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The QoI Fungicides, the Rise and Fall of a Successful Class of Agricultural Fungicides

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1. Introduction

Fungal diseases represent a major threat to crops. To cope with this problem, growers use enormous amounts of chemicals. Fungicides have long been used to reduce crop losses. Chemical control of plant diseases started to develop in the latter half of the nineteenth century when recommendations regarding the use of fungicidal preparations based upon the active ingredients sulphur, lime and copper sulphate were made. Up until the 1940s, the arsenal of available fungicides was very small. Chemical-based disease control continued to rely predominantly upon such inorganic chemical preparations that were frequently prepared by the user. The Second World War was a period of great advances in the chemical industries of most countries. The post-war period thus saw the introduction of new chemistry and new compounds based on pre-war chemistry (e.g., dithiocarbamates and phthalimides). Virtually all components were protectants i.e., they needed to be present on the crop at the time that the fungal infection arrived; once the infection was established, they were useless. A notable addition to these was the introduction in 1955 of an antibiotic designed in Japan specifically for rice blast control, blasticidin S. This was the first evidence that a systemic product could be applied on a field scale (Russell, 2005).

The 1960s was a time of considerable expansion in chemical crop protection. The start of this period saw some consolidation of previous years with further introductions from established areas of chemistry. Compounds such as mancozeb (a dithiocarbamate) and captafol (a phthalimide) were introduced with great success. Nevertheless, the major achievement of this decade was the introduction of the systemic fungicides thiabendazol and benomyl, both characterised by a methyl benzimidazole carbamate (MBC) mode of action, which marked the advent of internal plant therapy. In addition, chlorothalonil (a phthalonitrile), carboxin and oxycarboxin (carboxanilides), ethirimol (2-aminopyrimidine) and the first members of the morpholine fungicides, dodemorph and tridemorph, were introduced at this time (Russell, 2005). However, the 1970s was possibly the most significant decade for advances in crop protection chemistry. At this time the agrochemical market was growing at a rate of approximately 6.3% per annum in real terms (Finney, 1988). Fosetyl-Al, a phosphonate fungicide with the unique property of being phloem mobile, was one of the major discoveries of the 1970s. It was followed by metalaxyl, the first of the phenylamides,

and propamocarb, a carbamate fungicide. Options for disease control were expanded in the 1980s through the introduction of several triazoles, the first members of the sterol demethylation inhibitor (DMI) class of fungicides and several additional members of the morpholine group (Russell, 2005).

Over the last twenty years, the standards of disease control have been further improved by the development of the strobilurins (Bartlett et al., 2002). They are a truly remarkable group with activity against all major fungal genera. They exhibit protectant, systemic and eradicant action. The first strobilurin fungicides to reach the market were azoxystrobin and kresoxim-methyl; the development of similar compounds soon followed. Collectively, they are called the QoI group, a term derived from their mode of action in binding at the Qo site of cytochrome *b*. The strobilurins quickly became one of the most important agricultural fungicides, accounting for over 20% of the global fungicide market within the first ten years of their commercial introduction. However, one of the apparent strengths of systemic fungicides, their high specific mode of action, also proved to be a serious weakness. Soon after their introduction, QoI resistant isolates of *Blumeria graminis* f. sp. *triciti* on wheat and *Plasmopara viticola* on vines were documented (Heaney et al., 2000). Since then, resistant strains of over thirty different plant pathogens have emerged. This fungicide group is considered to be high risk; thus, strict anti-resistance strategies including limiting the number of treatments and using mixtures or alternations, must be taken. In most cases, resistance resulted from modification of the cytochrome *b* target site. However, an increasing amount of experimental evidence has suggested that QoI resistance can occur via other mechanisms (Fernández-Ortuño et al., 2008b). This chapter reviews our current knowledge of this successful class of agricultural fungicides and the mechanisms of resistance to QoI fungicides in phytopathogenic fungi, furthermore, it discusses the implications of the emergence of resistance and for risk assessment, including aspects such as the fitness cost associated with QoI resistance.

2. Discovery and structure of the QoI fungicides

Strobilurins are natural substances produced mainly by basidiomycete wood-rooting fungi such as *Strobilurus tenacellus* (Pers. ex Fr.) Singer and *Oudemansiella mucida* (Schrad. ex Fr.) Hohn, or by the gliding bacterium *Myxococcus fulvus* (Bartlett et al., 2002). As such, their name derived from the genus *Strobilurus*. Strobilurin A, the first QoI molecule, was isolated from liquid cultures of *S. tenacellus* by Anke et al. (1977). Similar compounds were subsequently identified and named in the order of their discovery (i.e., strobilurin B, C, D and so on). These compounds were isolated by chromatographic means, and their molecular structures were identified by high-resolution mass spectrometry. Further spectroscopic analyses were performed to determine their molecular structures as described in the work of Schramm et al. (1978). In fungi, these products are biosynthesised from phenylalanine via the shikimic acid cycle (Balba, 2007). Structurally, the basic common feature of all natural strobilurins is the presence of a methyl (E)-3-methoxy-2-(5-phenylpenta-2,4-dienyl) acrylate moiety, linked to the rest of the molecule at the α-position. They have therefore been named *β*-methoxyacrylates or MOAs (Sauter, 2007). They vary only in the aromatic ring substitutions at positions 3 and 4 (Fig. 1).

