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REVIEW ARTICLE

The Yin and Yang in plant breeding: the trade-off between plant growth yield and tolerance to stresses

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Abstract Plants have the ability to recognize and respond to biotic and abiotic stresses that are responsible for considerable yield losses in agriculture. Currently, a central goal of crop deployment is to develop the capacity to be tolerant to multiple stresses without a reduction in fitness. Still, many efforts to release such plants have failed because, frequently, there is a trade-off between growth and tolerance to stresses. Conventional breeding plays an essential role in crop improvement, but it is necessary to develop new tools, using for instance CRISPR, to produce new cultivars exhibiting tolerance to stress without significant yield penalty. In this short review we discuss novel strategies that can be employed to produce novel cultivars that would increase plant productivity without being hindered by potential negative effects of the immune response on plant development.

Introduction

During evolution, plants have acquired the competence to perceive pathogens and respond with robust defense responses. Pathogens include viruses, insects, nematodes, bacteria fungi and oomycetes that attack plants aiming at assimilating nutrients from them. However, in the absence of genetic resources or genetic variability to provide resistance against pathogens, there is an trade-off between performance and defense (Huot, Yao, Montgomery, & He, 2014; Karasov, Chae, Herman, & Bergelson, 2017). The constitutive expression of genes that increase resistance against pathogens may be costly for a plant in the absence of pathogens and it is important to understand the mechanism leading that balance the mechanisms involved in the trade-off among growth and disease tolerance. Plants can activate a very effective arsenal of defense responses, including genetically programmed suicide of infected cells, as well as tissue reinforcement and bioactive compound production at the site of infection (Kant et al., 2015). The plant immune

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Table 1 List of candidates for plant disease resistance.

Plant Species	Gene Modification	Resistance to pathogens	Reference
Rice	Overexpression of *NPR1*gene from Arabidopsis	*Rhizoctonia solani*	Molla et al. (2016)
Rice	Loss of function of *Bsr-k1*gene	*Magnaporthe oryzae* and *Xanthomonas oryzae* pv *oryzae*	Zhou et al. (2018)
Arabidopsis	*ian9* mutant	*Pseudomonas syringae* pv *tomato*	Wang et al. (2019)
Rice	Down-regulation of miR396 isoforms	*Magnaporthe oryzae*	Chandran et al. (2019)
Cowpea	Overexpression of RNAi-AC2, RNAi-AC4 and RNAi-AC2+AC4 stacked	Mungbean yellow mosaic India virus	Kumar et al. (2017)
Arabidopsis	*adr1* mutant	*Peronospora parasitica* and *Erysiphe cichoracearum*	Grant et al. (2003)
Rice	Pyramiding the Xa4, xa5 and Xa21 genes	*Xanthomonas oryzae* pv *oryzae*	Suh et al. (2013)
Rice	Pyramiding the xa13, xa5 and Xa21 genes	*Xanthomonas oryzae* pv *oryzae*	Kottapalli et al. (2010)
Cotton	Overexpression of *Tma12*gene from *Tectaria macrodonta*	*Bemisia tabaci*	Shukla et al. (2016)
Rice	*Pigm* locus containing a cluster of NLR genes	*Magnaporthe oryzae*	Deng et al. (2017)
Rice	Overexpression of *IPA1* gene	*Xanthomonas oryzae* pv *oryzae*	Liu et al., (2019)
Arabidopsis and rice	Overexpression of *BSR2* gene	*Rhizoctonia solani*	Maeda et al. (2019)
Rice	Overexpression of *MoSM1*gene from *Magnaporthe oryzae*	*Magnaporthe oryzae*	Hong et al., (2017)

