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REVIEW ARTICLE

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The role of exosome in autoimmune connective tissue disease

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ABSTRACT

Exosomes have generated significant interest in the last few decades owing to their important roles in a diverse range of biological pathways. They are nano-sized lipid bilayer membrane vesicles of endosomal origin, and are produced by a vast number of cell types. They are released into the extracellular environment and are found in most biological fluids. Exosomes can contain proteins, lipids and nucleic acids. The cargo of exosomes allows them to play roles in cell communication, antigen presentation, as biomarkers and in immune regulation. Substantial efforts have been made to understand their biology and potential clinical use in various diseases, including autoimmune connective tissue diseases (ACTD). In this review, we highlight the known functions of exosomes and detail recent advances made in the elucidation of the roles of exosomes in ACTDs with an emphasis on their potential use as a biomarker for disease diagnosis and as a therapeutic target.

KEY MESSAGES

- Exosome with the function of cell communication, antigen presentation, biomarkers, immune responses and immune regulation have become a hot area and have played an important role in several areas of science and technology especially in medicine.
- Exosomes play important roles in numerous biological processes as well as in the pathogenesis of ACTDs.
- Exosome comes into being the non-invasive procedure as potential biomarkers and excellent treatment means in ACTDs.

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1. Introduction

Exosomes were originally discovered in various normal and neoplastic cell lines in 1981 [1]. They are endosomal-derived nanovesicles that are defined by several characteristics, including their size (30–100 nm in diameter), density (1.13–1.19 g/ml), and morphology (they resemble flattened spheres or saucers under a transmission electron microscope). In addition, they are enriched in protein markers (including TSG101, ALIX, CD9, CD63, CD81, CD82, CD86, Hsp70 and Hsp90) that are unique to their cell of origin [2]. However, they were later found to be produced and secreted by a considerable number of other cell types, including dendritic cells (DCs), B cells, T cells, mast cells, tumour cells, neurons, astrocytes, haemocytes and epithelial cells. Once released into the extracellular environment, exosomes can be found in many biological fluids including plasma, urine, saliva, malignant effusions, synovial fluid, breast milk, bronchoalveolar lavage fluid and epididymal fluid.

Although they were initially thought to act as vehicles for the removal of cellular waste, exosomes were later identified to have an antigen-presenting function. More recently, researchers have revealed that proteins and nucleic acids contained within exosome phospholipid bilayers retain their functionality following the endocytosis of exosomal vesicles and the direct transfer of their contents into a recipient cell. In fact, exosomes have been shown to mediate intercellular communication by acting as signal-transmitting shuttles ("communicasomes") between cells [3]. In 2007, exosomes were found to carry specific messenger RNAs (mRNAs) as cargo, which are selectively packaged into vesicles by the donor cell [4]. A year later, a study by Altintas and colleagues revealed that exosomes are also able to carry and deliver double-stranded DNA [5]. Since then, independent studies have identified that nearly all cell types secrete exosomes: to date, 4563 proteins, 1639 mRNAs and 764 micro RNAs (miRNAs) have been identified as

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exosomal cargo from different tissues and species. Furthermore, exosomal contents vary between different originating cell types and the physiological and pathological conditions that prevail while exosomes are being packaged and secreted.

In 2013, three scientists, James E. Rothman, Randy W. Schekman and Thomas C. Südhof, were jointly awarded the Nobel Prize for their independent work elucidating the molecular mechanisms that regulate the transport of exosomes to their intended target cell(s) at the required time. In combination, their discoveries included: membrane protein monoubiquitination controls exosomal vesicle coat size and function; a series of genes is required for vesicle trafficking [6]; elucidation of the mechanism underlying how exosomes fuse with their target cell membranes, allowing the transfer of their "cargo" into the target cell cytosol [7] and how cellular signalling controls the transport of exosomes to a precise cellular location [8].

