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Genetics and breeding for resistance against four leaf spot diseases in wheat (*Triticum aestivum* L.)

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In wheat, major yield losses are caused by a variety of diseases including rusts, spike diseases, leaf spot and root diseases. The genetics of resistance against all these diseases have been studied in great detail and utilized for breeding resistant cultivars. The resistance against leaf spot diseases caused by each individual necrotroph/hemi-biotroph involves a complex system involving resistance (R) genes, sensitivity (S) genes, small secreted protein (SSP) genes and quantitative resistance loci (QRLs). This review deals with resistance for the following four-leaf spot diseases: (i) Septoria nodorum blotch (SNB) caused by *Parastagonospora nodorum*; (ii) Tan spot (TS) caused by *Pyrenophora tritici-repentis*; (iii) Spot blotch (SB) caused by *Bipolaris sorokiniana* and (iv) Septoria tritici blotch (STB) caused by *Zymoseptoria tritici*.

KEYWORDS

wheat, pathogens, sensitivity genes, resistance genes, necrotrophic effectors, PR proteins

Introduction

Wheat (*Triticum aestivum* L.) is the third most important staple food crop worldwide (the other two being maize and rice). According to FAO, during 2021-22, the total global wheat grain production was 778.6 million tonnes as against ~697 million tonnes in the year 2011-12, and 756.5 million tonnes in 2016-17 giving an annual increase of a mere 1.24% over the last 10 years and 0.83% over the last five years showing a decline in annual growth rate as against the desired rate of ~1.5% - 2% to meet the demand of growing world population. A variety of biotic and abiotic stresses are responsible for this bottleneck. The biotic stresses mainly include pathogens like fungi, viruses, bacteria, and nematodes, which cause a variety of diseases. Among these pathogens, fungal pathogens cause diseases like

rusts, mildew, blast, bunts, and blights, which are responsible for 15-20% yield loss (Figueroa et al., 2018). Among major classes of wheat diseases, the following are the four important leaf spot diseases, which are also described as blotch diseases (Figure 1): (i) Septoria nodorum blotch (SNB) caused by *Parastagonospora nodorum*, (ii) Tan spot (TS) caused by *Pyrenophora tritici-repentis*, (iii) Spot blotch (SB) caused by *Bipolaris sorokiniana* and (iv) Septoria tritici blotch (STB) caused by *Zymoseptoria tritici*. Among these four pathogens, *P. nodorum* and *P. tritici-repentis* are necrotrops, while *B. sorokiniana* and *Z. tritici* are hemi-biotrophs, since these are believed to need living tissue initially and later kill the host tissues and then feed and survive on the dead tissues of the host. The hemi-biotrophic nature of *Z. tritici* has, however, been recently questioned (Sanchez-Vallet et al., 2015; Friesen and Faris, 2021).

It has been shown that for most diseases in all crops including wheat, a gene-for-gene (GFG) model holds good between individual R genes of the host and the matching Avr genes in the pathogen (Flor, 1942; Flor, 1956). As a result, in the absence of a matching avirulance (Avr) gene in the prevalent race of the pathogen, the R gene can not provide resistance (Figure 2A). In contrast, the inverse gene-for-gene (IGFG) model (Fenton et al., 2009) assumes that a compatible interaction requires the presence of a matching susceptibility/S gene in the host and the corresponding necrotrphhic effector (NE) gene in the pathogen, so that in the absence of matching S gene in the host, an infection can not occur (Figure 2B; Friesen et al., 2007). Current knowledge suggests that in the same crop, both GFG and IGFG systems may operate synergistically, although this has not been widely discussed. Another class of genes include small secreted protein (SSP) genes, which have recently been shown to provide resistance against *Z. tritici* (Zhou et al., 2020); these SSP genes in wheat for other diseases have yet to be discovered. Quantitative disease resistance (QDR) may also occur together with S genes, R genes and SSP genes, although in some cases, one or more quantitative resistance loci (QRLs) have also been shown to represent S/R genes (for QRLs, see later). This makes the genetic systems for resistance against individual necrotrophs and hemi-biotrophs rather complex, but an interesting subject for research.

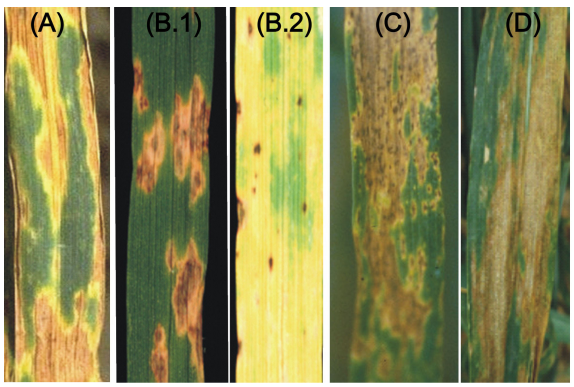

FIGURE 1
The visual symptoms of four necrotrophic and hemibiotrophic diseases. **(A)** SNB; **(B)** TS (**B.1** and **B.2** showing necrosis and chlorosis); **(C)** SB and **(D)** STB.

