MIR@NT@N

meta-regulation network models

a framework integrating transcription factors, microRNAs and their targets to identify sub-network motifs in meta-regulation network models
A single element does not support the function
A single element does not support the function
At least, 2 elements are needed...
A single element does not support the function
At least, 2 elements are needed...
... to create a function

The function is supported by the interaction between elements
Interactions between elements define the biological process and some regulations control the stability of this process.
Meta-Regulation Network

Meta-regulation network model

Martinez and Walhout (2009)

KEGG
Reactome
JASPAR
PAZAR
Transfac
miRBase
microRNA.org
Argonaute
IntAct
BIND
VisAnt

...
Meta-Regulation Network – microRNAs & TFs

Meta-regulation network model

at a transcriptional & post-transcriptional level

TF regulation mechanism

JASPAR
PAZAR
Transfac
oPOSSUM
...

tf

miRNA regulation mechanism

miRBase
microRNA.org
Argonaute
...

Martinez and Walhout (2009)
miRNA regulation prediction – miRBase & MicroRNA.org

miRNA→Gene


miRNA→Gene regulation prediction


miRNA definition

Stem-loop sequence M1000342

Accession: M1000342
ID: Heami-20Cb
Symbol: LGEC-MiP-2006
Description: Homo sapiens miR-20Cb stem-loop

Stem-loop

Get sequence

Comments: The mature sequence shown here represents the most commonly cloned form from large-scale cloning studies [4].

Genome context: Coordinates (GeneRIF): L1: 1092347-1092441 [+]

View: Ranking features

Clustered miRNAs: Clustered from heami-mir-200B

<table>
<thead>
<tr>
<th>Species</th>
<th>Gene Name</th>
<th>Transcript</th>
<th>Description</th>
<th>GO Terms</th>
<th>Score</th>
<th>Energy</th>
<th>Position</th>
<th>Length</th>
<th>Total Sites</th>
<th>No. Cons</th>
<th>Nr.mRNA</th>
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<td>Homo sapiens</td>
<td>KIAA1332</td>
<td>ENST00000281533</td>
<td>KIAA1332 (KIAA1332), miRNA [Source:RefSeq, db:Acc:NM_00128251]</td>
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<td>Homo sapiens</td>
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<td>ENST00000242741</td>
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<td>Homo sapiens</td>
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<td>ENST00000267112</td>
<td>Protein transport protein Sec23A (SEC23-related protein A1) [Source:Uniprot/SWISSPROT, Acc:O15345]</td>
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</tbody>
</table>

Transcription initiation factor IIE, subunit alpha (TFII-E, alpha) [Source:RefSeq, db:Acc:NM_00128251]
TF regulation prediction – PAZAR & JASPAR (TFBS)

TF→Gene

Sandelin et al. (2004)
Portales-Casamar et al. (2007)

TF→Gene regulation prediction (using JASPAR)

oPOSSUM

Ho-Sui et al. (2005)

oPOSSUM is a web-based system for the detection of over-represented transcription factor binding sites in the promoters of sets of genes.

TF definition (Position Frequency Matrix)

<table>
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<tr>
<th>ID</th>
<th>name</th>
<th>species</th>
<th>class</th>
<th>Sequence logo</th>
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<td>Homo sapiens</td>
<td>AP1</td>
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<td>Mxi</td>
<td>Mus musculus</td>
<td>I-HOG</td>
<td><img src="image" alt="Sequence logo" /></td>
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<tr>
<td>M40005</td>
<td>Agamous</td>
<td>Arabidopsis thaliana</td>
<td>MADS</td>
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<td>Araf-Ahr</td>
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<td>M40007</td>
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<td>NUCLEAR RECEPTOR</td>
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<td>Athb-1</td>
<td>Arabidopsis thaliana</td>
<td>HOMEODomain</td>
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</table>
Meta-Regulation Network – microRNAs & TFs

Meta-regulation network model

at a transcriptional & post-transcriptional level

TF regulation mechanism

JASPAR
PAZAR
Transfac
oPOSSUM
...

TF

miRNA

miRNA regulation mechanism

miRBase
microRNA.org
Argonaute
...

Protein

Protein
Meta-Regulation Network – microRNAs & TFs

Meta-regulation network model

at a transcriptional & post-transcriptional level

TF→miRNA

TF regulation mechanism

miRNA regulation mechanism

Published TF→miRNA
Mainly for Human & Mouse

Martinez and Walhout (2009)

Wang et al. (2009)

Qiu et al. (2010)

Alexiou et al. (2010)

Bandyopadhyay et al. (2010)
Meta-Regulation Network – microRNAs & TFs

Meta-regulation network model

at a transcriptional & post-transcriptional level

TF→miRNA

Promotor Prediction

TFBS Quality Score

Martinez and Walhout (2009)