These natural compounds break down rapidly in light and are therefore not reliable for disease control. However, knowledge of their structures and physical properties provided the starting point for independent research programmes within the chemical companies

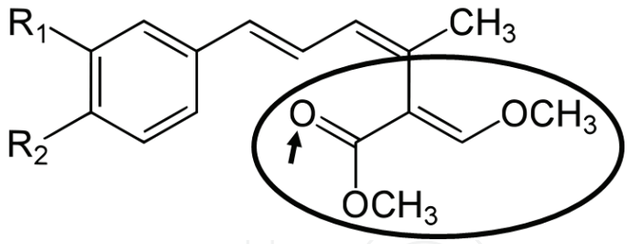

Fig. 1. The basic chemical structure of natural strobilurins. The *β*-methoxyacrylate moiety is highlighted with a circle and the carbonyl oxygen responsible for binding is indicated by an arrow. R_1 and R_2 represent radicals that are distinct in the different naturally-occurring strobilurins.

Syngenta and BASF. During the process of lead structure optimisation, thousands of QoI analogues were synthesised and tested before suitable photo-stable compounds with fungicidal activities were developed. Most of these attempts were focused on the modification of the α-substitution in the (E)-*β*-methoxyacrylate group. One of the important directions taken in the structural modifications was the replacement of the basic toxiphoric group of (E)-*β*-methoxyacrylate with a methoxyiminoacetate group. This modification was led by BASF. In 1992 the first QoI fungicides, azoxystrobin from Zeneca (now Syngenta) and kresoxim-methyl from BASF, were announced (Godwin et al., 1992; Ammermann et al., 1992). These fungicides were made commercially available in 1996 (Fig. 2).

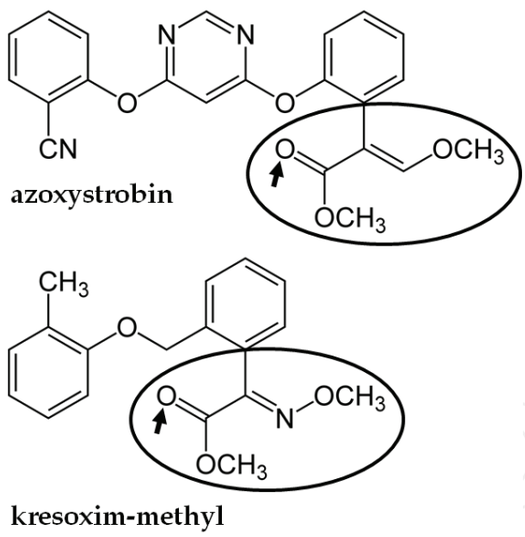

Fig. 2. The chemical structures of azoxystrobin and kresoxim-methyl. The (E)-*β*-methoxyacrylate group of azoxystrobin and the methoxyiminoacetate group of kresoxim-methyl are highlighted with circles and the carbonyl oxygen moieties responsible for binding are indicated by the arrow.

The development of similar compounds soon followed. A further modification was the replacement of the (E)-*β*-methoxyacrylate group with 2-methoxyiminoacetamide. This modification was marketed under the name metominostrobin. In addition to strobilurins, there are other compounds such as famoxadone and fenamidone (Fig. 3) that are chemically distinct from strobilurins but are part of the same QoI fungicide cross-resistance group.

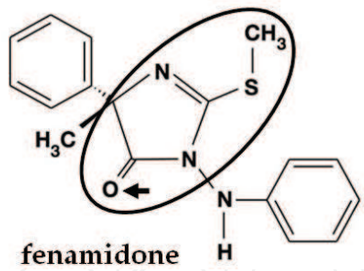

Fig. 3. The chemical structure of fenamidone. The toxophore moiety is highlighted with a circle and the carbonyl oxygen responsible for binding is indicated by an arrow.

Several products resulting from these development efforts are now commercially available. At present, based on structural similarities, eight chemical groups of Qo inhibitors can be distinguished, representing fifteen QoI active ingredients (Table 1). Commercial QoI fungicides are among the best-selling agricultural fungicides worldwide, and are used primarily as plant protectants against most major fungal and oomycete pathogens.

Classes	Fungicides	Current owner	First sales
Methoxyacrylates	Azoxystrobin	Syngenta	1996
	Picoxystrobin	Syngenta	2002
	Enestrobin	SS[a]	-
	Pyraoxystrobin	SRICI[b]	-
Oximinoacetates	Kresoxim-methyl	BASF	1996
	Trifloxystrobin	Bayer	1999
Oxazalidinediones	Famoxadone	DuPont	1997
Oximinoacetamides	Metominostrobin	Bayer	1999
	Dimoxystrobin	BASF	2004
	Orysastrobin	BASF	2006
Imidazolinones	Fenamidone	Bayer	2001
Methoxycarbamates	Pyraclostrobin	BASF	2002
	Pyrametostrobin	SRICI	-
Dihydrodioxazines	Fluoxastrobin	Bayer	2004
Benzylcarbamates	Pyribencarb	KCI[c]	-

[a]Sinochem Shanghai
[b]Shenyang Research Institute of Chemistry Industry
[c]Kumiai Chemical Industry

Table 1. The QoI fungicides.