Exosomal biogenesis starts within the endosomal system. Exosomes originate from early endosomes, which mature into multivesicular bodies (MVB) through invagination of the endosomal membrane to generate intraluminal vesicles (ILV). This is followed by fusion with the plasma membrane and release of the ILV into the extracellular space as an exosome. Exosomes contain many different collections of proteins, the composition of which can be distinct from the cells or tissues of origin owing to selective protein cargo loading [9]. For example, exosomes derived from antigen-presenting cells can contain immunostimulatory proteins, and tumour-derived exosomes can contain immunosuppressive proteins [10]. Therefore, several studies have investigated a therapeutic role for exosomes in the modulation of the immune system. Exosomes containing anti-inflammatory molecules could be used as immunomodulatory agents in the treatment of inflammatory, hypersensitivity and autoimmune disorders [11]. Therefore, we believe there is enormous future potential for the use of exosomes in the diagnosis and treatment of various diseases, production of immunosuppressive drugs and in many other applications.

Autoimmune connective tissue diseases (ACTDs) are chronic and complex inflammatory diseases that can affect multiple organs and tissues, and typically have a broad spectrum of clinical presentations. Examples of ACTDs include systemic or discoid lupus erythematosus, systemic sclerosis or scleroderma, dermatomyositis, and other conditions that cause chronic inflammation. Many studies have revealed that the dysregulation of exosomal function leads to the development of ACTDs. In this review, we will analyze the potential of exosomes in the diagnosis and treatment of ACTDs.

2. The biological functions of exosomes in ACTDs

2.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that is characterized by its clinical heterogeneity. It was first described as a typical skin lesion, and was later discovered to be a systemic disease caused by aberrant autoimmune responses, almost 100 years after its initial discovery [12]. The reported prevalence of SLE in the world is 20–150 cases per 100,000 people, and a male-to-female ratio of ∼1:9 [13]. Although SLE is currently incurable, patient survival rates and longevity have increased in recent decades owing to improvements in diagnoses and therapies. However, the long-term disease management and monitoring that is required for SLE patients does incur significant medical costs [14]. Lupus nephritis (LN) is a major cause of the morbidity and mortality of patients with systemic SLE. Indeed, 10–30% of LN patients have been reported to develop end-stage renal disease [15].

It is possible that exosomes may serve as novel biomarkers of SLE disease activity. Exosomes acting as potential intercellular messengers provoke a gradual inflammatory response in SLE patients, as the circulatory system enables exosomes to reach and activate immune cells at remote sites. Circulating exosomes purified from the serum of SLE patients were immunologically active and their relative levels correlated with disease activity in SLE patients [16]. Furthermore, another study discovered that the urine of SLE patients contained exosomal miRNAs. Interestingly, higher levels of exosomal miRNAs were detected in the urine of patients with active LN. These results indicate that inflamed organs or tissues are a potentially valuable source of exosomes. The levels of miR-29c in urinary exosomes are significantly down-regulated in LN patients with high degrees of renal chronicity, suggesting that it could be used as a non-invasive marker for the early progression of renal fibrosis [17]. Furthermore, another study observed an increase in miR-26a levels in urinary exosomes from LN patients compared with healthy controls that correlated positively with urinary protein levels, suggesting its potential use as a predictive biomarker of podocyte injury [18]. Exosomal miR-146a is also involved in renal inflammation and fibrosis [19]. LN patients have also

been observed to have high levels of glomerular miR-146a [20]. Together, these findings support a possible role for these miRNAs in SLE and LN pathogenesis: the levels and composition of circulating exosomes in SLE or LN patients could be associated with SLE and/or LN disease activity.

Circulating exosomes from SLE patients were observed to be immunologically active and were able to induce the production of inflammatory cytokines from healthy peripheral blood mononuclear cells. In addition, interferon-α (IFN-α) and tumour necrosis factor-α (TNF-α) production induced by SLE exosomes was significantly higher compared with an equivalent number of healthy exosomes [16]. These data suggest the possibility that the compositions and biological activities of exosomes are disease-specific. Indeed, microparticles from SLE patients have higher levels of immunoglobulins and complement factors [21]. These findings highlight the potential of using urinary exosomes as a non-invasive approach for diagnosing and monitoring SLE patients [22].

