Essay

Robustness of Biological Systems: A New Class of Compensation Mechanisms for Compromised Polycomb Function by miRNA-Dependent Feed-Forward Loops

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Posted Date: 24 March 2026

doi: 10.20944/preprints202603.1944.v1

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Robustness of Biological Systems: A New Class of Compensation Mechanisms for Compromised Polycomb Function by miRNA-Dependent Feed-Forward Loops

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Abstract

Biological systems such as gene regulatory networks (GRNs) acquire robustness by feedback and feed-forward loops. Although many adaptations and robustness of biological systems seem to be implemented through feedback loops, feed-forward loops were demonstrated computationally and in synthetic biology applications to be as effective as feedback loops.

Keywords: miR164B - CUC2; robustness of biological systems; compensation mechanisms; feed-forward loops; miRNAs in gene regulatory networks (GRNs)

1. Robustness of Biological Systems by Feedback and Feed-Forward Loops

Biological systems such as gene regulatory networks (GRNs) acquire robustness by feedback and feed-forward loops (Figure 1A-E). Positive feedback loops result in the gradient upregulation of their nodes (components). A well-known example in plants is the interaction of the floral activators LEAFY (LFY) and APETALA1 (AP1) (Figure 1A); their positive feedback regulation facilitates the sharp phase transition from vegetative to reproductive development (Liljegren et al., 1999). The main function of negative feedback loops is to maintain the homeostasis of biological systems, such as the negative feedback loop of the signal peptide CLV3 and the pluripotent transcription factor WUS, which maintains the homeostasis of shoot stem cell niches in Arabidopsis (Brand et al., 2000; Doerner, 2000). Although the *CLV3-WUS* negative feedback loop is often present as an elegant system balancing the expression of two genes (Figure 1B), ongoing research on *CLV3-WUS* signaling is discovering increasingly more modifiers and additional feedback loops that stabilize the system (Müller et al., 2006; Somssich et al., 2016; Müller-Xing and Xing, 2021). Therefore, it is reasonable to assume that the majority of biological systems are far more complex than the initially straightforward models of biological network architecture imply. Theoretically, coherent feed-forward loops with three nodes can have four different configurations (Figures 1C-F) (Mangan and Alon, 2003). There are also four types of incoherent feed-forward loops, but here we focus on the one with only negative interactions (repression) between the three nodes (Figure 1G). Although many adaptations and robustness of biological systems seem to be implemented through feedback loops, feed-forward loops were demonstrated computationally and in synthetic biology applications to be as effective as feedback loops (Le and Kwon, 2013; El-Samad, 2021; Weldemichael et al., 2022).