3. Biochemical mode of action of QoI fungicides

The QoI fungicides display a single-site mode of action that was elucidated in 1981 by Becker et al. The fungicidal activity of QoI fungicides relies on their ability to inhibit mitochondrial respiration by binding at the Qo site (the outer, quinol oxidation site) of the cytochrome bc_1 enzyme complex (complex III). This inhibition blocks the transfer of electrons between cytochrome *b* and cytochrome c_1, leading to an energy deficiency in the fungal cells by halting the production of ATP (Fig. 4), and ultimately leading to fungal death. The QoI target, cytochrome bc_1, is an integral membrane protein complex essential for

fungal respiration. In eukaryotes it comprises 10 to 11 different polypeptides with a combined molecular mass of roughly 240 kDa, and operates as a structural and functional dimer. Cytochrome *b*, cytochrome c_1 and the Rieske iron-sulfur protein (ISP) form the catalytic core of the enzyme. The catalytic mechanism, called the Q-cycle, requires two distinct quinone-binding sites: Qo, the quinol oxidation site, and Qi, the quinone reduction site (Fisher & Meunier, 2008). The location of the quinol/quinone binding sites of bc_1, both of which are located within the cytochrome *b* subunit has been resolved by X-ray crystallography using bound inhibitors. Detailed information about interactions between bc_1 and inhibitors has since become available for several QoI fungicides. It is now known that, despite differences in binding between the different Qo inhibitors, their fit to the enzyme pocket is very similar (Esser et al., 2004). The toxophore is similar in all compounds and always contains a carbonyl oxygen moiety (Figs. 1, 2 and 3) that is thought to be responsible for binding to the enzyme.

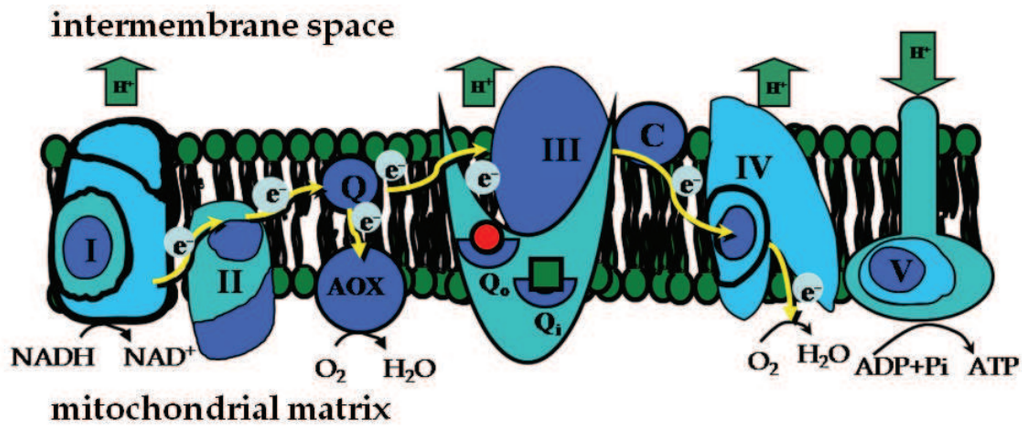

Fig. 4. Schematic representation of the mitochondrial electron transport system. I, II, III and IV are the different complexes of the transfer chain. V is the ATP synthase complex. Q is the ubiquinone pool and C is the peripheral protein cytochrome *c*. The yellow arrows inside the membrane indicate the direction of electron flow. The Qo and Qi binding sites of the cytochrome bc_1 enzyme complex (complex III) are delineated by a red circle and a green square representing Qo- and Qi-inhibitor molecules, respectively. In some fungi, inhibitors of the respiratory pathway induce the synthesis of alternative oxidase (AOX), an enzyme that diverts electrons at the ubiquinone pool (Q), but generates much less energy.

One important characteristic of the fungicidal action of this class of chemicals is their rapid activity. Studies performed using different QoIs have demonstrated that spore germination and zoospore motility are developmental stages of fungi and oomycetes that are particularly sensitive to QoI fungicides (Godwin et al., 1997; Leinhos et al., 1997). This can be explained by their biochemical mode of action, namely the disruption of energy production, with the consequence that they are particularly effective against these highly energy-demanding stages of development that are very critical for successful colonization of the plant (Fig. 5). The detailed understanding of the effects of QoIs on different stages of fungal development has been important for the optimisation of application timing to most effectively control of disease. QoIs are, therefore, best applied prior to infection or in the early stages of the disease cycle to capitalise on their potent effects as protectant or preventive fungicides (Bartlett et al., 2002).

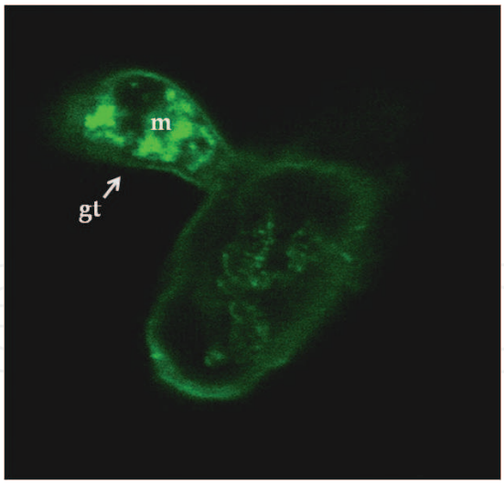

Fig. 5. Mitochondria in the germination tube of a phytopathogenic fungus. Mitochondria in germinating conidia of the cucurbit powdery mildew fungus *Podosphaera fusca* were labelled with MitoTracker Green FM (Molecular Probes). Green fluorescence indicates the presence of mitochondria (m) that are primarily located in the germination tube (gt). Germination is a physiological process that is highly dependent on energy; therefore, most of the conidial mitochondria are reallocated to the germination tube.

