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[1]. Our plan is to build a resource comprising high-quality, reliable functional annotations for cardiovascular-related miRNAs; annotations 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 (Fig. 1).

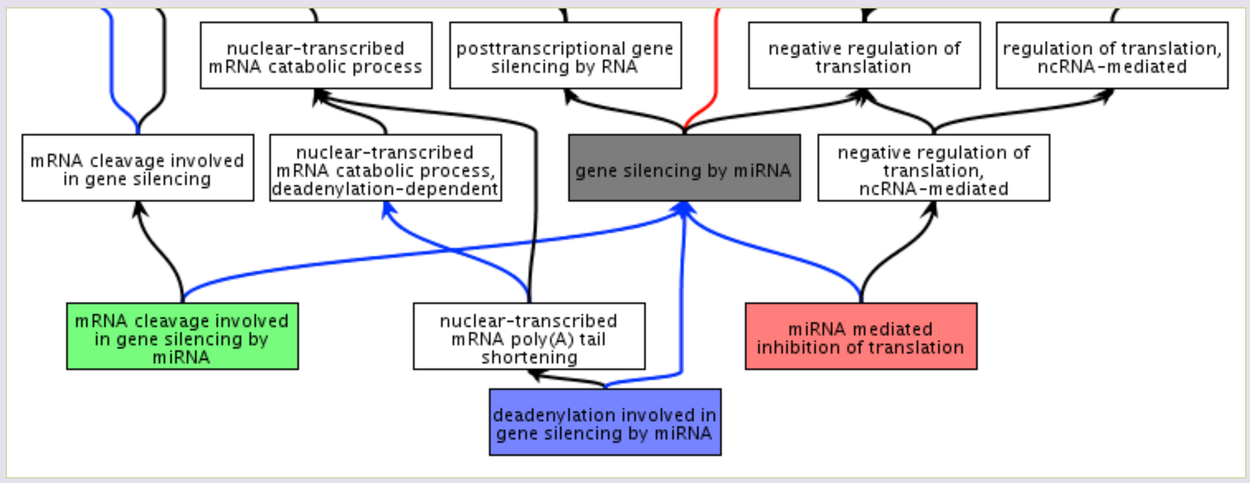


Figure 1. QuickGO view of the GO terms used for curation of the miRNA's role in gene silencing. If the exact mechanism of silencing is demonstrated, i.e. translational repression, deadenylation or mRNA cleavage, it is recommended to use the appropriate child terms of "gene silencing by miRNA". (www.ebi.ac.uk/QuickGO)

GO curation of cardiovascular-related miRNAs

We 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 roles of a miRNA and interpret large datasets.

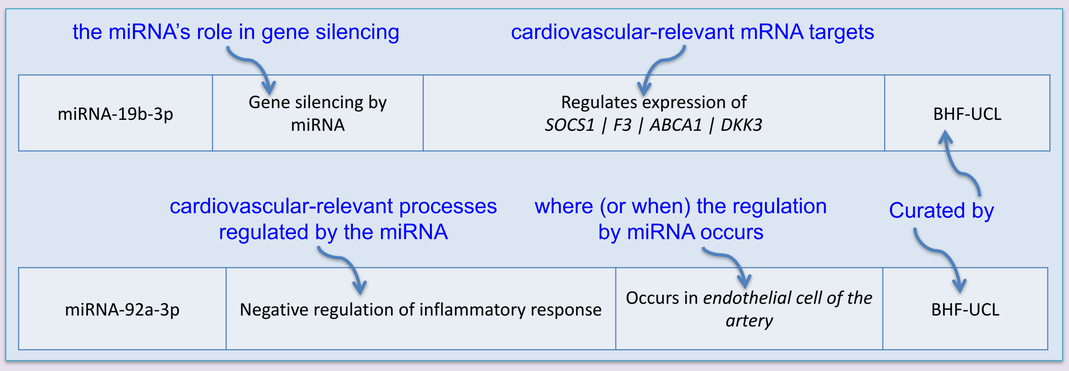


Table 1. GO annotation of the experimentally verified roles of miRNAs

Our focus is cardiovascular-related miRNAs, which are known to be important in cardiovascular disease and development (Fig. 2). We take a process approach, curating all miRNAs involved in a defined biological process or pathway. Our current projects include; ***cardiac electrophysiology***, ***aortic aneurysm*** (blood vessel integrity) *and* ***cardiac regeneration***.

