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Exosomes mediate myocardial regeneration of cardiac progenitor cells in a swine model of dilated cardiomyopathy

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Introduction- Stem cell therapy has been shown to improve cardiac function. The mechanisms of therapeutic efficacy are considered the secretion of paracrine factors but the details are still unknown. Hypothesis- Exosomes are extracellular vesicles containing bioactive substances such as proteins, messenger RNAs and micro RNAs. We hypothesized that exosomes may be the main paracrine factors to mediate therapeutic efficacy of cardiosphere-derived cells (CDCs). Methods- Farm pigs (30 kg, n=10) were treated by intracoronary administration of 10,000 microspheres (100-300 µm) into three vessels. Two weeks later, 9.0×106 CDCs pretreated by exosome inhibitor (EI; 20µM of GW4869) or DMSO as controls were selectively infused into three coronary arteries. Evaluation of ejection fraction (EF) was performed before cell infusion and 1 month after protocol treatment. Results- Pigs developed diffuse hypokinetic heart failure (baseline EF 37.1%±2.1%) and randomly assigned into two groups (CDCs with EI: n=5, CDCs with DMSO: n=5). No serious adverse events were found during the CDCs infusion. Significant improvement of EF was observed in CDCs with DMSO group (37.1%±2.1% to 42.5%±3.0%; P=0.01), whereas no change was found in CDCs with EI group (37.1%±2.4% to 36.2%±2.9%; P=0.58). Myocardial fibrosis stained by picrosirius red was significantly reduced in CDCs with DMSO group compared with CDCs with EI group (9.5±3.6% versus 17.3±5.3%; P<0.01). Conclusions- We confirmed the therapeutic efficacy of CDCs and these effects were mainly mediated by exosomes.