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Molecular characteristics and functional differences of anti-PM/Scl autoantibodies and two other distinct and unique supramolecular structures known as “EXOSOMES”

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Abstract

The term “exosome” has been applied to three distinct supramolecular entities, namely the PM/Scl autoantibodies or “RNA exosomes”, transforming DNA fragments termed “DNA exosomes”, and small size extracellular vesicles known as “exosomes”. Some of the molecular components of the “PM/Scl exosome complex” or “RNA exosome” are recognized by specific autoantibodies present in the serum from some Systemic Sclerosis (SSc), polymyositis (PM) and polymyositis SSc (PM/Scl) overlap syndrome patients. On the other hand, one of the most active focuses of laboratory investigation in the last decade has been the biogenesis and role of extracellular vesicles known as “exosomes”. The remarkable ability of these “exosome” vesicles to alter the cellular phenotype following fusion with target cells and the release of their macromolecular cargo has revealed a possible role in the pathogenesis of numerous diseases, including malignant, inflammatory, and autoimmune disorders and may allow them to serve as theranostic agents for personalized and precision medicine. The indiscriminate use of the term “exosome” to refer to these three distinct molecular entities has engendered great confusion in the scientific literature. Here, we review the molecular characteristics and functional differences between the three molecular structures identified as “exosomes”. Given the rapidly growing scientific interest in extravesicular exosomes, unless a solution is found the confusion in the literature resulting from the use of the term “exosomes” will markedly increase.

Keywords

Exosome; Autoimmune diseases; PM/Scl complex; Systemic Sclerosis; polymyositis; polymyositis Scleroderma overlap syndrome

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Declaration of Competing interests

The authors declare that they have no competing interests.

1. Background

The term “exosome” has been used in the scientific literature to refer to three distinct supramolecular entities, specifically the PM/ScI autoantibodies or “RNA exosomes”, “DNA exosomes” and the “extracellular vesicle exosomes”. The purpose of this review is to highlight and clarify a source of confusion in the scientific literature resulting from the use of the term “exosome(s)” to refer to these three distinct molecular structures. A recent publication discussed the inappropriate application of this term as a general category representing extracellular vesicles instead of a specific population of extracellular vesicles[1]. However, the nomenclature confusion has arisen owing to the fact that the term “exosome” has been utilized to refer to three distinct supramolecular entities: 1. DNA exosomes[2-5]; 2. RNA exosomes that contain a protein recognized by human PM/ScI autoantibodies[6, 7]; and 3. Small extracellular microvesicles known as exosomes[8-12]. It should be strongly emphasized that each of these supramolecular entities has a very well defined and quite distinct biological function and is comprised of unique complexes of distinct molecules. The various subcellular and molecular components being referred to by the term “exosome” in the scientific literature are depicted in Figure 1.

2. DNA exosomes

The term “exosomes” first appeared in the scientific literature in 1970 when A. Fox and collaborators described exogenous DNA fragments capable of entering *Drosophila melanogaster* cells[2-4]. These DNA fragments internalized by intact cells were able to modify the cell’s genetic output. The non-Mendelian inheritance of these exogenous DNA fragments due to occasional loss in subsequent generations supported the view that they were not readily integrated into the host genome. These exogenous DNA fragments were termed “exosomes” and their transforming effects were referred to as “the exosome model” of cellular transformation[2-4]. Once associated with their homologous chromosomal segments, the exosomes replicate in synchrony with these segments and are transmitted with them during the cell division processes of mitosis and meiosis. In addition, transcription and translation from the exosomes is possible, resulting in alteration of the host cell phenotype. Similar observations of DNA-fragment-mediated non-Mendelian genetic transmission were subsequently made in *Neurospora* species[5].

3. Exosome Microvesicles

Nearly a decade later, the term “exosome” was used by Johnstone et al. to describe membrane bound microvesicles released into the intercellular space from reticulocytes during their maturation[9-11]. In the initial publication in 1987, these “exosomes” were described as a mechanism for the shedding of membrane proteins during the maturation of sheep reticulocytes and it was suggested that these membrane bound extracellular vesicles were derived from endosomal membranes through a complex sorting process during endosomal membrane maturation[9, 13, 14]. It is now understood that exosome microvesicles are produced via invagination of cellular endosomes resulting in formation of multivesicular bodies that, instead of being shuttled to lysosomes for degradation, fuse to the

plasma membrane resulting in their release from the cells into the extracellular compartment and eventually into the circulation[12, 15-17].