A number of studies have also been conducted on QDR against each of the above four diseases. These studies mainly include identification of either the QRLs using linkage-based interval mapping, often involving biparental mapping populations [sometimes also involving multi-parent advanced generation inter-cross (MAGIC) populations] or the marker-trait associations (MTAs) using LD-based genome-wide association studies (GWAS) using association panels. In some cases, a QRL identified through interval mapping may also overlap a resistance R gene, as shown in the case of one or more of the four R genes (*Sb1-Sb4*) for resistance against *B. sorokiniana* (Kumar et al., 2015; Gupta et al., 2018a). The relative roles of QRLs/R genes and the sensitivity S genes have also been assessed, and it was shown that QRLs/R and not the S genes are the major source of resistance, although in certain parts of the world, resistance has also been found to be associated with absence of S genes like *Tsn1* (Cowger et al., 2020).

The occurrence of multiple disease resistance (MDR) involving resistance against more than one disease has also been reported (Zwart et al., 2010; Mago et al., 2011; Singh et al., 2012; Jighly et al., 2016; Pal et al., 2022). As an example, MDR for SNB and TS has been reported in some winter wheat cultivars, suggesting that MDR may be associated with winter habit and that diverse sources of resistance for multiple diseases can be made to hybridize to achieve MDR (Ali et al., 2008; Gurung et al., 2009; Gurung et al., 2014). Association among resistance to two or three diseases, namely SNB, SB, and STB has also been observed (Gurung et al., 2014). Such an association involving MDR could also be the result of unconscious selection for resistance to multiple diseases during wheat breeding programmes. GWAS-based MTAs, each associated with more than one disease, have also been identified, suggesting occurrence of either the pleiotropic genes or closely linked loci providing resistance to more than one disease (Gurung et al., 2014).

Meta-QTLs involving diseases caused by more than one necrotroph have also been recently identified (Saini et al., 2022). However, while the available literature on interactions between S genes and necrotrophic effectors (NEs), and also on cloning and characterization of the sensitivity genes in the host and the NE genes in the pathogen has been the subject of several reviews, the literature on the complex genetic system for disease resistance involving S genes, R genes, SSP genes and QRLs associated with more than one disease caused by necrotrophs has not been adequately reviewed (Cowger et al., 2020). However, it has been shown that durable resistance against the pathogen is generally achieved through a quantitative genetic system and that interactions between the products of the recessive alleles of S genes and the NEs play a minor role in providing resistance (Cowger et al., 2020). The S genes, S QTLs, R genes, and resistance QTLs identified through QTL interval mapping and GWAS are sown in Supplementary Figures S1, S2.

The present review is intended to provide an overview of the complex genetic system of resistance in wheat against each of the four different pathogens, mentioned above. While doing so, we recognize that the work involving GFG in biotrophs is widely known and regularly reviewed (Van Der Biezen and Jones, 1998;

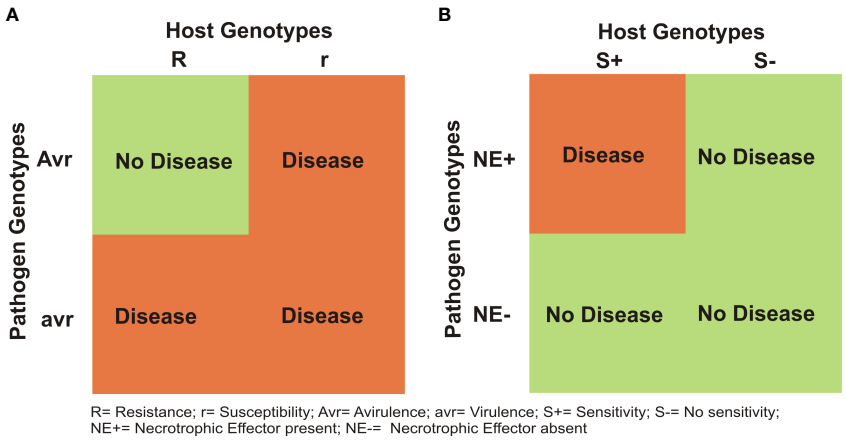

FIGURE 2
Two different models for host- pathogen interactions in plants: **(A)** gene-for gene (GFG) model, proposed by Flor (1956) and **(B)** an inverse gene-for gene (IGFG) model that was discovered recently in a number of necrotrophic diseases in wheat.

Kaur et al., 2021). Therefore, in this review, emphasis will be on the NEs and S genes involved in IGFG. In each case, the disease is caused by an interaction between NEs encoded by host-specific toxin (HST) genes of the pathogens and the proteins encoded by the corresponding S genes in the host, but resistance is largely quantitative in nature. The recent information on the genomics of all four pathogens will also be included in this review since whole genome sequences are now available for all four pathogens; this became possible only due to the availability of high through-put next-generation sequencing (NGS) technology (Syme et al., 2013; Moolhuijzen et al., 2018; Plissonneau et al., 2018; Richards et al., 2018; Syme et al., 2018; Aggarwal et al., 2019; Aggarwal et al., 2022). The present review on genetics and breeding for resistance against four leaf spot diseases in wheat should prove useful for geneticists, breeders and pathologists for further research targeted towards development of high yielding cultivars, resistant to these four foliar leaf spot diseases.