Furthermore, exosomes are promising candidates as nanocarriers for the accurate delivery of selected nucleic acids (miRNA, siRNA and mRNA), proteins, and therapeutic agents to their specific target cells [23]. Significantly, exosomes are highly stable in blood and have been shown to efficiently cross biological barriers such as the blood-brain barrier [24].

In combination, these findings strongly suggest a potential future role for exosomes in the diagnosis and treatment of SLE and LN.

2.2. Dermatomyositis

Dermatomyositis (DM) is a chronic inflammatory disease with symptoms including a distinctive skin rash and muscle weakness. In addition, up to 25% of DM patients will go on to develop an associated malignancy. Therefore, both the early diagnosis of DM and cancer screening are crucial for a favourable patient outcome.

Myositis-specific autoantibodies (e.g. anti-Jo-1 and anti-Mi-2) or myositis-associated autoantibodies (e.g. anti-PM/Scl) can often be found in exosomes isolated from the sera of patients with polymyositis (PM), a similar muscle inflammatory disease and DM. The presence of each of these autoantibodies appears to be associated with different disease manifestations and could be significant in disease classification and enabling early patient diagnoses. Recent studies have provided new information about several of these exosomal autoantibodies. Among the more important developments were the identification of a group of autoantibodies directed against aminoacyl transfer RNA (tRNA) synthetases, including histidyl tRNA synthetase (anti-Jo-1) [25]; the detection of anti-Jo-1 antibodies in over one-third of patients with confirmed myelitis; and the evaluation of distinctive histopathological features of anti-Jo-1 antibody-positive patients. In addition, new information regarding the cellular roles of the autoantibodies' antigens was discovered. For example, the Mi-2 antigen was discovered to be a helicase involved in chromosome-mediated regulation of transcription as part of a nucleosome remodelling deacetylase multi-protein complex [26]. Interestingly, polymyositis/scleroderma (PM/Scl) antibodies are directed against an exosome complex that is composed of nine proteins and several associated proteins that play a role in RNA processing and degradation [27]. Several studies have investigated the prevalence of anti-PM/Scl antibodies in ACTD patients: anti-PM/Scl antibodies are usually found only in patients with PM, DM or systemic sclerosis (SSc), an autoimmune disease characterized by fibrosis and vasculopathy. The highest incidence of anti-PM/Scl antibodies was observed in overlap syndromes of SSc with either PM or DM [28]. For many years, anti-PM/Scl reactivity could only be detected using indirect immunofluorescence and immunodiffusion techniques. However, in 1992, several components of the autoantigen complex were identified and characterized, including PM/Scl-75, PM/Scl-100 and a synthetic peptide (PM1-Alpha). This led to the development of reliable and sensitive assays based on recombinant proteins and peptides, which have allowed the development of a new generation of anti-PM/Scl tests with higher sensitivity and specificity. These novel assays, enzyme-linked immunosorbent assay (ELISA), line immunoassays (LIA) and addressable laser bead immunoassay (ALBIA), led to the introduction of modern, automated and multi-parametric assays for specific anti-PM/Scl screening [29].

DM patients with exceptional antinuclear antibody titres and PM/Scl specificity have been reported; these are rare serological cases with an acute monophasic course. However, the evidence does suggest that autoantibodies can be used as serological markers for accurate diagnoses of myositis-associated conditions and as a monitor of disease behaviour [30]. To date, little is known about the involvement of exosomes in DM and related diseases. However, as the exosome complex is targeted by autoantibodies, we can speculate that exosomes are involved in regulating immune responses.

