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Integrative network analysis reveals time-dependent molecular events underlying left ventricular remodeling in post-myocardial infarction patients

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ABSTRACT

To elucidate the time-resolved molecular events underlying the LV remodeling (LVR) process, we developed a large-scale network model that integrates the 24 molecular variables (plasma proteins and non-coding RNAs) collected in the REVE-2 study at four time points (baseline, 1 month, 3 months and 1 year) after MI. The REVE-2 network model was built by extending the set of REVE-2 variables with their mechanistic context based on known molecular interactions (1310 nodes and 8639 edges). Changes in the molecular variables between the group of patients with high LVR (>20%) and low LVR (<20%) were used to identify active network modules within the clusters associated with progression of LVR, enabling assessment of time-resolved molecular changes. Although the majority of molecular changes occur at the baseline, two network modules specifically show an increasing number of active molecules throughout the post-MI follow up: one involved in muscle filament sliding, containing the major troponin forms and tropomyosin proteins, and the other associated with extracellular matrix disassembly, including matrix metalloproteinases, tissue inhibitors of metalloproteinases and laminin proteins. For the first time, integrative network analysis of molecular variables collected in REVE-2 patients with known molecular interactions allows insight into time-dependent mechanisms associated with LVR following MI, linking specific processes with LV structure alteration. In addition, the REVE-2 network model provides a shortlist of prioritized putative novel biomarker candidates for detection of LVR after MI event associated with a high risk of heart failure and is a valuable resource for further hypothesis generation.

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1. Introduction

Left ventricular remodeling (LVR) after myocardial infarction (MI) is a strong predictor of heart failure and cardiovascular death [1]. In humans, imaging studies have confirmed a similar progressive left ventricular dilation after MI [1,2] but difficulties in accessing to myocardial samples in this setting have precluded a comprehensive assessment of the time-dependent changes occurring at the tissue level.

As an alternative to directly studying human myocardial biopsies, circulating biomarkers are easy to assess and may shed light on the pathophysiologic processes involved in heart failure and LVR [3]. Although a reasonable number of circulating biomarkers have been associated with LVR, most studies published so far have focused on one or few markers, and in most cases at a single time-point after MI [reviewed in [4]]. Therefore, the complexity and the time-dependent nature of LVR after MI in humans have not yet been addressed adequately.

It is now recognized that complex biological processes implicated in human diseases are often the result of multiple pathways interacting through interconnected networks that can best be studied using system biology approaches [5,6]. Therefore, in this study we set out to combine experimental data from a serial blood sampling throughout the first year post-MI with information contained in prior knowledge databases to allow more comprehensive, network-based mapping of the dynamic of LVR process in humans.

The aim of the present study was to gain insight into molecular mechanisms that are associated with LVR at different timepoints after MI and to discover putative novel biomarker candidates for detection of LVR after a MI event. To this end, molecular data collected in the REVE-2 study, a prospective cohort of 246 patients dedicated to the study of circulating biomarkers after anterior MI [7], has been integrated with known molecular interactions available in 12 public knowledge databases. The resulting network model has been analyzed to explore

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processes associated with LVR at different timepoints after MI and to generate hypotheses regarding putative novel biomarker candidates for timely detection of LVR after a MI event. Together, for the first time we gain mechanistic insights in post-MI LVR process in such comprehensive and dynamic way, paving the way for further testing of generated hypotheses.

2. Methods

2.1. The REVE-2 study

The design of the REVE-2 study has been published in detail elsewhere [7]; this prospective multicenter study was designed to analyze the association between circulating biomarkers and LVR. We enrolled 246 patients with a first anterior wall Q-wave MI. Inclusion criteria were hospitalization within 24 h after symptom onset and at least 3 akinetic left ventricular segments in the infarct zone at the predischarge echocardiography. Exclusion criteria were inadequate echographic image quality, life-limiting noncardiac disease, significant valvular disease, or prior Q-wave MI. The protocol required serial echographic studies at hospital discharge (baseline = day 3 to day 7), 3 months (3 M) and 1 year (1Y) after MI to assess LVR which was defined as a change in left ventricular end-diastolic volume between baseline and 1Y >20%. Serial blood samples were taken at baseline, 1 month (1 M), 3 M, and 1Y after MI. The institutional Ethics Committee (Centre Hospitalier Universitaire de Lille) approved the study; written informed consent was obtained from all patients.

The characteristics of the 246 patients included in the REVE-2 study are shown in Table 1. One-year echocardiographic follow-up was achieved in 226 (92%) patients; 87 (38.5%) patients had LVR.

2.2. Molecular data processing

The molecular REVE-2 network model was built based on the molecular data [7–13]. This included 24 molecular variables (18 proteins, 6 non-coding RNAs (5 miRNAs and 1 long non-coding RNA)), measured at 1 to 4 time points (depending on the variable, including baseline, 1 M, 3 M, and 1Y).

