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REVIEW ARTICLE

Improvement of Wheat Genetic Resistance to Powdery Mildew Retrospects and Prospects

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Abstract:

Powdery mildew is one of the most noticeable and harmful wheat diseases in countries with temperate climates and sufficient rainfall. The most efficient, economical, and environmentally friendly means to control powdery mildew is the growing of genetically resistant wheat cultivars. The genetic resistance of wheat is quickly overcome due to the evolution of the avirulence genes of the pathogen. The problem of enriching the genetic pool of wheat with new effective resistance genes is relevant. The objective of the work is to show that the basis of the organization of the genetic protection of wheat from powdery mildew cannot be related to the simple expansion of the wheat genetic pool due to new resistance genes. The gene transfer should be preceded by the study of the molecular nature of the resistance gene products. The work presented information about resistance types in wheat against powdery mildew and the molecular nature of *Pm* genes' products. They are NLR-immune receptors, tandem kinase proteins, receptor-like kinases, transporters, plant-specific proteins, and mitogen activated kinases. NLR, in interaction with the pathogen effectors, confers highly specific resistance; all the rest provide resistance of a wide spectrum. Characteristics of pathogen gene products are provided, and a model of interaction between *Pm* and *AvrPm* gene products is described. A certain number of *Pm* genes are present in the current genetic pool of common wheat. The effectiveness of some of the most common genes has already been overcome by the pathogen. This necessitates the renewal of resistance genes in wheat. Prospects for the improvement of wheat genetic resistance to powdery mildew are provided. The prospective direction of research for providing effective long-term wheat genetic resistance to the biotrophic pathogen *Blumeria* is molecular genetic studies of wheat plants and pathogen races. A clear understanding of the molecular nature of the plant protein conferring resistance and its role in the development of the molecular pattern of plant protection against the pathogen is necessary to assess the prospects of any resistance gene for transfer to the genetic pool of wheat in relation to its ability to confer effective and long-lasting powdery mildew resistance.

Keywords: Powdery mildew wheat, Diseases, Wheat cultivars, Wheat chromosomes, Horizontal resistance, Vertical resistance.

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1. INTRODUCTION

Powdery mildew is one of the most noticeable and harmful wheat diseases in countries with temperate climates and sufficient rainfall [1]. The disease begins to develop early in the vegetation season, affecting all plant's parts, and is amplified in favorable agronomic conditions [2]. Yield loss caused by powdery mildew could be evaluated as 5–40%, and in cases of early disease development [3 - 5], grain quality is decreased [6]. The disease in wheat is caused by the biotrophic fungal pathogen *Blumeria graminis* (DC) E.O. Speer f. sp. *tritici* Em. Marchal (*Bgt*) (syn. *Erysiphe graminis* DC f. sp. *tritici* Marchal) (*Bgt*), which is an obligate parasite [7].

The most efficient, economical, and environmentally friendly means to control powdery mildew is the growing of genetically resistant wheat cultivars [8]. Until recently, in com-

mon wheat (*Triticum aestivum* L.), durum wheat (*T. durum* Desf.) and their relatives from the subtribe Triticinae at least 90 genes (alleles) in about 50 loci have been identified as genes that prevent the development of powdery mildew spores on wheat leaves, thus conferring resistance of the plant to this pathogen [9, 10].

The resistance of wheat plants to powdery mildew can be horizontal, which is formed as a result of the deployment of a molecular pattern of the interaction of pathogen and host molecules as a result of the expression of several genes involved in ontogenetic processes [11 - 17]. The reaction is not specific to isolate the pathogen and sometimes the disease. Resistance can be vertical when developed in response to the interaction of the products of a particular *Pm* wheat resistance gene and the corresponding *AvrPm* pathogen gene. Such resistance is highly specific, and the vast majority of wheat genes identified today in its gene pool provide it. Products of genes *Pm* and *AvrPm* are components of the gene-for-gene system [18].

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In genotypes of modern commercial wheat cultivars, powdery mildew resistance is conferred by a limited variety of resistance genes, and almost all these genes confer vertical race-specific resistance. These include genes *Pm2*, *Pm3a,b,f*, *Pm4a*, *Pm30*, inherent to the common wheat genetic pool, and several introgressed genes: *Pm6*, *Pm8*, *Pm13*, *Pm21* [19, 20]. It has been reported that most of the indicated genes were overcome by the pathogen because new races of pathogen appeared with virulence genes, whose products were not recognized by the products of resistance genes [20 - 23]. This has been stated for widely grown cultivars in many regions of the world. That is the reason for the need for constant renewal of genes for resistance to powdery mildew in the cultivated wheat gene pool.

It is believed that the most prospective sources of new resistance genes are wheat wild relatives. They could provide genes for nonhost resistance, and these genes could be effective for a long time, while the pathogen evolves new avirulence genes on the background of positive selection of virulent mutants, which occurs when cultivars contain specific resistance gene (genes) [19, 24 - 29]. However, gene introgression is combined with the performance of a large amount of work and lasts a long time. In order to be sure that the long and hard work will not be in vain due to the rapid overcoming of the new wheat resistance gene by a virulent mutation of a pathogen gene from the gene-for-gene system, the optimal start to such work is the sequencing of the resistance gene to understand what resistance it provides. If vertical, the effectiveness of such a gene is not likely to be long-lasting [24]. If a gene provides broad-spectrum resistance, the effectiveness of such a gene in wheat genotypes can persist for decades [19, 24].

