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Hemodynamic activation of vascular cells in cardiac veins induce an equivalent of stimulus triggered acquired pluripotency in human cardiomyocytes

Reprogramming of cardiomyocytes require severe interference with normal signaling and cellular homeostasis. In contrast with molecular vectors and scientifically highly disputable stimulus triggered acquired pluripotency (STAP), use mechanical stress for induction which seems to induce regeneration by reiterating embryonic developmental pathways. Here, we show that epigenetic signaling via hemodynamic mechanotransduction on human venous vascular cells in cardiomyopathy hearts induces pluripotency marker Klf4, but not NANOG. Pressure controlled intermittent coronary sinus occlusion (PICSO) temporarily increases shear stress during backflow in cardiac microcirculation and via mechanical stretch of elevated pressures on vascular cells including pericytes create a pleiotropic signaling known as canonical pathway during morphogenesis of the heart. This intervention was applied in patients with end stage cardiomyopathy for 20 minutes. Sera of coronary sinus blood samples were co-cultured with human cardiomyocytes explanted from a patient with end stage cardiomyopathy during heart transplantation. Klf4 expression was measured as pluripotency marker. Sera of treated patients were able to significantly up-regulate Klf4 in cultured cardiomyocytes as compared to those taken before treatment and in untreated controls. In porcine myocardial specimen subjected to acute ischemia with and without PICSO also a significant increase of Ki67 and a reduction of p53 were observed. This indicates that direct mechanotransduction as well as the release of soluble factors act in accordance in the recovery of failing hearts mimicking similar pathways known during the development of the heart. We conclude that the STAP concept might have been abolished too early and that a clinically feasible transcatheter sinus intervention may induce a paradigm change in regeneration therapy.

Biography

Werner Mohl has graduated from the Vienna University, Medical School and received his PhD in Natural Science from the University of Vienna. He has received the Board of Surgery and the Academic License to teach Surgery. He is the Professor of Surgery at the University of Vienna. He has published more than 90 papers in reputed journals, book chapters and has been serving as an Editorial Board Member of several journals.

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