Pathosystems and genetics of disease resistance

As mentioned above, among the four pathosystems selected for this review, two pathosystems involve necrotrophs, while the other two involve hemi-biotrophs. The major differences between biotrophs and necrotrophs are listed in Table 1. The details of the

TABLE 1 A comparison of characteristics of biotrophs and necrotrophs (based on the link http://www.davidmoore.org.uk/21st_Century_Guidebook_to_Fungi_PLATINUM/Ch14_10.htm).

Biotroph pathogens	Necrotroph pathogens
Appressoria or haustoria produced	Appressoria/haustoria normally not produced
Resistance is controlled by SA-dependent host-defense pathways	Resistance controlled by SA, JA and Et-dependent host-defense pathways
Gene-for-gene (GFG) relationship	Inverse gene-for-gene (IGFG) relationship
Difficult to culture	Easy to culture
Entry, direct or through natural openings	Entry via wounds or natural openings
Survive on living tissues or as dormant propagules	Survive on living/dead tissue or as competitive saprotrophs
Host cells not killed rapidly; hypersensitive reaction (HR) in resistant genotype	Host cells killed rapidly; no hypersensitive reaction in resistant genotype
Few lytic enzymes/toxins are produced	Cell-wall-degrading (lytic) enzymes/toxins are produced
Often systemic	Seldom systemic
Attack vigorous plants; any stage	Attack weak, young/damaged plants
Narrow host range	Wide host range
Intercellular/Intracellular growth of pathogen	Intercellular/Intracellular growth of pathogen
Effectors: Avr proteins recognized by matching resistance (R) proteins	Effectors: host-specific or host-selective toxins (HST)
Disease caused by suppressing PTI/ETI	Disease caused either by suppressing PTI/ETI or by activation of sensitivity genes

four important pathogens (necrotrophs/hemi-biotrophs) and the wheat diseases caused by them are listed in Table 2. For each of the four diseases, S genes, R genes and QRLs identified either through interval mapping or through GWAS are summarised in Supplemantery Table S1, which also includes information on SSP genes for resistance against STB. More details for each of the four pathosystems under review along with genetics of disease susceptibility/resistance as well as interactions between S genes and NE genes are presented in this section.

P. nodorum-wheat pathosystem

The *P. nodorum*-wheat pathosystem involved in the disease SNB is the most extensively studied pathosystem involving necrotrophs. Therefore, it is also used as a model to study host-pathogen interactions involving NEs previously referred to as host selective toxins (HSTs), released by the pathogen and the products of S genes in the host. The disease SNB includes both leaf blotch and glume blotch (Figure 1A) that are common in warm and humid areas of the world, causing ~16% yield losses, which sometimes approach 60% under severe infection/epidemic conditions (Bhathal et al., 2003; Ficke et al., 2018; Shankar et al., 2021). The disease is particularly common in Australia, USA, parts of Europe and southern Brazil. The short incubation period enables the pathogen for multiple infection cycles within a season. The fungus can reproduce through asexual conidia as well as through sexual reproduction due to the availability of both mating types (MAT1-1 and MAT1-2).

NE genes, S genes, and the interactions

P. nodorum produces NEs, which contribute to variation in aggressiveness. The infection occurs only when a specific S gene of the host responds to the presence of a NE encoded by a gene in the pathogen. Nine S genes in the host and eight NE genes in the pathogen have been identified, which are involved in the following nine interactions: (i) *Tsn1*-SnToxA; (ii) *Snn1*-SnTox1; (iii) *Snn2*-SnTox2; (iv) *Snn3B1*-SnTox3; (v) *Snn3D1*-SnTox3 (vi) *Snn4*-SnTox4; (vii) *Snn6*-SnTox6; (viii) *Snn7*-SnTox7; (ix) *Tsn1*-SnToxA. A new NE named SnTox267, was later shown to represent three previously characterized NEs, namely SnTox2, SnTox6 and SnTox7, hence the name SnTox267 (Richards et al., 2021). Among the above nine interactions, the following interactions have been subjected to relatively detailed studies because the S genes and the NE genes involved in these interactions have all been cloned and characterized: *Tsn1-SnToxA, Snn1-SnTox1* and *Snn3-D1-SnTox3*.

The distribution of S genes involved in SNB in wheat populations differs in different wheat-growing regions of the world. However, maximum data is available from the USA, Europe (including UK and Norway) and Western Australia. The distribution of three NE genes (*SnToxA*, *SnTox1* and *SnTox3*) in a globally diverse collection of pathogen isolates, was reported by McDonald et al. (2013); the results are summarised in Table 3. These results, suggested that the gene *SnTox1* is the most widely distributed gene, occurring in 95.4% isolates from the USA (as above) and in 84% isolates worldwide. Similar frequencies (85%) were reported for the corresponding S gene *Snn1* in wheat germplasm; this was also confirmed in some independent surveys conducted for the distribution of different S genes in wheat cultivars (Tan et al., 2014; Phan et al., 2018; Hafez et al., 2020).