Here, we provide an overview of the current understanding of the possibilities of genetic improvement of wheat relative to resistance to powdery mildew. The objective of the work is to show that the basis of the organization of the genetic protection of wheat from powdery mildew cannot be related to the simple expansion of the wheat genetic pool due to new resistance genes. The gene transfer should be preceded by the study of the molecular nature of the resistance gene products.

1.1. Resistance Types in Wheat

Powdery mildew resistance, similarly to resistance to other pathogens, is firstly classified as passive and active. Passive resistance is conferred by the physical surface barriers of the plant. This type of resistance prevents the penetration of pathogens into plant cells and do not consider here. Active resistance depends on concrete genes and is realized in two main ways: the development of pathogen-associated molecular patterns (PAMP) triggers resistance in which pattern recognition receptors (PRR) are involved. PRRs localize in the plasma membrane and recognize conserved pathogen molecules. Although this resistance reaction is active, it is not specific and develops in response to any pathogen. Such a class of immunity is called “pattern-triggered immunity” (PTI) and may be suppressed by host-adapted pathogens by delivering effector molecules inside host cells [30, 31]. A second line of defense is an active specific reaction to the pathogen. It develops through the action of intracellular multidomain receptors carrying a stereotypical nucleotide binding site (NBS) and leucine-rich repeat (LRR). Their name is NLR (nucleotide-binding leucine-rich repeat) [32, 33]. They are known as immune receptors and are encoded by *R*-genes. Contact between pathogen’s elicitors and *R* gene products directly or with the participation of certain intermediate molecules gives rise to the development of ETI – effector triggered immunity [34].

1.2. *Pm* Genes Products

Genes that provide active resistance to powdery mildew are called *Pm* genes. Their products confer both specific and not specific resistance. Specific resistance is conferred by NLR-receptors, not specific resistance is conferred by tandem kinase proteins, receptor-like kinases, transporters and some other proteins. The functions of proteins encoded by resistance genes have been clarified after sequencing these genes. Currently, nucleotide sequences of more than 300 plant resistance genes are established [35, 36]. For wheat *Pm* genes, sequencing began in 2003, and the number of sequenced genes increases every year. Currently, 13 *Pm* genes are sequenced (Table 1).

Table 1. List of *Pm* genes in the wheat gene pool.

Gene/Reference	Chromosome	Source of Gene	Product of Gene/Reference
<i>Pm1 a</i> [37, 38]	7AL	¹⁾	NLR [39]
<i>Pm1 b</i> [40]		<i>T.monococcum</i>	No information
<i>Pm1c</i> [40] = <i>Pm18</i>	7AL	¹⁾	No information
<i>Pm1d</i> [40]	7AL	<i>T.spelta</i>	No information
<i>Pm1e</i> = <i>Pm22</i> [41, 42]	7AL	¹⁾	No information
<i>Pm2a,c</i> [43]	5DS	¹⁾	NLR [44]
<i>Pm2b</i> [45]	C-5DS	<i>Agropyron cristatum</i>	No information
<i>Pm3</i> [46]	1AS	¹⁾	NLR [47]
<i>Pm4a</i> [48, 49]	2AL	<i>T.monococcum</i>	Functional kinase [36]
<i>Pm4b</i> [48, 49]	2AL	<i>T.carthlicum</i>	Functional kinase [36]
<i>Pm4c</i> = <i>Pm23</i> [50]	2AL	¹⁾	No information
<i>Pm4d</i> [51]	2AL	<i>T.monococcum</i>	No information
<i>Pm5 a</i> ²⁾ , <i>b,d,e</i> ²⁾ [37]	7BL	<i>T.dicoccum</i>	NLR [52]

(Table 1) contd....