system comprises an intricate network of regulators and receptors aimed at maintaining cellular homeostasis in the absence of pathogen threat and responding rapidly to biotic stimuli in order to prevent infection (Ben Rejeb, Pastor, & Mauch-Mani, 2014). On the other hand, the immune response that is activated upon pathogen attack is modulated by the induced production of a hormonal blend in the plant (Vos, Moritz, Pieterse, & Van Wees, 2015). Plant hormones are important because they can modify plant development and regulate responses to a wide range of biotic and abiotic stresses (Verma, Ravindran, & Kumar, 2016). The changes in plant development have been attributed to a diversity of single or combined mechanisms that act, either accumulatively or in a cascade, leading to the activation of resistance R-proteins that recognize specific pathogen effectors (Dangl & McDowell, 2006; Zhang et al., 2019). Generally, hormonal responses, in association with activation of defense genes result in yield penalties. Therefore it is necessary that new genotypes could be developed to overcome the negative effects on plant development (Ning, Liu, & Wang, 2017; Vos, Pieterse, & Van Wees, 2013). In this short review we highlight several strategies adopted to increase broad-spectrum resistance and describe emerging genotypes that confer plant immunity to multiple pathogens without yield losses (Table 1).

Genes conferring resistance to pathogens with minimal or no yield penalty

Plant immunity is a complex process comprising two inducible layers of defense (Fig. 1). In the first layer, the plant defense mechanism depends on immune receptors found on the plasma membrane which sense the Pathogen Associated Molecular Patterns (PAMPs) leading to PAMP-Triggered Immunity (PTI) (Zhang & Zhou, 2010). In the second layer, the effector proteins from pathogens can be recognized by R-proteins, initiating Effector-Triggered Immunity (ETI) (Zhang & Zhou, 2010). Recent studies have shown that cerato-platanins (CP) function both as fungal virulence factors or plant defense elicitors (Baccelli, 2015). The CP protein which is also located at the cell walls of fungi, is moderately hydrophobic and has been reported to act as a PAMP (Martellini et al., 2013). In rice, overexpression of the CP protein from *Magnaporthe oryzae* (*MoSM1*) resulted in improved resistance against *M. oryzae* and *Xanthomonas oryzae*, affecting the balance of hormones jasmonic acid (JA) and salicylic acid (SA) (Hong et al., 2017). The transgenic plants contained upregulated genes related to JA and SA biosynthesis and elevated levels of these hormones involved in defense. Significantly, these plants did not show any yield penalty, with similar tolerance to abiotic stress when compared to control plants.

The majority of plant *R* genes contain a conserved nucleotide-binding domain (NB-ARC) and leucine-rich repeat domain (LRR) together with a coiled-coil (CC) domain or a TOLL/interleukin 1 receptor (TIR) domain defines two major types of plant nucleotide-binding leucine-rich repeat (LLR) termed the CNLs and the TNLs, respectively (Borrelli et al., 2018; Jacob, Vernaldi, & Maekawa, 2013). In plants, the NLR gene family is found in the genomes both as isolated genes as well as in clusters of different sizes (McHale, Tan, Koehl, & Michelmore, 2006). To understand the defense mechanism provided by R-proteins, the mutant for the gene *AtADR1* (CNL) was analyzed and exhibited resistance against the

