Breeding for durable resistance to downy and powdery mildew in grapevine

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Abstract

The current strategy to control grapevine downy and powdery mildew relies on chemical treatments. An alternative solution to the use of chemicals is the development of varieties resistant to pathogens. Several genetic factors derived from *Vitis* species closely related to cultivated grapevine and conferring protection against downy mildew or powdery mildew have already been identified. Nevertheless, many major resistance genes have been overcome by virulent strains of pathogens in various plant-pathogen interactions, and such resistance breakdowns have already been described in grapevine. Resistance genes are a limited resource, and their introduction in a new variety is a long-term and costly process. This is why the assessment and improvement of resistance durability is crucial, particularly in the case of a perennial species. The Inra-ResDur breeding program aims at creating varieties with durable resistance to downy and powdery mildew. The pyramiding strategy employed to limit the risk of resistance breakdown is described. Other innovative ways are proposed to enhance resistance durability.

Keywords: grapevine, genetics, breeding, resistance, durability

In Europe, viticulture uses 33% of the total amount of fungicide active substances (excluding inorganic sulfur) intended for agriculture (Muthmann, 2007). These treatments are mainly sprayed to control the oomycete *Plasmopara viticola* and the ascomycete *Erysiphe necator*, respectively the downy and powdery mildew agents, because of the very high susceptibility of traditional varieties to these two diseases. This practice is not only expensive, but is also a health and environmental concern that can affect the brand image of wines and promote the emergence of fungicide-resistant strains.

As *Vitis* species closely related to cultivated grapevine have already been shown to be potential sources of resistance, an alternative solution to the use of chemicals is the development of varieties resistant to pathogens (Boubals, 1959; Staudt and Kassemeyer, 1995; Cadle-Davidson, 2008). That is why Inra (French National Institute for Agricultural Research) decided in 2000 to launch a breeding program to create varieties combining durable resistance to downy and powdery mildew with berry quality suitable for the production of high quality wines (Merdinoglu *et al.*, 2009). However, the use of these resources in breeding programs is not trivial, partly because the varietal ideotype is complex and must meet several objectives in order to have a commercial future: display a high level of resistance to the two major diseases, downy and powdery mildew; show at least partial resistance to diseases that may emerge in the absence of phytosanitary treatments (black rot, anthracnose, etc.); provide not only effective but also durable resistance; and display a berry composition compatible with the production of high quality wines in a context of climate change. Regarding resistance to downy and powdery mildew, our strategy has aimed at optimizing both the efficacy and durability of resistance.

Sources of resistance to grapevine downy and powdery mildew and resistance durability

Several genetic factors conferring protection against downy mildew or powdery mildew have already been identified in grapevine (Table 1). The majority of them confer varying levels of partial resistance to downy and powdery mildew, but some of them, coming from *V. rotundifolia* and *V. piasezkii*, confer total resistance in the genetic context where they are studied. Whatever their effect, partial or total, most genetic factors identified until now are located in genomic regions rich in NBS-LRR-like resistance genes, called *R* genes (Di Gaspero *et al.*, 2007; Moroldo *et al.*, 2008), and the cloning of *Rpv1* and

Run1 confirmed that they belong to this family (Feechan *et al.*, 2013a). This observation means that most genetic factors identified until now are potentially involved in a gene-for-gene interaction with the pathogen. On the one hand, the situation seems very favourable: plenty of resistance sources are available and several resistance factors with various effects have already been discovered. But, on the other hand, we know that disease resistances are not necessarily stable traits: the protection offered by resistance genes can be overcome by a virulent strain of the pathogen. This is particularly the case when this control is based on a gene-for-gene interaction, due to the recognition of a protein encoded by the pathogen avirulence gene by the product of the corresponding plant resistance gene.

