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Cyclin G, Developmental Stability and Transcriptional Control

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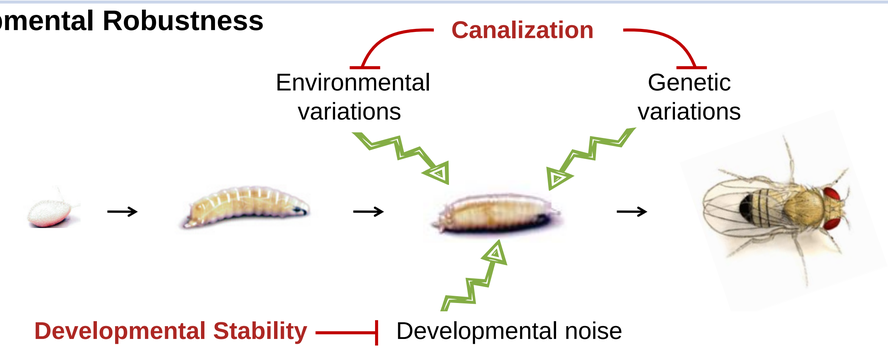
A central challenge in developmental and evolutionary biology is to understand how organisms cope with developmental noise, the stochastic variations of developmental processes. Nevertheless, **developmental stability**, the buffering of developmental noise, remains poorly understood. In bilaterians, developmental noise is estimated by **Fluctuating Asymmetry (FA)**, the random deviation from perfect symmetry within an isogenic population bred in a standardized environment. We recently reported that an individual gene, *Cyclin G* (*CycG*), encoding a cyclin involved in the regulation of transcription and in the cell cycle, plays a central role in developmental stability in *Drosophila* (Debat et al., 2011; Debat and Peronnet, 2013). Indeed, overexpression of *CycG* induces an unprecedented increase in developmental noise. Using *CycG* overexpression as a tool, we aim at highlighting gene networks underlying developmental stability.

Here, we investigate the role of *CycG* in transcription. Our data show that Cyclin G interacts with Polycomb and Trithorax factors as well as with components of the spliceosome. Furthermore, several mutations of both Polycomb/Trithorax members and components of the spliceosome increase *CycG*-induced developmental noise. Exploring the transcriptional targets of Cyclin G by RNA-seq, we have isolated a sub-network of 87 deregulated genes, mostly repressed by *CycG* overexpression, that is enriched in GO terms related to transcriptional activity. Such a sub-network might be involved in the control of developmental noise.

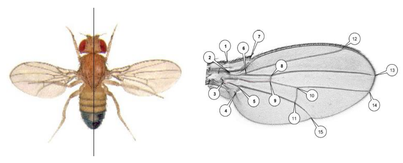
I - Developmental Stability and Fluctuating Asymmetry

Developmental Robustness

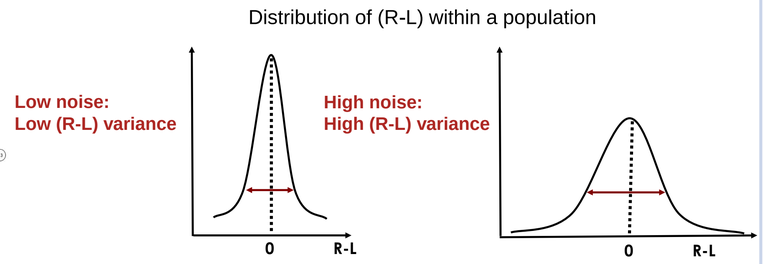


In bilaterians, developmental noise is assessed by Fluctuating Asymmetry (FA) in a population of isogenic flies raised in a standardized environment.

Measure of the centroid size of right (R) and left (L) wings using a set of 15 landmarks (geometric morphometrics)



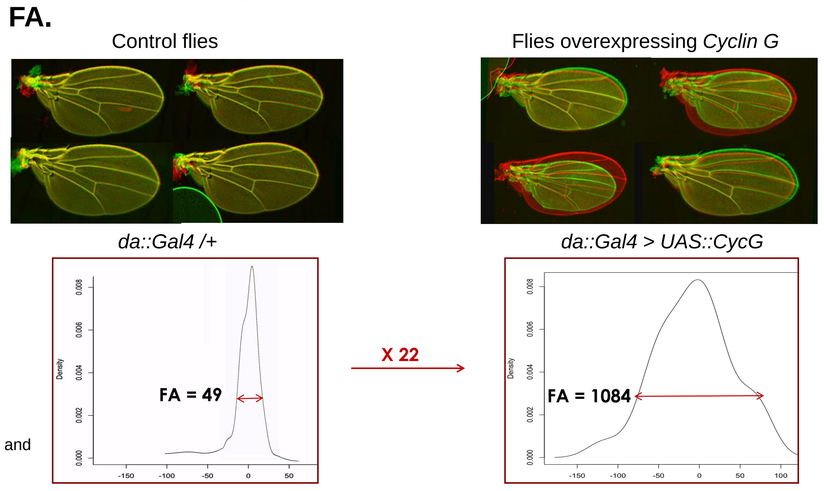
Distribution of (R-L) within a population



II - *Cyclin G* overexpression increases developmental noise

Overexpression of *CycG* in isogenic flies raised in a standardized environment induces high FA.

