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Cyclin G: A potential mitotic bookmark and its role in developmental stability through transcriptional regulation

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HAL Authorization

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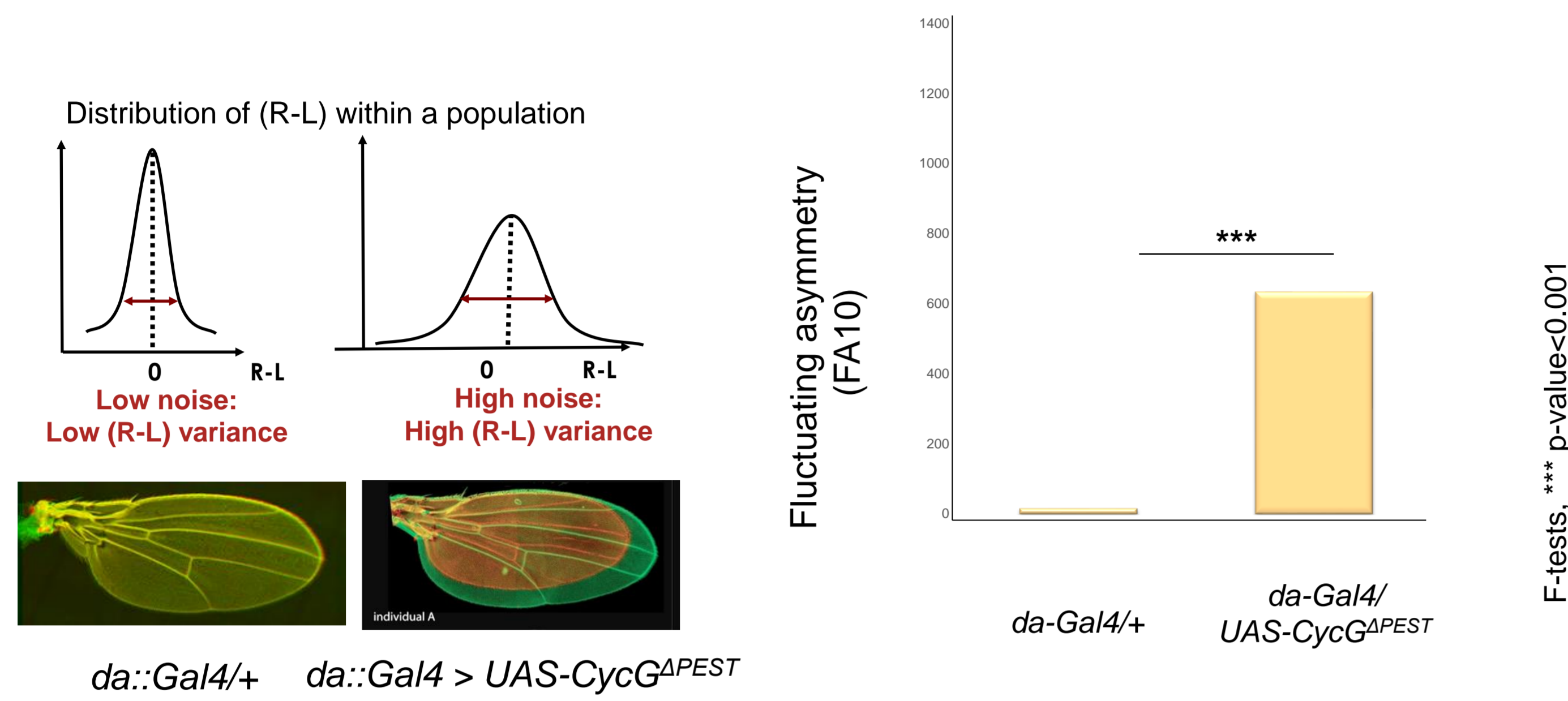
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In *Drosophila melanogaster*, the atypical cyclin, Cyclin G (CycG), is a transcriptional regulator that maintains cell growth homeostasis and developmental stability. The expression of a potentially more stable form of CycG, CycG^{ΔPEST}, has been shown to inhibit the G1/S transition of the cell cycle, slow development¹, and lead to a loss of correlation between cell size and total cell number in wings of flies². Furthermore, flies expressing CycG^{ΔPEST} have a high fluctuating asymmetry, notably of wings, indicating a high developmental noise². CycG also interacts genetically and physically with several subunits of the Polycomb PRC1 and PR-DUB transcriptional repressor complexes, which regulates developmental processes³. Mutants for these complexes exhibit increased CycG-induced fluctuating asymmetry in wings, with extreme effects in mutants for the ubiquitinase Sce of PRC1 and the deubiquitinase Calypso of PR-DUB. CycG physically interacts with both enzymes and can be ubiquitinated, suggesting that it might be ubiquitinated/deubiquitinated by PRC1 and PR-DUB, respectively. The regulation of CycG by ubiquitination might be crucial for developmental stability. Furthermore, RNA-seq experiments on wing imaginal discs expressing CycG^{ΔPEST} show that the expression of genes involved in metabolism and mitochondrial activity decreases whereas expression of genes involved in translation increases³. ChIP-seq experiments also reveal that CycG is enriched on the promoters of some of these genes. Strikingly, these promoters are bound by PRC1 in the same tissue. Interestingly, studies on HeLa cells suggest that promoters of homologous genes are bookmarked during mitosis by PRC1 ubiquitination of an unknown protein⁴. It is hypothesized that this ubiquitinated protein could be CycG that would serve as a mitotic bookmark on its transcriptional targets.

