

can mimic some of the effects of exercise is promising. This is particularly important for older people who might not always have the capacity for the level of exercise needed to promote optimal brain health.

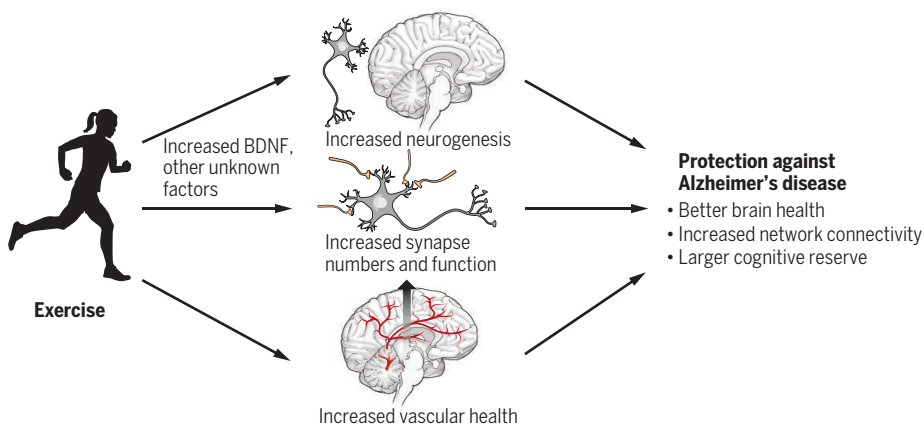
The study by Choi *et al.* also lends further support to the idea that amyloid plaques are a poor marker of disease progression and thus a poor choice of biomarker for clinical trials. The authors found that decreased plaque pathology was not necessary or sufficient to drive memory improvements. This adds to conflicting reports that environmental enrichment, including exercise, in some studies

during childhood (12). Overall, evidence suggests that at least low levels of neurogenesis occur throughout life. There have been several studies indicating that increased neurogenesis occurs in Alzheimer's disease (13), but whether this plays an important role in disease pathophysiology is unclear.

Moving forward, it will be important to understand how exercise, neurogenesis, and BDNF affect the brain at the synapse, cellular (neurons, glia, and vascular cells), and circuit level. Exercise causes new synapse formation and is excellent for cardiovascular health, both of which are relevant to

How might exercise protect against Alzheimer's disease?

Several pathways might explain how exercise protects the brain and prevents development of Alzheimer's disease. In mice, exercise enhances vascular health and increases the amount of BDNF in the brain, which promotes neurogenesis, survival of new neurons, and the formation of new synaptic connections.



decreased plaque pathology and increased it in others, despite most groups observing memory improvement (8, 9). Biomarkers that more closely track neural circuit integrity are much more promising, including structural magnetic resonance imaging to track brain atrophy and newer markers such as positron emission tomography ligands for synapses and synapse and neuron proteins in cerebrospinal fluid (10).

There are limitations of this work to consider. The authors used a single aggressive mouse model of familial Alzheimer's disease, which potentially exhibits nonphysiological mechanisms of cell death owing to overexpression of mutant proteins. Historically, studies of mouse models of Alzheimer's disease have not translated well in human clinical trials, particularly work in a single model, so this study will need to be replicated in other mouse models. There is also no direct evidence that these mechanisms are involved in human disease. Neurogenesis in human adult hippocampus has become a contentious issue. For example, one study found that neurogenesis occurred into older age (11), whereas another found that it stops

Alzheimer's disease because synapse degeneration is an important correlate of cognitive decline, and we are beginning to understand that nonneuronal cells (glia and vasculature) greatly affect this process (3, 14). In the best-case scenario, assuming these results are replicated in other models and are relevant to human disease, this study suggests that we could bottle the effects of exercise to prevent or treat dementia. ■

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PLANT BIOLOGY

To grow and to defend

A rice transcription factor's dual roles could improve yield and disease resistance