4. Agricultural use of QoI fungicides

Since their introduction, QoIs have become essential components of plant disease control programmes because their wide range of efficacy against many agriculturally important fungal diseases. QoIs have been registered in numerous countries for use on several different crops, including cereals, turf grass, grapevines, and a number of vegetables and ornamental plants. The individual active ingredients of QoIs have been the primary reason for their success, they are all characterised by one or more of the following attributes: broad-spectrum activity, control of isolates resistant to other fungicides, low use-rates and excellent yield and quality benefits (Bartlett et al., 2002). In a number of crops, QoIs have led to major changes in disease control programmes. For example, QoIs provided grapevine growers for the first time a single active ingredient to prevent both powdery (*Erysiphe necator*) and downy (*P. viticola*) mildews. In other crops such wheat and barley, QoIs exhibited increase yield and quality benefits over other classes of fungicides. QoIs have been important additions to the fungicide resistance-management armoury for many crops, particularly bananas. This class of fungicide has also proven particularly useful for the maintenance of protected horticultural crops; this was especially true in Europe where the number of available active ingredients is dwindling due to the high cost of maintaining a long list of registered uses. Furthermore, QoI fungicides are important not only as foliar-applied fungicides but also as seed-treatment applications and in-furrow treatments for soil-borne disease control (Bartlett et al., 2002).

All commercialised QoIs have been demonstrated to exhibit a broad spectrum of activity. Of particular importance is their activity against all four major groups of pathogens responsible for fungal-like diseases, namely Ascomycetes, Basidiomycetes, Deuteromycetes and Oomycetes. However, QoIs vary in their levels of activity against the different plant diseases, and not all of them exhibit high levels of control of these four major groups of

plant pathogens (Bartlett et al., 2002). Among other plant diseases, QoIs are effective in the protection of crops against powdery mildews (Fig. 6), brown rusts and downy mildews (Balba, 2007). Moreover, QoIs may exert some negative effects against the sexual stages of plant pathogenic fungi and oomycetes. Azoxystrobin has been shown to inhibit the production of viable ascospores and oospores of grapevine powdery and downy mildews, respectively (Godwin & Cortesi, 1999; Vercesi et al., 2002); thus, this QoI reduces the evolutionary potential of these important pathogens of vineyards.

Fig. 6. Disease symptoms of cucurbit powdery mildew on zucchini leaves elicited by *Podosphaera fusca*. Powdery mildew diseases are major targets for QoI fungicides. Unfortunately, they exhibit a high rate of resistance development and many cases of QoI-resistant powdery mildew fungi have been documented.

QoI fungicides may exhibit additional yield and quality benefits. Of particular interest has been the consistently greater yield of several crops, including wheat and barley, that are subjected to strobilurin-based fungicide programmes. This has been termed the strobilurin "greening effect", a phenomenon that refers to delayed leaf senescence and an increased grain-filling period that results in an enhanced biomass and yield (Bartlett et al., 2002). Two hypotheses have been presented to explain this phenomenon. The first hypothesis is related to the effects of strobilurins on non-disease-related physiological processes such as chlorophyll and phytohormone biosynthesis, stomatal aperture, water consumption in addition to modulation of nitrate reductase, photosynthetic and plant antioxidant enzyme activities. The second theory is related to the strong preventive activity of strobilurins, preventing the germination of pathogenic, non-pathogenic and saprophytic fungi and thereby preventing the initiation of energy intensive host defence responses. However, neither hypothesis has been unequivocally proven to be responsible for this phenomenon. It is possible that elements of both hypotheses contribute to these "unexpectedly positive" yield benefits resulting from the use of strobilurins (Bartlett et al., 2002). Moreover, some strobilurins, such as pyraclostrobin, may have priming-inducing activities on plants (Herms et al., 2002). In the primed condition, plants are able to "recall" previous infections, root colonisations or chemical treatments. As a consequence, primed plants respond more rapidly and/or effectively when re-exposed to biotic or abiotic stress; such improved responses are frequently associated with enhanced disease resistance (Goellner & Conrath, 2008). Findings made using pyraclostrobin suggest that this compound, in addition to

exerting direct antifungal activity, may also protect plants by priming them for increased activation of stress-induced defence responses.

Unfortunately, the single site mode of action of QoI fungicides results in a high intrinsic risk of development of resistance to this group of fungicides. Strict anti-resistance strategies, including treatment limitations and the use of mixtures or alternating fungicides, are therefore required (McGrath, 2001). In Spain, for example, there are cucurbit-growing areas where the cucurbit powdery mildew pathogen *P. fusca* has developed high levels of resistance (up to 74% in Murcia) to QoI fungicides. In these areas, disease control based on these compounds is virtually ineffective; these high rates of resistance are presumably the result of frequent use of these popular fungicides by growers (Fernández-Ortuño et al., 2006).

