Microbiomes & miRNA's: Analyzing miRNA & Gastrointestinal Tract Microbiota Interaction Studies for the Creation of a Pilot Relational Database Concept: miR.Gut

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INTRODUCTION

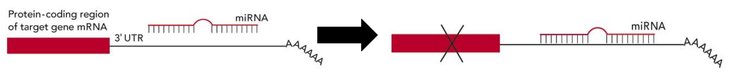
MicroRNAs(miRNA) are post-transcriptional suppressors of messenger RNA(mRNA) that promote mechanistic cleavage or translational inhibition of mRNA strands. Applications within gene expression studies, diagnostic testing, and therapeutic drugs have expanded upon the knowledge surrounding the utility of individual miRNAs.

Microbiomes are individual communities of microorganisms such as bacteria, archaea, fungi, and viruses, that inhabit areas ranging from plant roots to the human gastrointestinal tract. The human gut microbiome contains large biodiversity of microorganisms exceeding the total number of human cells; differing microbial compositions can have effects on immunity, digestion, and other aspects of the host.

Through fecal transplantation studies, researchers have concluded that foreign miRNA has the potential to affect gut microbial community composition and vice versa, offshooting studies investigating the role of host miRNAs on gut microbiota.[1]

Interaction studies between miRNAs and gut microbiota, as seen in Figure 1, have been mainly characterized by:

- **(1)** Gut microbiota products influencing miRNA gene expression in host cells,
- **(2)** Vesicle enclosed host miRNAs being taken up by microbes affecting microbe gene expression through RNA or genome binding.
- **(3)** Foreign miRNA's entering the host and then taken up by the gut microbiome.



WHY CREATE A DATABASE?

Expansion of microbiome and miRNA studies due to new sequencing technologies, has generated sets of interaction data that have yet to be organized into formal database formats.

The concept of miR.Gut, serves as a prototype database for storage, classification, and cellular effects/disease annotation of miRNA/gut microbiota interactions.

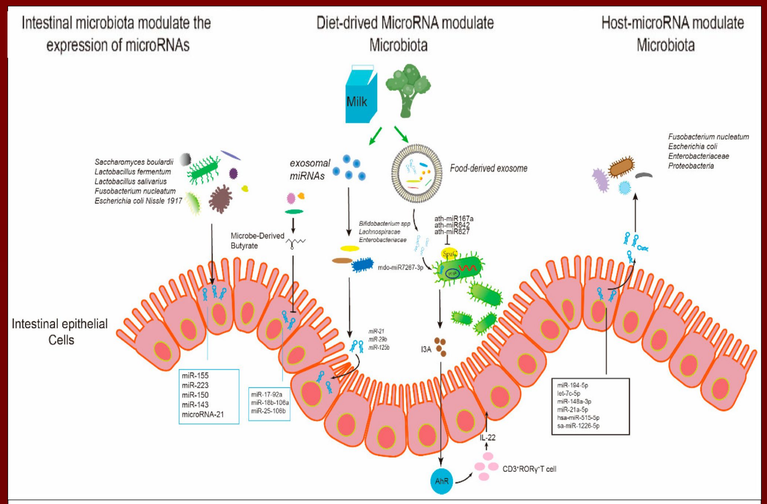


Figure 1. Representation of Commonly Studied MicroRNA/Gut Microbiota Interactions[2]

DATA IDENTIFICATION

NCBI E-Utilities, ESearch, and **NCBI Pubmed Search** were used to identify relevant literature. Using the terms, ((miRNA) OR (microRNA) OR (miR) OR (micro RNA)) AND ((microbe) OR (gut microbiota) OR (gut microbiome) OR (microbiome) OR (microbiota)), with a free text filter, 845 possible Pubmed articles were produced.

- **miRBase**: Primary miRNA database that stores miRNA sequence data, assigns naming conventions to different species miRNA
- **HGNC**: HUGO Gene Nomenclature Committee provides internationally standard naming conventions to genetic material for tracking across literature.
- **Disease Ontology**: The ontology of integrated biomedical terminology that assigns standard terms for characterization of human diseases
- **GMRepoV2**: The data repository storing names of human gut microbes along with associated disease/phenotypes, provided reformatted NCBI taxonomy tables.
- **miR2Disease**: Curated database providing comprehensive lists of all known miRNA and their associations to diseases.
- **Disbiome**: A database identifying microbial compositions associated with disease states, stores specific microbes experimentally proven to be related to a disease.