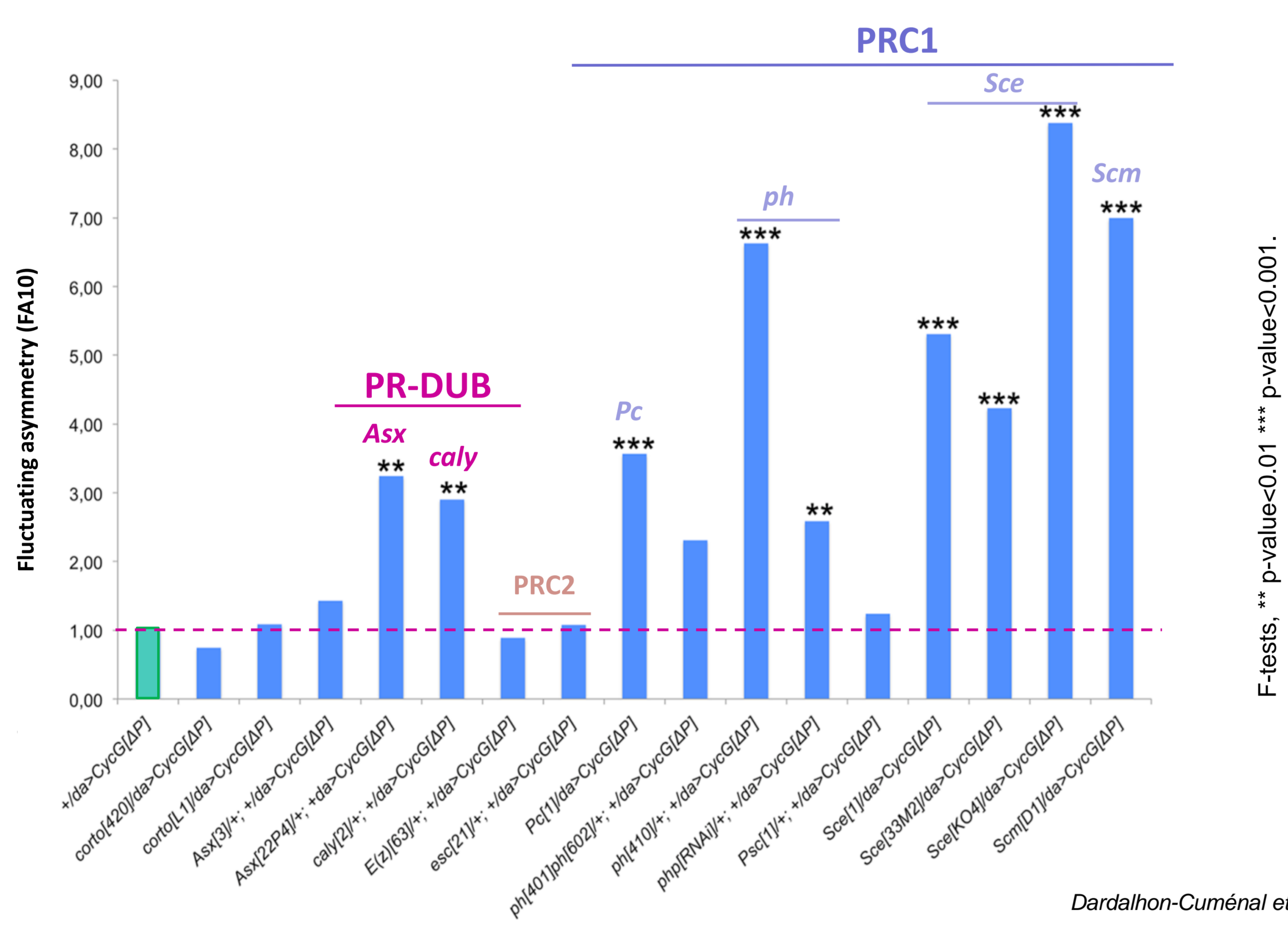
I - Developmental Stability and Fluctuating Asymmetry

