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Adaptation to fungicides in the wheat pathogen *Zymoseptoria tritici*: a multidisciplinary study of multi drug resistance.

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The ascomycete *Zymoseptoria tritici* is the causal agent of septoria leaf blotch on wheat. Disease control relies mainly on resistant wheat cultivars and on fungicide application. The fungus however displays a high potential to circumvent both methods. Resistance against all major fungicides has been observed and studied over decades. Especially the adaptation to DMIs, inhibiting sterol biosynthesis, implying modifications of the *CYP51* target gene has revealed a large spectrum of resistance mutations. Recently introduced fungicides are facing resistance through target gene mutations as well. A different type of resistance has evolved among *Z. tritici* populations affecting multiple chemical families (Leroux & Walker, 2011). Strains considered as multi-drug resistant have been isolated since 2009.

Multidrug resistance (MDR) is a common trait developed by many organisms to counteract chemicals and/or drugs used against them. MDR is relying on an overexpressed efflux transport system that actively expulses the toxic agent outside the cell. Our study aimed to validate MDR in *Z. tritici* field strains. We showed that active drug efflux was indeed at play and we identified the major-facilitator gene, *MFS1*, as principal player of this emerging resistance mechanism (Omrane et al., 2015). The *MFS1* gene was found overexpressed in all tested field strains. At the origin of the overexpression and the MDR phenotype is a 519 bp insert in the *MFS1* promoter, an LTR reminiscence of a recent retro-transposition event. The insert harbors four copies of a highly conserved transcription-factor binding-site that may explain *MFS1* overexpression. Besides this type of insert, we found a different type of promoter insert in more recent MDR strains. Interestingly, this last insert was found upstream of other genes in different *Z. tritici* strains. It also contains potential transcription factor binding sites. Finally, a 3rd type of insert was identified in two other *MFS1* overexpressing MDR strains.

Altogether, these results underline the extremely high adaptive potential of *Z. tritici* to fungicides through the plasticity of the *MFS1* promoter leading to its over-expression, to fungicide efflux and, ultimately, to MDR.

Leroux, P. & A.S. Walker, (2011) Multiple mechanisms account for resistance to sterol 14alpha-demethylation inhibitors in field isolates of *Mycosphaerella graminicola*. *Pest Manag Sci* **67**: 44-59.

Omrane, S., H. Sghyer, C. Audéon, C. Lanen, C. Duplaix, A.-S. Walker & S. Fillinger, (2015) Fungicide efflux and the MgMFS1 transporter contribute to the multidrug resistance phenotype in *Zymoseptoria tritici* field isolates. *Environmental microbiology* **17**: 2805-2823.

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