 doi:10.20944/preprints202603.1944.v1

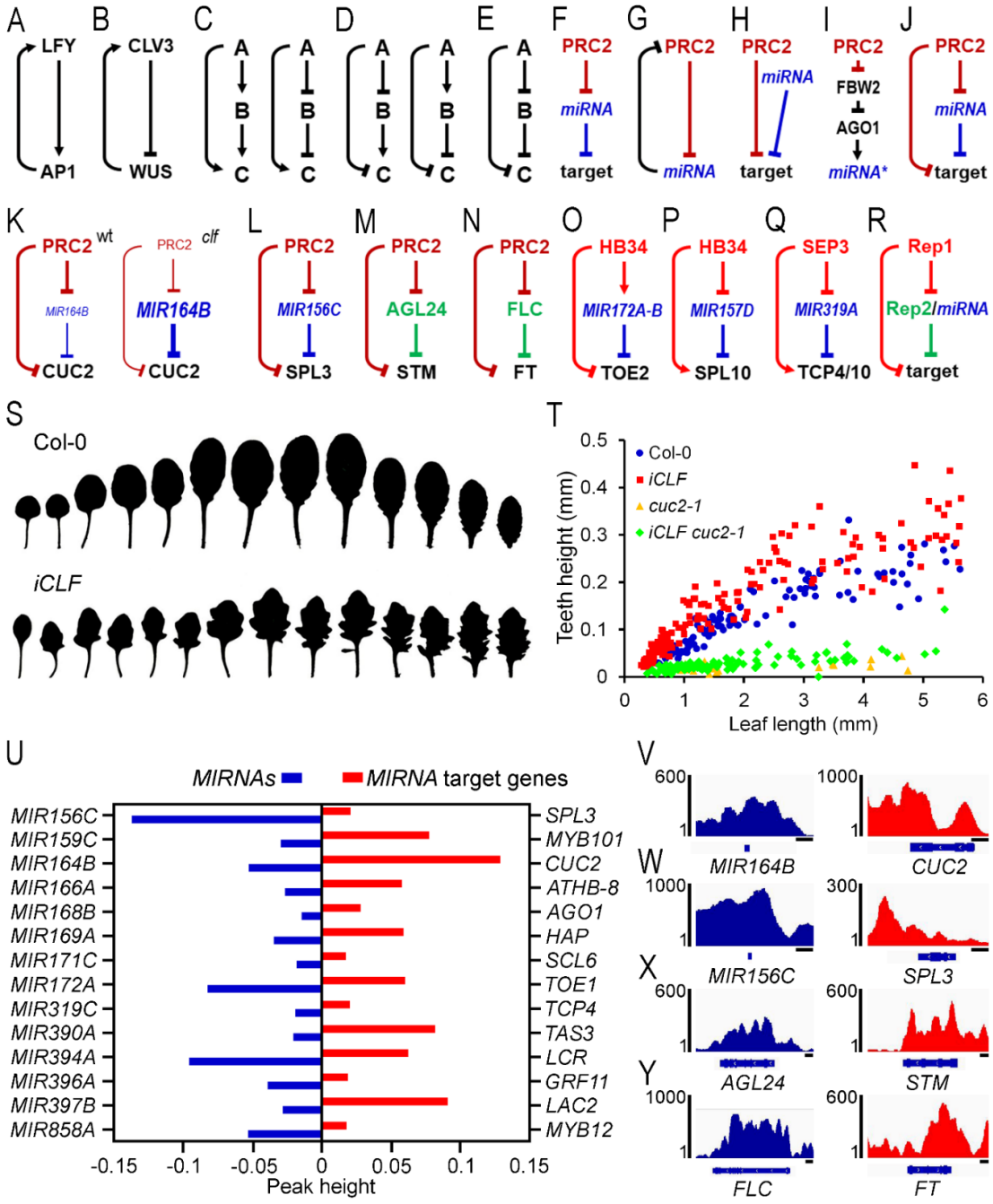

Figure 1. (A-E) Illustrative examples of feedback (A-B) and feed-forward loops (C-E): (A) LFY and AP1 form a positive feedback loop with 2 nodes; (B) CLV3 and WUS form a negative feedback loop with 2 nodes; (C) two types of coherent positive feed-forward loops with 3 nodes; (D) two types of coherent negative feed-forward loops with 3 nodes; (E) an incoherent feed-forward loop with 3 nodes (beside directly repressing C, A positively regulates C by repression of the repressor B; from a different perspective, B functions as a failsafe switch of A). (F-J) Diverse relationships between PRC2 and miRNAs: (F) PRC2 indirectly activates *miRNA* targets by repressing the corresponding *miRNA*; (G) double negative feedback loop between PRC2 and miRNAs; (H) simultaneous repression of a common target by PRC2 and a miRNA; (I) PRC2 represses the F-box gene FBW2 that in turn targets AGO1 that is required for miRNA (*) function in general; (J) PRC2-*MIRNA*-target incoherent feed-forward loop (compromised PRC2 function results in derepression of the *MIRNA* and target gene; the upregulation of the *miRNA* serves as a failsafe switch that ensures wild-type protein levels of the target). (K-N)