Many *R* gene breakdowns have been observed in various plant-pathogen interactions. But the first case of grapevine downy mildew resistance breakdown was recently described in the cultivar Bianca (Peressotti *et al.*, 2010). The Bianca resistance is mainly determined by the *Rpv3* factor (Bellin *et al.*, 2009). *Rpv3* confers to Bianca partial resistance to the majority of *P. viticola* strains. But after infection with the strain L collected in the Czech Republic, Bianca proves to be as susceptible as the susceptible cultivar Chardonnay (Peressotti *et al.*, 2010). This does not reveal a simple increase in aggressiveness of the strain L but a real change in virulence which is specific to Bianca. When both virulent and avirulent strains are inoculated to *V. rupestris*, which displays a partial resistance phenotype very similar to that of Bianca, no differences are observed between strains, the resistance level of *V. rupestris* remaining stable whatever the strain. So, it can be clearly concluded that the strain L specifically overcomes the *Rpv3* resistance factor. More recently, a similar situation was observed on *Run1*, a gene from *V. rotundifolia* conferring total resistance to powdery mildew (Feechan *et al.*, 2013a, 2015). In this case, a naturally occurring powdery mildew isolate, Musc4, originated from southeastern North America, is able to grow on vines bearing the *Run1* resistance gene and completely evade *Run1* recognition.

The fact that resistance genes are a limited resource and that their introduction in a new variety is a long-term and costly process makes the question of the assessment and the improvement of resistance durability crucial, particularly in the case of a perennial species. According to Johnson (1979), resistance is considered durable when it remains effective in a cultivar during its commercial use. Even if resistance durability is a retrospective judgment, some principles which allow to predict or limit the

risk of resistance breakdown can be stated. At the plant level, it is now admitted that pyramiding resistance genes – ie associating several resistance genes in the same variety –, using resistance genes with wide spectrum – ie capable to control a large range of pathogen strains – and combining various defense mechanisms are valuable strategies to increase resistance durability. At the pathogen level, the knowledge of its evolutionary potential, mainly determined by population size, gene flows or mating systems (McDonald and Linde, 2002), can help to assess the risk of breaking down resistance. At the host-pathogen interaction level, the fitness penalty associated to virulence (Leach *et al.*, 2001), or the knowledge of the selective constraints on the evolution of avirulence factors can help to predict the durability of the corresponding plant resistance genes. But durability also depends on environmental conditions and cultural practices, which influence the development of pathogen populations. From a practical point of view, the sustainable management of resistance aims then at reducing the selection pressure applied by the resistance genes on the pathogen populations thanks to potentially durable genetic constructions and resistance deployment strategies, including cultivation practices.

Pyramiding strategies to enhance the durability of resistant varieties

In order to pyramid several resistance factors in the same cultivar, the use of multiple sources of resistance was chosen in the Inra-ResDur breeding program. The resistance sources that we are currently using mainly come from *V. rotundifolia* and from other American and Asian *Vitis*. The molecular markers derived from genetic analyses have been integrated in the breeding process to assist both the selection of candidate varieties carrying the desired

Table 1. Resistance factors to downy and powdery mildew identified in grapevine.