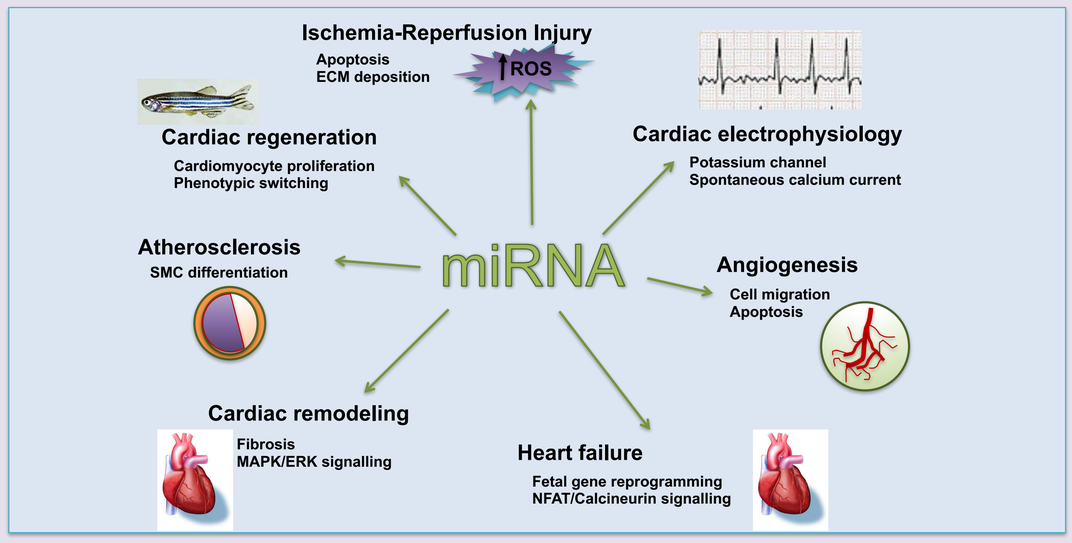


Figure 2. The cardiovascular development and disease processes known to be regulated by miRNAs.

Capturing the role of miR-29b in blood vessel extracellular matrix assembly

GO annotations describing the roles of miRNA-29b in extracellular matrix assembly were made by biocurators identifying evidence for the gene product:GO term association in the experimental literature. Contextual information, such as targets of processes, was also included (Table 2).

miRNA	Role	Target or context	Reference for evidence[2]	Curated by
miRNA-29b	Gene silencing by miRNA	Regulates expression of *COL1A1*	PMID:22269326	BHF-UCL
miRNA-29b	Negative regulation of extracellular matrix assembly	Occurs in *fibroblast of the aortic adventitia* Part of *blood vessel remodeling*	PMID:22269326	BHF-UCL

Table 2. GO annotations describing the role of miRNA-29b in gene silencing of collagen 1A1 and inhibition of extracellular matrix assembly. For clarity, not all fields of the annotation are shown, e.g. object identifiers, evidence codes.

The gene target information captured in GO annotations can be used to create a network of genes that are silenced by the miR-29 family (Fig. 3).

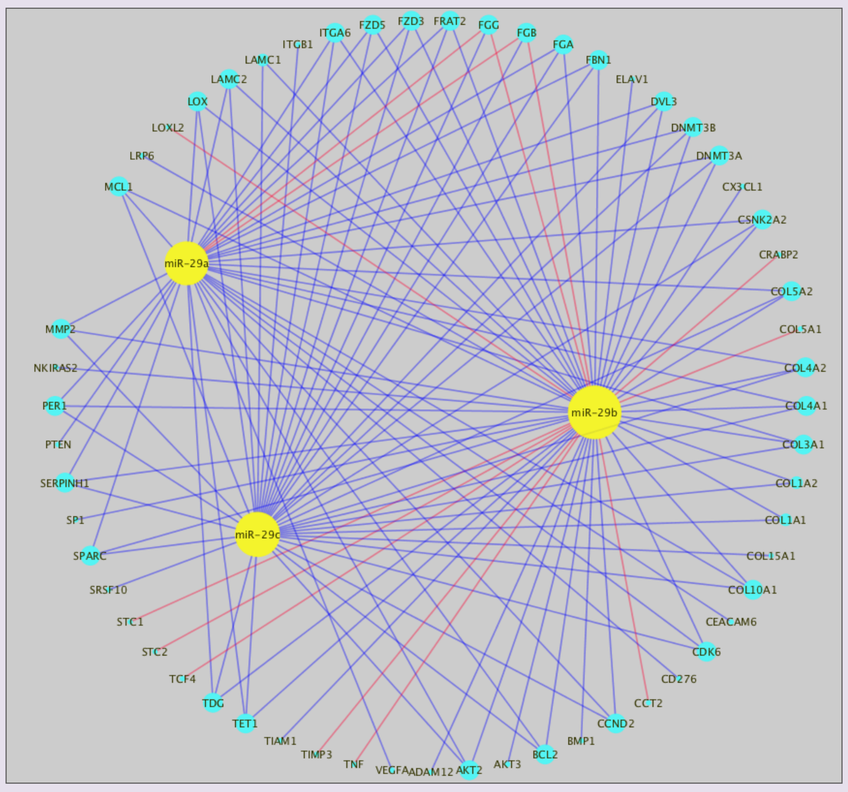


Figure 3. A network of miR-29 family target genes. Larger blue circles indicate all 3 miR-29 family members target that gene. Blue lines indicate direct targets, red lines are where the directness of the interaction is unknown. The network was created using Cytoscape (www.cytoscape.org).

