Cardiac cellular individuality across the spectrum of heart diseases with implications for new therapeutic targets

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Background

The human heart mainly consists of contractile cardiomyocytes, but also a range of supportive cell types responsible for tissue homeostasis. Heart tissue heals poorly, mainly as cardiomyocytes do not undergo mitosis, but a large proportion of cardiomyocytes are multinucleated thought to represent completion of the S-phase of the cell cycle without cytokinesis. Heart failure (HF) is the common clinical syndrome that represents the end-stage of all heart disease, caused by loss of viable cardiomyocytes and characterized by inability of the heart to maintain sufficient output to meet the demands of the body at normal filling pressures. The cellular and molecular mechanisms for HF development and progression across different etiologies remain incompletely understood.

Aims

To (i) develop methods to characterize global transcriptional profiles of individual cells from the human heart and to apply these methods to (ii) map the transcriptomes of healthy heart tissue and across several distinct disease states, (iii) study transcriptomic profiles of multinucleated and mononucleated cells, and finally (iv) to study the role of TSLP in HF, a cytokine which emerged from a GWAS of HF mortality.

Methods and results

First, we established an analytical framework for transcriptional analysis of individual heart cells through isolation of single nuclei (study 1). We are in the process of applying these methods to explore transcriptomic variability across healthy and a range of distinct disease states (study 2), as well as multinucleated as compared to mononucleated cardiomyocytes (study 3). Finally, we have applied this method and others to describe expression of TSLP in human cardiac fibroblasts, further revealing upregulation in response to strain, transcriptional regulation by NHLH1, and are currently exploring the impact of TSLP on myocardial immune and fibrotic processes (study 4).

Significance

The studies in this thesis provide a window on transcriptional heterogeneity in the human heart across diverse conditions and carry implications for development of new therapies. TSLP represents an intriguing therapeutic candidate in HF which in preliminary analyses appears to link strain from elevated filling pressure to myocardial inflammation and fibrosis.