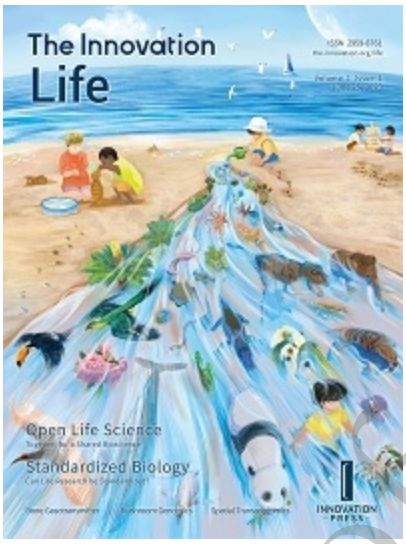

PCO-ERFVII: a hub coordinating flooding and post-flood stress

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PCO-ERFVII: A hub coordinating flooding and post-flood stress

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Climate change intensification drives increased flood frequency, posing a severe threat to crop yield stability and long-term productivity enhancement; thus, the development of flood-resilient crop varieties is urgently needed.[1] During flooding, plants experience a triphasic oxygen transition, normoxia–hypoxia–reoxygenation, driving tightly regulated, stage-specific fluctuations in reactive oxygen species (ROS) levels. Sustaining ROS homeostasis within a narrow physiological threshold window is critical for normal growth and development, disruption of this balance, whether through excessive accumulation or insufficient generation, compromises redox signaling fidelity and triggers developmental defects and cellular damage.

Previous studies have primarily focused on the mechanisms by which plants adapt to low-oxygen stress during the initial stages of flooding, while relatively little attention has been given to the explosive accumulation of ROS and the resulting oxidative damage triggered by the rapid increase in oxygen concentration during the reoxygenation phase after flood recede. Recently, Akter et al. demonstrated that the canonical PCO–ERFVII (PLANT CYSTEINE OXIDASE–group VII ethylene response factor) regulatory nexus, which has long been recognized for its central role in low-oxygen sensing and response during flooding, not only mediates hypoxia adaptation but also undergoes a functional switch during reoxygenation to transcriptionally activate antioxidant defense genes, thereby reinforcing cellular redox homeostasis and promoting recovery from oxidative damage.[1]

Under normoxic conditions, PCO catalyze the oxidation of the N-terminal cysteine residue in ERFVIIs, triggering their ubiquitination and subsequent 26S proteasome–mediated degradation. This regulatory mechanism suppresses the transcription of downstream hypoxia-responsive genes (HRGs), thereby permitting normal aerobic growth and development in plants.[2] During flooding-induced hypoxia, reduced O_2 availability inhibits PCO enzymatic activity, leading to stabilization of ERFVII proteins. Accumulated ERFVIIs translocate into the nucleus, bind to the HRPEs (Hypoxia-Responsive Promoter Elements) in the promoters of canonical HRGs (ADH1, PDC1, HB1, LBD41, HRA1, SUS1), and activate transcriptional programs that facilitate metabolic reprogramming toward anaerobic respiration, and thus ensuring energy homeostasis and sustaining plant survival under low-oxygen stress.[1,2] Upon flood recession, post-hypoxic recovery diverges depending on flood duration, following short-term

submergence, residual ERFVII is rapidly degraded via reactivated PCO N-degron pathway, enabling swift restoration of aerobic metabolism. Following prolonged submergence, rapid reoxygenation triggers a transient but pronounced burst of intracellular ROS, resulting in irreversible oxidative inactivation of PCO enzymes. Consequently, ERFVII proteins escape degradation and accumulate to functional levels. Critically, stabilized ERFVIIs engage the promoters of redox homeostasis–associated genes (RHAGs) not through their canonical DNA-binding CMVII-8 domain, but via distinct domains and driving transcriptional activation of antioxidant defense components, including *ZAT12* (a zinc finger transcription factor orchestrating ROS responses), *ATH8* (involved in sulfur-containing amino acid biosynthesis), and *GSTU24* (a glutathione S-transferase). This ERFVII-mediated transcriptional reprogramming bolsters cellular antioxidant defenses, mitigates reoxygenation-induced oxidative damage, and enhances plant resilience during the critical transition from hypoxia to normoxia. Meanwhile, chromatin immunoprecipitation assays revealed that ERFVIIs maintain stable occupancy at HRPEs within the promoters of HRGs under oxidative stress conditions, and actively repress the transcription of HRGs through selective recruitment of distinct subunits of the mediator complex (Figure 1A-C)[1]. These findings overturn the conventional paradigm by identifying, for the first time, a molecular mechanism wherein plant during reoxygenation following submergence，utilize H_2O_2 to directly inhibit PCO, thereby stabilizing the ERFVII transcription factors. This stabilization redirects ERFVIIs from transcriptional activation of hypoxia-responsive genes toward regulation of oxidative stress defense genes. Critically, the work redefines the plant oxygen-sensing pathway not merely as an O_2 sensor, but as a dual-signal integrator that coordinately processes inputs from both molecular oxygen and H_2O_2 to temporally discriminate between submergence and post-submergence recovery phases, thereby orchestrating stage-specific adaptive responses. Furthermore, it establishes H_2O_2-mediated functional reprogramming of transcription factors as a previously unrecognized signaling principle. These insights furnish genetically defined targets and a conceptual framework for precision molecular breeding strategies aimed at concurrently enhancing crop submergence tolerance and post-flood recovery capacity and offering a mechanistically grounded approach to mitigating escalating flood-related agricultural risks.