2.3. Scleroderma

Scleroderma is a chronic, systemic autoimmune disorder, which is characterized by excessive fibrosis caused by the abnormal growth of connective tissue supporting the skin and internal organs. Patients can exhibit vascular abnormalities as well as skin inflammation. The skin fibrosis is thought to be a result of excessive production of extracellular matrix proteins by dysfunctional dermal fibroblasts [31]. Two categories of scleroderma are known: systemic sclerosis (SSc), a chronic connective tissue disease characterized by inflammation, cutaneous sclerosis and visceral organ fibrosis, and localized scleroderma or morphea, which typically causes skin thickening and only occasionally affects the underlying muscle and tissue. Interestingly, increased expression of the exosomal markers, CD63, CD9 and CD81 has been observed in SSc dermal fibroblasts compared with normal fibroblasts, suggesting that increased levels of exosomes were present. The exosomes isolated from cultured SSc fibroblasts could stimulate type I collagen expression in normal fibroblasts. In addition, analysis of SSc fibroblast-derived exosomes revealed the dysregulation of collagen-related miRNA levels. Furthermore, serum exosome levels were significantly decreased in SSc patients compared with healthy control patients. Lower serum exosome levels positively correlated with the developments of vascular involvements such as skin ulcers or pitting scars. This could be the result of a disturbed transfer of exosomes from skin tissue to the bloodstream, with a wound healing delay caused by the additional down-regulation of collagen expression [32]. Skin ulcers are a frequent complication in SSc, which severely affects patients' quality of life. Recently, new therapeutic strategies for skin ulcers such as topical negative pressure therapy and platelet-rich plasma have been developed. In addition, serum-derived exosomes have been demonstrated to aid the healing of skin ulcers. This provides a further example of exosomal involvement in disease pathogenesis and their therapeutic potential.

2.4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common, systemic autoimmune disease that causes synovial hypertrophy and chronic joint inflammation. It can also cause multiple extra-articular manifestations that are associated with increased morbidity and mortality. Therefore, serological and proteomic biomarkers are required to be identified to allow an effective early RA diagnosis and subsequent monitoring of the disease [33]. In particular, exosomes have emerged as promising rheumatic disease biomarkers [34]; in particular, exosomes can carry disease-specific cargo, which can include metabolites, specific proteins, mRNA, miRNA and other non-coding RNAs. In addition, specific membrane proteins can enable exosome identity and selection [34].

Recently, research has focussed on long noncoding RNAs (lncRNAs) that are selectively sorted into exosomes. LncRNAs can regulate gene expression at multiple levels by interacting with DNA, RNA or protein and have roles in immune cell development, activation and function. Furthermore, lncRNAs are dysregulated in various diseases, including RA [35].

One of the first lncRNAs reported to regulate gene expression was HOX transcript antisense RNA (HOTAIR), which has a reverse transcriptional function. Studies by Wang et al. showed that the presence of serum exosomal HOTAIR was significantly correlated with clinical parameters of laryngeal squamous cell carcinoma (LSCC), suggesting its potential as a valuable biomarker for both the clinical diagnosis and monitoring of LSCC [36]. In addition, another study observed high expression levels of HOTAIR in blood mononuclear cells and serum exosomes from RA patients, resulting in the migration of activated macrophages. In contrast, significantly lower levels of HOTAIR were detected in differentiated osteoclasts and rheumatoid synoviocytes. Overexpression of HOTAIR in cultured osteoclasts resulted in lowered levels of the matrix metalloproteinases (MMP) MMP-2 and MMP-13. This indicates a role for HOTAIR in the regulation of the extracellular matrix and suggests that exosome-derived HOTAIR could be a valuable potential biomarker for RA diagnosis [37]. However, further studies are needed to fully understand the mechanisms of HOTAIR-mediated regulation of RA.

There is also immense research interest in synovial exosomes and their association with rheumatoid arthritis. Citrullinated proteins, known RA autoantigens, have been detected in exosomes isolated from the synovial fluid of RA patients. Citrullination is a post-translational modification process that converts arginine to citrulline. Proteins such as fibrinogen, fibrin and vimentin can be citrullinated during tissue inflammation. Anti-citrullinated protein antibodies (ACPA) can form immune complexes with citrullinated proteins and boost the inflammatory process. Therefore, exosomes could possibly play an important role in the distribution of auto-antigens and enhance immunogenicity. However, further studies are required to identify why citrullinated proteins are specifically recognized as autoantigens in RA [38].