5. Mechanisms of resistance to QoI fungicides

5.1 Mutations in the cytochrome *b* gene

The primary mechanism of QoI resistance is target site-based and involves mutations in the mitochondrial cytochrome *b* gene (*CYTB*), resulting in peptide sequence changes that prevent fungicide binding. Mutations that affect sensitivity to QoI fungicides have been found in two regions of *CYTB*, corresponding to amino acid positions 120-155 and 255-280 of the encoded protein. In the folded cytochrome b, these domains are close to each other and are important for ligand binding. Two amino acid substitutions, from glycine to alanine at position 143 (G143A) and from phenylalanine to leucine at position 129 (F129L), have been detected in the cytochrome *b* proteins of several phytopathogenic fungi and oomycetes that are resistant to Qo inhibitors (Gisi et al., 2002). Recently, an additional amino acid substitution, from glycine to arginine at position 137 (G137R), has also been linked to QoI resistance (Sierotzki et al., 2006). Isolates expressing F129L or G137R mutant proteins exhibit moderate (partial) resistance that is typically overcome by the recommended field levels of QoIs. In contrast, isolates expressing G143A mutant protein exhibit high (complete) levels of resistance that is always associated with the failure of QoI to control disease (Fig. 7). The G143A substitution has been detected in resistant isolates of more than twenty species, including phytopathogenic ascomycetes and oomycetes such as several powdery mildews and *Alternaria* species in addition to the major *Mycosphaerella* pathogens, *M. fijensis* and *M. graminicola* (for an updated list of plant pathogens in which the G143A substitution has been documented, please visit the web page of the Fungicide Resistance Action Committee, FRAC, QoI Working Group at www.frac.info). The G143A substitution is also present in strobilurin-producing basidiomycetes that are naturally resistant to these fungicides (Kraiczy et al., 1996).

Although many reports have attributed QoI resistance in plant pathogens to the G143A substitution, the role of this amino acid change in QoI resistance has been very difficult to investigate because the cytochrome *b* target is encoded by a mitochondrial gene. Consequently, functional genetic studies of this mutation have only been performed in *M. fijiensis* (Gisi et al., 2002). In light of the obstacles in investigating the role of *CYTB* mutations in QoI resistance using molecular approaches, most studies have focused on demonstrating a correlation between QoI resistance and the G143A substitution. However, this statistical approach has not always been as thorough as required due to the low number of resistant isolates analysed. Regardless, a correlation between QoI resistance and the G143A substitution has been clearly demonstrated in *Blumeria graminis* f. sp. *tritici*, *M. graminicola* and *Pyricularia grisea* (Fraaije et al., 2002; 2005; Kim et al., 2003).

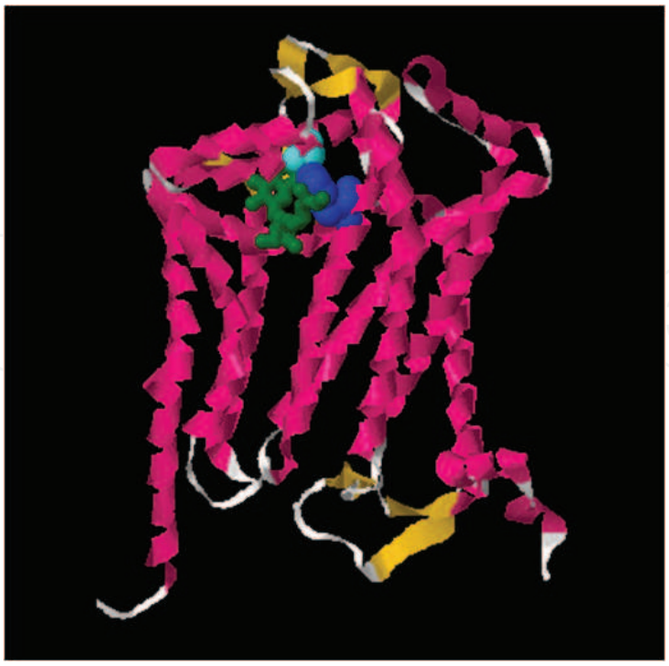

Fig. 7. Cytochrome *b* and QoI resistance. Molecular model of the cytochrome *b* protein of *Saccharomyces cerevisiae*. A QoI fungicide molecule bound to the Qo site of the cytochrome bc_1 complex is depicted in green. The amino acids substitutions G143A and F129L that are responsible for QoI resistance are depicted in cyan and blue, respectively. Note how these amino acids interact with the fungicide molecule.

5.2 Alternative respiration

The second mechanism of resistance to QoI fungicides is mediated by the induction of an alternative, cyanide-resistant respiration that is sustained by alternative oxidase (AOX) (Wood & Hollomon, 2003). In this rescue mechanism, mitochondrial electron transfer is diverted by circumventing the inhibitory site of QoI in the cytochrome bc_1 complex (Fig. 4). However, the energy provided by alternative respiration only seems to counteract QoI effects *in vitro* but not *in planta*. Under field conditions, alternative respiration appears to have a limited impact on the protective activities of QoI fungicides for two main reasons. First, this pathway provides low levels of ATP that represent only 40% of the normal efficiency for energy conservation. This is due to the fact that complexes III and IV of the mitochondrial electron transport system are bypassed, and AOX lacks proton pumping activity. Consequently, processes that demand large amounts of energy and are critical steps for successful colonization of the plant, such as spore germination and host-penetration, are not supported. Second, plant antioxidants, such as flavones, are released during infection and interfere with the induction of alternative respiration by quenching reactive oxygen species that are necessary to induce the *AOX* gene and are generated by QoIs (Wood & Hollomon, 2003).