By George H. Greene and Xinnian Dong

Feeding an expanding world population while sustaining an inhabitable environment represents the greatest challenge of our time. To meet this challenge, the scientific conundrum of increasing crop yield while protecting it from evolving pathogens must be resolved. Rice (*Oryza sativa*) contributes the majority of dietary energy for more than half of the world's population. The most devastating pathogen of rice worldwide is the fungus *Magnaporthe oryzae*, the causal agent of rice blast, which results in an estimated yield loss of 30% globally. Therefore, controlling *M. oryzae* infection is a key battlefield for improving global rice production (1). On page 1026 of this issue, Wang *et al.* (2) identify a mechanism by which Ideal Plant Architecture 1 (IPA1), a transcription factor previously identified for conferring high yield, can also promote immunity against rice blast. This discovery provides a great addition to the toolbox for rational breeding of rice varieties with both high yield and high disease resistance.

Disease resistance is mostly generated by introducing immune receptor genes from resistant cultivars or wild relatives into high-yield varieties to create "super varieties" (3). Many of these immune receptors recognize the presence of rapidly evolving, pathogen-specific virulence factors. Selection for new polymorphisms that allow pathogen effectors to evade perception can diminish the efficacy of these receptors within years (4). A common remedy for this deficiency is the stacking of multiple immune receptor genes in the host genome (5). However, expression of these receptor genes can lead to competition with yield-related traits for available metabolic resources (6). Alternatively, broad-spectrum disease resistance may be conferred through manipulation of central immune regulators downstream of pathogen recognition that control the expression of resistance-conferring genes. Constitutive

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activity of these core regulators is often associated with drastically diminished yield because of the inherent trade-offs between defense response and growth (7). Recent advances in engineering broad-spectrum disease resistance have focused on mitigating yield costs by making the immune response tunable to pathogen detection. Such strategies include the use of pathogen-responsive promoters (8), messenger RNA (mRNA) stability (9), and chromatin modifications (3). More recently, regulation at the level of translation was achieved through cis mRNA elements that allow transient translation of core immune regulators to establish optimal balance between defense and growth (10).

Although considerable effort has gone into understanding and minimizing the effects of immune regulators on growth, the extent to which growth-promoting regulators modulate immunity remains relatively unexplored. Yield is a complex trait that is determined by multiple factors, including the number of panicles (branched flower clusters), the number of filled grains per panicle, and overall grain weight (11). IPAI functions to reduce the number of unproductive rice tillers (panicle-bearing stems) and increase grain density in productive panicles (12), maximizing the number of grains per panicle and thus the yield of the plant. Alleles of *IPAI* from various cultivars are expressed at different amounts owing to variations in distinct regulatory mechanisms, including methylation of the *IPAI* promoter in the *wealthy farmer's panicle (WFP)* allele or microRNA (miRNA)-mediated repression of *IPAI* expression. The *ipa1-ID* allele contains a naturally occurring point mutation that escapes the miRNA-mediated repression, resulting in higher IPAI protein expression (13). Fine-tuning IPAI protein abundance allows for the ideal combination of panicle size and panicle number for maximum productivity. However, the value of such high-yield varieties is limited if losses to disease are not controlled.

Wang *et al.* investigated the yield output of *ipa1-ID* plants under *M. oryzae* challenge. Through large-scale field trials, they determined that plants with the *ipa1-ID* allele maintained the expected yield benefits of ~10% (compared with plants expressing the *IPAI* allele) in the noninfected field and showed an impressive 30% yield increase in the infected field.

This led the authors to hypothesize that IPAI promotes resistance to rice blast in addition to its yield-enhancing activity.

