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COMMENTARY

Triggering regeneration: A new recognized local wound signal in plants

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INTRODUCTION

"What controls organ regeneration?" is one of the 125 most challenging scientific questions proposed by Science magazine on 125th anniversary. The processes of wound healing and organ regeneration are often autonomous and unconscious. Meanwhile, the regenerative capacity is also strictly limited by internal factors such as species, age, the damaged part, and the degree of damage, as well as external factors such as nutrient supply, temperature, infection, etc. It is worth noting that this impressive regenerative capacity is strictly inhibited during the normal growth and development of organisms.

Plants are often subjected to various biotic and abiotic stresses due to sessile growth, resulting in various degrees of damage. In plants, wounding causes local and systemic defense responses. The activation and deployment of defense responses only take a few minutes, involving the release of primary wound-signaling molecules, the long-distance transport of defense-signaling molecules, as well as the activation of gene expression and protein synthesis related to defense.[1] In order to cope with injuries, plants have developed the abilities of tissue repair and organ regeneration during the evolution. Compared with most animals, plants exhibit strong regenerative abilities as new organs or even whole plants can grow from injured tissues through *de novo* organogenesis or somatic embryogenesis.

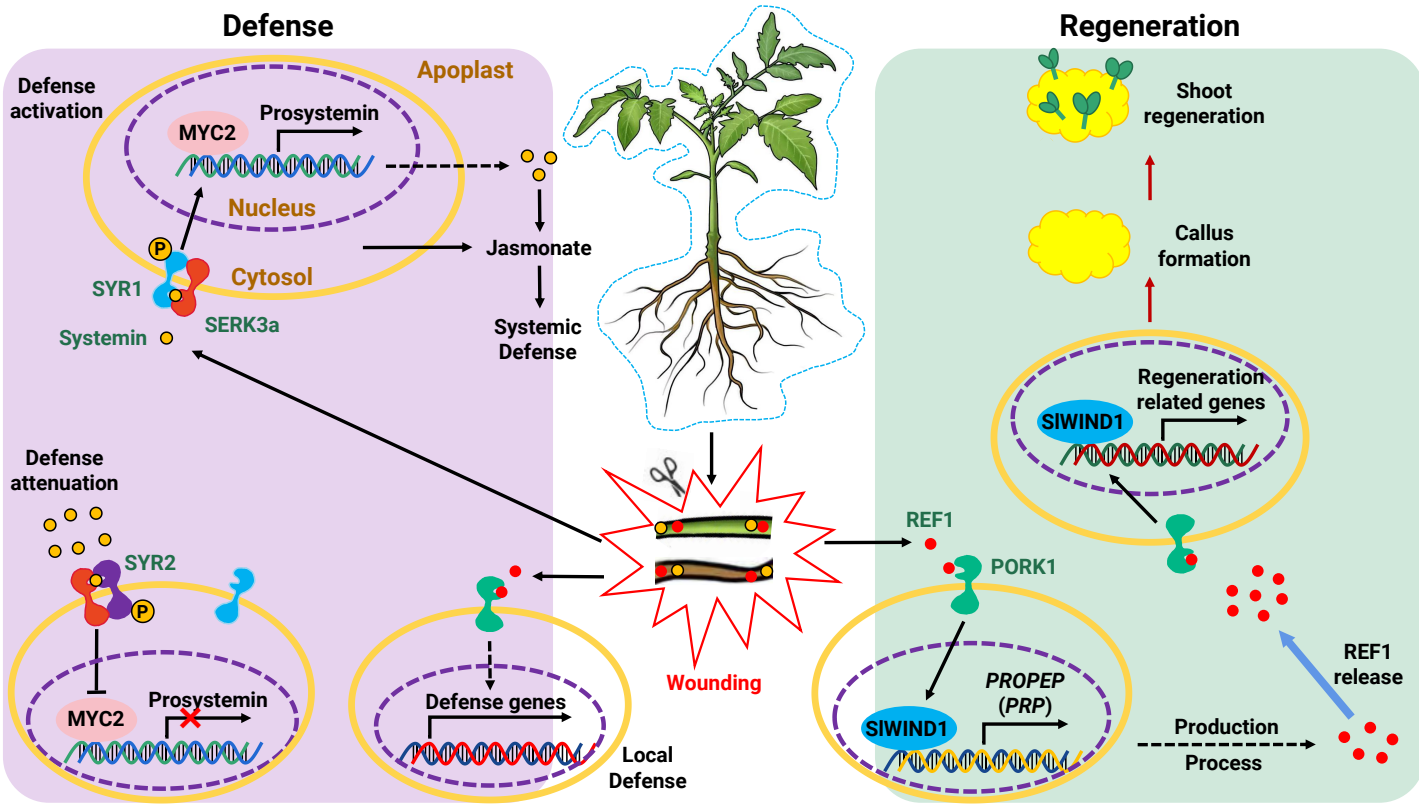

Figure 1. Plants initiate defense responses and trigger regeneration after suffering mechanical damage The rapid defense responses and regeneration are mediated by systemin and REF1, respectively. Left, systemin released by the wound interacts with the high-affinity receptors SYR1 and the co-receptor SERK3a to activate the expression of the systemin precursor gene *PRS* and defense-related genes. However, at higher concentrations of systemin, the low-affinity receptor SYR2 competes for the interaction between SYR1 and SERK3a, thereby attenuating the plant's systemic defense response. Right, upon tissue injury, REF1 binds to and activates PORK1 to initiate SlWIND1-dependent regeneration. In addition, activated SlWIND1 also upregulates the expression of the REF1 precursor gene *PRP* through promoter binding, thereby amplifying the local wound signal for regeneration.

Wound activates the defensive response