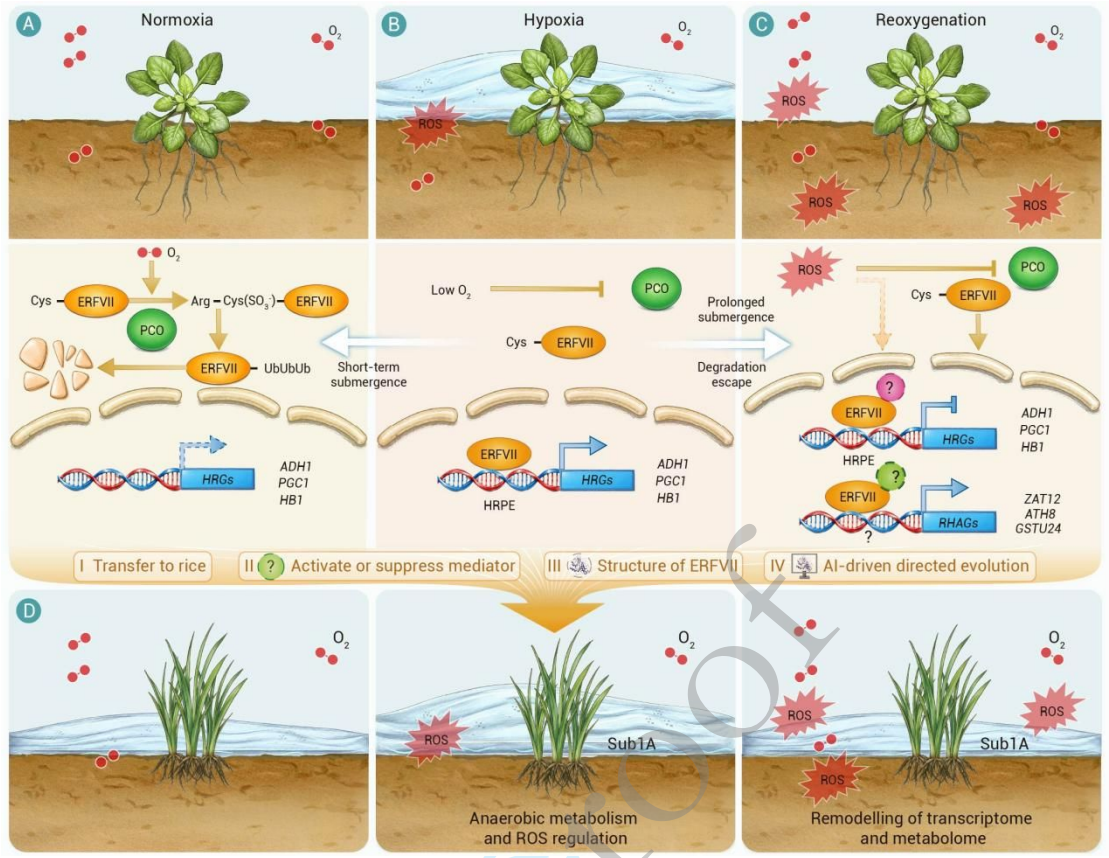

Figure 1. PCO-ERFVII: A hub coordinating hypoxic adaptation during Flooding and oxidative stress tolerance upon flood recession (A) Under normoxic conditions, ERFVIIs are degraded via the PCO-dependent Cys/Arg N-degron pathway, thereby preventing spurious activation of *hypoxia-responsive genes* (*HRGs*). **(B)** Upon flooding, oxygen limitation inhibits PCO activity, leading to rapid stabilization and nuclear accumulation of ERFVIIs, which bind HRPE cis-elements to drive *HRG* expression, orchestrating a metabolic shift toward fermentation and sustaining cellular energy homeostasis under hypoxia. **(C)** During post-flood recovery, the concomitant oxidative burst sustains PCO inhibition, preserving ERFVII protein levels; however, in this redox-altered context, ERFVIIs undergo functional reprogramming, recruiting distinct mediators to repress *HRG*s while activating *ROS-homeostasis-associated gene*s (*RHAG*s), thereby facilitating redox restoration and mitigating oxidative damage. Red double spheres indicate oxygen in A-C. **(D)** The issues that need to be addressed in transferring this theory to rice breeding and functional application. **I,** whether this biphasic, redox-gated transcriptional switch is conserved and functionally transferable to crop species remains an open question requiring systematic validation. **II,** critically, molecular characterization of the context-specific mediators that determine ERFVII's target selectivity, whether it functions as an activator or repressor, is essential to fully delineate its dual regulatory logic in flood adaptation and recovery. **III and IV,** ultimately, integrating high-resolution structural insights, functional genomics data, and AI-driven protein design holds strong promise for engineering optimized ERFVII variants with enhanced, condition-tunable activity, potentially enabling next-generation crops with coordinated resilience to both hypoxic stress during submergence and oxidative stress during reoxygenation.