Cloning of S genes and NE genes

Three S genes (*Tsn1*, *Snn1*, and *Snn3-D1*) and five NE genes (*SnToxA*, *SnTox1*, *SnTox3*, *SnTox5*, *SnTox267*) have also been cloned and characterized thus permitting a study of interactions between the products of sensitivity genes and NEs at the molecular level. Efforts are also underway for cloning of *Tsc1* gene. For this purpose, in a recent study, 58 molecular markers were identified delineating a 1.4 cM genetic interval spanning 184kb on chromosome 1AS, carrying *Tsc1* gene (Running et al., 2022). This short region carried only nine candidate genes that were mainly related to NB-ARC, protein kinase, LRR, retinal pigment epithelial membrane protein and pseudo-gliadin proteins. The information with details of the cloned S genes and NE genes is available in a number of individual original papers (Ciuffetti et al., 1997; Liu et al., 2009; Faris et al., 2010; Liu et al., 2012; Liu et al., 2016; Shi et al., 2016a; Shi et al., 2016b; Kariyawasam et al., 2021; Zhang et al., 2021) and summarized in several recent reviews (Wang et al., 2014; McDonald and Solomon, 2018; Faris and Friesen, 2020; Friesen and Faris, 2021; Lin and Lillemo, 2021; Peters Haugrud et al., 2022). The information is also summarized in Table 4 and Supplementary Figure S3.

TABLE 2 Necrotrophs and hemibiotrophs causing diseases in wheat.

Pathogen (teleomorph)	Pathogen (anamorph)	Disease caused	Reference
Parastagonospora nodorum (Berk.) Quaedvlieg, Verkley & Crous	*Stagonospora nodorum* [Berk.] Castellani & E.G. Germano)	Septoria nodorum blotch (SNB)	Weber, 1922; Sprague, 1950; King et al., 1983; Scharen et al., 1985
Pyrenophora tritici-repentis (Died.) Drechsle	*Drechslera tritici-repentis* (Died.) Shoemaker	Tan spot	Drechsler, 1923; Shoemaker, 1959; Shoemaker, 1962
Cochliobolus sativus (S. Ito & Kurib.) Drechsler ex Dastur	*Bipolaris sorokiniana* (Sorokin) Shoemaker	Spot Blotch (SB)	Dastur, 1942; Shoemaker, 1959
Mycosphaerella graminicola (Fuckel) J. Schröt.	*Zymoseptoria tritici* (Desm.) Quaedvlieg & Crous	Septoria tritici blotch (STB)	Desmazieres, 1842; Schroter, 1894

TABLE 3 Distribution (%) of three Tox genes among isolates of *P. nodorum* and sensitivity genes in wheat.

Distribution (%) of three Tox genes in *P. nodorum*				
Region	*SnToxA*	*SnTox1*	*SnTox3*	Reference
Fertile Crescent	95.0	97.0	72.0	Ghaderi et al., 2020
Norwegian	67.9	46.1	47.9	Lin et al., 2020b
Canada	69.2	80.7	76.9	Hafez et al., 2020
Norwegian	69.0	53.0	76.0	Ruud et al., 2018
World-wide collection	18.0	26.0	22.0	McDonald et al., 2013
Europe	12.0	89.0	67.0	McDonald et al., 2013
South-eastern United States	15.0	74.0	39.0	Crook et al., 2012
Distribution (%) of three sensitivity related genes in wheat				
	Tsn1	*Snn1*	*Snn3*	
Norwegian	30.0	7.6	15.3	Lin et al., 2020b
Canada	59.0	32.9	56.9	Hafez et al., 2020
Norwegian	45.0	12.0	55.0	Ruud et al., 2018
Russia	29.3	26.8	51.2	Phan et al., 2018
Kazakhstan	27.7	28.6	63.6	Phan et al., 2018
India	66.7	58.3	77.8	Phan et al., 2018
Pakistan	59.4	71.9	68.8	Phan et al., 2018
British French, German and Dutch	9.1	28.0	42.0	Downie et al., 2018
Australia	63.0	71.7	91.3	Tan et al., 2014
USA	32.0	0.0	64.0	Bertucci et al., 2014

Genetics of resistance

There are at least three genetic systems, which provide resistance against SNB, as also in other pathosystems; these three systems include the following: (i) recessive alleles or loss of S genes, (ii) classical R genes and (iii) QTLs/MTAs identified through interval mapping and GWAS. Some details of these three systems will be described.

S genes for resistance.

According to Cowger et al. (2020), some evidence is available, which suggests that during breeding programs, perhaps unconscious selection for resistance has been exercised against S genes (*Snn* genes in the case of *P. nodorum*) due to their role in conferring susceptibility. It is also assumed that some S genes were R-genes, which provided resistance against pathogens, but have

TABLE 4 A summary of cloned sensitivity and NE genes involved in SNB.

