From spheroids to organoids: the evolution of model system for human cardiac regeneration in a dish

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Two-dimensional (2D) culture systems represent the conventional approach to study cardiac differentiation, cardiac regeneration and disease modeling in a dish. For a long time, 2D cardiac spheroid generation from embryonic/induced pluripotent stem cells and adult multipotent cardiac stem cells supported the aims to generate in a dish committed and differentiated cardiomyocytes able to regenerate the infarcted myocardium when injected *in vivo* in murine models. Nevertheless, although they are undoubtedly useful for delineating the normal and disease conditions in cardiac cell biology, the key limitation of 2D culture systems is their suitability for translational or clinical human correlations. With this perspective, the recent advances in cardiac tissue engineering contributed to optimally reproduce the features of human cardiac tissue. Indeed, the innovative three-dimensional (3D) cardiac organoid culture technologies enhanced our ability of mimicking human organ reconstruction. Cardiac organoids as well as "Cardioids" were generated from human pluripotent stem cells (hPSCs) that self-organize into complex native-like organ structures. Cardioids mimic the cellular microenvironment of human tissues better than 2D cell culture systems and render more faithfully the tissue physiology. Furthermore, hPSC-derived 3D cardiac models including spherical aggregates of cardiomyocytes and other cardiac cell types have been established as promising high throughput tools for drug discovery. Finally, advances in patient-derived organoid culture further provides a unique perspective from which treatment approaches can be personalized.