Rice, as the staple food crop for over half of the global population, is predominantly cultivated in paddy systems and is frequently subjected to transient or prolonged submergence in rain-fed and irrigated lowland ecosystems, where plants encounter significant submergence stress throughout their developmental cycle.[3,4] Multiple genes, including *Sub1A*, *Sub1B*, and *Sub1C*, contribute critically to submergence tolerance in rice. Most cultivated rice varieties harbor the *Sub1B* and *Sub1C* loci, whereas the *Sub1A* gene is exclusively present in submergence-tolerant accessions. Upon submergence, *Sub1A* and *Sub1C* expression is rapidly and strongly induced. In contrast, *Sub1B* exhibits only marginal transcriptional responsiveness. Two functionally distinct alleles of *Sub1A* have been identified in natural populations: *Sub1A-1* conferring submergence tolerance, and *Sub1A-2* associated with submergence sensitivity. *Sub1A-1* is naturally found in tolerant cultivars, including the FR13A, and is robustly induced upon submergence to orchestrate adaptive transcriptional reprogramming. By contrast, *Sub1A-2* predominantly present in sensitive cultivars such as IR29 and shows negligible induction under submergence stress. As an ERFVII transcription factor, Sub1A directly binds the GCC-box in the promoters of downstream target genes, coordinately regulating diverse physiological pathways including anaerobic energy metabolism, ROS homeostasis, and delayed leaf senescence during submergence. Ectopic overexpression of *Sub1A-1* in the submergence-intolerant *Oryza sativa* ssp. *Japonica* significantly enhanced submergence tolerance, concomitant with transcriptional repression of *Sub1C* and induction of *Alcohol dehydrogenase 1* (*Adh1*), thereby establishing *Sub1A-1* as a master regulatory determinant of the submergence response.[3] Notably, *Sub1A* has also been shown to facilitate post-submergence recovery by remodelling of the transcriptome and metabolome. In fact, through integrated genetic, transcriptomic, and metabolomic analyses, the study demonstrates that *Sub1A* exerts sustained regulatory effects on the accumulation of key metabolites, including free amino acids, glucose, and sucrose in rice during post-submergence recovery, thereby supporting the restoration of metabolic homeostasis. In contrast, *Sub1A* has a minor effect on mRNAs related to growth and photosynthesis, resulting in a temporary attenuation of cellular processes underlying growth reactivation. Collectively, these coordinated actions enable efficient physiological recovery following submergence stress.[4] Nevertheless, it remains unclear whether *Sub1A* exerts this function through a mechanism analogous to that established in *Arabidopsis* ERFVIIs, namely, redox-dependent protein stabilization and switch to transcriptional activation of antioxidant defense genes.

Future should systematically uncover natural variation and functional diversity of ERFVII orthologs in major crops, and maximize the utilization of optimal haplotypes for breeding. Meanwhile, future studies should characterize the research prioritize high-resolution structural characterization of ERFVII transcription factors to resolve full-length proteins and domain-specific constructs, under defined redox conditions. Integrating these molecular-level insights with AI-driven directed evolution, utilizing deep learning models trained on experimentally validated sequence–structure–function datasets,[5] will facilitate the rational design of ERFVII variants that are both proteolytically stabilized and conditionally activated. Additionally, a systematic dissection is required to identify the distinct regulatory mediators that recruit by ERFVIIs under hypoxic versus reoxygenation conditions. Crucially, this analysis will elucidate, within each physiological context, the precise molecular mechanisms through which ERFVII governs target gene expression: specifically, (i) its activation of HRGs to confer flood tolerance during oxygen deprivation, and (ii) its transcriptional switch during reoxygenation, characterized by HRG repression and concurrent induction of RHAGs to restore redox balance and mitigate oxidative damage (Figure 1D). Critically, such engineered regulators would not merely maintain constitutive activity across the normoxia–hypoxia–reoxygenation transition but dynamically reconfigure transcriptional output at each physiological phase. Using rice as an example, enhancing anaerobic ATP synthesis and coleoptile elongation during waterlogged germination; attenuating ROS overproduction during prolonged hypoxia at the seedling and tillering stages; and accelerating expression of detoxification, DNA repair, and redox homeostasis genes upon reoxygenation. Collectively, these strategies will pave the way for breeding flooding-smart crops.

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AUTHOR CONTRIBUTIONS

Author F.X. was responsible for the conceptualization, and drafting of the initial manuscript. Author J.S. contributed to the engaged in discussions, and revised the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.