Gene/chromosome	Length (bp)	Protein (aa)	Reference	Figure
Sensitivity genes (wheat, *T. aestivum*)				
Tsn1 (5BL)	10,581	S/TPK-NBS-LRR	Faris et al., 2010	Supplementary Figures S3A, B
Snn1 (1BS)	13,045	GUB-WAK, EGF_CA, TM, PK	Shi et al., 2016b	Supplementary Figures S3C–F
Snn3–D1 (5DS)	1,977	PKMSP	Zhang et al., 2021	Supplementary Figure S3G
NE Genes (*P. nodorum*)				
SnToxA	534	13 kD	Ciuffetti et al., 1997	Supplementary Figure S3H
SnTox1	7,600	10.3 kD	Liu et al., 2012	Supplementary Figures S3I, J
SnTox3	693	25.8 kD	Liu et al., 2009	Supplementary Figures S3L, M
SnTox5	654	16.26 kDa	Kariyawasam et al., 2021	Supplementary Figure S3K
Sn267	2,086	74.5 kDa	Richards et al., 2021	Supplementary Figure S3N

been hijacked/corrupted by necrotrophs to provide susceptibility, thus becoming S genes (Nagy and Bennetzen, 2008; Faris et al., 2010; Gilbert and Wolpert, 2013; Shi et al., 2016b). For instance, during the cloning of *Tsn1* and *Snn1* genes, it was concluded that necrotrophs hijacked the R genes involved in resistance to biotrophs and altered them for their own benefit (Faris et al., 2010; Shi et al., 2016b). During interval mapping also, some QTLs were found to be located in the genomic regions occupied by S genes, thus suggesting that QTLs may also sometimes represent R genes hijacked by the pathogens.

Possible R genes

Wheat genome sequences were also utilized for the identification of R genes associated with the genomic regions occupied by QTLs that were earlier identified and mapped on 1BS and 5BL. The annotation of intervals in the reference sequence allowed identification and mapping of 13 R genes on 1BS and 12 R-genes on 5BL (Li D. et al., 2021), although no evidence was available showing that these R genes were involved in providing resistance against SNB. The analysis of R genes, however, resolved co-located QTL on 1BS into the following two distinct but linked loci: (i) *NRC1a* and *TFIID* mapped in one QTL on 1BS, and (ii) *RGA* and *Snn1* mapped in the linked locus; all these genes were found to be associated with SNB resistance, but only in one environment. Similarly, *Tsn1* and *WK35* were mapped on the same QTL on 5BL, with NETWORKED 1A and RGA genes mapped in the linked QTL interval.

QTLs/MTAs for SNB resistance (leaf blotch, and glume blotch)

As mentioned above, *P. nodorum* is responsible for two SNB diseases in wheat, *i.e.*, leaf blotch and glume blotch (involving flag leaf for leaf blotch and spikes for glume blotch). The inheritance pattern for resistance against the two diseases differs (Wicki et al., 1999; Xu et al., 2004; Shankar et al., 2008; Chu et al., 2010). However, in several genetic studies, no distinction was made between leaf blotch and glume blotch. QTLs for resistance against SNB have also been identified following both linkage-based interval mapping and LD-based GWAS.

Interval mapping involved both bi-parental and multi-parental (MAGIC) mapping populations, and resulted in the identification of ~170 QTLs including ~30 major QTLs, each explaining >20% of the phenotypic variation (Supplementary Table 2). These studies included the following: Czembor et al., 2003; Schnurbusch et al., 2003; Arseniuk et al., 2004; Liu et al., 2004a; Aguilar et al., 2005; Reszka et al., 2007; Uphaus et al., 2007; Shankar et al., 2008; Friesen et al., 2009; Gonzalez-Hernandez et al., 2009; Francki et al., 2011; Abeysekara et al., 2012; Shatalina et al., 2014; Ruud et al., 2017; Francki et al., 2018; Czembor et al., 2019; Singh et al., 2019; Lin et al., 2020a; Lin et al., 2021; (for a recent review, also see Downie et al., 2021).

The above QTL studies also included two recent major studies, each involving an independent MAGIC population, one used by Lin et al. (2020a) and the other used by Lin et al. (2021). Using these two MAGIC populations, 17 QTLs on the following chromosomes were identified: 2A, 2D, 5A, 5B, 6A, 7B and 7D. In these two studies, two QTLs, namely *QSnb.niab-2A.3* (UK MAGIC population, Lin et al., 2020a) and *QSnb.nmbu-2A.1* (German MAGIC population, Lin et al., 2021) were found in a short interval on chromosome 2A; these two QTLs could represent a hot spot controlling resistance against SNB. A QTL (*QSnb.niab-5B.2*) overlapping *Tsn1* was also identified on 5BL (Lin et al., 2020a; Lin et al., 2021).

The GWA studies for resistance to SNB were undertaken both at the seedling stage and adult plant stage (flag leaf and spike for glume blotch) and resulted in identification of MTAs on almost all 21 chromosomes. However, more studies were conducted at the seedling stage than at the adult stage (glume blotch). These association studies largely included the following: Adhikari et al., 2011; Korte and Farlow, 2013; Gurung et al., 2014; Gao et al., 2016; Pascual et al., 2016; Downie et al., 2018; Phan et al., 2018; Halder et al., 2019; Ruud et al., 2019; Francki et al., 2020; Phan et al., 2021; Lin et al., 2022). After due validation, the markers associated with QTLs and MTAs can be utilized for marker assisted selection (MAS) for resistance breeding.

High-resolution fine-mapping has also been undertaken for sensitivity genes. For this purpose, a high-density genetic linkage map was developed for a chromosome 2D region, which narrowed down the *Snn2* gene to a 4 cM region, thus facilitating the discovery of closely linked molecular markers for breeding and positional cloning of the *Snn2* gene (Zhang et al., 2009). Phenotypic variation (PV) for the disease was 47% for the interaction *Snn2-SnTox2*, 20% for *Tsn1-SnToxA*, and 66% for both interactions taken together, suggesting the utility of these interactions for breeding (Friesen et al., 2008).

