Extracellular vesicles: small but strong

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This editorial refers to ‘Induction of pulmonary hypertensive changes by extracellular vesicles from monocrotaline-treated mice’ by J.M. Aliotta et al., pp. 354–362, this issue.

Pulmonary arterial hypertension (PAH) is a disease affecting small pulmonary arteries characterized by hyperplasia and hypertrophy of vascular smooth muscle cells and enhanced proliferation of endothelial cells. These events result in a remodelling of pulmonary vessels leading to an increase in the mean pulmonary arterial pressure and right ventricle overload and, ultimately, death. Growing evidences based on data obtained in patients with PAH indicate that the severity of PAH is associated with an increase of circulating small extracellular vesicles released from cells undergoing apoptosis or stimulation. Several discrepancies have been described concerning the origin of these vesicles, probably due to the heterogeneity of patients. These drawbacks may be overcome by using animal models of PAH induced by chronic hypoxic conditions or by monocrotaline treatment. Besides being biomarkers, extracellular vesicles can also serve to transfer a large number of messages between cells due to their protein, lipid, and cytoplasmic contents (e.g. mRNA and miRNA).

In this volume of Cardiovascular Research, Aliotta et al. have studied the role of extracellular microvesicles from monocrotaline-treated mice on the induction of pulmonary hypertensive changes. These vesicles are heterogeneous in size (30–423 nm) and carry proteins characteristic of exosomes and microparticles. Interestingly, the authors have analysed (i) the composition of different types of vesicles isolated from the lung and from the plasma of mice treated with monocrotaline and (ii) their effects when injected into healthy mice. The main results indicate that lung- and plasma-derived vesicles generated from monocrotaline-injected mice are able to induce the increases in right ventricular mass and pulmonary vascular wall thickness resulting in PAH-like changes. One hypothesis to explain these results may be that vesicles packaged monocrotaline, such as described by other drugs. Indeed, these authors have shown that microparticles derived from apoptotic tumour cells in response to chemotherapeutic treatments can package and deliver drugs to other tumour cells, thereby leading to their timely death without typical drug-associated side effects. However, it is particularly interesting to note that Aliotta et al. detected neither monocrotaline nor monocrotaline metabolites into vesicles, suggesting that their effects are not related to monocrotaline itself but to other vesicle components.

Extensive analyses on the composition of extracellular vesicles during PAH-induced monocrotaline indicate that miRNAs from endothelial origin are overexpressed in vesicles isolated from the lung, but not from the plasma, suggesting that monocrotaline may damage selectively endothelium from pulmonary vessels leading to vesicle release. Also, extracellular vesicles from monocrotaline-treated mice display altered expression of a variety of miRNAs such as miR-145, miR-328, miR-451 that appear to be involved in pulmonary vascular remodelling associated with PAH pathogenesis. In addition, among the proteins identified in extracellular vesicles, phosphodiesterase-5 is increased in both lung- and plasma-derived vesicles from mice treated with monocrotaline. The use of phosphodiesterase-5 inhibitors represents a therapeutic approach in PAH. Since other studies have reported the effective use of drugs to reduce circulating microparticle levels, a strategy leading to target the diminution of release of vesicles carrying phosphodiesterase-5 may be attractive to fight against PAH. The present study needs to be transposed on the translational level by conducting further works on the analysis of composition of vesicles isolated from PAH patients to allow identifying the presence of phosphodiesterase-5 in human extracellular vesicles.

Interestingly, 30 min after tail vein injection into normal mice, fluorescently labelled extracellular vesicles are detected adjacent to pulmonary vascular endothelial cells, suggesting that they can be tracked down by the pulmonary microcirculation. Once injected (once daily for 3 days), only 2 weeks are needed for extracellular vesicles to generate pulmonary hypertensive changes, whereas the development of PAH by monocrotaline requires several injections during 4 weeks, suggesting that extracellular vesicles generated from monocrotaline-treated mice are even more deleterious than monocrotaline treatment. These data indicate that extracellular vesicles shuttle biological effectors accounting for the pathological consequences. It should be interesting to perform an exhaustive analysis of the possible effects related to 18 proteins and 3 miRNA identified in both extracellular vesicles obtained from monocrotaline—but not from vehicle-injected mice. Once again, the presence of phosphodiesterase-5 in extracellular vesicles from monocrotaline-injected mice might be associated with their deleterious effects. These findings are even more relevant when one takes into account that the effects evoked by extracellular vesicles are dependent on their composition and not on their number. Indeed, a same amount of extracellular vesicles generated in the absence of monocrotaline treatment affect neither right ventricular mass nor pulmonary vascular wall thickness.

Finally, the authors have analysed the effects of extracellular vesicles on differentiation and gene expression of bone marrow-derived...
progenitor cells. Extracellular vesicles from mononuclear-treated mice induce differentiation of bone marrow cells into endothelial progenitor cells that home to the lung when transplanted into healthy mice and may contribute to pulmonary vascular remodelling. The exact role of bone marrow-derived progenitor cells in PAH is not elucidated, but several reports have described the mobilization of bone marrow-derived progenitor cells and their recruitment to the lung and pulmonary vasculature in experimental hypoxia-induced PAH. In contrast, in PAH patients a relative deficiency of circulating endothelial progenitor cells and their recruitment in the lung and pulmonary vasculature has been described. Moreover, Aliotta et al. have observed that extracellular vesicles obtained from mononuclear-mice-induced bone marrow-derived progenitor cell up-regulation of endothelial markers and growth factors implicated in the pathogenesis of PAH. Most interestingly, transplantation of these cells into healthy mice caused right ventricular hypertrophy and increased muscularization of pulmonary vessels, suggesting a potential mechanism by which extracellular vesicles may induce pulmonary vascular remodelling via induction of bone marrow-derived endothelial progenitor cells.

Altogether, these findings demonstrate that extracellular vesicles from PAH mice can induce pulmonary hypertensive changes and probably contribute not only in the maintenance of this disease, but also in their pathogenesis (Figure 1). In this way, it might be beneficial to target vesicle production directly so as to restore production of physiological vesicles that do not display deleterious effects. Deciphering the mechanisms implicated in the generation of extracellular vesicles during pathological states is essential to allow specifically inhibiting mechanisms implicated in the generation of extracellular vesicles from monocrotaline-treated mice. These extracellular vesicles induce the increases in right ventricular mass and pulmonary vascular wall thickness resulting in PAH-like changes. H&E stainings of lung sections are reproduced from Aliotta et al. (with permission).