Gene/Reference	Chromosome	Source of Gene	Product of Gene/Reference
<i>Pm5c</i> [37]	7BL	<i>T.sphaerococcum</i>	No information
<i>Pm6</i> [53]	2BL.2GL	<i>T.timopheevii</i>	Several LRRs, a trans-membrane domain, and a Ser/Thr protein kinase domain [54]
<i>Pm7</i> [55]	4BL	<i>S.cereale</i>	No information
<i>Pm8</i> [56, 57]	1BL.1RS	<i>S.cereale</i>	Coiled-coil (CC), nucleotide-binding site ARC1 and ARC2 (NB-ARC) and leucine-rich-repeat (LRR) domain protein [58]
<i>Pm9</i> ²⁾ [59]	7AL	¹⁾	No information
<i>Pm10</i> [60]	1D	¹⁾	No information
<i>Pm11</i> [61]	6BS	¹⁾	No information
<i>Pm12</i> [62]	6BS6SS.6SL	<i>Ae. speltoides</i>	No information
<i>Pm13</i> [55]	T3BL.3BS-3S1 #1S	<i>Ae. longissima</i>	No information
<i>Pm14</i> [63]	6B	¹⁾	No information
<i>Pm15</i> [63]	7DS	¹⁾	No information
<i>Pm16</i> [64]	4A	<i>T.dicoccoides</i>	No information
<i>Pm17=Pm8</i> [65]	T1AL.1R#2S	<i>S.cereale</i>	See <i>Pm8</i>
<i>Pm18</i> [66]	7A	¹⁾	See <i>Pm1c</i>
<i>Pm19</i> [67]	7D	<i>Ae. tauschii</i>	No information
<i>Pm20</i> [68]	T6BS.6R#2L	<i>S.cereale</i>	No information
<i>Pm21</i> [69]= <i>Pm31</i> [70]	T6AL.6VS	<i>H.villosa</i>	serine and threonine protein kinase V, Stpk-V [71]
<i>Pm22= Pm1e</i>			See <i>Pm1e</i>
<i>Pm23= Pm4c</i>			See <i>Pm4c</i>
<i>Pm24a</i> [72]	1DS	¹⁾	(Tandem Kinase Protein, TKP) [13]
<i>Pm24b</i> [73]	1DS	¹⁾	No information
<i>Pm25</i> [74]	1A	<i>Triticum monococcum</i> subsp. <i>aegilopoides</i>	No information
<i>Pm26</i> ²⁾ [75]	2BS	<i>T.dicoccoides</i>	No information
<i>Pm27</i> [76]	6B-6G	<i>T.timopheevii</i>	No information
<i>Pm28</i> [77]	1B	¹⁾	No information
<i>Pm29</i> [78]	7DL	<i>Ae.ovata</i>	No information
<i>Pm30</i> [79]	5BS	¹⁾	No information
<i>Pm31</i> [80]= <i>Pm21</i> [70]	6VS/6AL	<i>H.villosa</i>	No information
<i>Pm32</i> [81]	1BL.1SS	<i>Ae.speltoides</i>	No information
<i>Pm33</i> [82]	2BL	<i>T.carthlicum</i>	No information
<i>Pm34</i> [82]	5DL	<i>Ae.tauschii</i>	No information
<i>Pm35</i> [83]	5DL	<i>Ae.tauschii</i>	No information
<i>Pm36</i> [84]	5BL	<i>T.dicoccoides</i>	No information
<i>Pm37</i> [85]	7AL	<i>T.timopheevii</i>	No information
<i>Pm38</i> [86]	7DS	¹⁾	ABC transporter [16]
<i>Pm39</i> [87]	1BL	<i>Ae.umbellulata</i>	No information
<i>Pm40</i> [88]	7BS	<i>Th. intermedium</i>	CC-NBS-NBS-LRR [89]
<i>Pm41</i> [90]	3BL	<i>T. dicoccoides</i>	Protein with domens CC-NBS-LRR (CNL) [91]
<i>Pm42</i> ²⁾ [92]	2BS	<i>T. dicoccoides</i>	No information
<i>Pm43</i> [93]	2DL	<i>Th. intermedium</i>	No information
<i>Pm44</i> [94]	3A	¹⁾	No information
<i>Pm45</i> [95]	6DS	¹⁾	
<i>Pm46</i> [96]	5DS	¹⁾	Hexose transporter [17]
<i>Pm47</i> [97]	7BS	¹⁾	No information
<i>Pm48</i> [98]	5DS		No information
<i>Pm49</i> [99]	2BS	<i>T.dicoccum</i>	No information
<i>Pm50</i> [100]	2AL	<i>T.dicoccum</i>	No information
<i>Pm51</i> [101]	2BL	<i>Th. ponticum</i>	No information
<i>Pm52</i> [102]	2BL	¹⁾	No information
<i>Pm53</i> [94]	5BL	<i>Ae. speltoides</i>	No information
<i>Pm54</i> [103]	6BL	¹⁾	No information

(Table 1) contd....

Gene/Reference	Chromosome	Source of Gene	Product of Gene/Reference
<i>Pm55</i> [104]	5VS.5DL	<i>D.villosum</i>	No information
<i>Pm56</i> [105]	T6RS.6AL	<i>S.cereale</i>	No information
<i>Pm57</i> [106]	T2BS.2BL-2SS #1L	<i>Ae.searsii</i>	No information
<i>Pm58</i> [107]	2DS	<i>Ae.tauschii</i>	No information
<i>Pm59</i> [108]	7AL	¹⁾	No information
<i>Pm60</i> [109]	7A	<i>T.urartu</i>	Proteins with domains NBS and LRR [110]
<i>Pm61</i> ²⁾ [111]	4AL	¹⁾	No information
<i>Pm62</i> [112]	2BS.2VL#5	<i>D.villosum</i>	No information
<i>Pm63</i> [108]	2BL	¹⁾	No information
<i>Pm64</i> [113]	2BL	<i>T.dicoicoides</i>	No information
<i>Pm65</i> [114]	2AL	¹⁾	No information
<i>Pm66</i> [25]	T4S'S-4BL	<i>Ae.longissima</i>	No information
<i>Pm67</i> [19]	T1DL.1VS#5	<i>D.villosum</i>	No information
<i>Pm68</i> [115]	2BS	<i>T.turgidum</i>	No information

Note: ¹⁾ Gene is attributable to *T. aestivum* ²⁾ Recessive gene ³⁾ Table 1 contains only genes with permanent names mapped to specific chromosomes using traditional methods of linkage mapping and physical mapping using bins. Genes mapped using the modern method of genome-wide association studies (GWAS), in our opinion, should be tested if they are alleles of known mapped genes, and only after this testing, these genes could get the permanent name of a new gene or a new allele, or the allele of the previously mapped *Pm* gene.