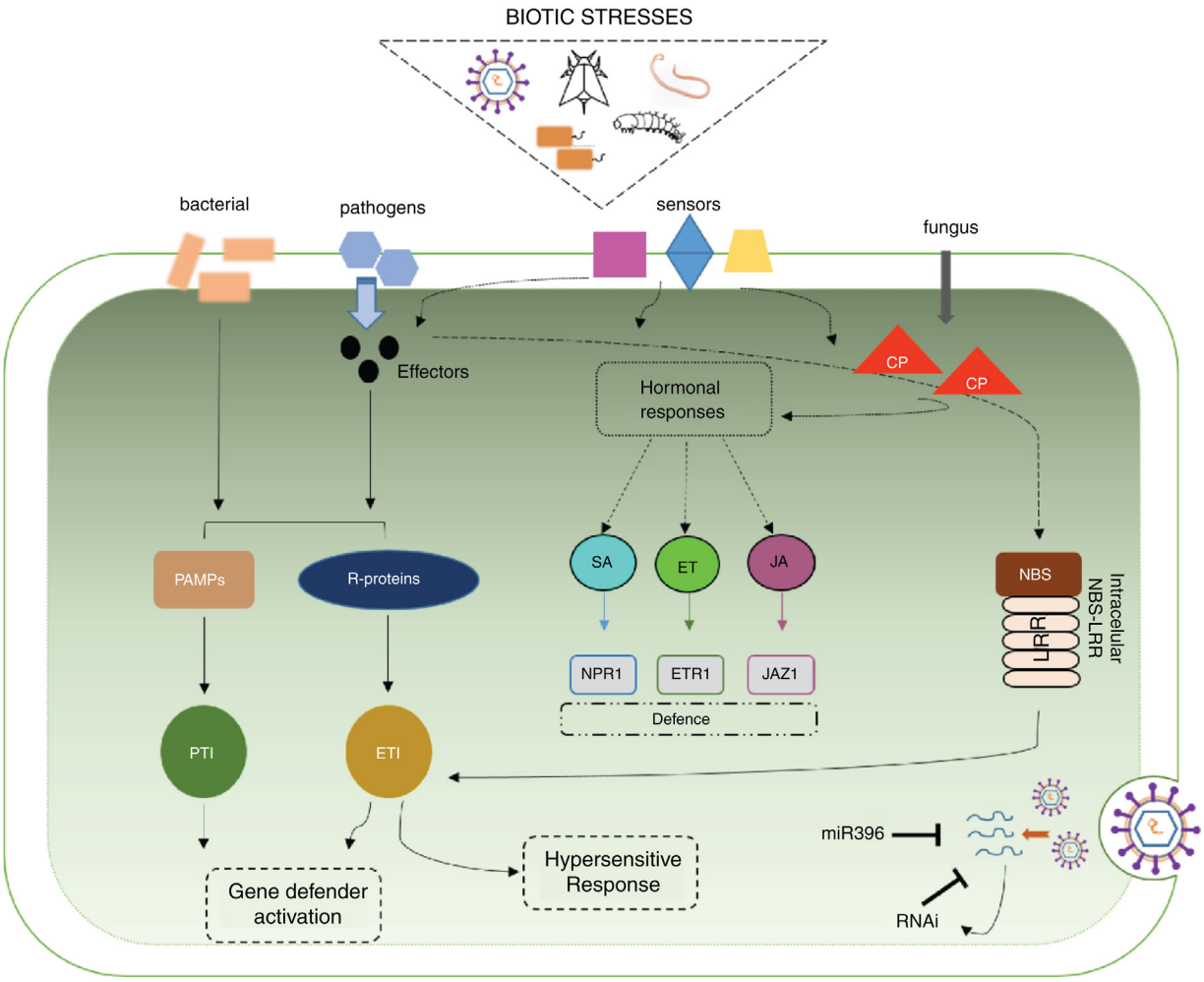

Fig. 1 Schematic illustration of the plant's response to biotic stresses. Upon perceiving the pathogen, extracellular receptors are activated and recognize effectors, pathogenic structures and also virulence factors that are released inside the cell. As a result, a signaling cascade is triggered to combat the invasion. The first defense mechanism is through the recognition of Pathogen Associated Molecular Patterns (PAMPs) leading to the PAMP-Triggered Immunity (PTI) response that will activate the defense genes. Then, pathogen-triggered effectors are recognized by R-proteins or by nucleotide-binding leucine-rich repeat (NLRs) intracellular sensors that stimulate the Effector-Triggered Immunity (ETI) response that can activate defense genes or a hypersensitive response. Proteins located in fungal cells when penetrated into the intracellular medium are quickly recognized and trigger hormonal responses that stimulate the increase in salicylic acid (SA), ethylene (ET) and jasmonic acid (JA) that regulate genes mediated in response to them. Moreover, other strategy is via RNA silencing.

biotrophic pathogens *Peronospora parasitica* and *Erysiphe cichoracearum* (Grant, Chini, Basu, & Loake, 2003). The *adr1* plants accumulated SA and expressed a number of distinct defense-related marker genes, besides SA depletion abolished resistance against both *P. parasitica* and *E. cichoracearum*.

Another approach to obtain plants tolerant to disease is to examine the *loci* that confer resistance to microbes in breeding programs (Deng, Zhu, Shen, & He, 2006). In China, the rice variety Gumei 4 was used in breeding programs to improve disease resistance as it contains a locus encompassing a cluster of genes encoding NLR receptors (*Pigm*) (Deng et al., 2017). Among the cluster genes, the *PigmR* (*R6*) under control of native or 35S promoters conferred resistance to the fungus *Magnaporthe oryzae* in Nipponbare without yield penalty, in contrast to others NLR- genes (Deng et al., 2017).