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Examples of incoherent feed-forward loops compensating compromised PcG activity in plants: (K) PRC2-*MIR164*-CUC2 in wild-type (wt) and *clf-81 sep3-2* (*clf*) mutants; (L) PRC2-*MIR156*-SPL3; (M) PRC2-AGL24-STM; (N) PRC2-FLC-FT. (O) HB34-*MIR172A/B*-TOE2 coherent negative feed-forward loop. (P) HB34-*MIR157D*-SPL10 coherent positive feed-forward loop. (Q) SEP3-*MIR157D*-SPL10 coherent positive feed-forward loop. (R) General model of an incoherent feed-forward loop with two (transcriptional) repressors or one repressor and one miRNA, which can function as a compensation mechanism. (S) Strong leaf serration in plant lines with strongly depleted PcG activity (*iCLF*: *clf-28 swn-7 CLF-GR*) compared to wild-type (Col-0). (T) Loss of *CUC2* suppresses leaf serration in *iCLF* also in the later phase. (U) H3K27me3 peak levels of selected PcG-targeted *miRNA* - *miRNA*-target pairs in Arabidopsis flowers, stage 6 (Müller-Xing et al., 2022). (V-Y) Browser screenshots of H3K27me3 levels in young flowers, stage 6; selected PcG target pairs: *MIRNAs*/Repressors and their targets: (V) *MIR164B* - *CUC2*, (W) *MIR156C* - *SPL3*, (X) *AGL24* - *STM*, (Y) *FLC* - *FT* (Müller-Xing et al., 2022).

2. Relationships of Gene Repression by Mirna and Polycomb Function

Polycomb (PcG) transcriptional and microRNA (miRNA) post-transcriptional gene repression exist in animals and plants and have been shown to be interconnected in various ways (Maugarny et al., 2024). POLYCOMB REPRESSIVE COMPLEX 2 (PRC2) silences target genes by catalyzing the methylation of Lys-27 on histone H3 (H3K27me3), a modification associated with transcriptional repression (Förderer et al., 2016), while miRNAs are short noncoding RNAs that mediate the repression of target transcripts (mRNAs) (Plotnikova et al., 2019). A first type of interaction, in which PRC2 indirectly activates miRNA-target genes through H3K27me3-mediated silencing of miRNA genes (Figure 1F), appears to be important for developmental phase transitions in plants (Xu et al., 2016). More precisely, PRC2 represses *MIR156A* and *MIR156C* by deposition of H3K27me3, which promotes vegetative phase change and floral transition (Picó et al., 2015). An animal-specific mode, in which PRC2 and miRNA pathways interact antagonistically by reciprocal inhibition, forming a double negative feedback loop (Figure 1G), leads to bistable systems contributing to cell fate decisions (Juan and Sartorelli, 2014). In a third type of interaction, PRC2 and miRNAs cooperate to provide additive repression of common targets at the transcriptional and posttranscriptional levels (Figure 1H). Although common in animals, examples in which PRC2 and a miRNA simultaneously repress a common target are still lacking in plants. Nevertheless, genes targeted by miRNAs tend to be also more frequently targeted by PRC2 than non-miRNA targets in plants (Lafos et al., 2011). In a fourth type, PRC2 prevents degradation of ARGONAUTE 1 (AGO1) that is essential for general miRNA function (Figure 1I) (Ré et al., 2020). A recent study reveals a fifth mode of interaction between PRC2 and miRNAs, in which a PcG-targeted miRNA compensates for compromised PRC2 function during Arabidopsis leaf development (Figure 1J-K) (Maugarny et al., 2024).

3. Maugarny et al. (2024) Present with mir164b-cuc2 a New Type of Compensation Mechanism for Compromised Polycomb Function by Mirna-Dependent Incoherent Feed-Forward Loops

In plants, *CUP-SHAPED COTYLEDON 2* (*CUC2*) is a key regulator of leaf serration by repressing growth in the leaf sinus and promoting outgrowth of the leaf teeth (Nikovics et al., 2006; Bilsborough et al., 2011). *CUC2* is targeted by the three members of the miRNA gene family *miR164* (*MIR164A-C*), which contributes to developmental robustness (Sieber et al., 2007). In their recent study, Maugarny et al. (2024) report an incoherent feed-forward loop that compensates for the depleted function of POLYCOMB REPRESSIVE COMPLEX 2 (PRC2), resulting in wild-type levels of CUC2 protein during early leaf morphogenesis, although *CUC2* is transcriptionally derepressed (Maugarny et al., 2024). PRC2 is a known regulator of leaf serration (Müller-Xing et al., 2014), while *CUC2* and *MIR164B* are strong H3K27me3 targets (Figure 1U,V) (Müller-Xing et al., 2022). Due to the loss of *CLF*, which encodes one of the three histone methyltransferases of PRC2, PcG function is partially compromised, leading to transcriptional derepression of *CUC2* and *MIR164B* (Maugarny et al., 2024). In this mechanism, the upregulation of *MIR164B* compensates for the misexpression of *CUC2* mRNA to

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provide wild-type CUC2 protein levels and normal leaf morphogenesis. To form this incoherent feed-forward loop, PRC2 may directly repress *MIR164B* via the deposition of repressive H3K27me3 marks (Maugarny et al., 2024).

