Functional annotation of cardiovascular microRNAs with GO

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http://www.ucl.ac.uk/functional-gene-annotation

Overview

MicroRNA (miRNA) regulation of developmental and cellular processes is a relatively new field of study, however, the data generated from such research has so far not been organised optimally to allow inclusion of this data in **pathway and network analyses** tools. The association of gene products with terms from the **Gene Ontology** (GO) has proven highly effective for large-scale analysis of functional data, but this is currently lacking for miRNAs. In order to address this issue we have prepared a set of comprehensive guidelines for curation of miRNAs and miRNA processing proteins, in consultation with experts in the field of miRNA research, to enable biocurators to provide consistent annotation. Using these guidelines we have built a **publicly accessible bioinformatic resource** comprising high-quality, reliable **functional annotations for cardiovascular-related miRNAs**; a resource that will be a valuable addition to the advancement of miRNA research in this field.

Gene Ontology for miRNAs

MiRNAs can directly silence mRNA targets by three main mechanisms; 1) mRNA cleavage, 2) mRNA deadenylation and 3) translational repression. GO terms are available for each of these mechanisms as child terms of "gene silencing by miRNA" (Figure 1).

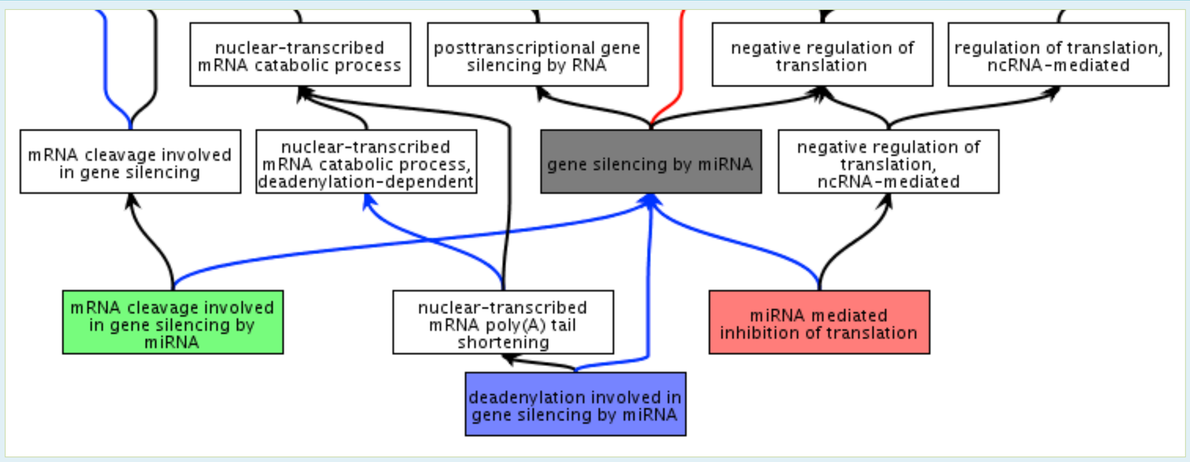

Figure 1. QuickGO view of the GO terms used for curation of the miRNA's role in gene silencing. If the exact mechanism of silencing is demonstrated, i.e. translational repression, deadenylation or mRNA cleavage, the appropriate child term of "gene silencing by miRNA" is associated with the miRNA (www.ebi.ac.uk/QuickGO).

Literature curation of cardiovascular-related miRNAs using GO

We curate primary experimental literature to capture both the role of the miRNA in gene silencing and the effect that the silencing event has on the cell or organism (Table 1), enabling researchers to easily find the biological roles of a miRNA and use these to analyse large datasets.