A promising approach to increase disease resistance for plant improvement is gene pyramiding, which is defined as a method aimed at assembling multiple desirable genes from multiple parents into a single genotype for a specific trait (Ye & Smith, 2008). Commonly, the pyramid lines show broader and higher levels of resistance than the lines carrying only a single gene (Fukuoka et al., 2015). Rice plants containing the R-genes xa5, xa13 and Xa21 were generated by multiple crosses, with resistant plants displaying minimal lesion lengths following inoculation with *X. oryzae* pv *oryzae*. Interestingly, durable disease resistance was conferred without any negative impact on yield (Kottapalli, Narasu, & Jena, 2010). In a similar approach, Suh et al. (2013) developed rice breeding lines with three resistance genes Xa4, xa5 and Xa21 and once again tested against the same pathogen. The rice genotype carrying Xa4+xa5+Xa21 exhibited very high resis-

tance to 18 isolates of *X. oryzae* pv *oryzae* from Korea and revealed that the accumulation of three-gene do not cause a yield penalty (Suh et al., 2013).

The guanosine triphosphatase (GTPase) family of proteins are key components of biological complexes which control growth and development of plants under normal and stress conditions (Wang & Li, 2009). Among all GTPases, the subfamily termed IMUNE-ASSOCIATED NUCLEOTIDE-BINDING/GTPases OF IMMUNITY-ASSOCIATED PROTEINS (IAN/GIMAP) has been reported to be associated linked with immunity, with the levels of *AtIAN8* high in response to the avirulent bacterial strain *Pseudomonas syringae* pv. *maculicola* expressing the effector AvrRpt2 (Reuber & Ausubel, 1996). To verify the importance of another Arabidopsis IAN member, a mutant of At*IAN9* (a membrane protein) was generated and tested against *P. syringae* (Wang et al., 2019). The *ian9* knockout seedlings and adult plants were visually indistinguishable from control and, when surface inoculation of *P. syringae* pv *tomato* DC300 was performed, the plants displayed increased disease resistance independently of SA signaling.

Other candidate genes include the cytochrome P450 monooxygenases, which catalyze a wide variety of monooxygenation reactions in primary and secondary metabolism in plants (Mizutani, 2012). In many cases, P450s mediate hydroxylations at nitrogen and sulfur heteroatoms, dehalogenations, dealkylations, deaminations, and epoxidations (Schuler, 1996). A variety of defense compounds are synthetized by P450, leading to improved physiological tolerance against pathogens and modulating plant development. One example is the P450 protein *BROADSPECTRUM RESISTANCE2* (*BSR2*) that confers resistance to *Rhizoctonia solani* in Arabidopsis and rice (Maeda et al., 2019). Although the mechanism of action is not clear, ethylene (ET) and JA signaling pathways are possibly involved, and *BRS2* may generate novel compounds that act in disease resistance (Maeda et al., 2019). Regarding phenotypic alterations, transformants displayed seeds longer in length than wild types, as well as slightly slower growth.

The development of new plant genotypes with ideal plant architecture (IPA) has been proposed as a means to enhance rice yield potential over that of existing high-yield varieties (Wang et al., 2017). IDEAL PLANT ARCHITECTURE1 (IPA1), a pleiotropic gene isolated through a map-based cloning approach, has been shown to be one of the key regulators that determine plant architecture (Lu et al., 2013). To determine the effects of high levels of IPA1, rice plants were transformed and the results showed an ideal plant architecture with a decrease in unproductive tillers and an increase in panicle branch number (Lu et al., 2019). Furthermore, overexpression of IPA1 increased disease resistance against *Xanthomonas oryzae* pv. *oryzae* and modulated the JA pathway without yield penalty.

