of movement, a loss of orthodontic reflexes and joint stiffness.[88] Currently, the treatment of PD is mainly limited to dopamine-like drugs and anticholinergic agents that aim to improve the balance

of neurotransmitters in the brain. These therapeutic drugs can only delay the progression of the disease, but fail to fundamentally improve its prognosis.[89] Similar to AD, it is difficult to effectively deliver drugs for the treatment of PD due to the need for those drugs to penetrate the BBB. Interestingly, drug delivery through nasal mucosa can bypass the BBB, allowing direct delivery of drugs into the brain and avoiding hepatic first pass metabolism.[90] The neuroactive peptide DNSP-11 is a synthetic 11-position aminated neuroactive peptide. After repeated intranasal administration, DNSP-11 can be detected in the striatum and substantia nigra of the brain within 30 minutes, suggesting that DNSP-11 preferably targets the dopaminergic system.[91] Similarly, intranasal administration of dopamine liposomes can promote the entry of dopamine into the CNS and have a significant effect on symptoms of PD.[92] Lu *et al*.[93] have reported that cavitation-mediated icariin nanoliposomes with ideal micromorphology and particle size distribution are transferred into the brain through the olfactory area of the nasal cavity. This improves the efficiency of icariin delivery into the brain, thereby enhancing the therapeutic efficacy of icariin for the treatment of PD. The therapeutic effects of this model of delivery have been confirmed in the rat model of PD, with significantly improved motor function and a repair action on the neuronal lesion.[94] In addition to these approaches, nanotechnology has been widely used to develop drugs for treatment of PD. For example, some new nanomaterial drug delivery systems have been shown to offer neuroprotective effects, including preventing oxidative stress and interfering with protein aggregation in animal models of PD.[95] These systems include the use of fullerenes (C60), magnetic nanoparticles (MNPs) and cerium oxide.[95] Thus, in the near future it is possible that the use of nanomaterials will enable improvements in the delivery of drugs for the treatment of PD, enhancing their therapeutic efficacy.

The role of targeted therapies in immune system diseases

Targeted treatment of systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex chronic autoimmune disease that affects multiple organs, including the skin, heart, kidney, joints, and brain. The clinical symptoms of SLE are complex and varied, and the patients are mainly women of childbearing age. The pathogenesis of SLE involves various factors, such as genetics, exposure to the environment and hormonal factors, but the specific mechanisms involved in the development and progression of SLE have not been fully clarified.[96] At present, the treatment of SLE mainly consists of glucocorticoids, antimalarials, and immunosuppressants, which can reduce organ injury and mortality. However, these drugs have a wide range of immunosuppressive effects and are associated with varying degrees of adverse reactions. In addition, these therapies do not improve the prognosis of critically ill or refractory patients.[97,98] Therefore, more effective immune-targeted drugs are urgently needed. In recent years, biologic agents and small molecule-targeted drugs have emerged which can inhibit B and T lymphocyte activation, block the interaction of different types of immune cells, and reduce cytokine production.[99] In 2011, the FDA and European Medicines Agency (EMA) approved belimumab for the treatment of SLE, the first drug to be specifically designed for the treatment of this condition.[100] Belimumab is a fully-humanized monoclonal antibody against B cell activator (BAFF) that binds soluble BAFF and inhibits it from binding to the BAFF receptor.[101] This leads to autoimmune B cell apoptosis, thereby reducing serum autoantibodies.[101] Other recently approved

treatment options include blisibimod and talabumab. Unlike belimumab, blisibimod binds to soluble, insoluble, and membranous BAFF, while talabumab binds to soluble and membranous BAFF.[99] Other drugs targeting B lymphocytes include atacicept, telitacicept, rituximab, and obinutuzumab. Abatacept is a selective T cell costimulatory modulator that inhibits T cell activation by binding to CD80 and CD86 on antigen-presenting cells. However, a phase II clinical trial for testing the therapeutic efficacy of abatacept failed to meet the primary/secondary endpoints. Although many such targeted treatments have not had their desired effects in initial clinical trials, there are increasing numbers of targeted therapies are undergoing clinical tests and additional targeted drugs may become available for the treatment of SLE in the future.

Targeted treatment of rheumatoid arthritis

Rheumatoid arthritis (RA) is a common systemic immune disease with an incidence rate of 0.5~1.0%, particularly in women of the age of thirty to fifty years. RA is characterized by chronic synovitis with inflammatory infiltrates, which produces a variety of clinical symptoms. The main clinical manifestations of RA are symmetric joint swelling, morning stiffness, and a continuous decline in activity levels. Continual progression of RA may cause joint deformity or even disability.[102] It is generally believed that RA involves genetic and environmental factors which activate immune cells that attack the synovial membrane, leading to inflammation and joint injury.[103] At present, the preferred drugs for the treatment of RA mainly include non-steroidal anti-inflammatory drugs, glucocorticoids, anti-rheumatism drugs, and biological agents. However, these drugs usually require high doses, frequent administration, and have severe adverse reactions, limiting their clinical application.[104] These barriers have encouraged the development of nano-targeted drug delivery systems for the treatment of RA. A recent study in arthritic mice has shown that nanoparticles can deliver these drugs in such a way that they selectively accumulate in inflammatory synovial tissues with high vascular permeability.[105] Researchers have also designed and developed four nano agents which are targeted either passively, actively, in response to the cellular microenvironment responsive, or via bionic targeting.[104] For example, Yang *et al*. have designed a passive targeting agent—consisting of folic acid-modified silver nanoparticles (FA-AGNPs), which accumulate in inflamed joints by binding to folic acid receptors that are highly expressed on M1 macrophages. This results in greater M2 maturation and inhibits inflammation in animals with RA without long-term toxicity. Hence, using techniques such as these to rebalance pro-inflammatory M1 and anti-inflammatory M2 macrophages can alleviate synovial inflammation. Furthermore, metabolites of this drug are cleared through feces and do not accumulate in other organs.[106] Oxidative stress in the synovium of the RA joint can promote the generation of reactive oxygen species (ROS) and aggravate synovitis. The manganese ferrite and ceria nanoparticle-anchored Mesoporous silica nanoparticles (MFC-MSNs) can synergistically remove ROS and produce O_2 to rebalance M1 and M2 macrophages for RA treatment.

