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Epicardium derived cells promote sympathetic ganglionic outgrowth towards myocardium in vitro

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Background: The autonomic nerve system is essential to maintain homeostasis in the body. In the heart, autonomic innervation is important for adjusting the physiology to the continuously changing demands such as stress responses. After cardiac damage, excessive neurite outgrowth, referred to as autonomic hyperinnervation, can occur which is related to ventricular arrhythmias and sudden cardiac death. The cellular basis for this hyperinnervation is as yet unresolved. Here we hypothesize a role for epicardium derived cells (EPDCs) in stimulating sympathetic neurite outgrowth.

Purpose: To investigate the potential role of adult EPDCs in promoting sympathetic ganglionic outgrowth towards adult myocardium.

Method: Fetal murine superior cervical ganglia were dissected and co-cultured with activated adult mesenchymal epicardium-derived cells (EPDCs) or/and adult myocardium in a 3D collagen gel culture system. Four experiment groups were included: Group 1: Vehicle cultures (ganglia cultured without EPDC/myocardium) (n=48); Group 2: ganglia co-cultured with EPDCs (n=38); Group 3: ganglia co-cultured with myocardium (n=95); and group 4: ganglia co-cultured with both EPDCs and myocardium (n=96). The occurrence of neurite outgrowth was assessed in each group. The density of neurites that showed directional sprouting (i.e. sprouting towards myocardium) was assessed as well with a semi-automatic quantification method. Finally, sub-analyses were made by taking gender into account.

Results: Cervical ganglia cultured with EPDCs alone (group 2) showed increased neurite outgrowth compared to vehicle cultures (group 1), however the neurites did not show directional sprouting towards EPDCs. When co-cultured with myocardium (group 3), directional neurite outgrowth towards myocardium was observed. Compared to the ganglia-myocardium co-cultures, directional outgrowth was significantly increased in co-cultures combining myocardium and EPDCs (group 4), and the neurite density was also significantly augmented. Comparison between males and female ganglia demonstrated that more neurite outgrowth occurred in female-derived ganglia than in male-derived ganglia under the same co-culture conditions.

Conclusion: Activated adult EPDCs promote sympathetic ganglionic outgrowth in vitro. Sex differences exist in the response of ganglia to EPDCs, and female-derived ganglia appear more sensitive to EPDC-signalling. Results support a role of EPDCs in cardiac autonomic innervation and open avenues for exploring of their role in ventricular hyperinnervation after cardiac damage.