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A new perspective on miRNA-mediated regulation

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$\longrightarrow$ microRNAs control every physiological process by fine-tuning some of its components.

First paradox

Computational programs identify tens or hundreds of targets for each miRNA, yet genetic studies identify a single one.

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miRNA	Genetic experiments		Number of computationally predicted targets	
	Target	Reference	TargetScan	PicTar
worm *let-7*	*lin-41*	Slack *et al.* (2000)	65	89
worm *lin-4*	*lin-14*	Ambros (1989)	22	32
fly *let-7*	*abrupt*	Ambros and Chen (2007)	50	68

Second paradox

MiRNA-mediated repression is much smaller than intrinsic, well-tolerated variations in gene expression.

Supplementary data

Third paradox

Computationnally-identified miRNA targets are poorly conserved.

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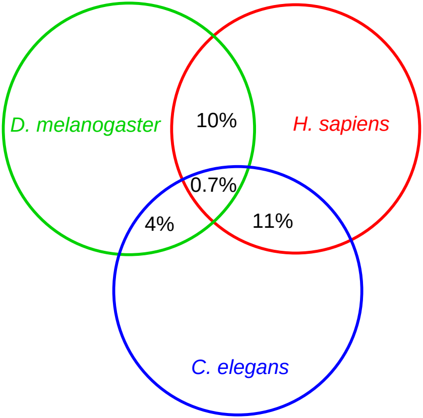

(Data from Chen and Rajewsky, 2006)

An alternative hypothesis

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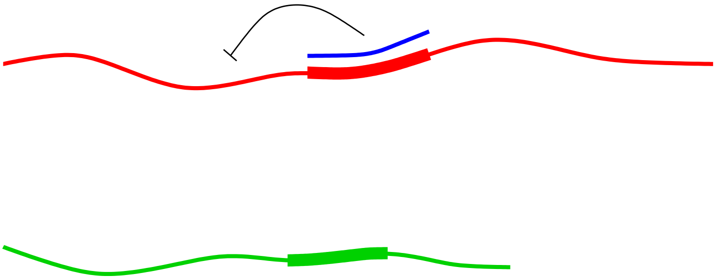

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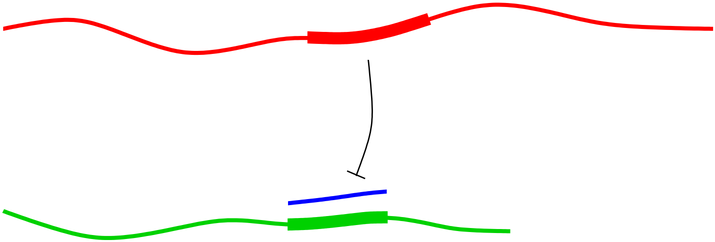

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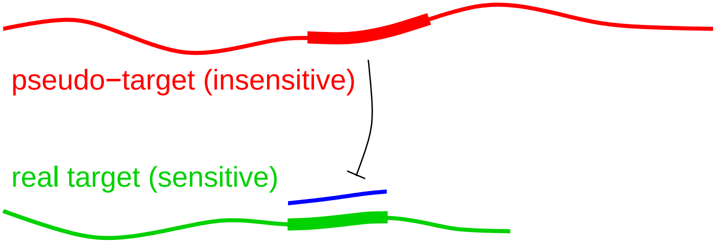

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Prediction: only dose-sensitive genes can be targeted by miRNAs.

An alternative hypothesis

Gene	Target for
worm *lin-14*	*lin-4*
worm *lin-41*	*let-7*
fly *abrupt*	*let-7*

An alternative hypothesis

Gene	Target for	Indication for dosage sensitivity
worm *lin-14*	*lin-4*	Formation of lateral alae at L4 molt is sensitive to *lin-14* dosage
worm *lin-41*	*let-7*	Worm viability is sensitive to *lin-41* dosage
fly *abrupt*	*let-7*	Dendritic branching in multiple dendritic sensory neurons is sensitive to *abrupt* dosage

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fly *abrupt*	*let-7*	Dendritic branching in multiple dendritic sensory neurons is sensitive to *abrupt* dosage
worm *cog-1*	*lsy-6*	Left/right ASE neuron asymmetry is sensitive to *cog-1* dosage
fly *hid*	*bantam*	Survival of eye bristle cells is sensitive to *hid* dosage
Mammalian myostatin	*miR-1* and *miR-206* in mutant sheep	Muscle mass and racing performance correlate with gene dosage in dogs
mouse *Ptbp1*	*miR-124*	Alternative splicing is sensitive to *Ptbp1* expression level

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A "systems biology" conception of miRNA-target interactions: functional output depends on complex interaction networks.

Integrating expression information of hundreds of genes on a single regulator.

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The pseudo-target theory could apply to every type of regulator/target interaction.

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Regulator/target relationships are not unidirectional.

Acknowledgements

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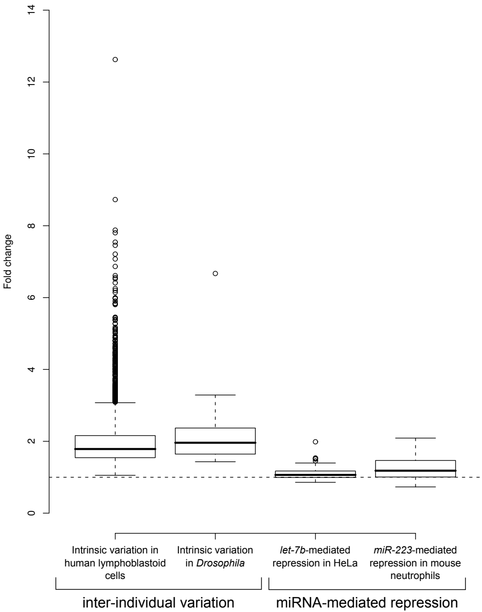
Acknowledgements

Supplementary data

- Robustness of biological pathways
- Additional support to the hypothesis
- Revisiting known properties of microRNA targets

Second paradox



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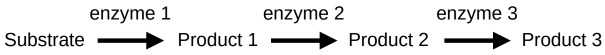

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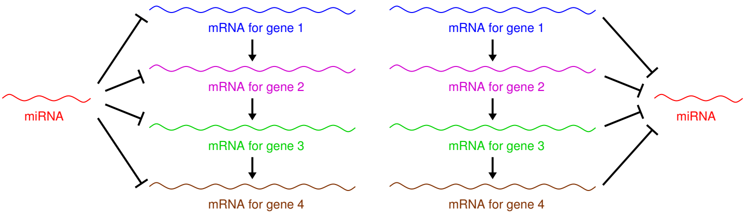
In *Arabidopsis thaliana*: microRNA-mediated repression of some targets is buffered at the macroscopic level (Allen *et al.*, 2010).

Revisiting known properties of microRNA targets



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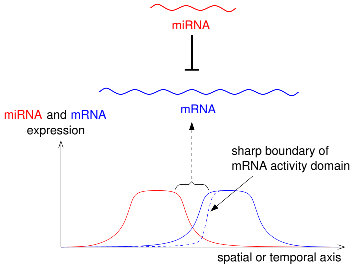

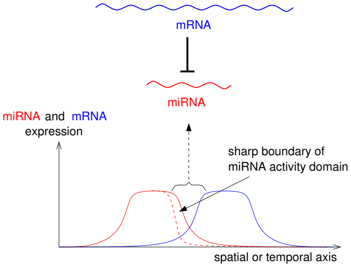

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