As research on the biogenesis of exosome microvesicles and on their role as intercellular messengers has progressed, it is now understood that they are but one distinct subtype of extracellular vesicle normally produced and released from cells during their normal activities; the other subtypes being microvesicles produced by budding from the plasma membrane, and apoptotic bodies[1, 12, 16-20]. Exosome microvesicles are distinguished from other extracellular vesicles based on their size (20-100 nm), the mechanisms of their biogenesis, their content of various protein components (e.g. tetraspanins such as cluster of differentiation (CD) antigens CD63, CD9, and CD81; flotillin 1; or annexin A5) with concomitant absence of cis-Golgi proteins such as GM130; and by the unique characteristics of their macromolecular cargo[1, 15-17, 21, 22].

Following their release from the exosome-producing cells, exosome microvesicles can be taken up by adjacent or distant target cells and their macromolecular contents released into the target cells resulting in alterations of their normal phenotypes[23-25]. Exosome microvesicles, therefore, can function as a novel form of intercellular communication[26, 27] inducing regulation and modification of numerous cellular processes including signal transduction[28], antigen presentation[25, 29], and the immune response[30]. The mechanisms by which the bioactive cargo macromolecules can impact the phenotype and function of target cells include: epigenetic reprogramming of target cells by functional RNA, protein, and lipid cargo molecules, transfer of activated receptors to recipient cells, and direct engagement of target cell surface receptors by exosome microvesicle surface-bound ligands[13, 19, 23, 25, 28, 29].

Alternatively, exosome microvesicles can diffuse into the circulation or be excreted in the urine or other biological fluids where they can serve as a non-invasive source of biomarkers for numerous diseases[12, 31, 32]. Indeed, changes in the macromolecular composition of the exosome microvesicles and of their cargo may reflect changes in the status of the cells that have produced them (e.g. quiescent, stressed, differentiated, transformed, or stem-like), allowing exosome microvesicles to serve as prognostic biomarkers for various human diseases. Interest in the paracrine signaling capability of exosome microvesicles and in their utility as disease biomarkers began in the field of cancer research but has expanded in the last decade to encompass a wide variety of human diseases including cardiovascular[33-35], renal[33-36], metabolic [37], and neurodegenerative diseases[38], as well as chronic inflammation[29, 30, 39, 40], cancer[30, 41, 42], and autoimmune disorders such as vasculitis[43] and SSc[31, 32, 44-46].

4. PM/ScI complex or RNA exosome complex

The third supramolecular structure labeled with the term “exosomes” occurs in the fields of autoantibodies and autoimmune diseases. These studies utilized the term “exosomes” to refer to specific molecular structures recognized by specific autoantibodies present in the serum of patients with various autoimmune diseases including SSc[7, 47]. The presence of autoantibodies that are reactive to various extracellular, nuclear and cytoplasmic

autoantigens in the serum of patients with SSc is considered a hallmark of the disease and the presence of specific autoantibodies can have diagnostic or prognostic significance[48-50]. Similarly, an array of myositic-specific and myositis-associated autoantibodies have been reported[51-54]. In 1977, a report by Wolfe et al. described an antigen (PM-1) precipitated from calf thymus protein extracts by incubation with serum isolated from PM patients[55]. Subsequently, in 1984 two independent groups reported that sera isolated from patients with an overlap syndrome with features of PM and SSc contained autoantibodies to the PM-1 antigen[56, 57]. Anti-PM/Scl antibody analyses revealed staining predominantly in the nucleolus[57-60]. Clinical correlation studies showed that only 2% of SSc patients demonstrated anti-PM/Scl positive staining, but remarkably, approximately 25% of those patients also had a PM/SSc overlap syndrome[57, 59]. Anti-PM/Scl staining can also be detected in the serum of patients with dermatomyositis and myositis[59-62]. Several clinical features are associated with the presence of anti-PM/Scl antibodies in SSc patients including overlap syndrome, involvement of the joints, and subacute myositis[63-65]. Anti-PM/Scl positive patients also tend to have earlier disease onset and display limited cutaneous disease and absence or low frequency of severe internal organ involvement[63, 64]. The cutaneous features include nailfold capillary distortion, hyperkeratosis on the fingers and calcinosis. Some also present with inflammatory arthropathy. The presence of Raynaud's phenomenon several years before other disease symptoms is common but digital ulceration with peripheral vasculopathy is less common[63, 64]. The presence of interstitial lung disease is less frequent but the age of onset of pulmonary involvement is lower compared with anti-PM/Scl-negative individuals and anti-PM/Scl-positive patients have higher progression-free survival rates[66-68]. Indeed, it has been suggested that the presence of antibodies against PM/Scl allows the separation of different subsets of SSc patients[67]. Anti-PM/Scl-positive SSc patients were considered to be highly responsive to immunosuppressive corticosteroid therapy although the evidence supporting this response is scant[69-75].