Epistatic interactions among fungal NE genes.

Epistatic interactions involving suppression of *SnTox3* by *SnTox1* in the pathogen were also demonstrated (Phan et al., 2016). In this study, the mapping population consisted of 177 double haploid (DH) lines, and an aggressive isolate (Sn15) of the pathogen with genes for three NEs, namely *SnToxA*, *SnTox1* and *SnTox3* and its two deletions (tox1-6 with a deletion for *SnTox1*, and toxa13 with deletion for all the three NE genes) were used; mutant strain toxa13 retained pathogenicity and necrosis-inducing activities in the culture filtrate (Tan et al., 2015); the virulence of this toxa13 on the mapping population at the seedling stage was comparable with that of Sn15.

The following observations also suggested epistatic suppression of *SnTox3* by *SnTox1* and that of *SnToxA* by *SnTox3* in the pathogen: (i) The mapping population segregated for S genes *Snn1* and *Snn3*, since parents of the mapping population differed for these two genes; (ii) When Sn15 was used for infection, *SnToxA–Snn1* interaction was most important for SNB development on both seedlings and adult plants, suggesting that *SnToxA* always functioned; no effect of the *SnTox3–Snn3* interaction was observed under Sn15 infection. (iii) When tox1-6 strain was used for inoculation, *SnTox3–Snn3* interaction was observed; (iv) When toxa13 strain was used for infection, it unmasked a significant SNB QTL on 2DS, where *Snn2* is located. This QTL was not observed in Sn15 and tox1-6 infections, thus

suggesting that *SnToxA* and/or *SnTox3* were epistatic. Additional QTLs responding to SNB sensitivity were detected on 2AS1 and 3AL.

Seedling and adult plant field resistance

In each above case, resistance has generally been examined at the seedling stage under controlled conditions using single isolates of the pathogen, but often also examined and compared with those under field conditions (with a mixture of isolates) at the adult plant stage. However, caution should be exercised during evaluation of resistance at the seedling stage for developing resistance under field conditions. Several studies have shown comparable results at the seedling and adult plant stages, when using the same isolate or mix of isolates. However, since the natural infections in the field involve complex pathogen populations with a mixture of isolates, care must be taken to choose representative isolates (see Ruud and Lillemo, 2018 and Peters Haugrud et al., 2022 for recent discussions on this topic).

Genetics and genomics of *P. nodorum*

Genetic variation among naturally occurring isolates and population genetics of *P. nodorum* has also been examined both at the national level in Sweden (Blixt et al., 2008), Western Australia (Murphy et al., 2000) and Norway (Lin et al., 2020b), and at the global level (Stukenbrock et al., 2005; Stukenbrock et al., 2006). Using RFLPs and SSRs as molecular markers for this purpose, it was shown that in general, *SnToxA* had a relatively higher frequency among *P. nodorum* isolates sampled in different studies (Lin et al., 2020b).

Whole genome sequencing has also been undertaken for *P. nodorum*. The pathogen is haploid with a genome size ranging from 28 Mb to 37 Mb with 23 chromosomes including an accessory chromosome, AC_{23} that is involved in virulence-related functions other than the functions assigned to NEs (Syme et al., 2013; Richards et al., 2018; Syme et al., 2018). A number of isolates, including the following four major isolates were used for genome sequencing: Sn15, Sn4, Sn2000, Sn79-1087. The number of genes in the genome was shown to range from 13,569 for the Sn15 reference genome to 13,294 in Sn79-1087 genome (Hane et al., 2007; Syme et al., 2013; Syme et al., 2016; Richards et al., 2018). Another study involved 197 isolates collected from durum wheat and spring/winter bread wheat from the USA (Richards et al., 2019). These studies together resolved a wide range of structural variations (SVs). A pangenome was also developed using multiple genome sequences (Syme et al., 2018).

P. tritici-repentis-wheat pathosystem

TS caused by *P. tritici-repentis* (Died.) Drechs. has been reported from different parts of the world, including Australia, Canada, the USA, Mexico, South America (Argentina and Brazil), Europe, Africa, and Central Asia (Kazakhstan and Tajikistan) (Singh et al., 2008; Ciuffetti et al., 2010). The epidemics for this disease have been reported to cause yield losses of up to ~50% (Rees et al., 1982). The disease is characterized by two distinct and independent symptoms, namely necrosis and chlorosis (Figures 1B.1, B.2).

NE genes, S genes, and interactions

There are three NE genes (*ToxA*, *ToxB* and *ToxC*) and three sensitivity genes (*Tsn1*, *Tsc2* and *Tsc1*) involved in TS. The sensitivity genes and the NEs encoded by three Tox genes are involved in the following three interactions: (i) *Tsn1*-ToxA interaction (this interaction is also known in two other pthosystems, namely wheat-*P. nodorum* and wheat-*B. sorokiniana* pathosystem). (ii) *Tsc2*-ToxB interaction; (iii) *Tsc1*-ToxC interaction (Ciuffetti et al., 2010).

There is strong evidence that *P. tritici-repentis* acquired the gene *ToxA* from *P. nodorum* through horizontal gene transfer (Friesen et al., 2006). Among the three NEs, *ToxA* causes necrosis, while *ToxB* causes chlorosis. However, *ToxC*, which also causes chlorosis, is not a protein but a non-ionic, polar, low molecular mass molecule (Effertz et al., 2002).