Despite the widely accepted minor role of AOX in QoI resistance, several reports using alternative oxidase-deficient mutants and specific inhibitors of this enzyme have revealed that alternative respiration also limits QoI effectiveness *in planta*, especially once the infection has been established (Olaya & Köller, 1999; Avila-Adame & Köller, 2003; Miguez et

al., 2004). A possible explanation is that a decreasing demand for energy efficiency during the later stages of the infection process, such as mycelial growth and sporulation, enables AOX to become more effective as an infection progresses (Wood & Hollomon, 2003). This is consistent with the lack of eradicant activity of QoI fungicides against many fungi; after visible symptoms have appeared, control is typically ineffective.

Moreover, alternative respiration may provide an opportunity for the selection of a point mutation in *CYTB* by decreasing levels of damaging reactive oxygen species and ensuring ATP synthesis. Both of these functions contribute to cell survival while selection increases the frequency of resistant mitochondria (Wood & Hollomon, 2003; Miguez et al., 2004). The QoI-targeted cytochrome *b* protein is encoded by mtDNA that is known to mutate at a higher frequency than nuclear DNA; this mutation frequency is increased by the accumulation of reactive oxygen species that result from the inhibition of the electron transport system by QoIs (Bohr & Anson, 1999). Under such circumstances, alternative respiration could represent an essential pathway for the transition from sensitivity to full resistance in phytopathogenic fungi in the presence of sub-lethal concentrations of QoI fungicides. Regardless, despite the lack of a clear-cut example in which AOX plays a role in field resistance to QoIs, the potential involvement of this enzyme in the development of QoI resistance should not be ignored (Wood & Hollomon, 2003).

5.3 Efflux transporters

Efflux transporters can enable fungi to survive exposure to toxic compounds, preventing the accumulation of compounds at toxic concentrations inside fungal cells. These membrane-bound proteins are known to provide protection against a wide range of natural toxic compounds and xenobiotics (Del Sorbo et al., 2000). The ATP-binding cassette (ABC) transporter family and the major facilitator superfamily (MFS) are the most important efflux pumps involved in the protection of fungi against fungicides (Fig. 8) (Stergiopoulos et al., 2003; De Waard et al., 2006). In agriculture, however, there are few obvious cases of multi-drug resistance to fungicides in plant pathogens. The first efflux transporter gene involved

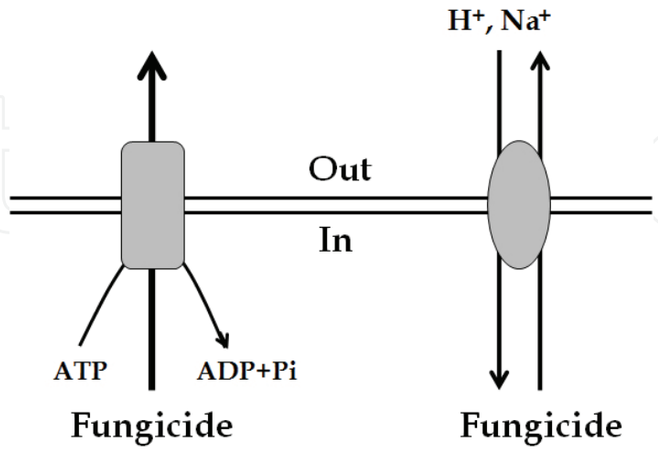

Fig. 8. Schematic representation of the two major classes of efflux transporters in fungi. ATP-binding cassette (ABC) transporters utilise the free energy of ATP hydrolysis to pump fungicides out of the cell. The transporters from the major facilitator superfamily (MFS) mediate the extrusion of fungicides in a coupled exchange with protons or sodium ions.

in QoI insensitivity to be reported in a plant pathogen was *MgMfs1*, a MFS transporter gene of *M. graminicola* (Roohparvar et al., 2007). Most natural isolates of *M. graminicola* resistant to strobilurins and over-expressing *MgMfs1* also contain the G143A substitution, suggesting that the contribution of *MgMfs1* to the QoI resistance in field strains should be small.
Prior to the isolation of *MgMfs1*, Reimann & Deising (2005) described an efflux transporter-mediated mechanism of resistance to QoI fungicides in field isolates of the wheat pathogen *Pyrenophora tritici-repentis*. The involvement of this type of mechanism in fungicide resistance was determined by using inhibitors of these membrane transporters, such as the hydroxyflavone derivative 2-(4-ethoxy-phenyl)-chromen-4-one, in combination with fungicides; such inhibitors shifted resistant isolates back to normal sensitivity levels, preventing infection of wheat leaves. In addition, those authors also reported the induction of efflux transporter activity under field conditions and after *in vitro* applications of sub-lethal doses of fungicides. Although data regarding resistance to QoI fungicides based on efflux transporters are scarce, the contribution of these energy-dependent mechanisms in the *in planta* adaptation to fungicides by phytopathogenic fungi should be seriously considered.

