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Editorial commentary: Extracellular vesicles in cardiovascular diagnosis and therapy

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Extracellular vesicles (EVs) are cell-released small lipid vesicles with diameters ranging between 40 and 5,000 nm. EVs are commonly subclassified by size into exosomes, microvesicles or microparticles (MP), and apoptotic bodies [1]. Different from apoptotic bodies generated only during programmed cell death, exosomes and MPs are sub-micron membrane vesicles that can be released from almost all eukaryotic cells constitutively as well as during cell activation. Serving as cell-cell and cell-extracellular matrix communication tools, EVs contain not just differential compositions of lipid, but also cargos of protein, mRNA, micro-RNA (miRNA), and long non-coding RNA (lnRNA). The lipid and cargos provide characteristic footprints and specific functions related to the EV's cells of origin. In the cardiovascular system, EVs are generated and released by a variety of cell types from stem cells to mature cardiomyocytes. Exploring biogenesis, the functional consequences of EVs, and the value of the cargo they contain is now an emphasis in this burgeoning era of cardiovascular medicine.

Cardiovascular EVs from biogenesis to cargo content

As discussed in the excellent accompanying review article [2], exosomes are the smallest vesicles that originate not from plasma membrane but from intracellular compartments. Exosomes are formed by inward budding of endosomal membrane and stored as intraluminal vesicles within a large multivesicular body (MVB). During exocytosis when MVB membrane fuses with plasma membrane, exosomes are released into the extracellular space. Distinct from exosomes, MPs are shed from outward budded plasma membrane through ectocytosis. Thus, unlike exosomes, MPs carry the cell-surface antigens of their respective parental cells.

The biogenesis of exosomes and MPs also involves different but not necessarily distinct cellular mechanisms. During MP biogenesis, the outward bending of plasma membrane is initiated by lipid scramblase / flippase-dependent [3] outward flipping of phosphatidylserine (PS) resulting in high PS concentration in MP membrane's outer leaflet. In contrast, exosomal membrane usually has non-detectable to low PS levels. However, accumulating evidence indicates that common cellular pathways are shared between exosome and MP biogenesis. Cytoskeleton actin, ESCRT complexes, and intracellular Ca^{2+} are all critical components required for the formation and release of both exosomes and MPs. For example, ESCRT complexes 0–III are involved in the full process of exosome formation from cargo-sorting, membrane bending, and fission events. Meanwhile, ESCRT complexes are also responsible for MP formation at various plasma membrane sites [4–6]. Over time, we expect that the distinction between exosomes and MPs will be increasingly blurred.

Therapeutic effects of exosome and MP cargo are becoming apparent. Cardioprotective effects have been reported for exosomal miRNAs secreted from stem cells including cardiac progenitors cells, cardiosphere-derived cells, and pluripotent stem cells [7]. Other exosomal molecules currently under intensive research are lnRNAs—which are also believed to have important functions. Future studies will be interesting to explore how these molecules act in synergy to maintain cardiovascular functional homeostasis, as well as how homeostatic balance is compromised in disease.

Ectocytosis generated MPs also contain lipid, protein, RNA, and miRNA. There are numerous studies indicating that MPs are messengers mediating cell-cell communication to regulate the pathology of cardiovascular diseases. Circulating pro-coagulant MPs are

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considered as markers of thrombosis. The role of exosomes and MPs in modulating cardiac muscle function and remodeling is much less explored and remains an interesting topic for future research.

Roles of EVs in heart failure diagnosis and therapy

Despite the large body of work focusing on EVs in cardiovascular disease pathology, studies on EVs derived from mature muscle cells remain limited. Only recently have researchers identified that healthy adult cardiomyocytes are not only passive recipients of EVs, but also active parental cells capable of releasing both exosomes and MPs [6].

Cardiomyocyte-derived EVs originate from mature heart muscle and can exert paracrine effects on myocytes and other cells in the heart, as well as cells in remote organs after circulating in the blood stream. Cardiomyocyte-derived EVs thus provide a unique opportunity to focus on cardiac muscle related disease management. It was recently reported that human cardiomyocytes release cardiac bridging integrator 1 (cBIN1)-MPs [6] that originate from the transverse-tubule cBIN1-membrane microdomains [8]. The release of cBIN1-MPs requires a coordinated interaction of cBIN1, an ESCRT-0 similar protein with capability of membrane bending, with actin and the ESCRT-II complex member CHMP4B. As part of cardiomyocyte homeostasis, cBIN1-MPs are released continuously from healthy hearts. At steady state, a normal blood concentration of cBIN1-MP is maintained and correlates to muscle content of cBIN1, allowing quantification of cardiac cBIN1 by a blood test measuring plasma cBIN1. Thus, blood available cBIN1 and related cBIN1 score (CS) can be used as an accurate index of cardiac cBIN1-microdomain, which undergoes negative remodeling as an early phase of heart failure progression [9,10]. In a clinical cohort of patients with heart failure with preserved ejection fraction, CS can help identify failing muscle and predict future clinical outcomes better than the B-type natural peptides [11]. Future studies are needed to understand the function of cBIN1-MPs and whether they can detect early preclinical failing myocardium. At present, it appears that CS will improve clinical management of existing ambulatory heart failure.

Additional research into the cargo content in cardiomyocyte-derived EVs can help us identify disease biomarkers such as cBIN1 and new targets for therapy development. It is unclear but likely that extracellular EVs can be re-absorbed by cardiomyocytes. Thus cargo molecules can modulate intracellular signaling and functional remodeling of local cardiomyocytes. More generally, can cardiomyocyte-derived EVs serve as a functional reservoir pool that provides a readily available supply source to recycle biological active molecules to nearby cardiomyocytes? If so, can we load these EVs with cardiomyocyte specific regulatory and stress-response proteins to be delivered to diseased cardiomyocytes to modulate, postpone, or reverse abnormal muscle remodeling? In a way much like virally mediated gene transfer in gene therapy, these EVs can be used as delivery vehicles to reintroduce proteins and RNAs to diseased muscle for functional rescue. In the future, it may be possible to replenish diseased cardiomyocytes with functionally critical yet expression deficient proteins such as the transverse-tubule microdomain organizing cBIN1, as well as cardioprotective proteins such as GJA1-20k [12] which provide trafficking and metabolic release during stress [13,14]. In addition, can cardiomyocyte-derived EVs impact on local non-myocytes and matrix to modulate inflammation, fibrosis, and other pathology of diseased heart remodeling? A recent study indicates that EVs in the ischemic myocardium can be taken up by monocytes and regulate inflammatory responses [15]. Further studies are needed to address these unanswered questions.

In conclusion, cardiac EVs, originating from cardiomyocytes and non-myocytes, are an interesting topic to be extensively explored in the following decades. While the excellent accompanying review [2] focused on exosomes, we note that studies are already emerging that MPs provide new clinical biomarkers of the health of cardiac muscle. Future investigations will likely find that EVs of both exosome and MP origin can be harnessed for therapeutic potential as well.

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