Biological therapies using inhibitors and antibodies to target inflammatory factors are effective in alleviating RA symptoms but are unable to reverse disease progression. While the therapeutic potential of novel gene therapy approaches for the treatment of RA in many animal models appears promising, it is still unclear whether they are safe and effective for human patients. However, recent research has revealed that immunosuppressive dendritic cell (DC)-derived exosomes, as well as blood plasma- and serum-derived exosomes elicited potent therapeutic effects in animal models of inflammatory and autoimmune diseases, including RA [39]. For example, immunosuppressive exosomes derived from transforming growth factor-β (TGF-β1) gene-modified DCs were able to attenuate murine Th17-mediated inflammatory disease via the induction of regulatory T cells [40]. In addition, exosomes produced by primary murine bone marrow-derived DCs expressing the immunosuppressive ligand FasL were able to suppress inflammation and the progression of established collagen-induced arthritis (CIA) in a murine model [41]. Furthermore, exosomes derived from immature DCs treated with the recombinant immunomodulatory cytokines IL-10 and IL-4 also significantly reduced inflammation and the onset of murine collagen-induced arthritis. As purified DC-derived exosomes are very stable vesicles, it is possible that exosomes could have a future clinical application as vectors to treat autoimmune diseases including RA [42]. Compared with traditional gene and cell therapies, an exosome-based method could provide a safe and effectual approach to treat inflammatory arthritis diseases [39]. In addition to exosomes derived from immunosuppressive DCs, other sources of suppressive exosomes may also have therapeutic potential. Indeed, many types of tissue- or body fluid-derived exosomes have immunoregulatory or tolerogenic activities. For example, exosomes derived from autologous conditioned plasma or conditioned serum have been found to reduce arthritic inflammation [43]. More research is required to ascertain if these endosome sources can be utilized for the treatment of autoimmune diseases.

2.5. Sjögren syndrome

Sjögren syndrome (SS) is a chronic autoimmune disorder of unknown cause. It triggers lymphocytic infiltration in lacrimal and salivary glands, which severely affects the body's moisture-producing glands.

Table 1. Literature about ACTD and exosomes.

Disease	Articles	Exosome cargo	Derivation	Marker
SLE	Salvi et al. 2018 [22]	microRNAs	Plasm	IFN-α
	Lee et al. 2016 [16]	IFN-α, TNF-α, IL-1β, and IL-6	Serum	IFN-α, TNF-α, IL-1β, and IL-6
		microRNAs	Urinary	miR302d, miR-335, miR-200c and miR-146a
		Osteoprotegerin (OPG)		miR-29b
		miR-29c	Urinary	miR-29c
			Urinary, kidney	miR-21
DM	Targoff 2000 [26]	Anti-Jo-1, Mi-2 antigen	Serum	
SSc		PM/Scl antibodies		
	Nakamura et al. 2016 [32]	Collagen-related microRNA	Serum, dermal fibroblasts	CD63, CD9, and CD81
RA		Exosomal amyloid A, lymphatic vessel endothelial hyaluronic acid receptor-1 (LYVE-1) proteins	Serum	
			Mesenchymal stem cells (MSCs)	
			Human synovial sarcoma cell line	IL-1β
	Song et al. 2015 [37]	lncRNAs	Serum	Hot air, MMP-2 and MMP-13
				CD63, immunoregulatory microRNA's (miR-30a, -223, -92a), PKH-67
	Skriner et al. 2006 [38]	BiP and heterogeneous nuclear RNP A2	Synovial exosomes	
	Bullerdiek and Flor 2012 [46]	microRNAs of "chromosome 19 microRNA cluster"	Placenta	
Overlap symdrome	Gutiérrez-Ramos et al. 2008 [30]	anti-PM/Scl-100		
	Mahler and Raijmakers 2007 [29]	PM/Scl complex		
		Anti-PM1-Alpha, PM/Scl-75c, PM/Scl-100		
		PM/Scl-75		MPP6, C1D, KIAA0052/hMtr4, hSki2, and hSki8
		PM/Scl complex	Serum	hRrp4p, hRrp40p, hRrp41p, hRrp42p, hRrp46p, hCsl4p

Symptoms include acute dryness of the eyes, mouth, skin and mucosa, with accompanying fatigue, arthralgia, neuropathies, and swelling of the salivary glands and lymph nodes.