Factor	Controlled disease	Origin of resistance	Chromosome	Resistance level	Reference
Rpv1	Downy mildew	*V. rotundifolia*	12	High	Merdinoglu *et al.*, 2003
Rpv2	Downy mildew	*V. rotundifolia*	18	Total	Wiedemann-Merdinoglu *et al.*, 2006
Rpv3	Downy mildew	*V. rupestris*	18	Partial	Bellin *et al.*, 2009; Welter *et al.*, 2007
Rpv4	Downy mildew	American *Vitis*	4	Weak	Welter *et al.*, 2007
Rpv5	Downy mildew	*V. riparia*	9	Weak	Marguerit *et al.*, 2009
Rpv6	Downy mildew	*V. riparia*	12	Weak	Marguerit *et al.*, 2009
Rpv7	Downy mildew	American *Vitis*	7	Weak	Bellin *et al.*, 2009
Rpv8	Downy mildew	*V. amurensis*	14	High	Blasi *et al.*, 2011
Rpv9	Downy mildew	*V. riparia*	7	Weak	Moreira *et al.*, 2011
Rpv10	Downy mildew	*V. amurensis*	9	High	Schwander *et al.*, 2012
Rpv11	Downy mildew	American *Vitis*	5	Weak	Fischer *et al.*, 2004
Rpv12	Downy mildew	*V. amurensis*	14	High	Venuti *et al.*, 2013
Rpv13	Downy mildew	*V. riparia*	12	Weak	Moreira *et al.*, 2011
Rpv14	Downy mildew	*V. cinerea*	5	-	Ochssner *et al.*, 2016
Run1	Powdery mildew	*V. rotundifolia*	12	Total	Pauquet *et al.*, 2001
Run 2.1	Powdery mildew	*V. rotundifolia*	18	Partial	Riaz *et al.*, 2011
Run 2.2	Powdery mildew	*V. rotundifolia*	18	Partial	Riaz *et al.*, 2011
Ren1	Powdery mildew	*V. vinifera*	13	Partial	Hoffmann *et al.*, 2008
Ren2	Powdery mildew	*V. cinerea*	14	Partial	Dalbó *et al.*, 2000
Ren3	Powdery mildew	American *Vitis*	15	Partial	Welter *et al.*, 2007
Ren4	Powdery mildew	*V. romanetii*	18	Partial	Riaz *et al.*, 2011
Ren5	Powdery mildew	*V. rotundifolia*	14	Total	Blanc *et al.*, 2012
Ren6	Powdery mildew	*V. piasezkii*	9	Total	Pap *et al.*, 2016
Ren7	Powdery mildew	*V. piasezkii*	19	Partial	Pap *et al.*, 2016
Ren8	Powdery mildew	American *Vitis*	18	Partial	Zyprian *et al.*, 2016

gene combinations as well as the introgression of a resistance gene into a cultivated genetic background.

Compared to phenotyping, marker-assisted selection (MAS) is undoubtedly a tool of choice to identify the genotypes which combine the desired resistance factors and, thus, to construct varieties with a high potential of durability. Indeed, in some cases, plants carrying two or three resistance factors are undistinguishable from those carrying only one resistance gene, for instance, when this gene alone confers total resistance. But according to the principles determining resistance durability, plants combining several resistance factors are expected to have greater resistance durability, even if they display the same level of resistance than those bearing only one factor. In addition, MAS allows creating varieties with very high or even total resistance by combining multiple genetic factors contributing only partial resistance.

MAS was applied to three series of crosses including as genitors of resistance back-cross lines derived from *V. rotundifolia*, the cultivar Regent (in collaboration with Julius Kühn-Institut, Siebeldingen), the cultivar Bronner (in collaboration with Staatliches Weinbauinstitut, Freiburg) and the cultivar Divico (in collaboration with Agroscope, Changins). MAS allowed following six resistance alleles, *Rpv1*, *Rpv3* and *Rpv10* for downy mildew, and *Run1*, *Ren3* and *Ren3.2* for powdery mildew. This strategy led to the development of candidate varieties bearing two or three genes to control each disease. The correlation between the observed phenotype and the resistance genotype was rather good. However, variations in resistance level were observed around predicted mean values, suggesting the presence of unidentified resistance factors that segregate in the breeding populations and bring minor but significant effects.

The selection process is organized into three steps: early selection, which is a rapid screening step in controlled conditions including MAS and early phenotyping, intermediate selection in the Inra-ResDur experimental network, and final selection in the VCU (value for cultivation and use) network, managed in collaboration with IFV (Institut Français de la Vigne et du Vin), the last two being trials including wine tasting and conducted in the vineyard. The whole assessment process of candidate varieties takes 16-17 years. In this framework, the objective was to propose the registration of ca 30 varieties with black or white berries between 2017 and 2024. Varieties with three different combinations of 4-6 resistance factors to downy and powdery mildew,