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



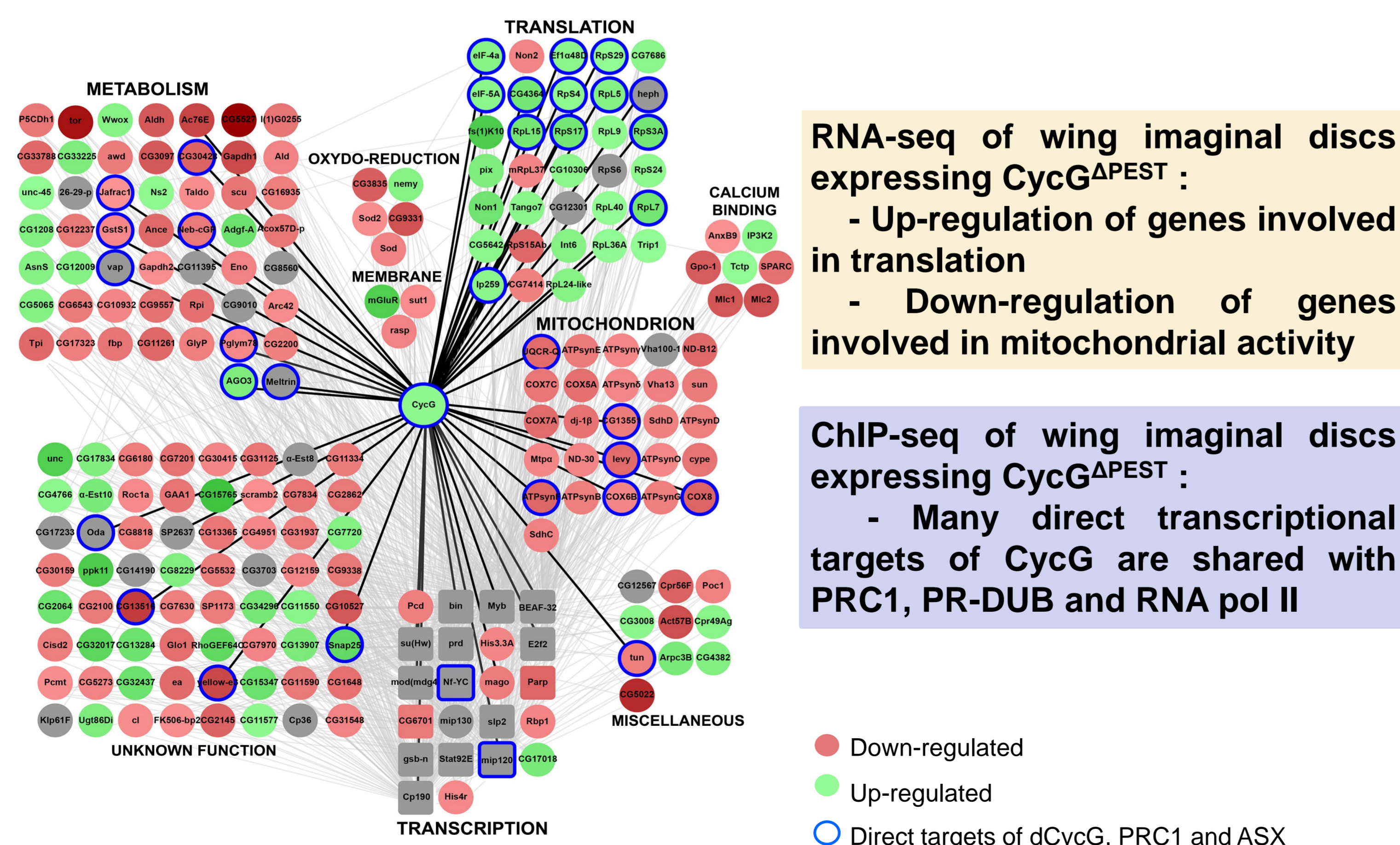
II - Cyclin G genetically interacts and shares transcriptional targets with PRC1 and PR-DUB