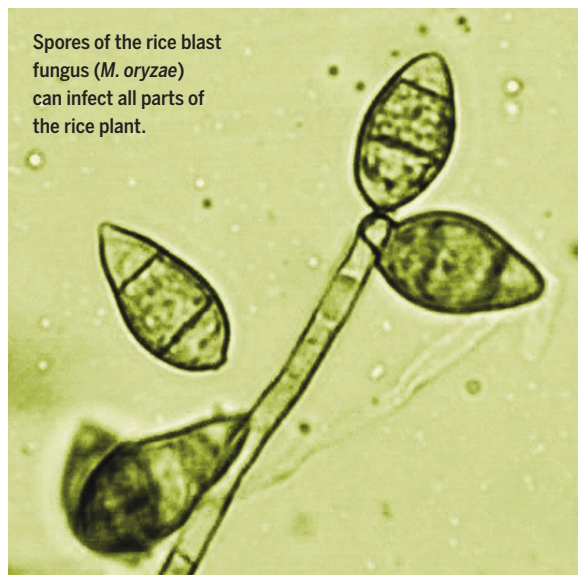
Through biochemical assays, the authors identified an inducible phosphorylation event on serine-163 in a conserved region of IPAI that occurs upon exposure to *M. oryzae*. In the absence of pathogen, IPAI binds to the promoters of growth-stimulating genes to drive their expression. Phosphorylated IPAI is repurposed as its DNA binding affinity is altered to favor defense gene promoters, including the promoter of WRKY DNA-binding protein 45 (WRKY45),

which encodes a broadly pathogen-responsive transcription factor involved in global transcriptional changes associated with plant defense (14, 15). The increased abundance of IPAI in the *ipa1-ID* plants accelerates WRKY45 accumulation, conferring enhanced resistance.

Moreover, phosphorylated IPAI in *ipa1-ID* plants returned to background-level amounts by ~48 hours after infection. This could result from turnover of the phosphorylated IPAI protein or an active dephosphorylation process when infection subsided. This rapid and transient IPAI

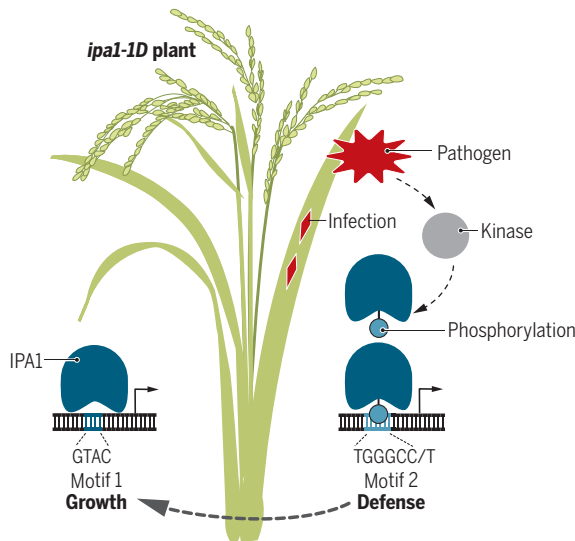
modification allowed *ipa1-ID* plants to have increased yield and enhanced *M. oryzae* resistance while avoiding the yield penalties that would occur if IPAI remained in its immune active form (see the figure). It warrants further investigation whether such pathogen-responsive phosphorylation of growth-regulating transcription factors is a widespread mechanism for rapid yet moderated response to infection.

The dual functionality of IPAI presents intriguing new opportunities for engineering disease resistance to other pathogens and in additional crops. This depends on the degree of conservation of the signaling components, from pathogen recognition to IPAI phosphorylation to the downstream defense targets. For example, if IPAI phosphorylation is dependent on pathogen recognition through a specific immune receptor, the use of IPAI may be limited to *M. oryzae* in rice. Nevertheless, further engineering through introduction of an IPAI overexpression allele, along with the necessary upstream components, may confer yield benefits that are retained under challenge by a broad spectrum of pathogens. ■



How IPAI promotes growth and resistance

IPAI normally binds GTAC DNA sequences (motif 1) to promote growth. Upon *M. oryzae* infection, IPAI is phosphorylated by an unknown kinase and switches its binding to TGGGCC/T (motif 2), which promotes immunity to *M. oryzae*.



After immune induction, IPAI rapidly reverts to its growth-promoting function (gray arrow), mitigating potential yield losses associated with unregulated immune responses.

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