respectively *Rpv1/Rpv3/Run1/Ren3*, *Rpv1/Rpv10/Run1/Ren3.2* and *Rpv1/Rpv3/Rpv10/Run1/Ren3/Ren3.2*, corresponding to the three series of crosses, will be released successively. Trials undertaken in intermediate selection have shown that all candidate varieties reach a very high resistance level in conditions of natural infection. One third of them display cultural and oenological traits compatible with the criteria of French wine production and the best of them, a wine quality comparable to that of control grape varieties (Chardonnay, Merlot) (Schneider *et al.*, 2014). Four candidate varieties have already been submitted for registration into the national list in 2018 (Catalogue Officiel des Variétés de Vigne). These varieties represent an innovation breakthrough not only in terms of breeding strategy but also in terms of vine-growing practices. Indeed, it is expected that the new varieties will allow reducing the average treatment frequency index from 12, currently observed for the traditional varieties, to 2 in the future vine-growing systems. The promotion and dissemination of these varieties will be ensured under the ENTAV-INRA® trademark.

Future prospects: innovative approaches to identify new resistance factors to strengthen resistance durability

Apart from the approach described above, new strategies designed to diversify the types of resistance factors used to control the main grapevine diseases are now available and seem worth exploring to strengthen resistance durability. By way of conclusion, the opportunities offered by three of them are briefly presented.

So far, resistance gene pyramiding has been essentially based on MAS to combine dominant resistance genes which are discovered by conventional phenotyping (ie a resistance bio-assay where plants or parts of plants are inoculated with a pathogen) and which putatively belong to one of the canonical families of *R* genes. Combining genes working through different mechanisms (ie dominant and recessive genes) has been proposed to increase the durability potential of resistant varieties. Genes whose loss of function confers recessive resistance have already been identified, like *DMR6* in the *Arabidopsis thaliana - Hyaloperonospora arabidopsidis* interaction or *Mlo* for barley resistance to powdery mildew. The screening of KO mutations for such recessive candidate resistance genes in the natural diversity of *Vitis* species or the creation of non-functional mutants by gene editing technologies appear as valuable alternative strategies to diversify the range of resistance genes available for grapevine

breeding. Indeed, the grapevine homologue of the barley *Mlo* gene has been identified, validating its function in resistance against powdery mildew (Feechan *et al.*, 2013b; Pessina *et al.*, 2016).

R genes recognize pathogen-encoded factors, so called avirulence genes (Avr), and trigger defense responses. Most oomycete Avr proteins known to date do belong to the RXLR family of effector proteins. RXLR effectors form a large fast-evolving family. Accordingly, most individual resistance genes deployed against oomycetes have been overcome by the pathogens, and, as has previously been shown for *Rpv3* (Peressotti *et al.*, 2010), grapevine is not an exception. Based on these concepts, we have proposed to use the most conserved components of the repertoire of oomycete effector genes as a way to identify potentially durable resistances. First, effector proteins were identified from *P. viticola* (Mestre *et al.*, 2012). Then, 45 expressed RXLR effectors were unveiled, including effectors conserved between oomycete species, thus potentially essential for the pathogen (Mestre *et al.*, 2016). These "essential" *P. viticola* RXLR effectors are currently used to detect resistance sources carrying *R* genes recognizing them and, thus, to identify *a priori* durable resistance genes.

MAS was shown to be successful to select resistances based on major genes. Nevertheless, field observations suggest that putative minor factors are involved in the expression of weak but significant effects that can enhance the protection conferred by major genes and improve their durability. Quantitative resistance based on several or even many minor genes is characterized by a diffused and complex genetic architecture, similar to agronomic traits such as yield. If MAS facilitates major resistance gene pyramiding, it looks not adapted to capture small-effect loci. Genomic selection is an approach based upon whole-genome prediction models using genome-wide molecular markers ((Meuwissen *et al.*, 2001). It looks ideal for traits with complex genetic architecture controlled by many small effects, and thus adapted to breeding for quantitative resistance. So, the implementation of genomic selection for grape breeding will certainly bring new opportunities to combine both major *R* genes and quantitative resistance and thus construct varieties with highly durable resistance.

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