Mutations in the Polycomb complexes PRC1 and PR-DUB increase CycG-induced Fluctuating Asymmetry



Dardalhon-Cuménal et al. 2018

Functional subnetwork identified in wing imaginal discs expressing CycG



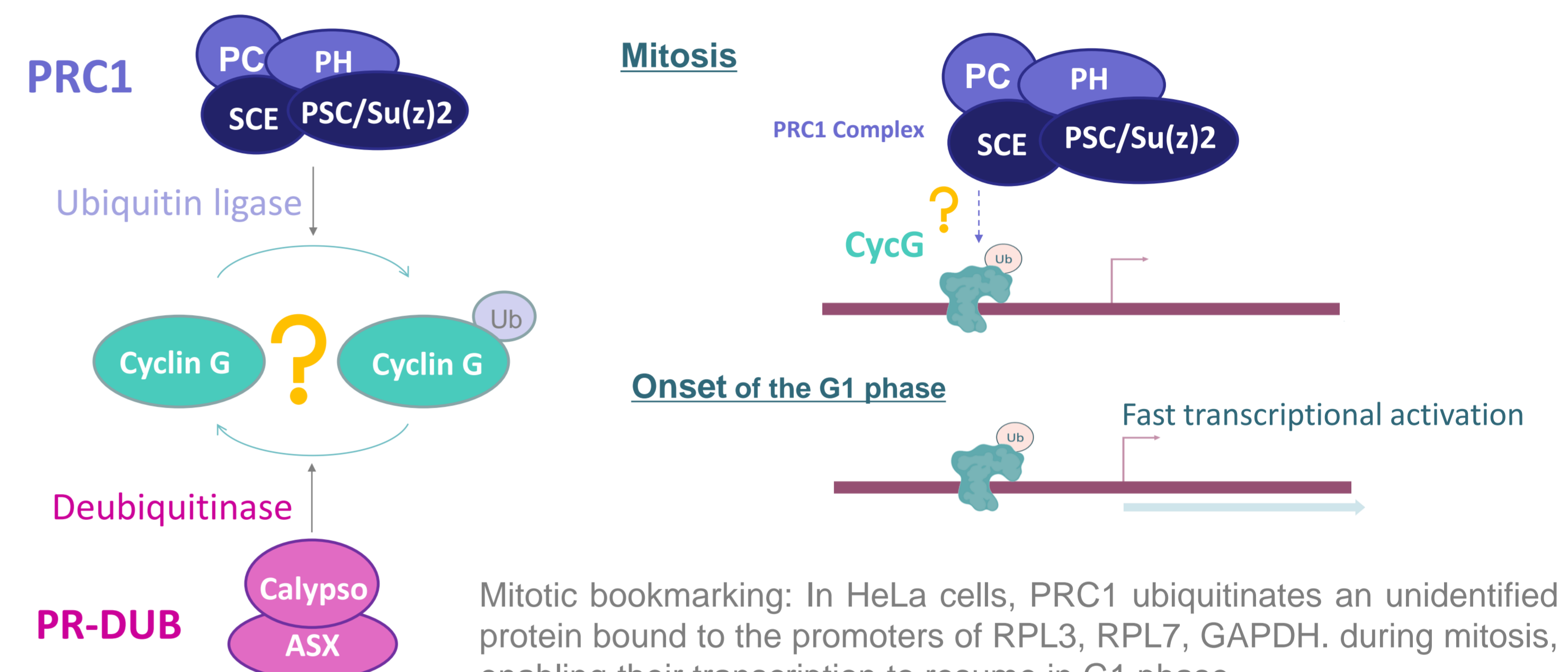
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- 4- Arora, M., et al. Nucleic Acids Res 44, 2136–2144 (2016).
- 5- Dupont CA et al. Epigenetics Chromatin. 2015 May 7;8:18. doi: 10.1186/s13072-015-0008-6.
- 6- Skene, P. J. et al. E life 6, e21856 (2017)