It has been subsequently determined that the PM/Scl antigen complex is actually the human counterpart to the yeast exosome, which is a predominantly nucleolar multiprotein complex consisting of 11-16 proteins[6, 59, 62, 76]. By 1990, two of the proteins in this complex, named PM/Scl-75 and PM-Scl-100 based on their molecular weights, had been cloned[77-79]. The RNA exosome was initially described as a complex involved in ribosomal RNA processing in the yeast *Saccharomyces cerevisiae* that is now known to function as an RNA processing complex for mRNA and several other small RNA species as well[6, 76]. Most RNAs transcribed in eukaryotes undergo multiple types of processing following their transcription [80-84]. For example, mRNAs processing entails 5' capping, 3' cleavage, intron splicing, and polyadenylation of the original transcript whereas primary microRNA undergoes a step-wise cleavage followed by 5' capping and polyadenylation[80-83]. Some mammalian mRNAs contain AU-rich elements (AREs) in their 3' untranslated region that target these RNAs for rapid degradation by the RNA exosome[85-94]. Small nuclear and small nucleolar RNAs undergo similar processing steps whereas ribosomal RNA undergoes precursor cleavage, base modifications and removal of 3' nucleotides and transfer RNA undergoes 5' and 3' cleavage, 3' capping, base modification, intron removal and attachment of its cognate amino acid [80-84].

The human RNA exosome, like its yeast counterpart, is a ribonuclease complex involved in the processing or degradation of various RNAs[6, 76, 80, 88-90, 94-98]. The RNA exosome consists of ten conserved core protein subunits arranged in a ring-like structure comprising a central 6-subunit ring, a 3-subunit cap, and a ribonuclease subunit associated with the central ring[6, 76, 88-90, 99-103]. Structural analysis has revealed that the RNA exosome complex forms a ring-like shape with a central pore opening through which the RNA to be processed enters[88]. Two additional proteins associate with this core complex and provide the catalytic activity for the RNA exosome[99, 100]. The ribonuclease subunit possesses both endoribonuclease and exoribonuclease activity[104-107] and is involved in maturation of the 5.8S ribosomal RNA[6, 108, 109], mRNA turnover[110, 111], and processing of various small nuclear and small nucleolar RNAs[112-114].

Human homologues of proteins comprising the yeast exosome were reported to correspond to the PM/Scl complex in human cells and it was further shown that two of the components of the yeast exosome, Rrp6p and Rrp45p, were homologous to the PM/Scl-100 and PM/Scl-75 autoantigens, respectively[6, 60, 76, 108, 115-117]. In addition, these core proteins of the PM/Scl complex/RNA exosome associate with other proteins for specific functions, e.g. ARE-binding proteins that recruit and promote degradation of unstable ARE-containing mRNAs[118].