5.4 Unknown mechanisms

In recent studies, resistance to QoI fungicides based on the G143A substitution has been deemed unlikely to evolve in phytopathogenic basidiomycetes (such as *Puccinia* spp.) or in several ascomycetes (such as *Alternaria solani*, *Monilinia fructicola* and *Pyrenophora teres*) because they carry a type I intron immediately after this codon. Consequently, a nucleotide substitution in codon 143 of the *CYTB* gene would prevent the splicing of the intron and lead to a deficiency in cytochrome *b*; such a mutation would likely be lethal mutation (Grasso et al., 2006). Indeed, serious resistance problems have not developed among *Puccinia* species, despite the extensive use of QoI on crop hosts of this group of pathogens. Nevertheless, one isolate of *Puccinia horiana* resistant to QoI has been reported to have *CYTB* sequences identical to sensitive genotypes, including the type I intron and, therefore, without the G143A substitution (Grasso et al., 2006). The case of *Botrytis cinerea* is different; two types of *CYTB* gene were found in Japanese populations of the grey mould pathogen, one with three introns and the other with an additional intron (Bcbi-143/144 intron) inserted between the 143rd and 144th codons. All QoI-resistant isolates showed the G143A mutation whereas the isolates possessing the Bcbi-143/144 intron were QoI-sensitive (Banno et al., 2009). The possession of such an intron may guarantee a low risk of QoI resistance but it might not always be fixed in pathogen populations.
There are a number of isolates from different fungal pathogens such as the above mentioned *B. cinerea*, *M. fructicola*, *P. fusca, Podosphaera aphanis* and *Venturia inaequalis*, in which the G143A substitution has not been always presented or has occasionally explained the QoI-resistant phenotypes (Ishii et al., 2001; Fountaine et al., 2006; Fernández-Ortuño et al., 2008a; Ishii et al., 2009; Lesniak et al., 2009; Schnabel, 2010). Moreover, in *P. fusca* and *V. inaequalis* the role of alternative respiration in resistance has been ruled out, though the mechanisms responsible for QoI resistance remain to be characterised (Steinfeld et al., 2001; Fernández-Ortuño et al., 2008a). In *P. fusca*, considering the pattern of cross-resistance to different Qo inhibitors, the high levels of resistance of the resistant isolates, and the absence of consistent mutations in *CYTB*, a structural change in the Rieske protein, the other protein component of the Qo site, has been suggested as the most plausible explanation for QoI resistance (Fernández-Ortuño et al., 2008a). Experimental evidence regarding the role of the Rieske

protein in the resistance to QoI fungicides has not yet been reported, though its nature as a nuclear-encoded target makes it an ideal candidate to explain QoI resistance in pathogens in which *CYTB* mutations have not been found.

6. Evolution and fitness costs associated with QoI resistance

The fact that QoIs inhibit a target site that is encoded by a mitochondrial gene implies several important differences in the way resistance to these fungicides evolved within fungal populations. The inheritance of *CYTB*-based QoI resistance is non-Mendelian and results in a 0:1 segregation at the single progeny and a 1:1 segregation at the population level. After homoplasmic resistant individuals have emerged, the selection process for QoI resistance in populations is expected to follow mechanisms similar to those of nuclear-encoded resistance; in particular, the key to effective resistance is the transition process from hetero- to homoplasmic cells. The evolution of QoI resistance in a fungal population must be the combined result of recurrent mutations and the selection process imposed by the fungicide. However, how this mutation is selected from within a population of wild-type, sensitive mitochondria, is not clear (Gisi et al., 2002). Some reports have described that mitochondrial heteroplasmy with respect to the G143A mutation results in different levels of QoI resistance (Lessemann et al., 2007). The question of how many mutated mitochondria per cell are required to produce a full QoI-resistant phenotype has not yet been answered. Moreover, the dynamics of mitochondria and the status of heteroplasmy in the mitochondrial genome encoding the *CYTB* gene can cause instability of the mutated gene over time, making it difficult to precisely monitor QoI resistance using molecular methods (Ishii, 2010). Heteroplasmy of *CYTB* genes has been described in several plant pathogenic fungi such as *B. cinerea*, *P. leucotricha* and *V. inaequalis* (Zheng et al., 2000; Fountaine et al., 2007; Ishii et al., 2007; Lessemann et al., 2007). In these studies, it was clearly shown that the sensitive isolates of these pathogens exhibited a low frequency of the mutated *CYTB* gene.

Evolution of resistance is closely related to the fitness costs associated with fungicide resistance. If fitness costs are associated with fungicide resistance, the frequency of resistant isolates will decline in the absence of fungicide. On this basis, Ishii et al. (2002) performed studies with cucumber powdery and downy mildews; they found that under both laboratory and commercial greenhouse conditions, QoI-resistant isolates persisted for a few years following the withdrawal of the selection pressure imposed by the fungicide. The authors proved that the homoplasmic mutated sequences in the *CYTB* gene of QoI-resistant strains may gradually revert to heteroplasmic status to include the wild-type sequences in the absence of fungicidal selection pressure, and that the proportion of mutated sequences rapidly increases in the high copy numbers of heteroplasmic *CYTB* gene when fungi are exposed to strong selection pressure by QoI fungicides.

