

## Cell-Derived Exosomes for Cardiovascular Therapies Y (Not) RNAs?

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See related article, pp 370–380

Hypertension is recognized as the leading pathophysiologic insult for atherosclerosis development and progression, for the development of cardiac, cerebrovascular, and peripheral vascular diseases, and for organ damage. It represents overall the major risk factor for heart failure, stroke, and kidney diseases. Current guidelines for hypertension management are mainly based on combination therapies.<sup>1</sup> However, a significant percentage of patients with hypertension still fails to achieve optimal blood pressure targets, and the prevalence of uncontrolled hypertension continues to rise. Under this perspective and because of its multifaceted pathogenesis, therapeutic modulation of hypertension could be more complex than expected and ascribable to more than one single aspect. Increasing evidence supports a complex interplay of immunity (both innate and adaptive) and inflammation in the development of hypertension. Ang (angiotensin) II—one of the key factors modulating blood pressure—has been described as a major trigger of inflammation in resistance vessels and kidney. Recently the interplay between immunity, inflammation, and Ang II has become evident as a main pathogenetic mechanism involved in the onset of hypertension.<sup>2</sup>

Among novel strategies for cardiovascular disease treatment, cardiac cell therapy has been considered in the past 15 years as a potential protective and regenerative approach for heart failure, rapidly reaching clinical evaluation with several completed and ongoing clinical trials.<sup>3</sup> Multiple cell types have been proposed, including extracardiac cell sources and also resident cardiac progenitor cells. Through the years, knowledge has been expanding on the therapeutic mechanisms involved in cardiac cell therapy, evolving from a direct cardiogenesis-centered perspective to a multitarget paracrine view.

In this issue, Cambier et al<sup>4</sup> provide yet a new insight on this complex mechanistic picture in a novel pathophysiological context, that is, hypertension. In particular, the authors describe a protective role played by exosomes secreted by cardiosphere-derived cells (CDCs; CDC-exo) through one

of their most abundant small RNA constituent: EV-YF1 (Figure). CDCs are a regenerative cell product, including resident cardiac progenitor cells and supporting stromal cells, which have been widely tested in preclinical settings<sup>5</sup> and also in phase I/II trial.<sup>6</sup> Besides directly differentiating into cardiomyocytes, endothelial cells, and smooth muscle cells, CDCs exert complex indirect beneficial effects on the endogenous myocardium, including proangiogenic, anti-apoptotic, and antifibrotic effects.<sup>7,8</sup> These are mediated by a plethora of secreted factors and microvesicles with a rich content, which includes numerous noncoding RNAs. Among the most represented species in CDC-exo, Y-RNAs represent 20% of the total RNA content.<sup>9</sup> Y-RNAs are still largely mysterious molecules that are emerging as potential biomarkers. They are mainly known to regulate DNA replication but appear to be able to modulate RNA transcription and splicing as well, by binding important proteins, such as RoBPI (Ro-binding protein 1).<sup>10</sup>

Extracellular vesicle-mediated cell transfer of the Y-RNA fragment EV-YF1 has been described from CDCs to macrophages,<sup>9</sup> accounting for a peculiar cardioprotective polarization characterized by increased IL (interleukin)-10 secretion (Figure). This effect may not be limited only to the heart, where it promotes cellular postconditioning and protects from ischemia/reperfusion injury.<sup>11</sup> Indeed, Cambier et al<sup>4</sup> provide now evidence that CDC-exo could mediate local IL-10 protective mechanisms in the myocardium, as well as in the kidney in the setting of hypertensive damage induced by Ang II infusion in mice. Interestingly, the authors have tested an early intervention, with CDC-exo injection after 2 weeks of hypertension induction, exploring a midcourse direct strategy to locally block the detrimental pathogenesis of kidney damage. Of note, the beneficial effects observed seem to be mediated again by IL-10, thus downstream of altered pressure control, possibly bypassing the issue of the *Primum Movers* in hypertension pathogenesis.

This study<sup>4</sup> contributes to the increasing body of knowledge on the interplay between immunomodulation and cardiovascular diseases progression, with the challenging aim of identifying novel effective therapeutic strategies. Notwithstanding the complexity of human hypertension pathogenesis compared with the animal model, these findings suggest an attractive possibility: targeting resident macrophage polarization through cardiac progenitor cell-derived exosomes as a potential strategy to counteract Ang II-induced end-organ damage. Microvesicles, and exosomes in particular, may represent a potent therapeutic tool because they can combine their bioactive carrier function with pleiotropic effects due to their variegated molecular content. Nonetheless, several limitations still exist, particularly

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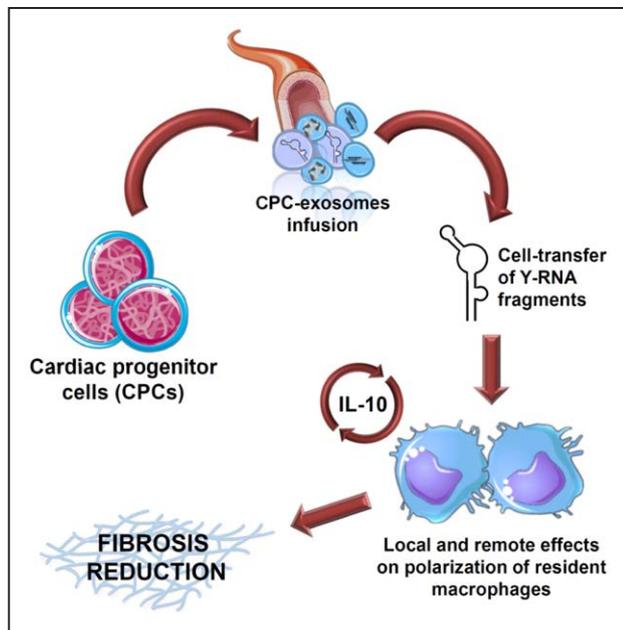
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**Figure.** Schematic representation of the proposed mechanism of action of cardiac progenitor cell (CPC)-derived exosomes in Ang (angiotensin) II-induced hypertension. Infusion of CPC-derived exosomes can mediate cell transfer of the Y-RNA fragment EV-YF1 to resident macrophages. This transfer induces a peculiar IL-(interleukin)10-mediated antifibrotic polarization of macrophages, sustaining antifibrotic effects in endogenous target tissues, such as the myocardium and the kidney. Figure was prepared using images from Servier Medical Art by Servier (<https://smart.servier.com>), which is licensed under a Creative Commons Attribution 3.0 Unported License.

concerning the knowledge about Y-RNA's mechanisms of action. Basic research on Y-RNA's molecular biology will be essential in elucidating the details of the signaling pathways involved. In fact, despite solid experimental observations of CDC-exo beneficial effects in the animal model, direct *in vivo* mechanistic evidence is still missing, together with thorough specificity assessment of such mechanism.

The association between immunity and hypertension continues to emerge even from the cognate research field of cardiovascular regeneration. Multiorgan bioactive targeted therapies will be likely the most successful ones in the fight against cardiovascular diseases and their main risk factor, that is hypertension.

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## Disclosures

None.

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