Autoantibodies directed against the Ro/SSA and La/SSB autoantigens have been detected in sera from SS patients. A study in 2005 revealed that resting and viable salivary gland epithelial cells both constitutively release exosomes that contained Ro/SSA, La/SSB and Sm ribonucleoproteins (SmRNPs). Significant expression of these RNPs was invariably observed in exosomes derived from SS patients and non-SS disease controls [44]. It is possible that exosomes participate in the presentation of intracellular autoantigens, such as RNPs, to the immune system. Loading of professional antigen-presenting cells (APCs) by RNP-containing exosomes is a feasible mechanism for the intracellular transfer and efficient antigen presentation to autoantigen-specific T cells [45].

Comparatively fewer studies have investigated exosomal miRNAs as potential diagnostic biomarkers for SS. Bullerdiek and colleagues reported that mimics of chromosome 19 microRNA cluster (C19MC)-derived miRNAs could be developed as useful drug candidates for the treatment of autoimmune diseases such as SS and also could be administered to prevent transplant rejection. In addition, as some tumours have been reported to overexpress C19MC miRNAs, these miRNAs may be suitable targets for treatment with appropriate antagonists [46]. Interestingly, Michael et al. described the isolation and initial characterization of miRNA-carrying exosomes from saliva and proposed that the protein and miRNA content of salivary exosomes could be used to detect SS [47]. Indeed, miRNAs have been reported to be promising candidate biomarkers of inflammation and salivary gland dysfunction in SS patients [48]. Further studies are required to assess the potential of using salivary exosomal miRNA analysis for the diagnosis and prognosis of SS.

3. Conclusion

In addition to their vital role in intercellular communications, recent research studies have highlighted the ability of exosomes to stimulate immune responses, and their vast potential as biomarkers to detect autoimmune disorders and as therapeutic agents for treating a variety of ACTDs. It is now known that exosomes play important roles in numerous biological processes as well as in the pathogenesis of ACTDs. Although it is well established that exosomes are able to modulate the autoinflammatory response, our knowledge of the involvement of the exosome, its individual components, or any associated factors in disease initiation and progression is still very much in its infancy. Compared with other diseases, comparatively fewer studies have investigated the regulation of immune responses by exosomes in autoimmune disease pathogenesis. Future studies directed at unravelling the exact mechanisms of action of exosomes in chronic inflammatory and autoimmune diseases will undoubtedly provide new insights into disease diagnoses and therapies (Table 1).

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References

[1] Trams EG, Lauter CJ, Salem N, Jr, et al. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. Biochim Biophys Acta. 1981;645:63–70.
[2] Lin J, Li J, Huang B, et al. Exosomes: novel biomarkers for clinical diagnosis. Sci World J. 2015;2015:1.
[3] Zhang X, Yuan X, Shi H, et al. Exosomes in cancer: small particle, big player. J Hematol Oncol. 2015;8:83.
[4] Lotvall J, Valadi H. Cell to cell signalling via exosomes through esRNA. Cell Adh Migr. 2007;1:156–158.
[5] Altintas A, Cil T, Pasa S, et al. Clinical significance of elevated antinuclear antibody test in patients with Hodgkin's and Non-Hodgkin's lymphoma: a single center experience. Minerva Med. 2008;99:7–14.
[6] Jin L, Pahuja KB, Wickliffe KE, et al. Ubiquitin-dependent regulation of COPII coat size and function. Nature. 2012;482:495–500.
[7] Söllner T, Whiteheart SW, Brunner M, et al. SNAP receptors implicated in vesicle targeting and fusion. Nature. 1993;362:318–324.
[8] Kaeser PS, Deng L, Wang Y, et al. RIM proteins tether Ca2+ channels to presynaptic active zones via a direct PDZ-domain interaction. Cell. 2011;144:282–295.
[9] Chlebowski A, Lubas M, Jensen TH, et al. RNA decay machines: the exosome. Biochim Biophys Acta. 2013;1829:552–560.
[10] Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nat Rev Immunol. 2009;9:581–593.
[11] Yáñez-Mó M, Siljander PR, Andreu Z, et al. Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles. 2015;4:27066–27125.