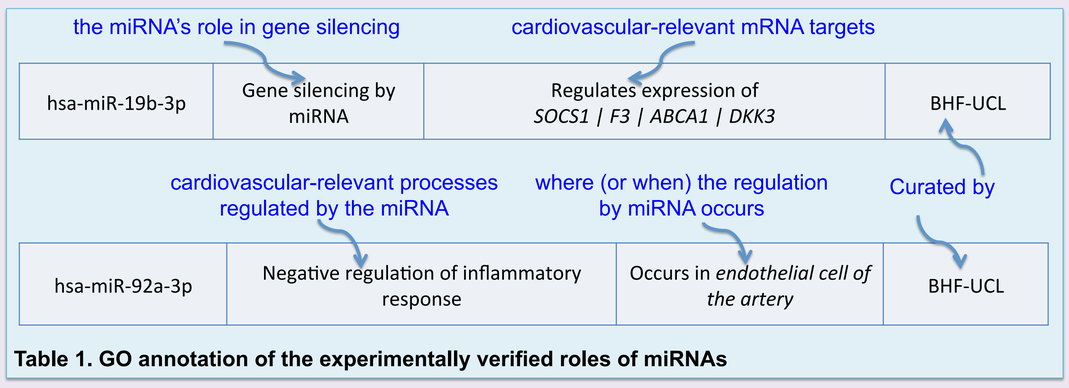

Table 1. GO annotation of the experimentally verified roles of miRNAs

Our focus is cardiovascular-related miRNAs, which are known to be important in heart disease and development (Figure 2). We take a process approach, curating all miRNAs involved in a defined biological process or pathway. Making this knowledge computationally accessible will improve interpretation of miRNA functional and network analyses.

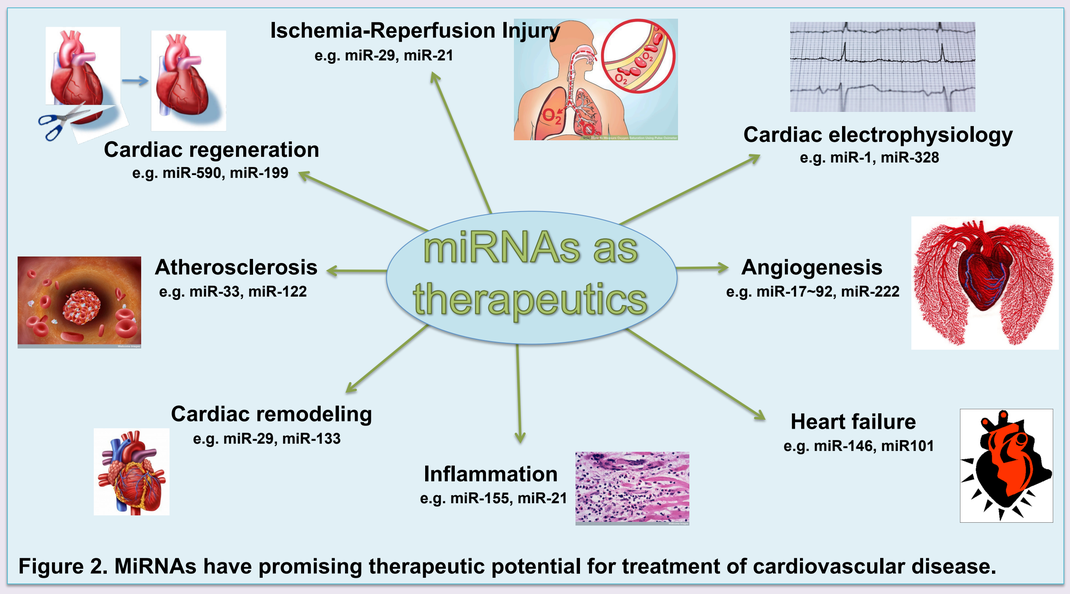

Figure 2. MiRNAs have promising therapeutic potential for treatment of cardiovascular disease.