The study of Maugarny et al. (2024) focused on one PcG gene using the *clf-81* mutation in *sep3-2* background that prevents leaf curling (Lopez-Vernaza et al., 2012). However, PRC2 contains at least four core components; two of them are encoded from three genes each (Khan et al., 2025). In contrast to plant lines with strongly depleted PcG activity that have strong leaf serration, such as *iCLF* (Figure 1S), *clf-81* mutants have a weak serration phenotype that can be more easily compensated for. Since the phenotypes and the loss of H3K27me3 levels strongly vary between different PcG mutants (Schubert et al., 2005; Lafos et al., 2011), future studies should examine the level of compensation of *CUC2* derepression by *MIRNA164B* in the various PcG mutants. In *clf-81* mutants, the H3K27me3 levels were not significantly reduced neither at the *MIR164B* nor at the *CUC2* gene locus (Maugarny et al., 2024). Therefore, PRC2 could also act indirectly via another factor that is directly repressed by PRC2 and H3K27me3; this factor would in turn repress *MIR164B*. Nevertheless, *MIR164B* is essential for the compensation mechanism since simultaneous impaired *MIR164B* and *CLF* functions lead to even higher CUC2 protein levels and stronger leaf serration. Therefore, the derepression of *MIR164B* can negatively regulate CUC2 during leaf morphogenesis (Figure 1K). This incoherent feed-forward loop generates a *MIR164B*-dependent compensation mechanism following compromised PRC2 function, which provides robustness to CUC2 protein levels under all environmental conditions tested, though with varying strength (Maugarny et al., 2024).

Furthermore, Maugarny et al. (2024) showed that the stronger leaf serration by compromised PRC2 activity, which occurs later in *clf-81* leaf development, cannot be related to an increased CUC2 function, since the CUC2 protein was no longer expressed during this secondary morphogenesis phase (Maugarny et al., 2024). This seems not to be the case in lines with strong depleted PRC2 activity, since loss of *CUC2* strongly suppresses leaf dissection also in late leaf morphogenesis (Figure 1T). In conclusion, the pivotal research of Maugarny et al. (2024) presents currently the best evidence for a miRNA-dependent incoherent feed-forward loop that can compensate for compromised PcG function. This raises the question whether further miRNAs participate in incoherent feed-forward loops in plants.

4. Other Putative Mirna-Dependent Feed-Forward Loops in Plants

Among PcG target genes in plants, transcription factors form a major class of H3K27me3 targets, while miRNA genes are more frequently targeted by H3K27me3 than protein-coding genes (Zhang et al., 2007; Lafos et al., 2011). To explore the possibility of further miRNA-dependent feed-forward loops compensating compromised PcG function in plants, we searched for miRNA - miRNA-target pairs that are both targets of the repressive PcG mark H3K27me3 in young flower tissues (Müller-Xing et al., 2022). Promising miRNA - miRNA-target pairs, which are both H3K27me3 targets, are listed in Figure 1U. PcG proteins directly repress only specific transcription factor families, while others seem largely not regulated by H3K27me3, including the *miR156/157*-targeted *SQUAMOSA-PROMOTER BINDING LIKE* (*SPL*) genes in vegetative shoot apical meristems and leaf tissues (Lafos et al., 2011). Nevertheless, we found that *SPL3* is a weak H3K27me3 target in young flowers and can therefore form a feed-forward loop with the *miR156/157* family, such as *MIR156C* (Figures 1L,W). This hypothesis is supported by the expression pattern of *MIR156c* and *SPL3* in various PcG mutants. Although *SPL3* is misexpressed in most PcG mutants, *SPL3* is less misexpressed in strong PcG mutants in which *MIR156c* is more strongly upregulated (Picó et al., 2015). This suggests that PRC2-*MIR156C*-SPL3 could build a similar feed-forward loop as PRC2-*MIR164B*-CUC2, compensating for compromised Polycomb function (Figure 1S). This hypothesis and other putative PRC2-miRNA-target (Figures 1J,T) should be investigated in future studies.