1.3. NLR-receptors

Most of the sequenced resistance genes code NLR, which provide vertical resistance to the pathogen [35, 116]. They are classified into two main types depending on the structure of their N-terminal domain (NBS): TIR (Toll and IL-1 receptors) and non-TIR. The majority of non-TIR NLRs have CC (coiled-coil) domain on their N-terminus. It was demonstrated that dicot plants have both TIR and non-TIR NLR, while monocot plants, including wheat, have only non-TIR NLR [116, 117]. When NLR specifically recognizes pathogen's effectors through the LRR domain, structural changes occur in the NB-ARC domain which is a functional ATPase. The binding of nucleotides to the NBS regulates the activity of the R protein. Activated R protein conducts a signal for the subsequent resistance development. Usually, NLR-induced resistance is associated with hypersensitive response – local cell death in the site of pathogen penetration in order to prevent the spread of biotrophic pathogens such as *Blumeria graminis* f.sp. *tritici* [109, 116]. In wheat, NLR-receptors are encoded by the genes *Pm1*, *Pm2*, *Pm3*, *Pm5*, *Pm8*, *Pm40*, and *Pm60*.

1.4. TKP (Tandem Kinase Orotin)

In wheat, the *Pm24* gene encodes a tandem kinase protein (TKP) with a predicted kinase pseudokinase domain, which is named WHEAT TANDEM KINASE 3 (WTK3) [13]. *Pm24/WTK* gene confers wheat resistance to 92 Chinese *Bgt*, therefore gene ensures broad-spectrum resistance [51]. A rare 6-nucleotide deletion of Lysine-Glycine codons in kinase domain 1 (Kin I) was identified to be important for the resistant phenotype. This mutation was identified only in wheat from Shaanxi province in China. It is predicted that the absence of these two amino acids could provide the formation of a more compact loop in the kinase structure, which could be important for subsequent protein-protein interactions and signal transduction for resistance development [13].

1.5. RLK (Receptor-like Kinases)

These kinases initiate broad-spectrum resistance (PTI) [14,

15]. Genes of receptor-like kinases *TaRLK1* and *TaRLK2* were identified in the genome of *T. aestivum/T. timopheevi* introgressive line [54]. The genes encode a protein with a signal peptide, several LRRs, a transmembrane domain, and a serine-threonine kinase domain. The lines with *TaRLK1* and *TaRLK2* overexpression demonstrated an increase in the levels of endogenous hydrogen peroxide (H₂O₂) under pathogen invasion sites [54]. This could indicate the possibility of a hypersensitivity reaction, very effective in resistance development, not only due to the immune receptors NLR, but also with the participation of genes with a wide spectrum of action. This makes RLK genes prospective for the development of plants with genetic resistance to powdery mildew. Genes of both kinases are localized in the long arm of wheat chromosome 2B [54], where previously the *Pm6* gene was mapped, but in another region [53, 118, 119]. Perhaps it will be difficult to clearly distinguish the *Pm6* gene from the genes *TaRLK1* and *TaRLK2* through their introgression origination (*T. timopheevi*). Three genes may be members of one gene cluster [119].

1.6. Transporters

Long-term nonspecific resistance to a broad spectrum of pathogens is conferred by transporter proteins. Resistance genes encoding transporters include: *Lr34/Yr18/Pm38/Ltn1* (7DS), which encodes ABC (ATP-binding cassette)-transporter [16], and *Lr67/Sr55/Yr46/Pm46/Ltn* (5DS), which encodes hexose transporter [17]. These genes are valuable as they confer effective, potentially long-term resistance to several important wheat pathogens: leaf rust (*Puccinia triticina*), stripe rust (*P. striiformis*), powdery mildew (*Blumeria graminis* f. sp. *tritici*), as controls a trait of leaf tip necrosis (Ltn1) [16]. The gene has been effective for more than 50 years. ABC transporter could provide resistance development through the export of metabolites affecting fungal pathogens' growth [16]. Developed durum wheat (*T. turgidum*) transgenic lines for the common wheat *Lr34/Yr18/Pm38/Ltn1* gene were resistant to leaf rust, stripe rust and powdery mildew at the seedling stage, and the resistance correlated with transgene expression [120].

Lr67/Sr55/Yr46/Pm46/Ltn3 gene encodes a hexose transporter [17] and confers resistance to the three mentioned before pathogens, and to stem rust. Hexose transporter transports hexoses through the plasma membrane [17, 121]. The gene is mapped in 5DS in wheat.

Fundamentally different groups of genes for active resistance are *Mildew Resistance Locus (MLO)* and *Enhanced Disease Resistance 1 (EDR1)*. Firstly, the recessive alleles of these genes are effective for conferring resistance; secondly, these genes provide broad-spectrum resistance (to different pathogens and races of pathogens), and this resistance has long-term efficiency within the temporal persistence of this genotype. This type of resistance is mediated by loss-of-function mutations in negative regulators of resistance, particularly to powdery mildew.

1.7. Plant-specific Proteins

Resistance of this type was described in 30-40 years of the XX century, and in 1972 loss-of-function mutation was characterized in barley [122]. *MLO* genes encode plant-specific proteins with several transmembrane domains and a specific C-terminal calmodulin-binding domain [11, 123]. Loss-of-function mutation in *MLO* was characterized as universal, conferring permanent resistance to all known barley powdery mildew races. Recently, such mutations were identified in almost all plant species of agricultural importance [124, 125]. They attract attention as potential objects for gene engineering using modern techniques of *in situ* genome editing [126 - 128]. Wheat also has *MLO* genes in the chromosomes of the first homoeologous group [129], therefore, recessive mutations of these genes could be identified (or constructed) in wheat, and they could confer resistance to a broad spectrum of powdery mildew races [127, 128, 130].