In the pathogen populations, eight races (races 1 to 8) have been recognized on the basis of the types of susceptibility lesions using six differential wheat genotypes (chlorosis or necrosis) and HSTs/NEs produced (Lamari et al., 2003; Ciuffetti et al., 2010; Table 5). Each race produces one or more NEs in a combination, which differs for different races. For instance, races 1, 6, and 7 produce two NEs each (race 1 with ToxA and ToxC, race 6 with ToxB and ToxC and race 7 with ToxA and ToxB). Races 2, 3, and 5 each produce only one NE (race 2 with ToxA, race 3 with ToxC and race 5 with ToxB); race 8 produces all the three NEs, while race 4 is known to produce none (Faris et al., 2013; Guo et al., 2018). In addition to the above three toxins, as many as 38 novel necrosis inducing toxins called 'triticones' have also been identified, although only triticone A and triticone B have been purified from Ptr (Rawlinson et al., 2019).

Geographic distribution of Ptr NE genes

The distribution of the genes encoding three different NEs (ToxA, ToxB and ToxC) and the wheat genotypes with corresponding S genes involved in interactions differs widely in different parts of the world. Of these, ToxA is the most widely distributed, present in ~80% of the world's Ptr isolates (Lamari et al., 1998; Ali and Francl, 2002; Friesen et al., 2006).

Cloned NE genes for TS

Among NE genes, the gene encoding PtrToxA (a 13.2-kDa protein) has been characterized by several independent research groups, and was the first to be cloned (Ballance et al., 1996; Ciuffetti et al., 1997). The gene encoding PtrToxB (6.61 kDa) occurs as multiple copies, and carries a 261-bp open reading frame (ORF) within its sequence (Martinez et al., 2001). PtrToxC has not been

TABLE 5 Reaction of eight races of *P. tritici-repentis* on four bread and two durum wheat differential lines.

Differential genotypes	Race (with Toxin) and reaction of six differential genotypes							
	1	2	3	4	5	6	7	8
	ToxA, C	ToxA	ToxC	None	ToxB	ToxB, C	ToxA, B	ToxA, B, C
Bread wheats								
Glenlea	S1	S1	R	R	R	R	S1	S1
6B662	R	R	R	R	S2	S2	S2	S2
6B365	S	R	S2	R	R	S2	R	S2
Salamouni	R	R	R	R	R	R	R	R
Durum wheats								
Coulter	S1	S1	S1	R	S1	S1	S1	S1
4B1149	R	R	R	R	R	R	R	R

R indicates resistant, S1 indicates susceptible (necrosis), and S2 indicates susceptible (chlorosis).

fully characterized and purified; the mode of action of this NE is also not known. However, its partial characterization has been done as low molecular weight, non-ionic polar molecule (Effertz et al., 2002).

Cloned sensitivity genes for TS

Tsn1 (common for susceptibility to three necrotrophs) was cloned and characterized rather early (Supplementary Figures S3A, B; Faris et al., 2010). The other two S genes, *Tsc1* and *Tsc2*, are yet to be cloned and characterized, but markers have been developed for these two other sensitivity genes also (Supplementary Table S1). The variety 'Maris Dove' was also identified as the historical source of *Tsc2* alleles in the wheat germplasm (Corsi et al., 2020). A minor S QTL was also identified on chromosome 2A (Corsi et al., 2020) in this line. The marker developed in this study can be used for MAS to select insensitive genotypes exhibiting disease resistance (Corsi et al., 2020).

Attempts are also underway to clone *Tsc1* gene. For this purpose, in a recent study, two biparental populations were used leading to the delineation of *Tsc1* candidate gene region to a 1.4 centiMorgan (cM) interval, which spanned 184 kb region on the short arm of chromosome 1A. Mapping of the chlorotic phenotype, development of genetic markers, both for genetic mapping and MAS, and the identification of *Tsc1* candidate genes in this study provide a foundation for map-based cloning of *Tsc1* (Running et al., 2022)

Genetics of resistance

Assessment of sensitivity

In a recent study, 40 Australian spring wheat varieties were examined for sensitivity to ToxA and disease response to a race 1 specific wild-type Ptr isolate carrying *ToxA* and *ToxC* (See et al., 2018). *ToxA* sensitivity was generally associated with disease susceptibility (compatible interaction) but did not always produce symptoms (See et al., 2018). When wild type and *toxA* mutant isolates were used for infection, most *Tsn1* varieties exhibited low disease scores with *toxA* mutants (as expected). However, several varieties exhibited no distinct differences between wild-type and *toxA* mutant (See et al., 2018). This pattern suggested that ToxA is not the sole major cause of TS disease and that the appearance of the disease partly also depends on the background of the host (See et al., 2018). It is thus apparent that ToxA may need additional factors to cause infection (See et al., 2018).

