Breeding a fungal gene into wheat

An ancient cross-kingdom gene transfer enables wheat resistance to a fungal toxin

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Every year, infection of wheat by the fungus *Fusarium graminearum* results in losses of ~28 million tons of wheat grain (*1*), valued at $5.6 billion. The fungus reduces yields, but also contaminates harvests with trichothecene toxins such as deoxynivalenol (DON, also called vomitoxin because of its effects on mammals) that render grain too poisonous to use. The disease is becoming more prevalent due to increasing cultivation of maize (also a host for the fungus) and reduced tillage (ploughing) agriculture, which promotes fungal survival on last season's plant debris. On page XXX of this issue, Wang *et al*. (*2*) reveal the molecular identity of the *Fusarium head blight 7* (*Fhb7*) gene, which encodes a glutathione S-transferase that detoxifies DON. This gene was acquired through a "natural" fungus-to-plant gene transfer in a wild wheat relative. This naturally-occurring genetically modified (GM) wheat strain is therefore exempt from regulation and can be grown directly by farmers.

Annual yield losses due to *Fusarium* head blight are second only to leaf rust (*1*). Despite screening thousands of wheat lines, little resistance to *Fusarium* has been found. Wild grassy relatives of wheat, however, represent a rich source of genetic diversity, which has long been mined for resistance genes by interspecific crosses. The *Fhb7* gene was introduced into wheat from tall wheat grass (*Thinopyrum ponticum*) and provides major, semi-dominant resistance (*2*), unlike most *Fusarium* resistance in wheat, which is typically conferred by polygenic minor-effect genes that are difficult for breeders to track (*3*).

The identification of *Fhb7* by Wang *et al*. reveals an enzyme that detoxifies DON by conjugating it to glutathione (see the figure). This explains the resistance conferred by *Fhb7*, because DON is an important virulence factor required for *Fusarium* growth on infected tissue (*4*). One could now engineer *Fhb7* for DON detoxification to elevate resistance to *Fusarium* species causing head blight in other cereals (such as barley and rye) or crown rot in wheat and ear rot in maize.

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The study of *Fusarium* head blight in wheat has been hindered by a disease resistance trait that is difficult to measure, a paucity of variation for resistance, and recent controversy concerning *Fhb1*, the first *Fusarium* head blight resistance gene to be cloned in wheat. Although one study identified *Fhb1* as a pore-forming toxin-like gene, two subsequent studies reported a histidine-rich calcium binding protein, but disagreed about the mode of action (*5*). Given the strong evidence presented by Wang *et al.,* including gain- and loss-of-function studies and a biochemical mechanistic dissection, hopefully *Fhb7* will evade such controversy. Optimal control of wheat head blight may require breeders to combine *Fhb7* with *Fhb1*, but this remains to be rigorously tested.

The most extraordinary aspect of *Fhb7* concerns its origin in *Epichloë*, a widely distributed ascomycete fungal genus that colonizes leaves of many grasses. Some species make alkaloid neurotoxins that render ryegrass poisonous to sheep in New Zealand (*6*). Because *Epichloë* primarily colonizes leaves, how DNA from *Epichloë* could enter the *Thinopyrum* germline remains a mystery. The *Fhb7* gene was found to have 97% identity with its homolog in *Epichloë*, but was otherwise absent from grass genomes, except within the *Thinopyrum* genus, suggesting the gene transfer event arose after divergence of *Thinopyrum* from other grasses ~5 million years ago (*2*). Horizontal gene transfer events (the transfer of genetic material between species) are rare but have been recorded before, for example, between Agrobacteria and sweet potato (*7*) and between sorghum and parasitic *Striga* (*8*). In these cases, no beneficial function was associated with the transfer. Additional such horizontal gene transfers likely exist and might be revealed by bioinformatic searches. Moreover, why *Epichloë* evolved a DON detoxification gene is unknown; perhaps it detoxifies one of its own toxins, or helps *Epichloë* compete with *Fusarium* for grass colonization.

What does the natural transfer of *Fhb7* into a grass mean for the discussion on GM crops? This natural GM product may be as good as or better than any that could have been created in the lab (see the figure), although conceivably, *Fhb7* could be even more effective if highly expressed from other promoters (*2*). Despite concerns from some, GM crop cultivation is increasing. 10% of the worlds arable land is used for GM soy, maize, cotton, and canola (*9*), which along with GM potato, papaya, eggplant (aubergine) and sugar beet provide pest, disease, and herbicide resistance. In rice, many GM traits have now been approved (*10*). However, wheat, the world's most widely grown crop—and a source of 20% of the calories and protein consumed by humankind—is a "GM orphan" (*11*).

Important opportunities are being missed by postponing GM wheat. Pests and diseases limit wheat production by ~20% globally (*1*). This number masks regional epidemics that can cause complete local crop failure, which is devastating for smallholder farmers in developing countries. It is now possible to rapidly discover and clone disease resistance genes from wild crop relatives (*12*) and engineer this resistance into domesticated varieties (*13*). Combinations ("stacks") of multiple broad-spectrum resistance genes will likely provide durable disease resistance. With conventional breeding, such stacks would be almost impossible to create and maintain.

Can *Fhb7* be used as an example to sway public opinion on anti-GM arguments? If plant breeders can take advantage of a "natural" horizontal gene transfer such as *Fhb7* to reduce crop losses, why not a deliberate horizontal gene transfer for the same reason? The world is heading towards a projected population of 9.6 billion in 2050 and increases in crop yields are not keeping pace with growing demand. To meet this demand, and sustainably increase agricultural output, a concerted effort from breeders, agronomists, biotechnologists and policymakers, and effective public engagement from scientists about the "naturalness" of horizontal gene transfer is needed.

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Two paths to *Fusarium*-resistant wheat

Fusarium head blight-resistant domesticated wheat has been produced by ancient horizontal transfer of the *Fusarium head blight 7* (*Fhb7*) gene between *Epichloë*, a fungal endophyte, and wild wheatgrass. This gene could also be engineered into domesticated wheat, but would be regulated as a genetically modified (GM) crop.

Insert: The Fhb7 enzyme neutralizes deoxynivalenol (DON) by conjugating a glutathione (GSH) onto its toxic epoxide moiety.