Meanwhile, methotrexate-based MFC-MSNs enable continuous release of the anti-rheumatism drug to enhance its therapeutic effect.[107] Bionic targeting of nano agents utilizes endogenous proteins, viruses, and cells gathering to the inflammatory site to inhibit inflammation.[104] As an example, An *et al*.[108] have developed a cell-carrier nanoparticle as an anti-inflammatory platform to inhibit the inflammatory response of LPS-induced RAW264.7 cells. In an inflammatory animal model, administration of these nanoparticles resulted in accumulation of inflammatory lesions,

inhibiting signaling through Notch1 and NF-κB pathways, reducing clinical symptoms, inflammatory infiltration, bone erosion, and serum inflammatory factors.

Targeted treatment of psoriasis

Psoriasis is a chronic inflammatory skin disease with a global prevalence of about 2%. Its main symptoms are well-defined plaques on the trunk, limbs, and scalp that are accompanied by itching, burning, and pain. Continuous inflammation leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation, which triggers psoriasis.[109] Psoriasis can be associated with various complications, such as arthritis, coronary artery disease, hyperlipidemia, obesity, and depression.[110] In recent years, molecular targeted therapies for the treatment of psoriasis have been developed that can be divided into three main categories: 1) targeted cytokines, 2) receptors involved in the pathogenesis of psoriasis, and 3) small molecule inhibitors targeting intracellular signaling molecules.[111] Given that Th17 cells and the IL-23/Th17 signaling axis is crucial for the pathogenesis of psoriasis, targeted agents currently being developed for the treatment of psoriasis have mainly been focused on Th17-related cytokines, such as TNF, IL-23, and IL-17.[112] IL-23 inhibitors are safe and effective in treating psoriasis and psoriatic arthritis without obvious adverse effects. Since 2004, the U.S. FDA has approved 11 biologically-targeted agents to treat plaque psoriasis, including etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, certolizumab, and risankizumab.[113] In the future, biologically-targeted drugs may be an effective alternative to treat psoriasis.

Targeted therapies for other Chronic Diseases

Targeted treatment of chronic myelogenous leukemia

Chronic myelogenous leukemia (CML) is a malignant disease originating from bone marrow hematopoietic stem cells with chromosomal abnormalities. It results from the ABL proto-oncogene on chromosome 9 joining the BCR gene on chromosome 22 to form the BCR-ABL fusion gene, resulting in the expression of a BCR-ABL fusion protein with high tyrosine kinase activity.[114] Prior to 2000, the treatment of CML relied on non-specific drugs, such as busulfan, hydroxyurea, and interferon-α (IFN-α).[115] However, more recently, the development of tyrosine kinase inhibitors (TKIs) has changed the history of CML therapy. TKIs can effectively inhibit the phosphorylation of tyrosine residues and inactivate this enzyme, inhibiting the excessive proliferation of white blood cells and achieving targeted treatment of CML. One such treatment, imatinib, has a potent effect on the early chronic stage of CML in children, with mild adverse reactions and a good tolerance and safety profile.[116] However, many patients with CML develop resistance to imatinib. Subsequently, drugs based on other targets have been developed, including tipifarnib and lonafarnib. These are two selective farnesyltransferase inhibitors with potential anti-leukemia activity in patients with CML. Studies have demonstrated the safety of lonafarnib combined with imatinib in the treatment of chronic myelogenous leukemia. Another treatment approach is the use of histone deacetylase inhibitors, which can reduce levels of BCR-ABL protein expression and induce apoptosis of imatinib mesylate-resistant BCR-ABL positive cells, potentially forming useful treatments for CML.[117] Another approach is the use of aurora kinase inhibitors (AURK-IS), which inhibit the activity of the

AURK family of serine kinases that regulate cell mitosis and are potential therapeutic targets for anticancer drug development.[118]

Future directions

Targeted therapies for many chronic diseases are currently being tested in clinical trials, with many displaying beneficial effects. However, developing appropriate delivery systems for targeted drugs has proven to be difficult because the pathogenesis of many chronic diseases remains unclear. Several questions need to be addressed urgently. At present, the pathogenesis of many chronic diseases is not entirely understood, but uncovering the molecular mechanisms underlying the pathogenesis of individual chronic diseases will help to identify disease-related targets for developing targeted drugs. The ability to develop appropriate delivery systems for targeted drugs in the future will undoubtedly enhance the treatment of various chronic diseases.

Conclusions

Chronic diseases have seriously affected human life and health and their incidence is increasing, including in younger people.[119] Given the chronic nature of these conditions, patients with chronic diseases depend on continual drug treatment, which is associated with an ongoing risk of adverse effects. Developing appropriate delivery systems for targeted drugs can promote the accumulation of targeted drugs in pathogenic lesions, reducing systemic adverse effects and improving patient outcomes. In addition, targeted delivery systems can help deliver drugs to specific immune-privileged tissues by passing through the BBB and other similar barriers. This technology provides many promising avenues for the future treatment of chronic diseases.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Manuscript writing (JYQ, CJP), literature search (ZFJ, DYJ), review and editing (CJP, TCW), supervision (TCW, CCQ). All authors have read and agreed to submit the manuscript.

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