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Systems approaches in integrative cardiac biology: Illustrations from cardiac heterocellular signalling studies

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ABSTRACT

Understanding the complexity of cardiac physiology requires system-level studies of multiple cardiac cell types. Frequently, however, the end result of published research lacks the detail of the collaborative and integrative experimental design process, and the underlying conceptual framework. We review the recent progress in systems modelling and omics analysis of the heterocellular heart environment through complementary forward and inverse approaches, illustrating these conceptual and experimental frameworks with case studies from our own research program. The forward approach begins by collecting curated information from the niche cardiac biology literature, and connecting the dots to form mechanistic network models that generate testable system-level predictions. The inverse approach starts from the vast pool of public omics data in recent cardiac biological research, and applies bioinformatics analysis to produce novel candidates for further investigation. We also discuss the possibility of combining these two approaches into a hybrid framework, together with the benefits and challenges. These interdisciplinary research frameworks illustrate the interplay between computational models, omics analysis, and wet lab experiments, which holds the key to making real progress in improving human cardiac wellbeing.

1. Introduction

The complexity of biological systems is epitomized by large numbers of functionally diverse, and frequently multifunctional, sets of elements that interact selectively and nonlinearly to produce coherent behaviours (Kitano, 2002). The heart exemplifies this complexity, maintaining homeostasis and resilience via multifactorial regulatory systems, mediated through multiple specialised cell types (Fig. 1). Understanding the structure/function relationships between these cell types in the healthy heart is a critical precursor to any effective treatment for cardiovascular pathologies. While progress has been made to understand the role of individual components in the heart, the question of how these components function as an integrated system remains largely unanswered.

This review focuses on the diverse cell types of the adult heart, from their individual functions to their intercommunication and integration in homeostasis and disease (Fig. 1). Multiple cell types have been identified within the heart structure, but although direct contacts between these cell types have been established in mammalian hearts (Fig. 1A, black connectors), their exact function and inter-relationships are largely unclear. Furthermore, under certain conditions, cells can trans-differentiate into new functional types (Fig. 1A, blue arrows), although there is still much controversy regarding the trans-differentiation from mesenchymal stem cells to cardiomyocytes (Fig. 1A, blue dashed arrow with question mark). Experimental determination of these structural and functional relationships is extremely difficult. At this time, many cell types cannot be isolated *in vitro* or identified within *in vivo* models due to a lack of unique, specific biomarkers.

Integrative cardiac biology seeks to expedite and enhance laboratory-based approaches by also employing mathematical and computational techniques to elucidate functional relationships. While computational prediction cannot substitute for experimental validation of biological conclusions, novel biological insights can arise from carefully designed experiments based on modelling (Quinn and Kohl, 2013). In studying the cell type-specific structure and function of the adult heart, computational tools and models

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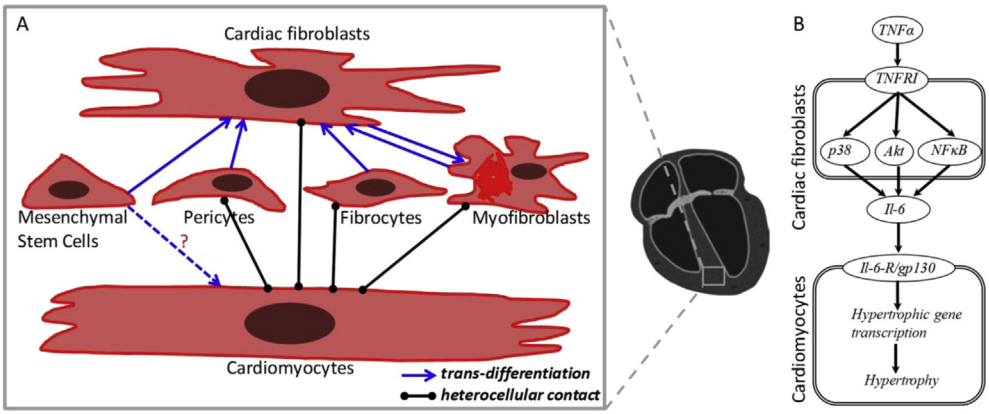

Fig. 1. The requirement for a systems-level understanding of cardiac biology. (A) The heart is a structurally and functionally complex system, which is composed of a diverse cell population dominated by cardiomyocytes by volume, and fibroblasts by number. (B) A simplified model of intercellular signalling between cardiac fibroblasts and cardiomyocytes, as mediated by Il-6. We constructed this model from multiple sources of evidence in the current literature, illustrating the power of an integrative approach for obtaining systems-level insight.

have successfully been integrated to help the design of wet lab experiments, and identify targets for further validation (Carapella et al., 2014).