To identify genes involved in rice resistance to pathogens, Zhou et al. (2018) performed a mutant screening and found a tetratrico peptide repeat (TPR) domain RNA-binding protein, named BSR-K1. The TPR domain is involved in a variety of biological processes and the motif consists of 3–16 tandem-repeats of 34 amino acid residues (Zeytuni & Zarivach, 2012). In rice, loss of function of the *Bsr-k1* gene enhanced resistance to *M. oryzae* and *X. oryzae* pv *oryzae* and resulted in mRNA accumulation of multiple *OsPAL* genes (Zhou et al., 2018). The *bsr-k1* mutant plants maintained key agronomic traits and carried broad-spectrum disease resistance, despite the normal levels of SA (Zhou et al., 2018).

Systemic acquired resistance (SAR) is an inducible form of plant defense conferring broad-spectrum immunity to secondary infection of plant tissues, involving the upregulation of a subset of pathogenesis-related (PR) genes (Fu & Dong, 2013). Through studies with Arabidopsis mutants, Non-Expressor of PR1 (NPR1) was identified as the master regulator that controls SA-mediated gene activation in response to SAR activated by pathogens and therefore a strong candidate gene for genetic engineering for disease resistance (Fitzgerald, Chern, Navarre, & Ronald, 2004). Although the AtNPR1 gene conferred disease resistance, constitutive expression of the gene had a negative impact on growth (Quilis, Peñas, Messeguer, Brugidou, & San Segundo, 2008). More recently, rice plants expressing *AtNPR1* were generated whereby the gene was under the control of the green tissue-specific promoter $P_{D540-544}$ (Molla et al., 2016). This approach resulted in the activation of downstream defense-related genes associated with the resistance of the plant to *Rhizoctonia solani*, whilst maintaining typical plant phenotypic characteristics.

The non-coding RNNAs (ncRNAs) also serve as potential molecules that can be manipulated to improve plant productivity. One member of the ncRNAs are the miRNA, which represent a class of small, 18- to 28-nucleotide-long noncoding RNA molecules that are important regulators of gene expression (Felekkis, Touvana, Stefanou, & Deltas, 2010). Li et al. (2014) characterized the miR396 family members in rice, uncovering differences in expression profiles upon *M. oryzae* infection between resistant and susceptible accessions. Transgenic plants expressing the target mimicry of miR396 - consisting of a noncleavable RNA that forms a nonproductive interaction with a complementary miRNA - exbibit low levels of miR396 isoforms, showed enhanced resistance to *M. oryzae*. In addition, these plants exhibit significant increase in yield-traits such as the panicle branches and grain size (Chandran et al., 2019).

RNA interference (RNAi) is a naturally occurring mechanism for gene silencing induced by the presence of short interfering RNA (siRNA), and it is a primary and effective antiviral defense (Guo, Liu, Smith, Liang, & Wang, 2016; Sledz & Williams, 2005). With the aim to study their potential in plant defense, Kumar, Tanti, Patil, Mukherjee, and Sahoo (2017)) employed a RNAi strategy to control infection by the Mungbean yellow mosaic India virus (MYMIV). The virus genome encodes nine ORFs, with AC2 and AC4 genes selected for RNAi assays. Transgenic lines of RNAi-AC2, RNAi-AC4 and RNAi-AC2+AC4 stacked constructs were analyzed, with no yield penalties observed with any construct and only the RNAi-AC4 expressing lines displaying characteristic symptoms of viral infection after five weeks (Kumar et al., 2017).

Among the many methods under evaluation for control of plant pathogens, the use of insecticidal proteins from certain plant species has gained importance (Jerga et al., 2019). Shukla et al. (2016) screened diverse ferns to identify proteins that are insecticidal against the whitefly species *Bemisia tabaci* and identified the gene *Tma12* from *Tectaria macrodonta*. Cotton plants overexpressing *Tma12* exhibited resistance to whitefly and were protected from infection by

the cotton leaf curl virus (CLCuKoV-Bu) with no detectable yield penalty (Shukla et al., 2016). The gene *Tma12* is recommended for pyramiding with others to develop GM plants resistant to multiple pathogens.

