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Multi-drug-resistance (MDR) in septoria leaf blotch.

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Context: Multidrug resistance (MDR) is a common trait developed by many organisms to counteract chemicals and/or drugs. The basic MDR mechanism relies on an overexpressed efflux transport system that actively expulses the toxic agent. In fungi, MDR has been extensively studied in *Saccharomyces cerevisiae*, but also plant pathogenic fungi, e.g., *Botrytis cinerea*, are concerned by this phenomenon. In agriculture, it is currently under investigation if MDR strains may threaten the efficacy of fungicide treatments. MDR strains were detected in septoria leaf blotch (*Zymoseptoria tritici*) field populations since 2008 (Leroux & Walker, 2011). These strains are cross resistant to fungicides with different modes of action.

Results: We have shown that this resistance is due to active fungicide efflux, potentially through the overexpression of one membrane transporter gene, *MgMFS1* (Omrane et al., 2015). The inactivation of *MgMFS1* abolished the MDR phenotype in at least one field strain. A bulk-segregant analysis (BSA) of two MDR isolates coupled to next generation sequencing showed a clear co-segregation between the MDR phenotype and the left arm of chromosome 7 covering *MgMFS1* (Fig.1). We identified a 519 bp insert (LTR-like) in both MDR strains as well as in other MDR field strains. Genotyping of the progenies for the promoter insert showed a clear, but not exclusive correlation between the *MgMFS1* promoter insert and the MDR phenotype. Current investigations are underway to analyze if the LTR-like insert - alone or in combination with a second mutation - confers the MDR phenotype through *MgMFS1* overexpression.

Conclusions: MDR is new resistance phenomenon in *Z. tritici*. It operates through fungicide efflux and involves overexpression of at least one major membrane transporter. Its evolution may be due to retrotransposon reminiscence, but additional mutations may be involved. The combination of *mdr* mutation(s) to target site mutations may threaten most fungicide treatments against septoria leaf blotch.

Fig. 1: A/ Flow chart of the applied BSA procedure; B/ Region of chromosome 7 with the highest distortion. SNPs and INDELS inducing non-synonymous substitutions are indicated by the stars.

Leroux & Walker (2011) Pest manag. sci. 67 (1):44-59.

Omrane et al. (2015) *Env. Microbiol.*, in press