In 1972, Professor Clarence Ryan first discovered the systemic defense phenomenon induced by insects or mechanical damage in tomato and potato.[2] Systemin, processed from a 200-amino-acid precursor named prosystemin (PRS), is a polypeptide containing 18 amino acids (AVQSKPPSKRDPPKMQTD) isolated from tomato leaves. It is regarded as the main systemic signal and can induce the expression of more than 15 defense genes in tomato plants at the fmol level.[1] The following studies confirmed that systemin and the phytohormone jasmonic acid (JA) regulate the systemic defense responses through a common signaling pathway.[1] Systemin functions through its receptors and leads to the release of linolenic acid, which is subsequently converted into JA.[3] Upon damage, JA rapidly spreads from the damaged leaves to the whole plant, completing the activation from local defense response to systemic defense response, resulting in the rapid synthesis and accumulation of proteinase inhibitors (inhibiting the activity of intestinal proteases in herbivores), and also the activation of other defense-related genes (Figure 1).[1]

Wounding signals trigger regeneration

Many plants exhibit remarkable developmental plasticity and the ability to regenerate new organs after being damaged. During shoot regeneration, a

wound-induced AP2/ERF transcription factor, WOUND-INDUCED DEDIFFERENTIATION 1 (WIND1), promotes callus formation and shoot organogenesis by up-regulating the expression of the *ENHANCER OF SHOOT REGENERATION1* (*ESR1*) gene. Within 2 h of leaf detachment, jasmonates are produced as a wound signal to activate *ETHYLENE RESPONSE FACTOR109* (*ERF109*), which in turn up-regulates the auxin biosynthesis gene *ANTHRANILATE SYNTHASE α1* (*ASA1*) to promote *de novo* root regeneration. Laser-assisted elimination can re-activate the root stem cell pathways beside the damaged cells, and the newly divided cells obtain the correct cell fate to replace the missing cells. Damage in the root apical meristem also induces JA signaling. JA activates the activity of quiescent center cells by regulating the RBR (RETINOBLASTOMA-RELATED)-SCR (SCARECROW) molecular network and the expression of *ERF115*. Meanwhile, ERF109 acts upstream of ERF115 and activates the expression of the cell-cycle regulator *CYCD6;1*. Auxin and JA accumulate near the wound and jointly regulate the reprogramming of damage-repair genes. Ectopic activation of the WUSCHEL (WUS) and DORNRÖSCHEN (DRN; or ESR1) promotes the regeneration of *Arabidopsis* mesophyll cell protoplasts and the acquisition of complete plants. Although these findings emphasize the direct connection between damage stimuli and ectopic activation of cell fate remodeling, what is regarded as damage signal which triggers regeneration remains elusive.