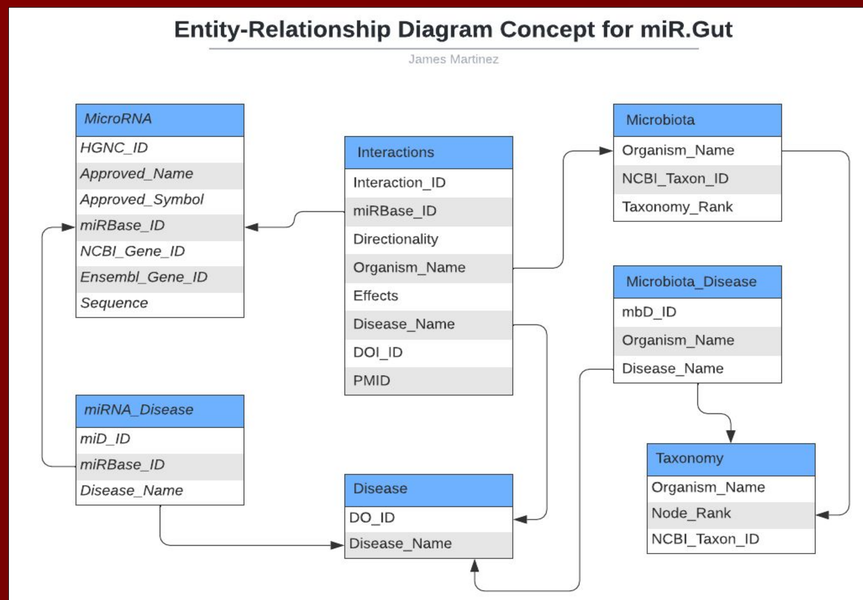


Figure 2. ER Diagram Representation of miR.Gut Based on PostgreSQL Architecture

DISCUSSION

Attempting to manually curate data did highlight aspects of literature searching:

- Reviews may contain well-condensed list of interactions for simple database insertion.
- Refinement of search parameters is necessary to improve data collection and save time.

The database was conceptualized primarily for viewing human host microRNA and human gut microbes. The problem is that many of the discovered interactions were experimentally verified through mice models. In such cases, **miRViewer** was used to identify homology levels between miRNAs from human and the experiment species to determine significance. Microbiota were also cross-checked with **GMRepoV2**.

Research has yet to determine exact mechanisms of how miRNA is able to change microbiota and vice versa. However, interest in the field is greatly developing and new studies are continuously unfolding the mystery. Workflows to experimentally observe and characterize these interactions through fecal transplantation are predicted to expand the amount of literature to come in the current decade.[3]

Interaction ID	miRBase ID	Directionality	Organism Name	Effects	Disease Name	DOI ID	PMID
MIG000001	hsa-mir-155-1	→	Fusobacterium nucleatum	Increased Proliferation, Disease Decrease	Colitis	10.1016/j.chom.2015.12.005	26764595
MIG000002	hsa-mir-1226	→	Escherichia coli	Increased Proliferation, Disease Decrease	Colitis	10.1016/j.chom.2015.12.005	26764595
MIG000003	has-mir-139	→	Blautiatia	Increased Proliferation, Disease Decrease	Colorectal Cancer	10.1128/mSystems.00205-17	29795787
MIG000004	hsa -let-7b	←	Escherichia coli O83:H1 str. NRG 857C	Decreased Expression, TLR4 Over Expression, Disease Increase	Crohn's Disease	10.1016/j.bcp.2018.08.029	30142321
MIG000005	hsa-mir-146	←	Herpes simplex virus-1	Increased Expression, NF-KB Activation, Disease Increase	Alzheimer's Disease	10.3389/fneur.2018.00145	29615954

Figure 3. Sample of Storage Format of the Interaction Table

FUTURE DEVELOPMENT AND RESEARCH

Both the database design and data acquisition have been successful, leading to the actual creation of a viewable web-interface to be the next step of the process. The website would include:

- Searchable Table View for Interactions as seen in Figure 3.
- Disease Correlation Interaction Map created through **Cytoscape**.
- Statistics Page summarizing data inside database.

Predictive RNA-RNA interaction algorithms offer increased utility:

(1) Integrated Microbial Genomes Database, and **Ensembl Bacteria** which provide whole genome scaffolds of microorganisms, can be used to create target templates for an miRNA-target prediction algorithm from scratch.

(2) Incorporating previously created algorithms is an alternative, **IntaRNA** can call upon Prokaryotic Refseq Genomes to identify mRNA targets to be targeted by either sRNAs or miRNAs, the predictions are based on interaction site availability and seed constraints.[4]

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