1.8. Mitogen Activated Kinases

Gene *EDR1* encodes MAPKKK – mitogen activated kinases with nuclear localization. *EDR1* functions as negative regulators of MAPK cascade in plants of wild type and plays a role in the transduction of signals from the elicitor to plant cell molecules. The function of these genes was characterized in resistance to the pathogen in Arabidopsis mutants [131]. This pathway is considered very conservative in plants, and the gene could be used for the development of new ways of conferring resistance to pathogens, particularly to powdery mildew in plants. In the wheat genome, this gene, *TaEDR1*, was identified in 2005 through cloning using PCR with primers developed from the sequence of the Arabidopsis gene [12]. It was used as a target gene for CRISPR/CAS *in situ* editing with a positive result: *Taedr1* recessive gene wheat plants showed resistance to powdery mildew without significant pleiotropic effects on plant development. The gene is considered very promising for developing stable lines through targeted mutagenesis [126].

Consequently, all genes whose products are involved in ensuring the resistance of wheat to powdery mildew form two groups: genes of the immune receptors NLR, highly specific to individual races of the pathogen, and genes whose products are involved in the organization of basic processes of interaction of cells and molecules. They form the resistance of a wide

spectrum and are now considered the most promising for ensuring the genetic protection of wheat from powdery mildew.

1.9. Blumeria Effectors

Blumeria fungi, from the order Erysiphales, division Ascomycota, are a monophyletic group originating from Leotiomycetes over 120 million years ago. They are obligate biotrophic plant pathogens [132]. Similarly to other biotrophic pathogens, they are able to develop only in the living tissues of the host plants. For the realization of its life cycle, the powdery mildew pathogen must overcome host resistance and switch cellular metabolism to meet its own needs [133, 134]. This is achieved through the action of effector proteins produced by the pathogen and acting as virulence factors [135]. These effectors are considered the main determinants of the interaction between plant and powdery mildew fungus and are classified as candidate secreted effector proteins (CSEPs) [136]. Effectors are secreted via the fungal endoplasmic reticulum. Some of them stay in the plant's apoplast, while other enter the plant cells and are directed to organelles, particularly the nucleus [137]. Blumeria effector candidate (BEC) proteins were identified in high concentrations in isolated haustoria [138]. According to literature [139], the composition of CSEPs and BECs is almost the same. CSEPs are currently classified into two groups: the so-called RNase-like effectors [140], and proteins with structural homologies to the MD2-related lipid-recognition (ML) domain, ML-like CSEPs [141]. RNase-like effectors bind to NLR immune receptors [142 - 144], and currently, more than one hundred genes encoding them are identified in *Bgt* genome [140, 144 - 146]. ML-like CSEPs bind to specific lipids [147].

Genome sequencing of wheat and barley powdery mildew pathogens identified a reduction of gene content compared to other ascomycetes and an expansion of gene complements encoding putative effectors [136, 148]. Currently, at least 35 CSEP genes are cloned. They encode proteins of 63 to 314 amino acid residues, all of which have a secretion signal [142, 144, 149 - 151]. Except for this signal, effector proteins have few similarities, and only one common motif YxC has been identified [152]. This confirms the assumption that effector proteins have different partners for interaction among plant proteins and have different functions [148, 153]. Considerable polymorphism of gene sequences is observed even on the population level, which indicates independent evolution of different alleles of effector genes through various molecular mechanisms [142, 146, 150, 151, 154].

Effector proteins' action is considered to overcome PTI; the first level of plant's nonspecific defense from pathogens. The following defense level is realized when specific *R* genes are present, which encode immune receptors and confer race-specific resistance. Fungal genes encoding effectors activating a specific response in plants are named *Avr* genes.

In *Bgt* genome, currently several *Avr* genes are cloned: *AvrPm3a2/f2*, *AvrPm3b2/c2*, and *AvrPm3d3*, which are recognized by *Pm3a/Pm3f*, *Pm3b/Pm3c* and *Pm3d* gene products, respectively [142, 150]; *AvrPm2* recognized by *Pm2* product [144]; *AvrPm1a* recognized by *Pm1a* product [151];

AvrPm17 recognized by *Pm17* gene product [146]. *Blumeria* AVR effectors are small proteins of 102-130 amino acid residues with N-terminal signal peptide, a very conservative motif after signal sequence, and conservative cysteine residues towards the C-terminus. Similarly to other CSEPs, they are highly variable [140, 145, 150, 154].

Consequently, pathogen effectors play a determinant role in initiating processes that culminate in wheat injury by powdery mildew or the development of a resistance reaction. The initiation of the process lies in the interaction of effectors with the products of plant resistance genes.

1.10. Interaction of *Pm* Gene Products with Pathogen Effectors (*Avr* Gene Products)

For their development in living plant tissues, biotrophic pathogens need to suppress the protective reactions of the plant. For this purpose, pathogens use their effectors, which overcome PTI. Subsequently, pathogen effectors are recognized by NLR plant proteins, and ETI resistance reaction is activated. Plant resistance acquired as a result of NLR protein and pathogen effector interaction is usually associated with local cell death (hypersensitive response) [155].

