



## EDITORIAL COMMENT

# One more piece in the puzzle of stem cell therapy in cardiovascular diseases

## Mais uma peça para o puzzle da terapia com células estaminais nas doenças cardiovasculares

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Stem cell-based therapy has been considered the “holy grail” in regenerative medicine in numerous areas. Also, in cardiovascular diseases (CVDs), which are still the leading cause of death worldwide, stem cells are a promising therapeutic option. Among stem cells, mesenchymal stem cells (MSCs) exhibit major potential as they possess the ability to differentiate between various types of cells such as cardiomyocytes, endothelial cells, and smooth muscle cells. Furthermore, these cells release several mediators that can play a role in the regulation of apoptosis, fibrosis, and neovascularization. Another key advantage of these cells is their limited likelihood of triggering an immune response, along with their ability to modulate the immune system.<sup>1</sup>

In this context, the study by Gu et al.,<sup>2</sup> published in this issue of the journal, provides new insights into the potential therapeutic role of MSCs in mitigating the development of cardiac fibrosis and hypertrophy, two pathophysiological processes present in most CVDs. In their study, authors cocultured rat MSCs with rat cardiac fibroblasts (CFs) or rat cardiomyocytes (CMs) to investigate the effects of MSCs in

these types of cells. The findings suggest that MSCs can promote cell cycle progression, proliferation and inhibit apoptosis in CFs and CMs under angiotensin II (Ang II) treatment. Additionally, MSCs reduced cytokine (IL-6, IL-1 $\beta$ , and TNF- $\alpha$ ) secretion and alleviated CF fibrosis and CM hypertrophy induced by Ang II.

These findings align with the results of previous studies. For instance, our group recently investigated the effectiveness of intracoronary administration of human umbilical cord matrix-derived MSCs as an adjuvant treatment for reperfusion injury in a swine model of acute myocardial infarction. Our findings demonstrated that these cells enhanced the contraction of cardiomyocytes, improved left ventricular function, and led to positive changes in the remodeling of cardiac tissue.<sup>3</sup>

It is worth noting that the benefits these cells can provide seem to be mainly achieved through paracrine actions. Lai et al.<sup>4</sup> were the first to show the efficacy of MSC-derived exosomes in reducing infarct size in a mouse model of myocardial ischemia/reperfusion injury. Other studies support the role of MSC-derived exosomes in modulating diseases such as atherosclerosis, and heart failure. Furthermore, biomolecules such as microRNAs (miRNAs) present in the secreted exosomes were suggested as key mediators of the cardioprotective effects of MSCs.<sup>5,6</sup>

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Of note, the study by Gu et al. also sheds light on the role of the arginine/serine-rich 3 splicing factor (SFRS3) in the context of cardiac fibrosis and hypertrophy. This protein regulates the splicing of several mRNAs, mRNA cytoplasmic transport, and processing of miRNA. The high expression of this protein has been associated with the development of cancer, and SFRS3 seems to play a role in the promotion of cell proliferation, progression of the cell cycle, and inhibition of apoptosis.<sup>7</sup> Importantly, only recently the role of this protein has begun to be investigated in the heart. SFRS3 was found to be fundamental for heart development in mice. Loss of SFRS3 in adult cardiomyocytes leads to decapping and degradation of mRNAs encoding proteins involved in cardiac contraction, resulting in severe systolic dysfunction.<sup>8</sup> Also, Dumont et al.<sup>9</sup> found that the localization and splicing activity of SFRS3 was regulated by p38 MAPK in cardiomyocytes. The same research group then found that this splicing factor plays a role in the regulation of cardiomyocyte mitochondrial integrity and function.<sup>10</sup> In the study by Gu et al., MSCs were found to induce SFRS3 expression in CFs and CMs, and overexpression of SFRS3 in CFs and CMs mirrored the effects of MSCs in promoting cell cycle progression, proliferation and reducing apoptosis induced by Ang II. The study suggests that MSCs, through increasing SFRS3 expression, can mitigate Ang II-induced cardiac fibrosis and cardiomyocyte hypertrophy.

This work opens new avenues for future studies, such as investigating the secretome of MSCs co-cultured with CFs and CMs and examining the effects of MSCs derived from various sources, including bone marrow, adipose tissue, and umbilical cord. Although the exact mechanism underlying the interactions between MSCs and SFRS3 in CFs and CMs requires further investigation, this study highlights the importance of continuing research into the role of MSCs and SFRS3 in the cardiovascular system. It also emphasizes the potential benefits of MSCs-based therapy in treating cardiac fibrosis and hypertrophy. Clarification of the molecular mechanisms involved in MSC actions will uncover new pathways that can contribute to improving the management of CVDs, by supporting clinical trials, and ultimately contributing to reducing the burden of these diseases on global public health.

## Conflicts of interest

Authors have no conflicts of interest to declare.

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