[12] Duarte C, Couto M, Ines L, et al. Epidemiology of systemic lupus erythematosus. In: Lahita RG, Tsokos G, Buyon J, Koike T, editors. Systemic lupus erythematosus. 5th ed. London: Elsevier; 2011. p. 673–696.
[13] Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110–2121.
[14] Li T, Carls GS, Panopalis P, et al. Long-term medical costs and resource utilization in systemic lupus erythematosus and lupus nephritis: a five-year analysis of a large medicaid population. Arthritis Rheum. 2009;61: 755–763.
[15] Ortega LM, Schultz DR, Lenz O, et al. Review: lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions. Lupus. 2010;19: 557–574.
[16] Lee JY, Park JK, Lee EY, et al. Circulating exosomes from patients with systemic lupus erythematosus induce an proinflammatory immune response. Arthritis Res Ther. 2016;18:264.
[17] Solé C, Cortés-Hernández J, Felip ML, et al. miR-29c in urinary exosomes as predictor of early renal fibrosis in lupus nephritis. Nephrol Dial Transplant. 2015;30: 1488–1496.
[18] Ichii O, Otsuka-Kanazawa S, Horino T, et al. Decreased miR-26a expression correlates with the progression of podocyte injury in autoimmune glomerulonephritis. PLoS One. 2014;9:e110383.
[19] Lu J, Kwan BC, Lai FM, et al. Glomerular and tubulo interstitial miR-638, miR-198 and miR-146a expression in lupus nephritis. Nephrology (Carlton). 2012;17: 346–351.
[20] Ostergaard O, Nielsen CT, Iversen LV, et al. Unique protein signature of circulating microparticles in systemic lupus erythematosus. Arthritis Rheum. 2013;65: 2680–2690.
[21] Cloutier N, Paré A, Farndale RW, et al. Platelets can enhance vascular permeability. Blood. 2012;120: 1334–1343.
[22] Salvi V, Gianello V, Busatto S, et al. Exosome-delivered microRNAs promote IFN-α secretion by human plasmacytoid DCs via TLR7. JCI Insight. 2018;3:pii: 98204.
[23] Figueroa FE, Cuenca Moreno J, La Cava A. Novel approaches to lupus drug discovery using stem cell therapy. Role of mesenchymal-stem-cell-secreted factors. Expert Opin Drug Discov. 2014;9:555–566.
[24] Alvarez-Erviti L, Seow Y, Yin H, et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011;29:341–345.
[25] Zhou JJ, Wang F, Xu Z, et al. Secreted histidyl-tRNA synthetase splice variants elaborate major epitopes for autoantibodies in inflammatory myositis. J Biol Chem. 2014;289:19269–19275.
[26] Targoff IN. Update on myositis-specific and myositis-associated autoantibodies. Curr Opin Rheumatol. 2000;12:475–481.
[27] Pagnini I, Vitale A, Selmi C, et al. Idiopathic inflammatory myopathies: an update on classification and treatment with special focus on juvenile forms. Clin Rev Allergy Immunol. 2017;52:34–44.
[28] Vandergheynst F, Ocmant A, Sordet C, et al. Anti-pm/scl antibodies in connective tissue disease: clinical and biological assessment of 14 patients. Clin Exp Rheumatol. 2006;24:129–133.
[29] Mahler M, Raijmakers R. Novel aspects of autoantibodies to the PM/Scl complex: clinical, genetic and diagnostic insights. Autoimmun Rev. 2007;6:432–437.