Pathogen effectors (*Avr* gene products), which are recognized by plant R-proteins, are often polymorphic for different fungal isolates. For the recognition of different pathogen effectors, plants have various resistance genes or different alleles at one locus. The set of *Blumeria graminis* isolates includes many sub-lineages, which are named *formae speciales* (*f.sp.*). Belonging to a certain sub-lineage depends on the specificity of certain cereal species which could be affected, and this type of resistance is named host resistance. In the case when wheat is affected, this is *B.g. tritici formae speciales* (*Bgt f.sp.*), for rye – *B.g. secalis formae speciales* (*Bgs f.sp.*), for barley – *B.g. hordei formae speciales*. If effectors *Bgs f.sp.*, for example, may be recognized by wheat immune receptors, this kind of resistance is named nonhost [156]. It is assumed that in the presence of host resistance to *Bgs f.sp.* in wheat, effectors of *Bgs f.sp.* are not subject to selection on the background of wheat immune receptors and these *formae speciales* remain nonadapted [150].

Several studies have been conducted for the *Pm3* gene to understand the mechanisms of interaction between plant's *Pm* gene and pathogen's *AvrPm* gene products. The study has been conducted by mapping populations from crosses of different *Blumeria* genotypes (different *Bgt f.sp.*), modern methods of analyzing DNA sequences, including rapid genotyping methods and development of genetic constructions with the studied elements controlling virulence/avirulence trait using transient expression systems in *Nicotiana benthamiana* after agrobacterial transformation [142]. Wheat *Pm3* gene is recognized as contributing to both host and nonhost resistance, because the products of its alleles are recognized by not only *Bgt f.sp.*, but also *Bgs f.sp.* According to a study [149], these effectors are ancient conservative virulence factors, and they have been present in genotypes of *Bgt f.sp.* even before the introgression of the *Pm17* gene into the wheat genome. *Pm8* (in 1BS.1RL translocation) and *Pm17* (in 1AL.1RS translocation) resistance genes were introgressed from rye into

the wheat genome; these genes are homologous to wheat *Pm3* gene, and are likely of orthologous origin [146]. For this reason, race-specific resistance conferred by these genes has been rapidly overcome by the virulent effector *AvrPm17*, encoded by two paralogous genes mapped in dynamic effector clusters specific to *Bgs* and *Bgt* genomes [146].

For the *Pm3* locus, currently, the greatest number of alleles (17) were identified (*Pm3a-g: Pm3k-Pm3t*) [157, 158]. Protein products of these different alleles have high sequence similarity (>97%), however, they recognize effectors of different *Bgt* isolates [158]. Studies of the interaction of wheat *Pm* genes' products (particularly different *Pm3* alleles) with *Bgt* pathogen effectors are an important model for understanding the mechanisms underlying resistance specificity [145, 150]. *Pm3a*, *Pm3b*, *Pm3c*, *Pm3d*, *Pm3e*, and *Pm3f* alleles of the polymorphic *Pm3* gene were studied in wheat genotypes for their response to corresponding *AvrPm* alleles in fungal genotypes [143, 150]. For the determination of genetic control of avirulence/virulence trait, the results of F_1 segregation were studied. F_1 generations were obtained from crosses of pathogen genotypes with alternative trait manifestation: one genotype was avirulent for plants with any of the specified *Pm3* alleles, while the other genotype was virulent. It was determined that depending on plant resistance allele pathogen avirulence could be conferred by one (alleles *AvrPm3^a*, *AvrPm3^c*, *AvrPm3^e*), two (haplotype *AvrPm3^{f1}-AvrPm3^{f2}*), or three (haplotypes *AvrPm3^{b1}-AvrPm3^{b2}-AvrPm3^{b3}*, *AvrPm3^{d1}-AvrPm3^{d2}-AvrPm3^{d3}*) loci. Each of these proteins is specifically recognized by the corresponding *Pm3* alleles. On the part of the pathogen, another gene is involved in controlling the virulence reaction, *SvrPm3^{a1/f1}* [143]. The product of this gene acts as a suppressor of recognition of avirulence effectors *AvrPm3a^{2/f2}*, *AvrPm3^{b2/c2}* and *AvrPm3^{d3}* by-products of plant *Pm3a-f* allele [142].

Pathogen avoidance from recognition by immune receptors occurs in case of its change that it is not recognized by the plant receptor. Mechanisms of changes of the effector gene include missense mutations with a change of at least one amino acid [150, 154], truncation or deletion of the *Avr* gene [145, 146], and, as it was demonstrated for the interaction *AvrPm3-Pm3*, involvement of one more gene in the control of recognition reaction. That is gene *SvrPm3*, the product of which suppresses recognition of the respective effector [149]. The other type of polymorphism, which underlies the gain of virulence, is effector gene duplication, which enables independent diversification of the two virulence genes [158].

So, to date, it has been experimentally proven that the development of ETI is the result of the interaction of products of highly specific plant *Pm* genes and *AvrPm/SvrPm* genes of the pathogen. There may be more than one gene on both sides. A long, multi-stage experiment involving alleles of the plant gene *Pm3* and the corresponding effectors of the pathogen showed that to understand the genetic basis of a highly specific reaction between immune receptors and pathogen effectors for each individual case, the task is very difficult and, as it seems to us, will not acquire practical significance.