Control flies — Flies overexpressing *Cyclin G*



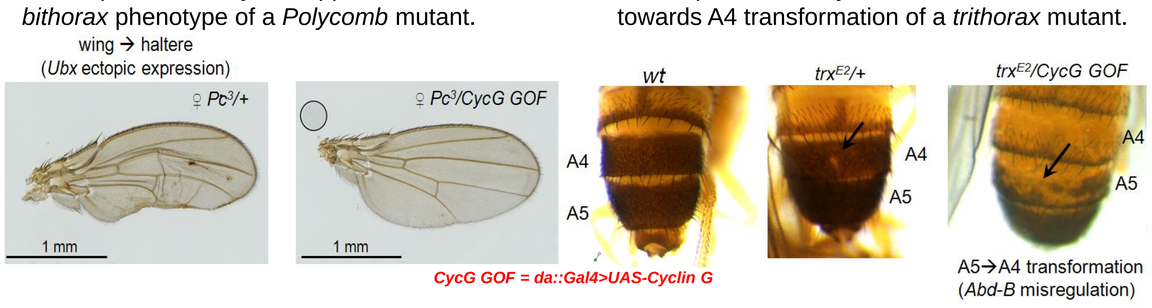
(Debat *et al.* 2011; Debat and Peronnet, 2013)

III - Cyclin G interacts with Polycomb and Trithorax factors

1) *Cyclin G* behaves as a Polycomb gene in the regulation of homeotic genes.

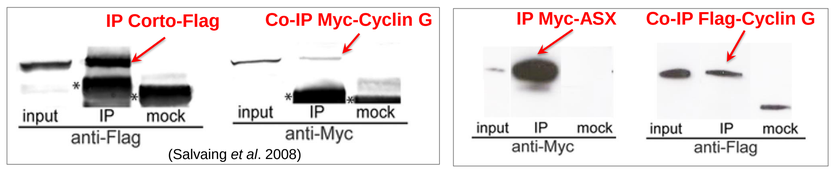
Overexpression of *CycG* suppresses the *Contra-bithorax* phenotype of a *Polycomb* mutant.

Overexpression of *CycG* enhances the A5 towards A4 transformation of a *trithorax* mutant.



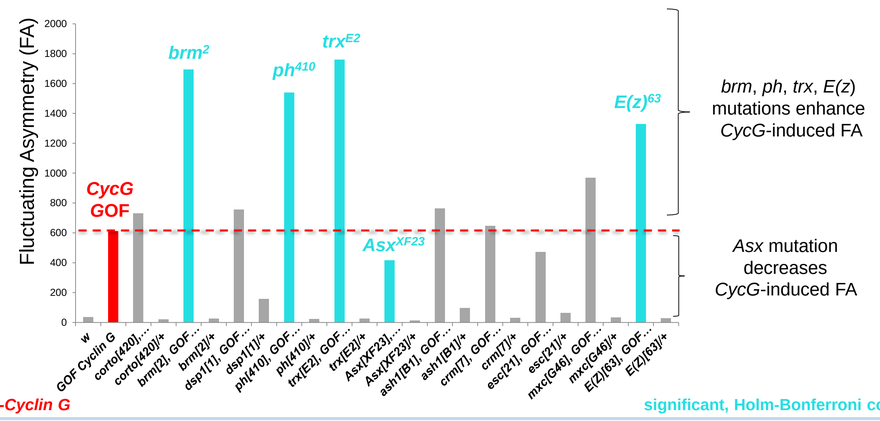
CycG GOF = da::Gal4>UAS-Cyclin G

2) Cyclin G directly interacts with two chromatin regulators of the Enhancers of Trithorax and Polycomb family (Corto, ASX).



(Salvaing *et al.* 2008)

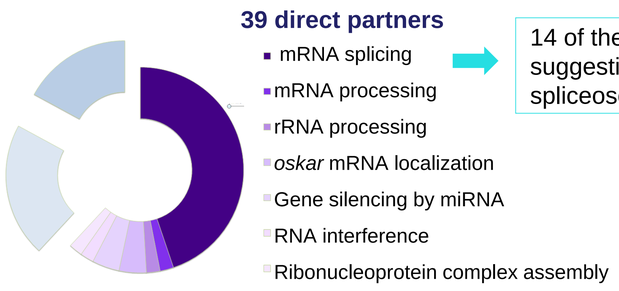
3) Several mutations of Polycomb and Trithorax genes increase *CycG*-induced FA whereas an *Asx* mutation decreases it.



