

Host Induced Gene Silencing (HIGS), a Promising Strategy for Developing Disease Resistant Crops

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Short Commentary

RNA interference (RNAi) is a powerful tool for elucidating gene function in plants and altering gene expression for desired traits [1-3]. Host-induced gene silencing (HIGS) is an RNAi-based process where small RNAs made in the plant silence genes of pests or pathogens that attack the plant. The small RNAs are generally made by producing double stranded RNA (dsRNA) in transgenic plants but for experimental purposes the dsRNA can be introduced into plant cells with agrobacterium or viruses that replicate through dsRNA. Gene silencing approaches for pest resistance in plants have only been commercialized for virus resistance to date. However, HIGS has emerged as a promising strategy for improving plant resistance to insects and nematodes by targeting genes essential to these pests. Transgenic maize plants expressing a dsRNA construct targeting the vacuolar H⁺ATPase showed significant reductions in feeding damage of western corn rootworm [4]. Similarly, Mao et al. [5] generated cotton (*Gossypium hirsutum*) plants expressing dsRNA of the cytochrome P450 gene CYP6AE14 which enhanced resistance to bollworms. Genes in sedentary root-knot and cyst nematodes can also be silenced by expressing dsRNAs in plants and silencing of essential genes can reduce their pathogenicity and thus make the plant more resistant. The efficiency of a variety of genes has been demonstrated for this purpose including those coding for secreted effector proteins, neuropeptides, and proteins involved in RNA processing [6-10].

Plant pathogenic fungi vary in their modes of pathogenicity from biotrophs like rusts and mildews, which invaginate living plant cells with haustoria, to necrotrophs like *Sclerotinia sclerotiorum*, which derive nutrients from dead or dying cells. Initial reports of HIGS-mediated resistance to fungi described resistance to *Fusarium verticillioides* in tobacco plants [11] and the powdery mildew fungus (*Blumeria graminis*) in cereals [12]. Additional work has demonstrated the utility of HIGS in suppressing diseases caused by the cereal rust fungi (*Puccinia species*) [13-16], other *Fusarium* species [17,18], *S. sclerotiorum* [19], and even the oomycete pathogen causing lettuce downy mildew [20]. The variety of genes that have inhibited disease development when silenced includes those essential for structural components like chitin and ergosterol, developmental regulation, primary or secondary metabolism and pathogenicity. The effectiveness of HIGS silencing has also provided insights into specific mechanisms that different fungi use for pathogenicity. For example, silencing of a gene involved in biosynthesis of the plant auxin hormone IAA indicated it was an essential process for full pathogenicity of the cereal rust fungi [14]. Inhibition of an essential process in a pathogen can often be difficult by silencing a single gene because of functional redundancy, when the products of different genes can perform the same role. This is particularly true when targeting genes coding for pathogenicity effectors since most fungal pathogens have large arsenals of effector genes and silencing one may have little effect on pathogenicity. Another drawback of the approach is the incomplete silencing that generally results from RNAi. If an essential gene can perform its function with only a fraction of its normal levels of the encoded protein, it may not be an appropriate target for engineering resistance. Thus, considerable trial and error may be involved in finding an appropriate target gene. The use of transient silencing assays that can be used to quickly test

candidate genes can therefore be useful, especially for plant species that are difficult to transform [15].

What are the potential advantages of HIGS-mediated disease resistance over the disease resistances commonly incorporated into crop varieties by plant breeders? For some pathogens, like *S. sclerotiorum* and some of the *Fusarium* species, naturally occurring resistance is not available in the crop plant's germplasm base and the diseases are typically controlled with fungicides. In other cases, like most of the rust and mildew diseases, resistance genes are widely available but provide resistance to only specific strains of each pathogen. These pathogens are notorious for their rapid evolution and ability to overcome the resistances bred into crop varieties. While only time will tell for sure, HIGS mediated resistance has the potential to be more difficult to overcome since multiple, conserved and essential pathogen processes can be targeted. Numerous challenges exist to commercializing HIGS as a tool in crop plants, including precise selection of the target sequences with no unintended effects on the host or non-target organisms, difficulties in making stably-expressing transgenic in many crops, assessment of safety aspects, and consumer preferences against transgene technology. However, there is reason for hope that in the near future HIGS technology will be used to develop crops with effective and long lasting resistance to important fungal diseases to replace costly and environmentally suspect chemical protection.

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Received October 02, 2015; Accepted October 19, 2015; Published October 21, 2015

Citation: Yin C, Hulbert S (2015) Host Induced Gene Silencing (HIGS), a Promising Strategy for Developing Disease Resistant Crops. Gene Technol 4: 130. doi: 10.4172/2329-6682.1000130

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This article was originally published in a special issue, [Molecular Pathology](#) handled by Editor(s). Dr. Fahd Al-Mulla, Kuwait University, Kuwait.