Recently, Yang *et al.* reported a signal transduction network in which a local wound signal promotes plant tissue repair and organ regeneration (Figure 1).[4] Using tomato as a model plant, they analyzed the plant systemic defense signal pathway co-regulated by systemin and JA, and obtained a series of tomato mutants with changes in the systemin signaling pathway. Among them, a mutant *spr9* (SUPPRESSOR OF PROSYSTEMIN-MEDIATED RESPONSE 9) with defects in both defense and regeneration has been identified. The *spr9* mutants exhibit an intermediate local defense and an intermediate systemic defense in response to injury, and SlPep and systemins collaboratively regulate both local and systemic defense responses. Map-based cloning showed that the *SPR9* gene encodes the precursor protein of the peptide SlPep (23 amino acids), the sole tomato homologue of the immunomodulatory peptides in the plant elicitor peptide (Pep) family, previously reported in Arabidopsis.[5] Wounding induces influx of Ca^{2+} in the cytosol, triggering metacaspases to cleave PROPEP1 and to release mature Pep1 peptide, and Pep1 is perceived by neighboring cell via Pep receptors (PEPRs), triggering local defense responses.[5] Knocking out *SPR9* causes seedlings to lose the ability to form callus, while over-expressing *SPR9* can significantly improve the regeneration ability. In addition, exogenous application of the SlPep significantly improves the regeneration ability. Therefore, SlPep is renamed as REGENERATION FACTOR1 (REF1). Further research has confirmed that PEPR1/2 ORTHOLOG RECEPTOR - LIKE KINASE 1 (PORK1) is the receptor of REF1. When cell damage occurs, REF1, as the primary wound signal molecule, is specifically recognized by the receptor PORK1, and transcriptionally activates the key regulator of cell reprogramming *SlWIND1*, thereby initiating the plant tissue repair and organ regeneration processes. In addition, the activated SlWIND1 can also bind to the promoter of the REF1 precursor gene to activate its expression, thereby producing more REF1 peptides to amplify the REF1 signal (Figure 1). This positive feedback regulation of REF1-SlWIND1 may be needed for propagating wound responses and wound-induced regeneration. In future studies, it is interesting to understand how to mitigate the positive feedback regulation, and whether phytohormones and other factors play a role in it.

The discovery of the wound signaling molecule REF1 reveals a precise system in plants that recognizes injury stimuli and triggers wound healing and organ regeneration, which is a significant progress. The effect of REF1 could be conserved as the REF1 peptides and their receptors can be found in various dicotyledonous and monocotyledonous plants. Indeed, exogenous application of REF1 can significantly improve the regeneration ability and genetic transformation efficiency of crops such as soybean, wheat and maize that are difficult to transform.[4] The application of REF1 provides a convenient and universal scheme for improving crop transformation efficiency and potentially breaking species and genotype dependence in molecular design breeding.

FUTURE PERSPECTIVES

Defense and regeneration are two inseparable aspects of the plant's response to injury.[4] As a primary wound-signaling molecule, REF1 plays a dual role in regulating damage-triggered local defense responses and regeneration processes. It would be interesting to investigate how REF1 coordinates local defense and regeneration in response to stress. In addition, the study by Yang et al. reveals a conserved phytocytokine pathway that promotes regeneration and provides a robust and efficient method for improving the regeneration and transformation efficiency of recalcitrant crops. In the future, testing the effect of REF1 in different regeneration systems (e.g., root tip regeneration, *de novo* root regeneration, etc.) will help to uncover the complex molecular interactions in various regeneration signaling pathways, and clarify the regeneration pathways from injury to healing. In-depth analysis of the intracellular molecular network mediated by wound signals may reveal how plants balance growth and defense, and contribute to a deeper understanding of the adaptive strategies of plants for changing over time and space.

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DECLARATION OF INTERESTS

The authors declare no competing interests.