[30] Gutiérrez-Ramos R, Gonz Lez-Díaz V, Pacheco-Tovar MG, et al. A dermatomyositis and scleroderma overlap syndrome with a remarkable high titer of anti-exosome antibodies. Reumatismo. 2008;60:296–300.
[31] Uitto J, Kouba D. Cytokine modulation of extracellular matrix gene expression: relevance to fibrotic skin diseases. J Dermatol Sci. 2000;24:S60–S69.
[32] Nakamura K, Jinnin M, Harada M, et al. Altered expression of CD63 and exosomes in scleroderma dermal fibroblasts. J Dermatol Sci. 2016;84:30–39.
[33] Mohan C, Assassi S. Biomarkers in rheumatic diseases: how can they facilitate diagnosis and assessment of disease activity? Bmj. 2015;351:h5079.
[34] Pant S, Hilton H, Burczynski ME. The multifaceted exosome: biogenesis, role in normal and aberrant cellular function, and frontiers for pharmacological and biomarker opportunities. Biochem Pharmacol. 2012;83: 1484–1494.
[35] Shi X, Sun M, Liu H, et al. Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett. 2013;339:159–166.
[36] Wang J, Zhou Y, Lu J, et al. Combined detection of serum exosomal miR-21 and HOTAIR as diagnostic and prognostic biomarkers for laryngeal squamous cell carcinoma. Med Oncol. 2014;31:148–155.
[37] Song J, Kim D, Han J, et al. PBMC and exosome-derived Hotair is a critical regulator and potent marker for rheumatoid arthritis. Clin Exp Med. 2015; 15:121–126.
[38] Skriner K, Adolph K, Jungblut PR, et al. Association of citrullinated proteins with synovial exosomes. Arthritis Rheum. 2006;54:3809–3814.
[39] Yang C, Robbins PD. Immunosuppressive exosomes: a new approach for treating arthritis. Int J Rheumatol. 2012;2012;573528.
[40] Cai Z, Zhang W, Yang F, et al. Immunosuppressive exosomes from TGF-β1 gene-modified dendritic cells attenuate Th17-mediated inflammatory autoimmune disease by inducing regulatory T cells. Cell Res. 2012; 22:607–610.
[41] Schorey JS, Bhatnagar S. Exosome function: from tumor immunology to pathogen biology. Traffic. 2008;9:871–881.
[42] Bianco NR, Kim SH, Morelli AE, et al. Modulation of the immune response using dendritic cell-derived exosomes. Methods Mol Biol. 2007;380:443–455.
[43] Ostman S, Taube M, Telemo E. Tolerosome-induced oral tolerance is MHC dependent. Immunology. 2009; 116:464–476.
[44] Kapsogeorgou EK, Abu-Helu RF, Moutsopoulos HM, et al. Salivary gland epithelial cell exosomes: a source of autoantigenic ribonucleoproteins. Arthritis Rheum. 2005;52:1517–1521.

[45] Routsias JG, Tzioufas AG. Autoimmune response and target autoantigens in Sjogren's syndrome. Eur J Clin Invest. 2010;40:1026–1036.

[46] Bullerdiek J, Flor I. Exosome-delivered microRNAs of "chromosome 19 microRNA cluster" as immunomodulators in pregnancy and tumorigenesis. Mol Cytogenet. 2012;5:27.

[47] Michael A, Bajracharya SD, Yuen PS, et al. Exosomes from human saliva as a source of microRNA biomarkers. Oral Dis. 2010;16:34–38.

[48] Alevizos I, Alexander S, Turner RJ, et al. MicroRNA expression profiles as biomarkers of minor salivary gland inflammation and dysfunction in Sjögren's syndrome. Arthritis Rheum. 2011;63:535–544.