CycG GOF = da::Gal4>UAS-Cyclin G — significant, Holm-Bonferroni correction

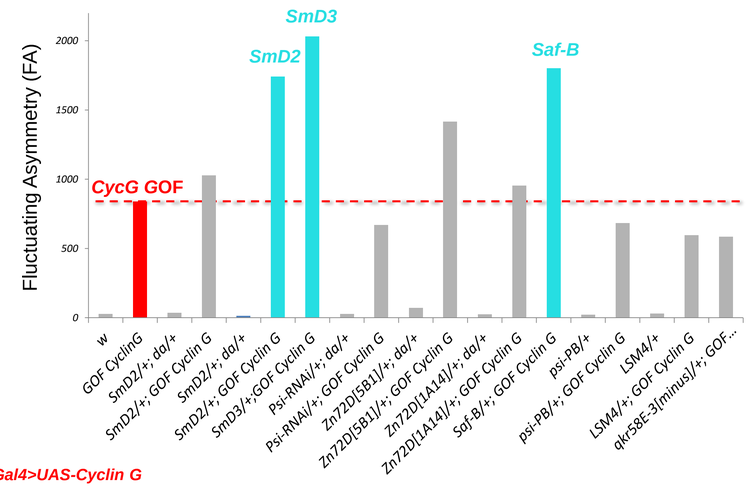
IV - Cyclin G interacts with components of the spliceosome

1) Direct partners of Cyclin G identified by pull-down and mass spectrometry (*Drosophila* Protein Interaction Map; *interfly.med.harvard.edu*)



14 of these partners are involved in mRNA splicing, suggesting that Cyclin G might interact with the spliceosome.

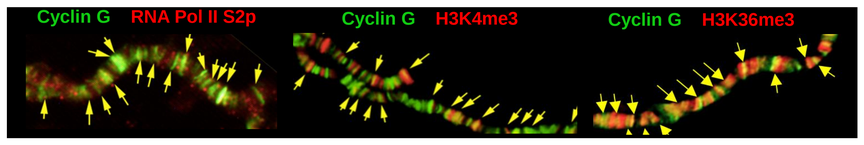
2) Several mutations of genes encoding components of the spliceosome increase *CycG*-induced FA.



CycG GOF = da::Gal4>UAS-Cyclin G

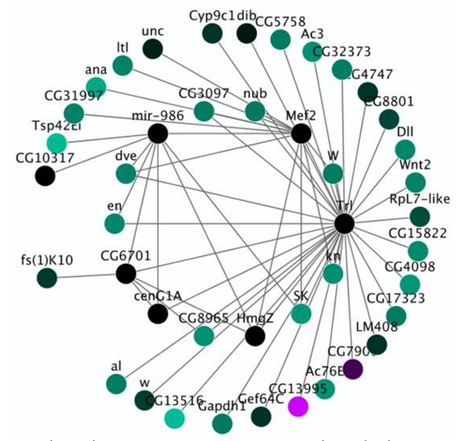
V - Cyclin G has many transcriptional targets

1) Cyclin G co-localizes at many sites with RNA Pol II, and with the active marks H3K4me3 and H3K36me3 on polytene chromosomes.



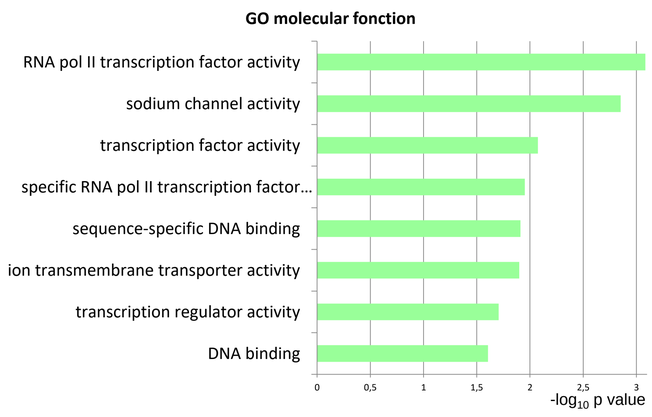
2) However, RNA-seq analysis of wing imaginal discs overexpressing *CycG* suggests that Cyclin G represses transcription of many genes; GO analysis of these genes shows an enrichment in terms related to transcriptional regulation.

Sub-network of 87 genes (Active module)



sd::Gal4 > UAS::CycG versus sd::Gal4 /+
Up-regulated genes, Down-regulated genes,
Unmodified genes
jActiveModules, Cytoscape 3.0

Gene ontology analysis of this sub-network (DAVID)



Ongoing projects

- ✓ Determine genome-wide binding sites of Cyclin G (Chip-Seq), to identify its direct transcriptional targets by correlation with RNA-seq.
- ✓ Analyze alternative transcripts in *CycG* overexpressing flies.
- ✓ Test the role of genes belonging to the identified sub-network in developmental stability.

References

Debat, V., Bloyer, S., Faradji, F., Gidaszewski, N., Navarro, N., Orozco-Terwengel, P., Ribeiro, V., Schlötterer, C., Deutsch, J.S., and Peronnet, F. (2011). Developmental Stability: A Major Role for Cyclin G in *Drosophila melanogaster*. PLoS Genet 7, e1002314.

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