Wasserman et al. (2004)
Meta-regulation network – MIR@NT@N model & database

Meta-regulation network model

TF

miRNA

Gene

Meta-regulation network database

JASPAR
PAZAR
oPOSSUM

miRBase
MicroCosm
microRNA.org

Ensembl
UniHI

Full model available for 7 species
Caenorhabditis elegans
Danio rerio
Drosophila melanogaster
Gallus gallus
Homo sapiens
Mus musculus
Rattus norvegicus
...
Meta-regulation network – MIR@NT@N model & database

Meta-regulation network model

TF

miRNA

Gene

Meta-regulation network database

JASPAR
PAZAR
oPOSSUM

miRBase
MicroCosm
microRNA.org

Ensembl
UniHI

Contextualization
with TFs/miRNAs/Genes
up-regulated
down-regulated

focus on major regulators and targets
and detect sub-networks motifs
Meta-regulation network – MIR@NT@N application

Meta-regulation network model

Meta-regulation network application

- Transcription Factors regulation
- miRNA regulation
- Meta-regulation Network

M@IA

Le Béchec et al. (2008)
MIR@NT@N – major TF regulators on targeted miRNA

Epithelium-Mesenchyme Transition

miRNA 200 family

hsa-mir-200a
hsa-mir-200b
hsa-mir-200c
hsa-mir-429
hsa-mir-141

Gregory et al. (2008)

Epithelium

Mesenchyme
MIR@NT@N – major TF regulators on targeted miRNA

Transcription Factors regulation

Epithelium-Mesenchyme Transition

Epithelium

TF

miRNA

Mesenchyme

Cano and Nieto (2008)

Bracken et al. (2008)

hsa-mir-200a

hsa-mir-200b

hsa-mir-429

ZEB2

ONECUT1

GABPA

NFYA

Cano and Nieto (2008)

Bracken et al. (2008)

hsa-mir-200a

hsa-mir-200b

hsa-mir-429
MIR@NT@N – major miRNA regulators on targeted genes

miRNA

miRNA regulation

Gene

Epithelium

Epithelium-Mesenchyme Transition

miRNA 200 family

Mesenchyme

hsa-mir-200a
hsa-mir-200b
hsa-mir-200c
hsa-mir-429
hsa-mir-141

Regulated genes

(132 Up or Down)

Gregory et al. (2008)

Vetter and Le Béchec et al. (2009)
MIR@NT@N – major miRNA regulators on targeted genes

miRNA regulation

Epithelium-Mesenchyme Transition

Epithelium

Mesenchyme

Cochrane et al. (2009)
Wellner et al. (2009)
Zhao and Rivkees (2004)
MIR@NT@N – networks generation

Meta-regulation Network

Epithelium-Mesenchyme Transition

Epithelium

Mesenchyme

TF

miRNA

Gene

hsa-mir-200a
hsa-mir-200b
hsa-mir-200c
hsa-mir-141

hsa-mir-429

ZEB2
NFYA
GABPA
ONECUT1
Meta-regulation Network

Epithelium-Mesenchyme Transition

MIR@NT@N – networks generation
MIR@NT@N – networks generation & analysis

Meta-regulation Network

Network motifs detection

Feed Back Loop

Feed Forward Loop

Baitaluk (2009)

Shalgi et al. (2007)

Hornstein and Shomron (2006)

Tsang et al. (2007)
MIR@NT@N – networks generation & analysis

Meta-regulation Network

Network motifs detection

Feed Back Loop

Feed Forward Loop

Burk et al. (2008)

Wellner et al. (2009)

Liu et al. (2010)

Shalgi et al. (2007)
MIR@NT@N – Literature validation

Published TF→miRNA regulations

43% TF→miRNA found by MIR@NT@N

Feed Back Loop

Feed Forward Loop

Emmrich and Putzer (2010)
Sylvestre et al. (2007)
Bendoraitė et al. (2010)
Bracken et al. (2008)
Wang et al. (2008)

Chang et al. (2008)
Wang et al. (2008)
Mott et al. (2010)
MIR@NT@N – Future plans

Integrate **expression data** to improve regulation predictions and increase the **quality** of generated networks

Take into account **Context/Time dimension** to develop a **dynamic network approach**
**MIR@NT@N**

miRNA and Transcription Factor Analysis Network

**MIR@NT@N**

### Conclusion

**Regulation of miRNA by TF**

**Meta-regulation Network**

**Network motifs detection**

Le Béchec et al. (in revision)

http://mironton.uni.lu
Thanks

Pr. Evelyne Friederich
Dr. Guillaume Vetter
Dr. Michele Moes
Aliaksandr Halavatyi

Pr. Wyeth Wasserman
University of British Columbia
Elodie Portales-Casamar

Dr. Pierre-Joachim Zindy
University of Montréal

Dr. Charles Lecellier
IGMM – UMR5535

Pr. Charles Thellier
IRCM
Dr. Anne Saumet
Questions?