In addition to the association of autoantibodies to PM/Scl-75 and PM/Scl-100 with SSc, myositis and dermatomyositis, mutations in the protein subunits comprising the PM/Scl complex/RNA exosome have been identified in various other human disorders, particularly neurodegenerative disorders[91, 102]. Missense mutations in EXOSC2 or RRP4 that prevent this RNA exosome structural cap subunit from binding to other proteins in the PM/Scl complex result in a novel syndrome recently named Short stature, Hearing loss, Retinitis pigmentosa and distinctive Facies (SHRF) in which defective autophagy may play a role[119, 120]. Mutations in another structural cap protein subunit (EXOSC3 or RRP40) have been implicated in the neurodegenerative disease pontocerebellar hypoplasia (PCH) type 1b that causes degeneration of spinal motor neurons, Purkinje cell abnormalities, and progressive atrophy of the pons and cerebellum beginning at birth[121-123]. Mutations in the core protein EXOSC8/Rrp43p are associated with the neurodegenerative disease PCH type 1c that is characterized by abnormal myelination of the central nervous system as well as cerebellar and corpus callosum hypoplasia from infancy[124]. Mutations in a third core protein, EXOSC9/Rrp45p are associated with a PCH-like neurodegenerative disorder of early onset with progressive spinal muscular atrophy-like motor neuropathy and cerebellar atrophy but with normal pons morphology[125]. Finally, mutations in the catalytic subunit DIS3 have been linked to various features of multiple myeloma including compromised immune function[126-133].

5. Discussion

The indiscriminate use of the term “exosome” to refer to three distinct supramolecular entities has given rise to a remarkable confusion in the scientific literature. This confusion is of particular relevance for clinical investigators and researchers focusing on the role of extracellular vesicle exosomes in autoimmune diseases such as SSc. For a researcher or

student unfamiliar with these fields, a simple search employing a search engine such as PubMed, Medline or Google for the term “exosome” would yield thousands of publications. The majority of these publications describe extracellular vesicle exosomes but studies investigating the other two supramolecular entities would also be included. This overlap would not necessarily be evident upon cursory examination of the search results. Since research on the role of the human exosome complex and on extravesicular vesicles are still very active areas of interest, the potential for this confusion caused by the imprecise use of the same term for distinct molecular entities will persist and increase.

6. Potential suggestions for a solution

The solution to the ensuing confusion is not readily apparent and will not be not easy to implement. It would require modification of the search parameters used to the PubMed algorithm to ensure separation between these terms. The only other apparent solution would be to increase awareness within the research community of the existence of this exosome nomenclature overlap and to indicate that the term “exosome” should be qualified by addition of the term “microvesicles” or “extracellular vesicle”. Investigators, authors, medical, and scientific journals publishers, editors, and reviewers must be encouraged to avoid the use of the term “exosome” to refer to DNA transforming complexes or to proteins involved in RNA processing including references to the human autoantibodies recognizing some of these proteins (exosome complex or RNA exosomes). We truly wish that the scientific community would favorably consider these suggestions to avoid further confusions, which is the ultimate goal we are attempting with this review.

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Abbreviations

ARE	AU-rich element
PH	pontocerebellar hypoplasia
PM	polymyositis
PM/Scl	polymyositis/Scleroderma
SHRF	Short stature, Hearing loss, Retinitis pigmentosa, and distinctive Facies
SSc	Systemic Sclerosis

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Highlights

- The term “exosome” in the scientific literature refers to three distinct supramolecular structures with unrelated functions.
- The PM/Scl exosome complex that is also known as the “human exosome” or “RNA exosome” is a multiprotein complex involved in the processing and degradation of various types of RNA.
- Autoantibodies to components of the PM/Scl complex are present in the serum of patients with Systemic Sclerosis, polymyositis, and polymyositis Scleroderma overlap syndrome.
- The term “exosome” is also used to refer to transforming DNA fragments and to a certain size of extracellular microvesicles.
- The scientific community needs to be aware of the multiple entities bearing the name “exosome” and to precisely define and differentiate the molecular entity under investigation with additional descriptors.

Figure 1. Subcellular and molecular components referred to as "exosomes" in the scientific literature.

A. "DNA Exosome": DNA fragments taken up by *Drosophila* embryos associate with homologous chromosomal regions and are capable of complex non-Mendelian modification of strain phenotypes. **B.** The autoantigenic complex, also termed "the human exosome" or "RNA exosome" is one of the polypeptide components of a multiple protein complex with 3'-5' exonuclease activity involved in ribosomal RNA (rRNA) processing. **C.** Extracellular vesicle exosomes are produced by fusion of multivesicular bodies to the plasma membrane and the subsequent release to the extracellular space of 20-100 nm lipid bilayer bound vesicles with a cargo comprised of a diverse collection of cell-derived macromolecules with the potential to affect the cellular phenotypes following uptake by target cells.