GO annotations and their contextual information can only go so far in describing a process or pathway. The GO Consortium have developed a tool, Noctua, which can be used to link together GO annotations and their associated evidence in order to give a more complete picture of the biological roles and activities of gene products (Fig. 4).

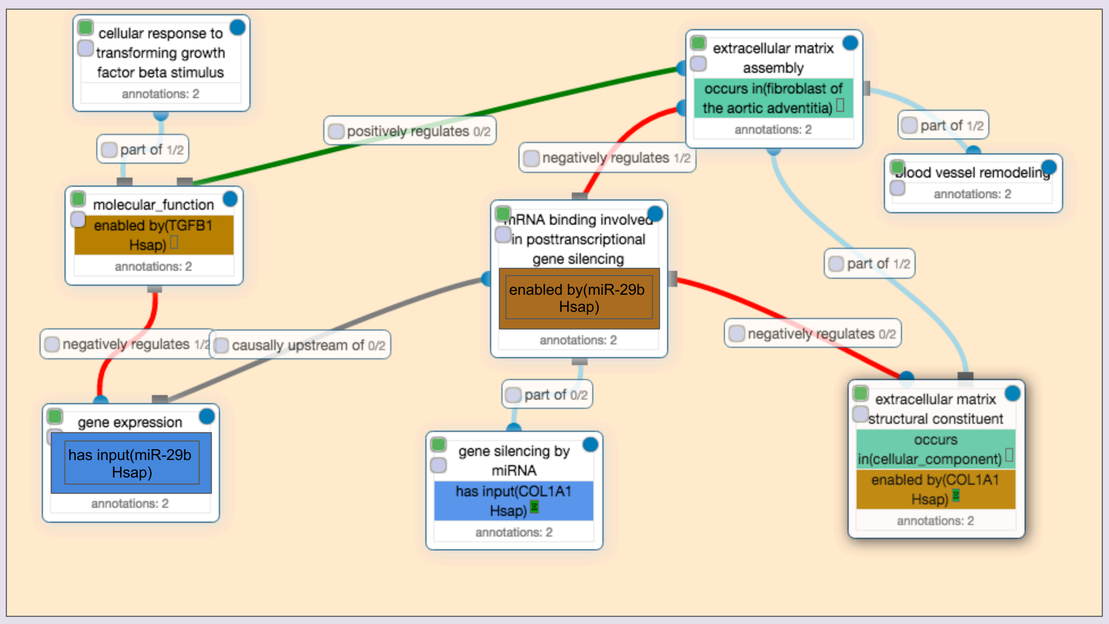
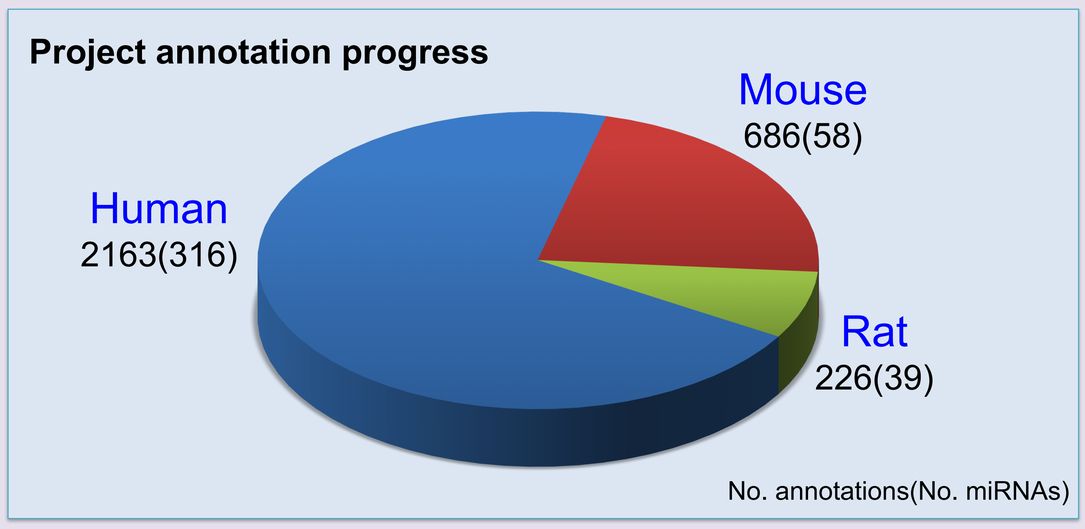


Figure 4. TGFβ1:miRNA-29b pathway model. TGFβ1 regulates expression of miRNA-29b, which subsequently regulates expression of collagen 1A1 causing a negative effect on extracellular matrix assembly in fibroblasts of the aorta[2]. The model was created using Noctua (noctua.berkeleybop.org).



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Reference:
1. Huntley *et al*. Guidelines for the functional annotation of microRNAs using the Gene Ontology. RNA. 2016 May 22(5).
2. Maegdefessel *et al*. Inhibition of microRNA-29b reduces murine abdominal aortic aneurysm development. J. Clin. Invest. 2012 Feb 122(2).