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Research Highlight

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Multi-chamber cardioids—A paradigm shift in heart research

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ABSTRACT

In the quest to understand the complexities of human heart development and the genesis of congenital heart defects (CHDs), the study by Schmidt et al. presents a paradigm-shifting approach. The development of a multi-chamber cardioid platform provides a novel in vitro model that captures the nuances of embryonic cardiac compartments, offering unprecedented insights into the genetic and environmental underpinnings of CHDs. This system not only advances our comprehension of early cardiac morphogenesis but also serves as a robust tool for high-throughput screening of potential teratogens and therapeutics.

KEYWORDS

cardioids, organoids, heart development, multi-chamber, cardiac progenitors, congenital heart disease

The human heart's developmental journey is a symphony of orchestrated events, with the potential for disruptive missteps leading to CHDs[1]. The intricate interplay between genetic, molecular, and environmental factors has been challenging to decipher due to the inaccessibility of the embryonic heart and the limitations of existing in vitro models. The quest to overcome these challenges has been significantly advanced by the advent of organoid technology. Organoids, self-organized three-dimensional (3D) tissue cultures, have emerged as invaluable tools in developmental biology and disease modeling[2]. The recent development of multi-chamber cardioids by Schmidt et al. represents a giant leap in this field, offering a more sophisticated model that closely mimics the human heart's complexity[3].

The innovation of this platform lies in its ability to recapitulate the developmental trajectories of distinct cardiac progenitor populations: the first heart field (FHF), anterior second heart field (aSHF), and posterior second heart field (pSHF). By manipulating key signaling pathways such as WNT, Nodal/Activin, and BMP, the authors efficiently generate progenitor subsets with specific regional identities, paving the way for the formation of cardioids with in vivo-like gene expression profiles, morphologies, and functions.

A pivotal aspect of this study is the functional characterization of the five cardioid subtypes, which exhibit distinct patterns of contraction and calcium signaling, mirroring the early stages of human cardiogenesis[4]. The platform's utility is further underscored by its application in genetic and teratogenic studies, where the authors demonstrate the system's sensitivity to mutations in key cardiac transcription factors, such as ISL1, TBX5, and FOXF1, resulting in compartment-specific defects reminiscent of in vivo observations.

Moreover, the multi-chamber integration of cardioid subtypes provides insights into the self-sorting potential of cardiac progenitors and their ability to co-develop and functionally connect, akin to the *in vivo* scenario[5]. This feature is particularly valuable for studying the molecular underpinnings of cardiac morphogenesis and the directional propagation of electrochemical signals during early heart development.

The study's findings are corroborated by single-cell RNA sequencing (scRNA-seq) analysis, which offers a detailed comparison between the cardioid subtypes and in vivo cardiac embryonic chambers[6], further validating the platform's physiological relevance. The integration of scRNA-seq data with existing datasets also reveals novel markers and gene modules that contribute to our understanding of early human heart specification.

In addition to genetic studies, the cardioid platform is employed to investigate the effects of teratogens and drugs on cardiac development. The authors demonstrate the system's sensitivity to compounds such as thalidomide and retinoids[7], which induce compartment-specific defects, providing a valuable tool for teratogenicity screening and drug discovery.

Notably, this study's methodology is a masterclass in precision, utilizing a combination of two-dimensional (2D) and 3D differentiation techniques to generate progenitor subsets with distinct identities, as well as involving the temporal modulation of key cardiogenic signaling pathways to develop three main cardiac progenitor lineages, which were then differentiated into five subtypes of cardioids enriched with mature cardiomyocytes.

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Moreover, the capacity of multi-chamber cardioid with compartment-specific gene expression profiles, morphologies, and functions can facilitate a detailed investigation of the ontogeny of signal and contraction propagation between chambers[6]. Last but not the least, the platform's utility extends to pharmacological research, offering a high-throughput screening system for drug discovery and cardiotoxicity assessment. The multi-chamber cardioid's sensitivity to various compounds, as demonstrated by the study's electrophysiological and calcium transient analyses, highlights its superiority over traditional models in predicting drug effects on human cardiac tissue[8].

Schmidt et al.'s multi-chamber cardioid platform is more than an incremental step in cardiac research—it is a transformative leap. This model's ability to encapsulate the heart's developmental complexity, its susceptibility to genetic mutations, and its response to environmental factors positions it as a cornerstone for future investigations in cardiac biology. As we stand on the precipice of a new era in heart research, the implications of this work are profound, offering a robust and versatile tool for disease modeling, therapeutic development, and regenerative medicine.

Research ethics and patient consent

Not applicable

Availability of data and material

Not applicable

Declaration of conflicting interests

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Dr. Hu contributed to the study conception and design. The first draft of the manuscript was written and commented on previous versions of the manuscript by Dr. Hu. Dr. Hu s read and approved the final manuscript.

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