Computational biology and mathematical approaches in cardiac biology take many forms, ranging from text mining to constructing machine-readable models to high-throughput data analysis (Smith et al., 2007). Among the various cell types that work in concert to maintain heart homeostasis (Fig. 1), modelling studies have focused on cardiomyocytes and cardiac fibroblasts. Cardiomyocytes account for the majority of the heart tissue by volume, due to their large size, despite comprising less than 30% of the total cell number (Frangogiannis, 2012). The much smaller cardiac fibroblasts are reported to be the most prevalent cell type in the heart (Brown et al., 2005; Porter and Turner, 2009) and are often highly active during heart injuries that cause fibrosis.

The interactions between cardiac fibroblasts and cardiomyocytes are crucial to heart development and disease, although the details of these processes are not yet fully delineated (Tian and Morrisey, 2012). Even less is known about the roles and interactions of these cells in maintaining homeostasis in the adult heart (Kakkar and Lee, 2010). This is where an integrative, or systems approach becomes very powerful. For example, co-cultured adult cardiac fibroblasts excrete several growth-related cytokines (Il-6, Il-1a) that promote hypertrophy in adult cardiomyocytes (Ieda et al., 2009). In cardiac fibroblasts, TNF-alpha induces Il-6 expression via p38, Akt and NF-kappaB (Turner et al., 2007). In cardiomyocytes, introduction of Il-6 induces activation of membrane receptors Il-6-R/gp130 that promotes hypertrophic gene transcription causing cardiomyocyte hypertrophy (del Vescovo et al., 2012). Taken together, we integrate this evidence to enable the modelling of Il-6 as a potential messenger for intercellular signal transduction between cardiac fibroblasts and cardiomyocytes (Fig. 1B).

Systems physiology of the heart is also becoming increasingly feasible with advances in computational and quantitative technologies (Noble, 2002). Mathematical modelling has been particularly successful in explaining abstract biological rules in the heart, such as metabolic aspects of the Frank-Starling law (Saks et al., 2006; Saks et al., 2009). As far back as the 1960s, researchers have turned to mathematical and computational approaches to help resolve and give insight into the complexity of heart function; the first heart models were built to address electrophysiological aspects of the heart (Hutter and Noble, 1960; Noble, 1960). A more sophisticated model was then developed to describe action potentials in the heart ventricles (Noble and Rudy, 2001). A more recent model of cardiomyocyte force and lengths was built using ordinary differential equations (Rice et al., 2008). Enormous progress has been made towards organ-level modelling of the heart (Trayanova, 2011). Ultimately, modelling of cardiac cells and tissues has promoted tremendous advances to the Cardiac Physiome, a quantitative framework of heart physiology (Bassingthwaighte et al., 2008; Clayton et al., 2010; Fink et al., 2010).

Computational modelling and methods are most effective when integrated with conventional cardiac laboratory experiments. Integration of computational models and methods into the research plan in a hypothesis-model-experiment cycle reduces the number of costly experiments and improves research outcomes. This integration produces a very powerful cross-disciplinary framework that can dramatically speed up biological discovery. There are two main approaches to mathematical modelling and computational prediction of experimental outcomes and analysis of large-scale data (Fig. 2). First, knowledge-driven modelling, which broadly resembles the mathematical forward approach where a set of equations produces a series of predictive outputs, constructs computational models based on known evidence (canonical knowledge) to predict noteworthy network properties and future experiments. This approach makes use of high-confidence data, which is often sparse, and moves towards a systems-level, or big picture, conceptual framework (Fig. 2A). Second, data-driven bioinformatics, which resembles the mathematical inverse problem where outputs are used to determine the set of equations, analyses transcriptomic and proteomic data to identify statistical and biological patterns, such as a highly abundant protein, or a set of co-expressed genes, under a certain biological context. This approach begins from a pool of high volume but low confidence data, and moves towards an exploratory, or 'promising new lead', conceptual framework (Fig. 2B).

Most scientific articles describe the end point of a complex research process, but do not necessarily capture or articulate the collaborative and integrative experimental design process. Here we present a series of case studies derived from our own collaborative research program, and that of other groups, to illustrate how the inclusion of systems biology in the experimental design provides biologists with a new conceptual framework for cardiac biology research. They demonstrate the objectives and complementarity of the forward and inverse approaches, as applied to cardiac research. We focus on the regulatory pathways of the cardiac fibroblast, to understand how they contribute to cardiac homeostasis in intracellular activity, and intercellular communication with cardiomyocytes. The function of cardiac fibroblasts in normal adult hearts is ideally suited to both a forward and inverse computational