III - Cyclin G, a mitotic bookmark?

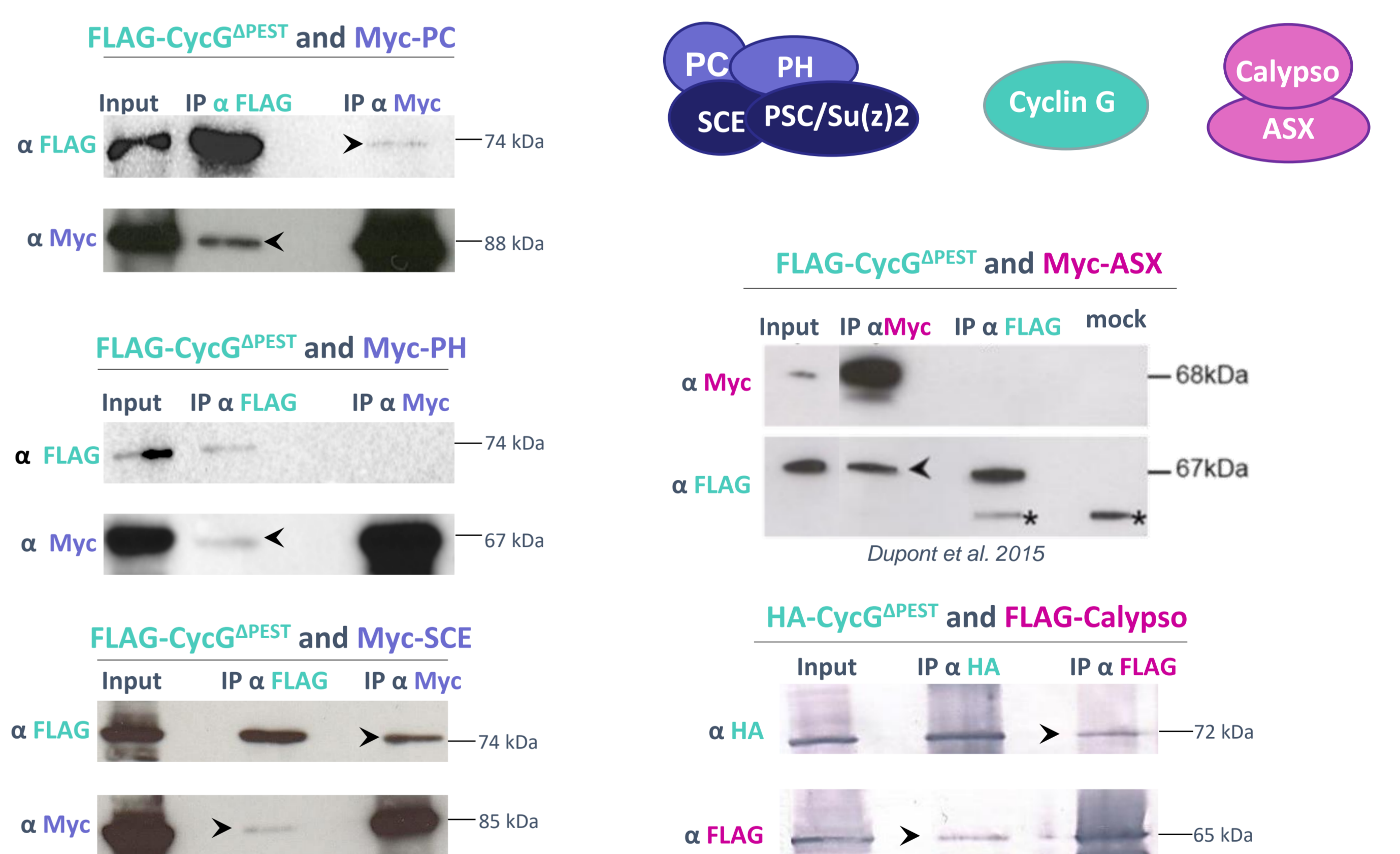
Hypothesis:

CycG, ubiquitinated by PRC1, would bind its transcriptional targets during mitosis and act as a bookmark that triggers activation of their transcription in early G1 phase.

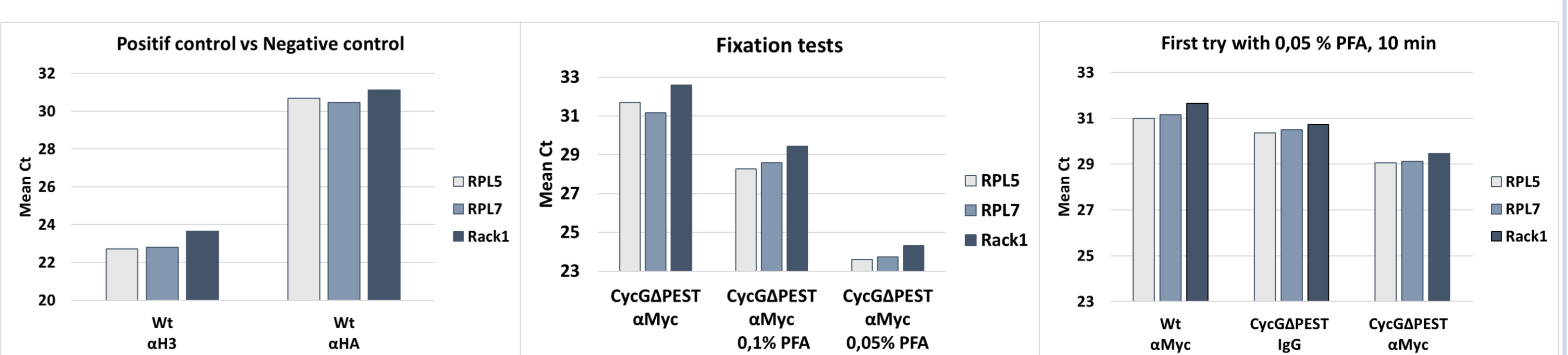
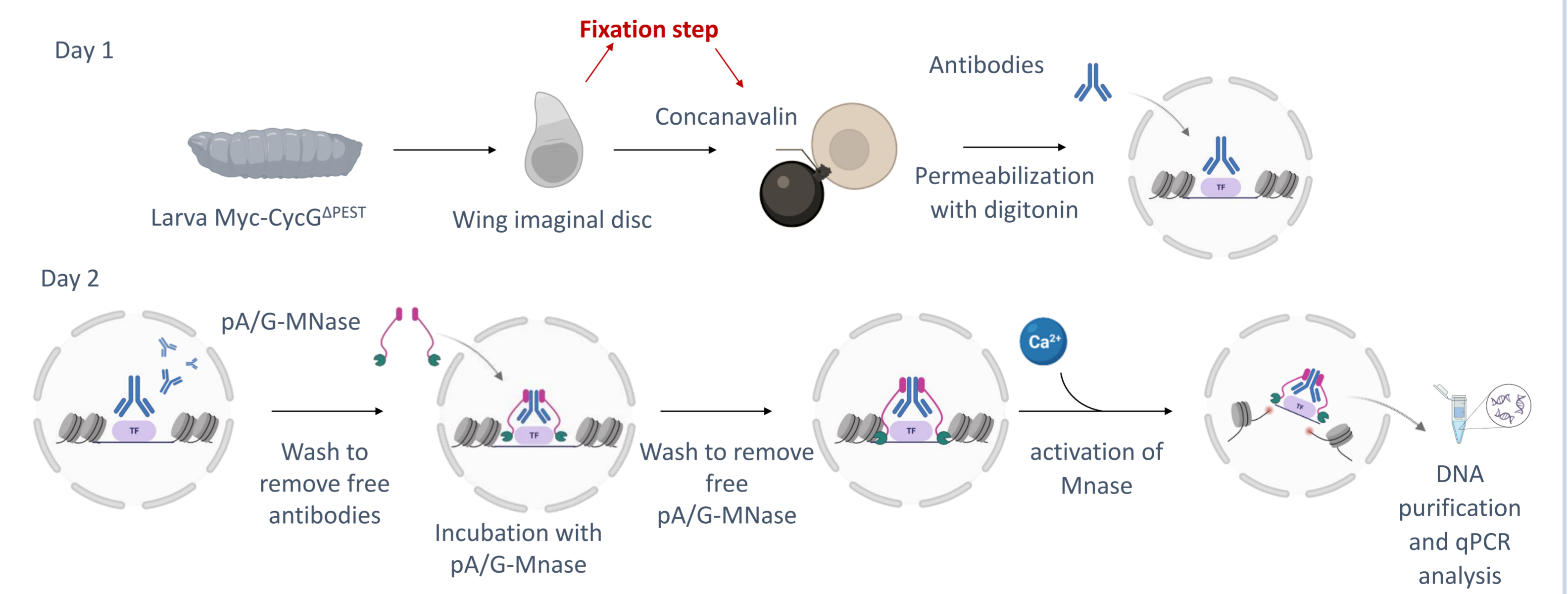


Mitotic bookmarking: In HeLa cells, PRC1 ubiquitinates an unidentified protein bound to the promoters of RPL3, RPL7, GAPDH. during mitosis, enabling their transcription to resume in G1 phase. In *Drosophila*, the promoters of homologous genes are targets of CycG and PRC1.

CycG physically interacts with PRC1 and PR-DUB



Development of the CUT&RUN technique to study the presence of CycG on its transcriptional targets during the cell cycle



Ongoing projects

- ✓ Analysis of CycG ubiquitination : Is CycG ubiquitinated/deubiquitinated during the cell cycle? and if so, are PRC1 and PR-DUB involved in this process?
- ✓ Binding of CycG to its transcriptional targets along the cell cycle by CUT&RUN on flow cytometry sorted cells : Is CycG involved in mitosis bookmarking of these genes?