Despite its practical relevance, little is known about the fitness cost associated with QoI resistance conferred by the G143A substitution. Fitness penalties have been observed in QoI-resistant field isolates of *P. grisea* and *P. viticola*, and laboratory mutants of *Cercospora beticola* (Avila-Adame & Köller, 2003; Malandrakis et al., 2006). In contrast, fitness penalties are not apparent in QoI-resistant field isolates of *B. graminis* and *B. cinerea*, and laboratory mutants of *Penicillium digitatum* (Heaney et al., 2000; Chin et al., 2001; Banno et al., 2009; Zhang et al., 2009). To test the fitness costs associated with *CYTB*-based QoI resistance, Fisher & Meunier (2008) used *S. cerevisiae* as a model system. Specific residues in the Qo site of yeast cytochrome *b* were modified to obtain new forms that mimicked the Qo binding site of

several fungal plant pathogens and to study the impact of the introduction of the G143A substitution on bc_1 complex activity. As expected, the G143A substitution resulted in high levels of resistance to QoI fungicides. However, the G143A substitution also led to a slight reduction of bc_1 complex activity in most of the Qo site mimics (e.g. *P. fusca*) but not in *B. graminis* f. sp. *tritici*. Based on these observations in the yeast model, the authors suggested that the G143A substitution might affect the fitness of plant pathogens differentially. It has been also widely assumed that fitness costs are fixed. However, the cost of resistance to QoI fungicides seems to vary with environmental conditions, such as temperature; fitness costs are higher in growth conditions that are sub-optimal for the fungus, as shown for *B. graminis* and *M. graminicola* (Brown et al., 2006). Thus, although the G143A substitution can confer resistance to QoI fungicides, in the absence of such compounds it may also cause some degree of fitness penalty, because of the possible effect on mitochondrial respiration.

Virtually no data exist describing the fitness costs associated with other mechanisms involved in QoI resistance. For *B. cinerea*, the usefulness of QoI fungicides is very limited and restricted to certain crops. It is interesting to note that, in liquid cultures, *B. cinerea* produces high levels of AOX in the absence of any external stimulus; therefore, it may be better adapted for the loss of complexes III and IV of the mitochondrial electron transport chain than species in which AOX is only induced as a rescue mechanism (Wood & Hollomon, 2003). Moreover, for the MFS transporter gene of *M. graminicola MgMfs1* it has been suggested that the increased strobilurin efflux activity provided by this transporter may be a condition for normal fitness because the efflux may prevent strobilurin accumulation in fungal membranes, thus, safeguarding normal membrane function. Therefore, it would be interesting to analyse the fitness costs associated with the different mechanisms of QoI resistance in fungal plant pathogens where QoI fungicides are still in use. Such studies would likely provide relevant information that may be used for the rational design of anti-resistance strategies

7. Conclusions

The QoIs are an outstanding class of agricultural fungicides that exhibit excellent properties in a number of areas, including human and environmental safety. QoI fungicides have been extremely successful because of the benefits associated with their use and are clearly one of the most valuable classes of single-site fungicide discovered by the agrochemical industry. However, one of the apparent strengths of these fungicides, their high specific mode of action, is also a serious weakness. The group is considered a high risk one in terms of resistance development; therefore, strict anti-resistance strategies, including the limitation of treatments and the use of mixtures or alternating compounds, should be followed to maintain the high efficacy of this class of fungicides. Although their use is no longer recommend in some crops, such as cereals, in many other crops if recommended use-patterns are strictly followed, the dependence of crop protection on the QoIs is likely to continue for many years into the future. A single point mutation in the *CYTB* gene that causes a G143A substitution in cytochrome *b* confers resistance to QoIs in many plant pathogens. While there is an extensive literature that emphasises the contribution of the G143A substitution in QoI resistance, this fact has not been always clearly substantiated. Although important insights into the mechanisms influencing the evolution of *CYTB*-based QoI resistance have been gained in recent years, many basic questions remain. Most of the unanswered questions are related to the mitochondrial nature of the cytochrome *b* gene.

Interestingly, an increasing amount of experimental evidence attributes the phenomenon of QoI resistance to mechanisms that are distinct from cytochrome *b* mutations, such as alternative respiration, efflux transporters and other unknown mechanisms. Thus, the cause of QoI resistance in phytopathogenic fungi may be more complex than a simple point mutation, and the widely accepted role of cytochrome *b* in QoI resistance should be reevaluated. In the microbial world, there are examples of microbes that can develop resistance to a given antibiotic through different mechanisms, and this could also be the case for QoIs. Therefore, we should avoid making general assumptions and carefully clarify the molecular basis of QoI resistance for single pathogen species before developing rapid diagnostic methods that will help to maintain the high efficacy of this important class of agricultural fungicides for as long as possible.

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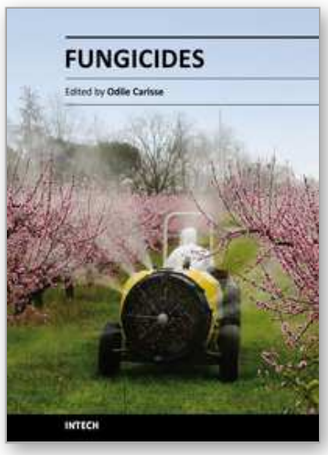

Fungicides

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Plant and plant products are affected by a large number of plant pathogens among which fungal pathogens. These diseases play a major role in the current deficit of food supply worldwide. Various control strategies were developed to reduce the negative effects of diseases on food, fiber, and forest crops products. For the past fifty years fungicides have played a major role in the increased productivity of several crops in most parts of the world. Although fungicide treatments are a key component of disease management, the emergence of resistance, their introduction into the environment and their toxic effect on human, animal, non-target microorganisms and beneficial organisms has become an important factor in limiting the durability of fungicide effectiveness and usefulness. This book contains 25 chapters on various aspects of fungicide science from efficacy to resistance, toxicology and development of new fungicides that provides a comprehensive and authoritative account for the role of fungicides in modern agriculture.

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