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Review article

Nanotherapeutics relieve rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease associated with persistent multiarticular synovitis, cartilage destruction, and even loss of joint function. Although remarkable progress has been made in the clinical treatment of RA, long-term administration of anti-rheumatic drugs still suffers quite a few drawbacks, including high dose and high frequency of drug use, as well as dysfunction of the heart, liver, kidney, and so forth. For the above problems, nanotherapeutic agents are developed to avert non-specific binding and upregulate the efficacy by improving the accumulation of drugs in lesion tissues. In this article, some of the most frequently used anti-RA agents were summarized, and the recent treatment of RA with passive or active targeting nanotheranostics was systematically illustrated. In addition, the prospect of nanovehicles in clinical therapy of RA was discussed and predicted.

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1.. Introduction

1.1. Overview of rheumatoid arthritis (RA)

RA, a chronic inflammatory pathology, is showing a dramatic increase in morbidity [1–3]. Nearly 1% of the populations throughout the developed countries are affected by RA, characterized by sustained synovitis, progressive cartilage destruction, and osteoporosis, and some patients may also suffer from complications in other organs [2,4]. Although its pathogenesis is not completely understand, RA is considered as a complicated disease associated with various causes, including infection, disorder of sexual hormones, genetic sensitivity, and environment factors. Activation and recruitment of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and transforming growth factor-β (TGF-β), were also involved in the pathological process of RA by

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Table 1
Current therapeutic agents for RA.

Classification	Instance	Mechanism of action	Side effects
DMARDs	MTX, HCQ, SSZ, CLO	Immunosuppression, inhibition of genetic materials synthesis	Myelosuppression, gastrointestinal reaction, dysfunction of liver and kidney, *etc.*
GCs	DEX, HC, PN, BUD	Impact on levels of inflammatory cytokines, immunosuppression	Hyperadrenocorticism, infection, hypertension and atherosclerosis, osteoporosis and osteonecrosis, *etc.*
NSAIDs	ASP, CEL, IPF, IDT	Inhibition of COXs	Gastrointestinal reaction, dysfunction of kidney, *etc.*
Biological agents	ETA, INF, ADA, GOL	Antagonism of TNF-α	Infection, tuberculosis
	AKR	Antagonism of IL-1 receptor	Infection
	TCZ	Antagonism of IL-6 receptor	Infection, gastrointestinal perforation
	ABA	Downregulation of T cells activation	Infection, malignancy
	RIT	B-cell depletion	Infection, hypertension

Abbreviations in the table only: ASP, aspirin; BUD, budesonide; CEL, celecoxib; IDT, indometacin; IPF, ibuprofen.

disrupting one's immune balance. More specifically, TNF-α and IL-1β stimulate the release of tissue degrading matrix metalloproteases (MMPs) from synovial cells, and TNF-α exacerbates the development of osteoclasts. In addition, the infiltration of macrophages, B cells, T cells, synoviocytes, and fibrocytes in inflamed joints triggers the proliferation of synovial tissues and osteoclasts, and invasion of synovium, and ultimately leads to the erosion of cartilages and bones [5].

1.2. Current treatment strategies for RA

Studies over the years have largely improved our understanding about RA and constantly helped optimize the treatment methods toward this agnogenic disease. Currently, the therapeutic agents for RA are basically divided into four categories, namely disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs), and biological agents (Tables 1 and 2).

Table 2
Features of nanocarriers in references.

Classification	Drug	Nanocarrier	Mean size (nm)	Delivery strategy	Reference
DMARDs	MTX	Liposome	100	EPR	[24]
			210–253		[27]
		HA		CD44/macrophages	[95,128]
		PAMAM dendrimer	5.9–6.1	FR	[80]
		PLGA/Au NP	100–115	$\alpha_v\beta_3$-Integrin	[93]
GCs	PNL	Liposome	450–500	EPR	[31]
			90–100		[32]
			108.5		[33]
	MPHS, BMHS	NSSL	~80		[34]
	PNL	Liposome	90–110		[35]
	DEX		100		[36]
	BM	PLGA NP	100–200		[38]
	MP	NSSL	~80		[39]
		CDP NP	27		[40]
	DEX	HPMA PM	50–100		[41]
		Liposome	96		[42]
		PM	53		
		HPMA copolymer-slow	5.0		
		HPMA copolymer-fast	5.9		
	DEX	Liposome	283–310		[43]
	PNL, BUD		90–110		[44]
	DEX, PNL, BUD		90–100		[44]
NSAIDs	IND	PM	65–412.4	EPR	[46–48]
		Nanocapsule	240		[49]
		PEI-CD NP	205		[51]
		MC-CD solid NP	76–83		[52]
	DCFS	Fe-EC NP	350	EPR/magnetic field	[53]
Biological agents	ETA	SPL nanocomplex	250	EPR	[54]
	TCZ	HA-Au NP	64.83		[56]
Others	Gal-1	Au-NP	15	EPR	[57]
	SOD	Liposome	100–200		[60]
			90–110		[61]
	TRAIL	HA nanocomplex	182		[66]
			100		[67]
	sCT	HA-chitosan nanocomplex	163–193		[68]
	PSs	HA-chitosan nanogel	40–140		[129]
	None	DS-PCL	200.6	SRs	[71]
	FUM	PFC NP	~250	$\alpha_v\beta_3$-Integrin	[115]
		PFOB NP	~250		[116]
			230–260		[117]
		PFC NP	230		[118]
	CPT	SSM	13	VIP	[104]

Abbreviations in the table only: BMHS, betamethasone hemisuccinate; DCFS, diclofenac sodium; EC, ethylcellulose; HPMA, *N*-(2-hydroxypropyl) methacrylamide; MC, methylcellulose; MPHS, methylprednisolone hemisuccinate; PNL, prednisolone.