A resource for experimentally validated miRNA targets

The molecular interactions we capture as GO annotations are exported to a PSICQUIC-compatible file, "EBI-GOA-miRNA"[1] (Table 2), that enables creation of interaction networks in tools such as Cytoscape.

miRNA	Interaction detection method	Reference	Interaction type	Target gene
hsa-miR-221-3p	experimental interaction detection	PubMed:19962668	physical association	human PTEN
hsa-miR-29b-3p	experimental interaction detection	PubMed:20657750	association	human MMP2

Table 2. Molecular interactions between miRNAs and their target genes. A simplified representation of the PSICQUIC-compatible file "EBI-GOA-miRNA" that includes the identifiers of the miRNA and target gene, the evidence of the interaction as experimental and the type of interaction, i.e. "physical association", applied when the miRNA is demonstrated to bind the mRNA listed; "association", applied when the experimental data does not demonstrate direct miRNA:mRNA binding.

As an example, the curated molecular interactions were used to create an interaction network of the targets that are experimentally proven to be silenced by human miR-21-5p (Figure 3).

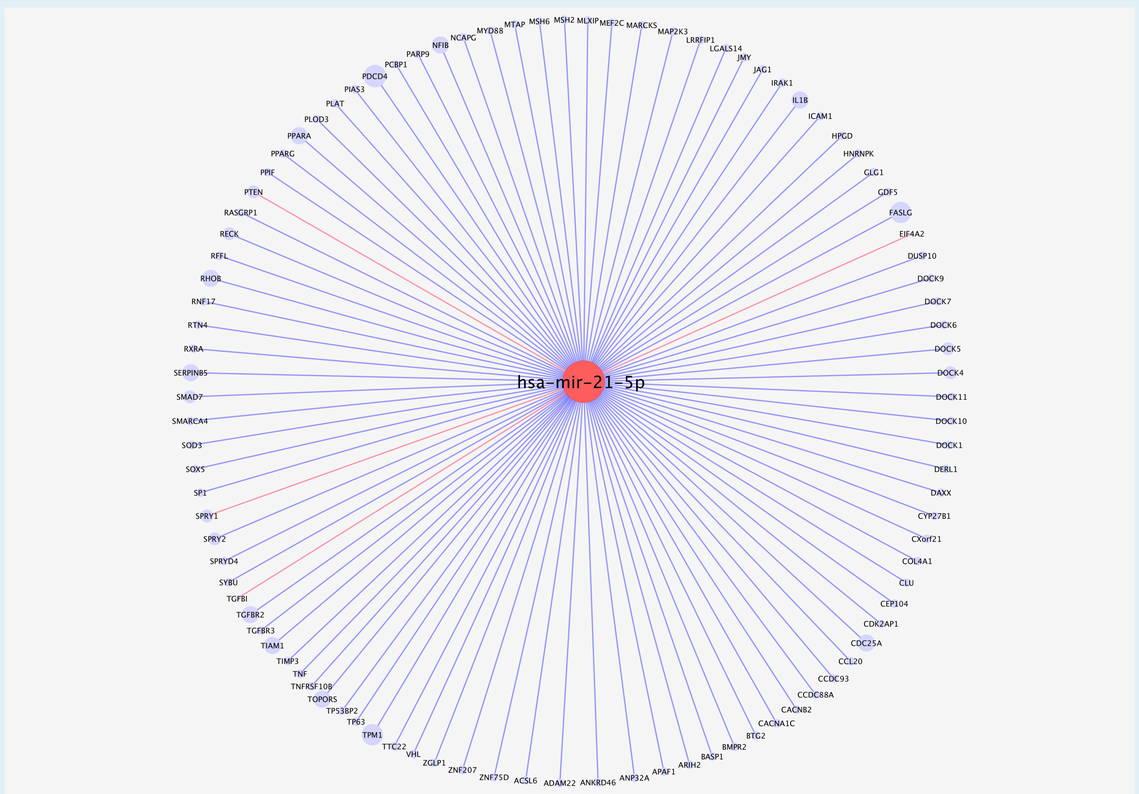

Figure 3. A network of miR-21-5p target genes. Size of nodes correlates with number of times the interaction has been captured as an annotation. Physical associations are indicated by blue edges, associations by red edges (see Table 2). The network was created using Cytoscape v3.2.1 (www.cytoscape.org) and the EBI-GOA-miRNA interaction file.