Molecular mechanisms regulating the trade-off between growth and disease resistance

There is growing evidence emerging in incompatible responses in different pathosystems for reduced growth when disease resistance is triggered. In the absence of abundant data, a general hypothesis is that plants turn off growth in order to save energy to fight attack from microbes. Indeed, there are clear examples of plants tunneling energy to fight disease (Kempel, Schädler, Chrobock, Fischer, & van Kleunen, 2011; Züst, Rasmann, & Agrawal, 2015). Another pathway is through regulation of Gibberellin accumulation by the DELLA protein. In the absence of pathogens, the DELLA protein is destabilized, and growth is promoted. On the other hand, upon an attack by a pathogen Gibberellins are destabilized and repression of growth mediated by DELLA is restored (Navarro et al., 2008). Resistance genes (*R genes*) play important roles in plant defenses, inducing Hypersensitivity (HR) (reviewed by Karasov et al., 2017). However, lesions induced by HR reduce yields. To avoid the penalties caused by HR plants try to fine tune the expression of *R genes* reducing their expression to basal low expression levels, being induced upon infection with pathogens. Another elegant mechanism described by Xu et al. (2017) is the translation regulation of *R genes*. The authors have shown that the presence of a purine rich sequence in the 5′ region of *R genes* (R motif) regulates translation of this class of genes. In non-infected plants, the mRNA is present, but it is not translated. Upon infection, the R motif regulates translation and the plant accumulates the protein. Finally, a recent study has shown that at least part of fitness costs that are associated with growth or disease responses could be credited to the differential accumulation of ROS species in the apoplast (Neuser et al., 2019).

Conclusion

Although the employment of genetically modified plants expressing genes effective in controlling pathogen invasion and disease development is an important strategy today enabling improved agricultural productivity, disease resistance at the expense of yield resistance must also considered. Considering the expected increased global population, and 15-20% increase in food demands (FAO, 2009), the identification of appropriate gens to increase agricultural production must become a priority, with breeders able to balance the advantages of modifying traits to escape disease against any reduction in yield or performance.

Although plants, unlike mammals, lack adaptive immunity, they possess an innated immune system in each cell with systemic signaling capability from infection sites. While PTI can be suppressed by pathogen effectors delivered into the host cell, this immune response suppression can be overcome through ETI to re-establish resistance. NLR-encoding *R genes* are known to interact directly or indirectly with specific pathogen effectors, resulting in NLR-triggered immunity. Although a reduction in growth and yield can be associated with such resistance, *R genes* are responsible for effective resistance in numerous species, including introgression through backcrossing for gene pyramiding (Deng et al., 2017; Grant et al., 2003; Kottapalli et al., 2010; Suh et al., 2013).

Yield and defense are also affected by hormonal regulation during attack. Plant hormones and their interactions have been shown to play pivotal roles on plant growth and development because the elaborate hormone signaling networks and their ability to crosstalk make them responsible for mediating defense responses to the detriment of growth. The regulation and execution of both PTI and ETI proceed via the biosynthesis of metabolic signals such as the hormones SA and JA. Both are the focus of infection studies in plants and understanding how plants produce a highly specific blend of these defense hormones is critical for choosing potential resistance systems. In this context, most of the studies presented in this review analyze the levels and the metabolic pathways related to these hormones to understand positive responses to different pathogens without yield penalties.

Additional key players in plant defense include ncRNAs. are also key players in plant defense. The miRNAs play pivotal roles in ETI and PTI pathways, regulating post-transcript or translation level of defense genes. In terms of resistance development without yield trade-off, Chandran et al. (2019), for example reported transgenic-derived resistance to blast disease with target mimicry of miRNA396 positively regulating Growth Regulating Factors GRF6, 7, 8.

RNAi approaches also offer potential and durable defense against plant virus, with RNAi constructs, including stacking, offering durable resistance without yield penalties. Kumar et al. (2017) demonstrated that the use of stacking constructs can be a clever solution for durable resistance without yield penalty.

Yield penalties in resistant cultivars developed in the past were likely greater than those observed in cultivars which are under development today base on our knowledge of genes and trade-off risks. Transgenic host resistance breakdown due to pathogen evolution, however, continues to threaten yield over time, resulting in losses to farmers and limiting available resistant cultivars. Although several successful examples have been presented in this review, continued research on plant mechanisms controlling disease resistance and yield is necessary, in the context of disease resistance breakdown avoidance.

Conflicts of interest

The authors declare no conflicts of interest.

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