 doi:10.20944/preprints202603.1944.v1

5. Other Incoherent Feed-Forward Loops in Plants

Besides miRNAs, transcriptional repressors have been shown to work as a compensation mechanism for compromised PcG function in plants. The majority of MADS transcription factors that control flower development are encoded by target genes of PRC2 (Lafos et al., 2011). Therefore, most of these MADS transcription factor genes should be derepressed and misexpressed in plant lines with strongly depleted PcG activity such as *emf2-10 vrn2-1* (Müller-Xing et al., 2014; Müller-Xing et al., 2015). Surprisingly, derepression of the transcriptional repressor gene *AGL24* results in the downregulation of *AP1*, *PI*, *SEP3*, and *AGL15* (Müller-Xing et al., 2022). Furthermore, ectopic expression of the PcG target *AGL24* prevents up to fourfold upregulation of the PcG target *STM*, forming the incoherent PRC2-AGL24-STM feed-forward loop that compensates for compromised PcG function (Figure 1M,X) (Müller-Xing et al., 2022). Similarly, derepression of the PcG target *FLC* prevents the ectopic upregulation of the PcG target *FT*, and removal of *FLC* function restores wild-type levels of *FT* in plant lines with strongly depleted PcG activity (Figure 1N,Y) (Müller-Xing et al., 2014). Therefore, in incoherent feed-forward loops that compensate for compromised PcG function, the derepression of transcriptional repressors can be as effective as that of miRNAs (Figure 1R).

Theoretically, incoherent feed-forward loops can also compensate for the compromised function of transcriptional repressors other than PRC2, but no such incoherent feed-forward loop has been described in plants. Nevertheless, there are several examples of coherent miRNA-dependent feed-forward loops without PRC2, such as HB34-*MIR172A/B*-TOE2 (Figure 1O), HB34-*MIR157D*-SPL10 (Figure 1P), and SEP3-*MIR319A*-TCP4/10 (Figure 1Q) (Chen et al., 2018; Lee et al., 2022). This suggests that also in incoherent feed-forward loops PRC2 can be replaced by a transcriptional repressor (Figure 1R).

6. Conclusions and Outlook

In animal research, descriptions of incoherent feed-forward loops are rare, and only a few recent examples are known to depend on miRNAs, but none of them also include PRC2 (Dai et al., 2024; Xu et al., 2024). Maugarny et al. (2024) revealed a new class of compensation mechanisms for compromised Polycomb function by miRNA-dependent incoherent feed-forward loops in plants, PRC2-*MIR164B*-CUC2 (Figure 1K). We here showed that there are candidates for miRNA-dependent incoherent feed-forward loops in Arabidopsis, such as PRC2-*MIR156C*-SPL3 (Figure 1L). Transcriptional repressors can replace the miRNAs in the compensation mechanisms for compromised Polycomb function by incoherent feed-forward loops. Furthermore, the here-presented type of incoherent feed-forward loops seems a very efficient compensation mechanism for compromised repressor function in general (Figure 1,R). Future studies should investigate how these incoherent feed-forward loops contribute to the stability of gene regulatory networks (GRNs) and might even participate in adjusting global gene expression in plants but also other eukaryotic systems.

Author Contributions: RM-X conceived the manuscript. YZ and RM-X wrote the article with the help of HQ. All authors contributed to the article and approved the submitted version.

Funding: This work was kindly funded by the National Natural Science Foundation of China (project Nos. 32460150, 31640054 and 31771602), the Jiangxi Province Recruitment Program of Foreign Experts (Project No jxsq2023104003), a Starting Grant of the Lushan Botanical Garden, the Chinese Academy of Sciences, Jiujiang (Grant Nos. 2021ZWZX24), the High-Level Foreign Experts Project (G2021022004) from the Chinese Ministry of Science and Technology, and the National Demonstration Platform for Attracting Talents and Intelligence (project no YZJD2023020) to R.M.-X.

Conflicts of Interest: The authors declare no conflict of interest.

 doi:10.20944/preprints202603.1944.v1

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