1.11. *Pm* Genes Present in the Current Genetic Pool of Common Wheat

The first *Pm* gene in wheat was identified in the Thaw cultivar by Australian researcher Waterhouse in 1910 [159], and currently, the identification of new resistance genes and alleles continues. Resistance genes, first of all, could be classified into two groups: genes from the native genetic pool of common wheat and genes introgressed from cultivated and wild relatives (Table 1).

As can be seen from Table 1, some parts of *Pm* genes identified in modern cultivars and local varieties of common wheat have an introgression origin. This is the result of long-lasting work using initially only cytogenetic methods of work with plant material obtained by wide hybridization of wheat with numerous wild relatives. Later studies in this area became optimized by the use of molecular genetic markers and methods of work with DNA sequences. Significant interest in resistance gene introgression to the common wheat genome could be explained by two reasons. Firstly, among researchers of the last century, the idea of the impoverishment of the common wheat genetic pool by resistance genes has arisen, and this impoverishment involved resistance genes to biotic stresses [160]. This was explained, on the one hand, by the hypothesis of monophyletic wheat origin; however, this hypothesis is not supported by all researchers [161 - 164]. Possible monophyletic wheat origin by itself could be the reason to believe that the wheat genetic pool did not include many resistance genes, and its resistance could have quite a limited variety of molecular genetic mechanisms. On the other hand, as it is always indicated, the genetic pool of modern cultivars is limited by the variability inherent to commercial varieties and local landraces or lines, which could be used for intraspecific hybridization [165, 166]. Quite a long time ago, the assumption was made [167, 168] that for the wheat genetic pool widening, its numerous wild relatives could be used, including those having genomes different from wheat. This idea turned out to be constructive, and for several decades the common wheat genome, and, to a lesser extent, the durum wheat genome, were artificially supplemented by genes (alleles), which had not been naturally inherent to these species. Wheat genetic pool became enriched in resistance genes to many devastating diseases, including powdery mildew (Table 1). The second reason making introgression popular was very widespread at the beginning of such work confidence that genetic resistance introgressed from wild relatives could be more long-lasting compared to resistance controlled by wheat genes [24]. Practical experience over several decades demonstrated that this was not always the case.

Resistance genes introgressed from wild relatives have limitations in their use in wheat cultivars' resistance improvement, because they are often part of alien chromatin of some amount, which could also contain genes deteriorating cultivars' agricultural traits (linkage drag) [169]. For the separation of resistance genes from other genes with negative effects, many backcrosses are usually needed; moreover, recombination between alien chromosomes of wild relatives and wheat homoeologous chromosomes is limited by *Ph* (pairing homoeologous) gene [106, 114]. To obtain

recombination between alien chromosome fragments containing resistance genes and wheat chromosomes, *ph* gene mutants could be used [106]. In the case when sexual hybridization and recombination of genetic material in hybrid genomes are, for some reason, impossible, genetic engineering and transformation of plant cells could be used. Clearly, for the development of genetic constructs with particular resistance genes, these genes must be cloned and available for use as nucleotide sequences [170, 171].

Thus, the main characteristic of modern wheat varieties relative to powdery mildew resistance genes is the limited number of effective genes in the genetic pool of these varieties. This creates favorable conditions for overcoming plant resistance through the positive selection of pathogen isolates with such mutations in the *AvrPm* genes that their products are no longer recognized by the plant's immune receptors. The most common conclusion in the relevant literature is the belief of researchers in need to constantly replenish the genetic pool of wheat with new genes of resistance to powdery mildew.

1.12. Prospects for Improvement of Wheat Genetic Resistance to Powdery Mildew

The review of the present literature on wheat genetic resistance to powdery mildew demonstrates that the transfer of resistance genes from wild relatives to wheat remains an urgent problem. Genetic engineering methods began to be used to develop constructs containing target resistance genes. However, resistance genes must be previously cloned and available for constructs' development [170, 171]. Furthermore, currently, introgressive hybridization has been associated with the induction of plant genome variability [172, 173], and due to this, rearrangements of common wheat genetic material could arise in its genome with the following formation of a new allele of the resident resistance gene [89], and changes in transcription regulation could occur [106]. Many NBS-LRR encoding resistance genes are known to be localized in plant genomes in clusters [174, 175]. These gene clusters and repeated sequences (encoding LRR-repeats) provide more opportunities for recombination and gene conversion, which could provide the formation of new resistance alleles and new races of the pathogen [176], and alien chromatin could be a trigger of these processes. Furthermore, it has been demonstrated that nonfunctional resistance genes (pseudogenes) are widespread in plant populations, and they could promote the formation of new functional genes [177]. Alternative splicing of mRNAs of many NBS-LRR genes also adds complexity and variety to plant defense reactions [175, 176]. All information mentioned above does not add confidence that the resistance of descendants from distant crosses is conferred exactly by the alien resistance gene. Nevertheless, according to modern research, it could be predicted that wild relatives would be further used for wheat gene pool enrichment in resistance genes to powdery mildew.

Compared to previous decades, when attention was focused on resistance genes' introgression, currently, the search of new resistance genes in wheat genotypes has been activated. Wheat landraces and local varieties which have limited distribution, possibly would not create a genetic

background for high selective pressure for the new virulent fungus mutant's evolution [97, 108, 111, 114, 178, 179]. In addition, their use is more convenient at least because the transfer of resistance genes is not associated with linkage drag, an integral part of distant hybridization [114, 180, 181].