A resource for functional analysis of miRNAs

The GO annotations provided by this resource[2] can be used in functional and network analyses to give a better picture of the roles of miRNAs and their targets in a specified biological process. Figure 4 shows the network of human miR-21-5p targets involved in epithelial to mesenchymal transition-related processes, created using molecular interaction and GO annotation data.

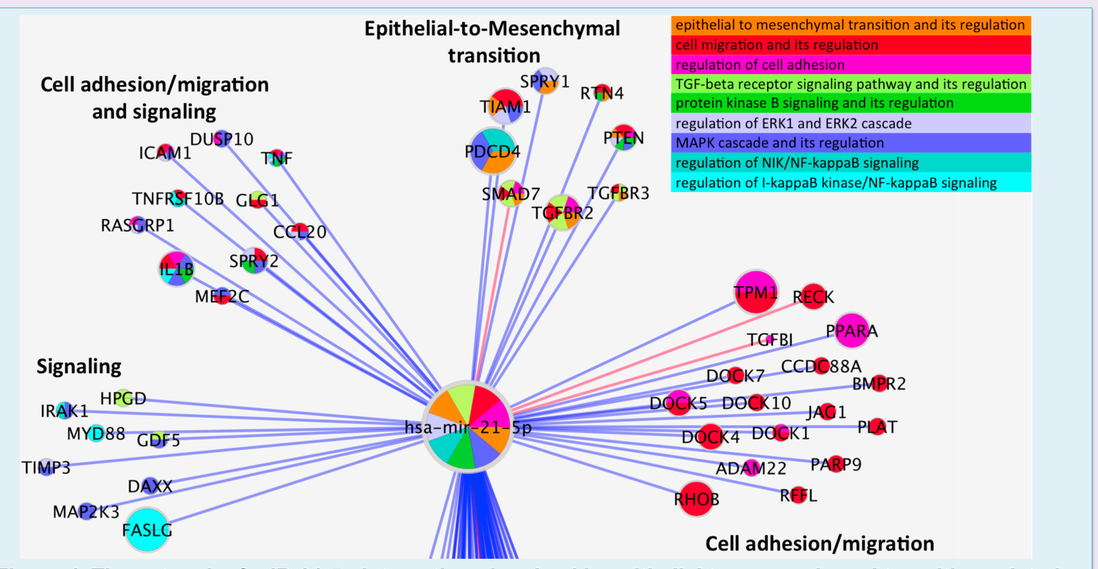

Figure 4. The network of miR-21-5p interactions involved in epithelial to mesenchymal transition-related processes. The miR-21-5p interaction network from Figure 3 was overlaid with GO annotations for miRNAs and their targets using the BinGO plugin for Cytoscape. We are working with other GO term enrichment tool providers to enable more tools to utilise miRNA annotations from our resource.

Summary

- MiRNA functional analysis is hampered by lack of bioinformatic resources
- We have created a novel resource of functional data for cardiovascular-relevant miRNAs
- Using the Gene Ontology we capture primary experimental information regarding:
  - validated miRNA targets
  - the biological roles that miRNAs regulate or are involved in
- These annotations have a positive impact on miRNA functional analysis; users can
  - reliably identify experimentally validated miRNA targets
  - determine the direct effects of miRNA function

>420 papers curated — yielding → **>3,300 GO annotations** — for → **>440 miRNAs**

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Access: 1. EBI-GOA-miRNA molecular interactions can be accessed from PSICQUIC or within Cytoscape and are available as a webservice http://www.ebi.ac.uk/QuickGO/psicquic-rna/webservices/current/search/interactor/*
2. miRNA GO annotations are available from ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/ and http://www.ebi.ac.uk/QuickGO-Beta/annotations?geneProductType=miRNA