Based on the skewed distributions, the data for all molecular variables were log2 transformed. For variables containing zero or negative values, an offset was applied before transformation by adding the minimum and first non-zero value to the data. To test for significant changes in the measurements between the groups of patients with high LVR versus the group of patients with low LVR, an unpaired, two-sided *t*-test was performed for each variable at each given time point. The resulting *p*-values were corrected for multiple testing using the Benjamini-Hochberg FDR control procedure [14]. Unless specified otherwise, all statistical analyses were performed in R version 3.2.0 (http://www.r-project.org/).

Table 1
Characteristics of the patients included in the REVE-2 study[1].

Age, y (mean ± SD)	57 ± 14
Women	46 (19%)
Diabetes mellitus	51 (21%)
First anterior myocardial infarction	246 (100%)
Initial reperfusion therapy	
– Primary percutaneous coronary intervention	128 (52%)
– Thrombolysis alone	28 (11%)
– Thrombolysis and rescue percutaneous coronary intervention	59 (24%)
– No reperfusion	31 (13%)
Left ventricular ejection fraction, % (mean ± SD)	49 ± 8
Medications at discharge	
– Antiplatelet therapy	246 (100%)
– β-blockers	238 (97%)
– Angiotensin-converting enzyme inhibitors	238 (97%)
– Statins	231 (94%)
One-year echocardiographic follow-up	
– No. of patients with follow-up	226 (92%)
– Left ventricular remodeling[2]	87 (38.5%)

[1] Of the 226 patients with echocardiographic follow-up.
[2] Defined as a > 20% change in left ventricular end-diastolic volume between baseline and 1 year.

2.3. Building the network model

To construct the REVE-2 network model, the knowledge platform *EdgeBox* (EdgeLeap's proprietary knowledge platform) was used as a resource of public knowledge on molecular interactions. This result in embedding REVE-2 variables into their molecular context based on 12 public databases (Supplemental Table 1): ENCODE (http://encodenets.gersteinlab.org), EnsemblGenes (http://www.ensembl.org), HMDB (http://www.hmdb.ca), Microcosm (http://ebi.ac.uk/enright-srv/microcosm), miRBase (http://mirbase.org), miRecords (http://c1.accurascience.com/miRecords), miRTarBase (http://mirtarbase.mbc.nctu.edu.tw), Reactome (http://www.reactome.org), STRING (http://string-db.org), TargetScan (http://www.targetscan.org), TFe (http://www.cisreg.ca/cgi-bin/tfe/home.pl) and WikiPathways (http://www.wikipathways.org).

The REVE-2 network model embeds the REVE-2 molecular variables in an integrated network of known interactions ("edges") between molecules ("nodes"). To enable linking the variables measured in REVE-2 study to their corresponding molecules in the network model, the variable names were manually annotated to a structured identifiers database. Each variable was mapped to a corresponding entity in Ensembl Genes [15], the Human Metabolome Database [16], and miRBase [17]. In addition, the proteins were annotated to Medical Subject Headings (MeSH) [18], Ensembl Phenotypes (http://www.ensembl.org/Homo_sapiens/Phenotype/All), Disease Ontology [19], and DrugBank [20]. All variables were mapped to a database entity. In case multiple entities were identified for a single variable (e.g. when multiple genes encode for the measured protein), all annotations were included. These annotations were used to build the molecular network model.

Firstly, a set of seed nodes was retrieved from *EdgeBox*, including: 1. All molecule nodes mapping to one or more REVE-2 variables; 2. All molecule nodes that are direct neighbors of the nodes defined in step 1 and 3. All molecule nodes that are part of the shortest paths up to 3 edges between any of the nodes defined in step 1. Here "molecule nodes" are defined as nodes representing genes, miRNAs and metabolites (type "protein_coding", "processed_transcript", "miRNA", or "metabolite").

Secondly, all edges between these nodes were queried. If multiple edges between two nodes exist (e.g. multiple sources of evidence for an interaction), they were bundled into a single edge. Furthermore, three quality criteria were applied to filter out low confidence interactions: for edges representing miRNA target interactions, edges were included only when either the target has been validated experimentally (data source is miRTarBase), or the target was predicted in at least three prediction resources (Microcosm, miRecords, and TargetScan); for edges originating from STRING, edges were included only for a STRING confidence score > 800; and for edges originating from WikiPathways, edges with type "in_group" were excluded. The resulting network forms the REVE-2 molecular network model, consisting of 1310 nodes and 8369 edges.

The REVE-2 molecular network model is an exploratory model which is not built towards a specific prediction, but is aimed towards uncovering potentially relevant relations ("give me all that is known about") and generating testable hypotheses based on this model.

2.4. Topology based cluster analysis

Network clustering was performed using the InfoMap algorithm as implemented in the igraph R package (version 0.7.1) (http://igraph.org/r/) for an optimal cluster structure detection in the network. As

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