For the search of new resistance genes and their characterization, modern methods of direct genome analysis are increasingly involved. To map the resistance genes within the wheat genome, a variety of molecular genetic markers designed for different types of cereals [106, 111, 130, 182], and fine mapping of *Pm* genes [183 - 186]. The most modern map-based cloning method could be used, which is essentially the method of position cloning: a resistance gene is identified only through its localization in a particular chromosome or its part through the association of the desired phenotype (resistance) and a number of molecular markers, previously mapped on the chromosomes of the genome. That is, the candidate region is identified by the traditional linkage analysis with the following sequencing of the region of interest and identification of the DNA fragment with different sequences for two alternative phenotypes [13, 25, 45, 52, 73, 96, 182, 185, 187, 188]. Next fine mapping enables the identification of all polymorphisms in the region of interest and the determination of haplotypes (combination of particular genetic elements) associated with resistance [182, 184, 186, 189]. Both the data on the sequencing of the resistance gene and the determination of the haplotype associated with resistance provide information about the molecular nature of the product of the resistance gene and its participation in the initiation of the plant's protective reaction against the pathogen. The use of the RNA-Seq method could be especially effective, because this method enables the comparison of transcriptomes obtained in the conditions of pathogen attack or without pathogen. This enables the identification of the gene of interest and the determination of its function without the mapping of this gene in the genome [89, 109, 190]. Modification of this method BSR-Seq (bulked segregant RNA sequencing) allows to work with segregating populations and to determine the localization of resistance genes in the genome using molecular markers with known localization and polymorphic for different resistance phenotypes [52].

The results of sequencing of resistance genes and their products have demonstrated that there was a fundamental difference in the structures of protein products conferring race-specific and broad-spectrum resistance. It was demonstrated that race-specific resistance controlled by *R* genes is based on the molecular level of mutual recognition of plant immune receptors and pathogen's effectors. Effector is avirulent as long as this recognition occurs. When the effector gene mutates (this process is random and permanent) and the effector becomes no longer recognizable by the plant immune receptor, a resistance reaction does not develop. The main and determining factor for developing a strategy for the genetic protection of plants is that the plant gene acts as a passive element. Certainly, a plant gene can also mutate, however, its mutation is also random, the probability that the new mutation will provide complementation (recognition) of the mutated effector is insignificant, and expecting this mutation is not a promising method to deal with the problem. Other types of proteins

participating in conferring resistance are kinase proteins. Usually they confer broad-spectrum resistance, like receptor-like kinases *TaRLK1* and *TaRLK* [54], whose products initiate a non-race-specific hypersensitive response in plants. This means that the effectiveness of the effector mutation is lost. *Pm21* gene product is a serine/threonine kinase with nonspecific action [71]. This gene was transferred to the wheat genome from *Haynaldia* and was effective against powdery mildew for about 20 years despite its wide distribution in wheat cultivars. The *Pm24/WTK* gene also encodes kinase; this gene was identified in wheat local landraces of provinces of China and conferred resistance to many *Bgt* races. The effectiveness of this gene depends on the presence of a rare 6-bp deletion in the kinase domain [13]. Such molecular structure of the resistant allele makes it prospective to artificially modified susceptible alleles of this gene through the introduction of deletion, possibly using the *CRISPR/Cas* method of genome editing [126, 130]. The example given confirms the effectiveness of studding rare wheat genotypes as prospective sources of useful genes. These genes, unlike resistance genes of wild relatives, are also prospective because they could be transferred to commercial wheat cultivars easily, with any recombination level, and without linkage drag. They emphasize the significance of the determination of the molecular nature of a resistance gene product for making predictions about its prospects for introgression to the wheat genetic pool because this work requires much time and effort. In our opinion, simply increasing the number of introgressed to wheat genetic pool resistance genes without determination of the molecular nature of their products could appear to be a direction with reduced prospects.

CONCLUSION

The prospective direction of research for providing effective long-term and controlled wheat genetic resistance to the biotrophic pathogen *Blumeria* is molecular genetic studies of wheat plants and pathogen races. For this, it can be applied both traditional methods of crossing and mapping populations' development for plants and fungi, and modern methods of genome analysis for direct (not through phenotype) genotyping of members of segregating populations of plant or fungus. Clear understanding of the molecular nature (structure and function) of the plant protein conferring resistance, and its role in the development of the molecular picture of plant protection against the pathogen, will enable to evaluate any new gene (introgressed to the wheat genetic pool or identified in wheat local varieties, or edited *in situ* using corresponding technologies) on how prospective could this gene be for introduction into commercial wheat cultivars for conferring reliable and long-lasting powdery mildew resistance.

LIST OF ABBREVIATIONS

PAMP	=	Pathogen-Associated Molecular Patterns
PRR	=	Pattern Recognition Receptors
PTI	=	Pattern-Triggered Immunity
NBS	=	Nucleotide Binding Site
LRR	=	Leucine-Rich Repeat

TKP	= Tandem Kinase Protein
GWAS	= Genome-Wide Association Studies
WTK3	= Wheat Tandem Kinase 3
Ltn1	= Leaf Tip Necrosis
MLO	= Mildew Resistance Locus
EDR1	= Enhanced Disease Resistance 1
CSEPs	= Candidate Secreted Effector Proteins
BEC	= Blumeria Effector Candidate
ETI	= Effector Triggered Immunity

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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