R genes for resistance

Resistance genes (R genes or major QTLs) providing resistance against TS have also been identified. Most studies on the genetics of TS are based on bi-parental mapping populations (Faris et al., 2013). Among R genes, *Tsr7* locus was also identified in tetraploid wheat using a set of Langdon durum-wild emmer (*Triticum turgidum* ssp. *dicoccoides*) disomic chromosome substitution lines (Faris et al., 2020). Four user-friendly SNP-based semi-thermal asymmetric reverse PCR (STARP) markers co-segregated with *Tsr7* and should be helpful for MAS (Faris et al., 2020).

QTLs for resistance

Several QTLs have been identified, mainly corresponding to the available S-genes (Liu et al., 2020a). The QTL studies resulted in the identification of as many as >160 QTLs; a number of these QTLs explained >20% phenotypic variation (Supplementary Table S2). A meta-QTL analysis was also conducted, leading to the identification of 19 meta-QTLs derived from the results of 104 QTL studies (Liu et al., 2020a; Liu et al., 2020b). Three race nonspecific meta-QTLs were also identified, one each on chromosomes 2A, 3B and 5A. These three meta-QTLs had large phenotypic effects, each responsible for resistance to multiple races infecting bread and durum wheat races, thus suggesting their utility for marker-assisted selection (MAS).

GWAS for resistance

A number of GWA studies involving the identification of MTAs for TS resistance are also available (Patel et al., 2013; Kollers et al., 2014; Liu et al., 2015; Juliana et al., 2018; Dinglasan et al., 2019; Galagedara et al., 2020; Kokhmetova et al., 2020; Muqaddasi et al., 2021). These studies led to the identification of >240 MTAs, although many of these could be false positives (Supplementary Table S3). Candidate genes were found for 16 out of 19 meta-QTLs; the candidate genes for each meta-QTL ranged from 2 to 85, with most of them being on chromosome 2B. Many of these potential genes encoded NBS- and/or LRR-like proteins and were found near the *Tsc2* S gene (Liu et al., 2020a). However, none of these candidate genes could be actual *Tsc2* gene, because the genomic sequence used to identify candidate genes belonged to Chinese spring (CS) wheat, insensitive to Ptr ToxB. (Liu et al., 2020a).

Genetic studies at seedling and adult plant stage under field conditions

The genetics of resistance against TS in wheat has been examined both at the seeding and adult plant stages. For instance, in a study of ~300 accessions from Vavilov collection, seedling but not adult plant disease response corresponded with ToxA sensitivity; ToxA-sensitive accessions that were susceptible at the seedling stage, carried adult-plant resistance (APR) (Dinglasan et al., 2017). In a follow-up GWAS, they identified 11 QTL, of which were associated as follows: 5 with seedling resistance, 3 with all-stage resistance, and 3 with APR. Interestingly, the novel APR QTL was effective even in the presence of host sensitivity gene *Tsn1* (Dinglasan et al., 2019).

Genetics and genomics of *P. tritici-repentis*

The genetic studies on isolates of *P. tritici-repentis* from different parts of the world have also been conducted using molecular markers. It was shown in several studies including one from Oklahoma in USA that race 1 was the predominant race in most regions (Ali and Francl, 2003; Friesen et al., 2005; Kader et al., 2022).

The Ptr genome is 40.9 Mb in size and has already been fully sequenced (Moolhuijzen et al., 2018). As much as 98% of the genome has been mapped on 10 or more chromosomes, carrying 13,797 annotated genes (Moolhuijzen et al., 2018). The *Ptr ToxA* is a single copy gene (Ballance et al., 1989; Tomas et al., 1990; Tuori et al., 1995; Ballance et al., 1996; Zhang et al., 1997; Ballance et al., 1998), producing a 19.7 kD protein precursor (Ballance et al., 1996; Ciuffetti et al., 1997). *Ptr ToxB*, on the other hand, is a multi-copy gene (1-3 Kb in length; Martinez et al., 2004) that encodes a 6.6 kDa host selective toxin (Strelkov et al., 1999; Martinez et al., 2004). When the genome of a race 5 Tox-B isolate was sequenced, ten identical *ToxB* gene copies were identified (Moolhuijzen et al., 2020). Multiple *ToxB* gene loci on chromosome 10 were separated by 31-66 kb long segments and exhibited an alternating pattern involving forward and reverse DNA strands. Also, the gene is flanked by transposable elements (Moolhuijzen et al., 2020; Supplementary Figure S4).

B. sorokiniana-wheat pathosystem

B. sorokiniana is a hemi-biotroph, which causes several important wheat diseases, namely SB (Figure 1C), common root rot (CRR), black point and crown rot; these diseases are responsible for significant yield losses in several parts of the world (Gupta et al., 2018a; Gupta et al., 2018b). The correlations between these diseases in wheat seem to be poor and mechanisms for resistance against these diseases seem to differ (Conner, 1990; Al-Sadi, 2021). However, we will restrict our discussion to only spot blotch.

The gene *ToxA* initially reported in *P. nodorum* and *P. tritici-repentis* (Tuori et al., 1995; Friesen et al., 2006), has also been identified in some *B. sorokiniana* isolates from USA (South Central Texas), Australia, India, and Mexico. It was also shown that a *B. sorokiniana* isolate harbouring *ToxA* (dominant alleles of S gene) is more virulent on wheat lines carrying the S gene *Tsn1* (McDonald et al., 2018; Navathe et al., 2020).

NE gene, S gene, and the interaction

A solitary sensitivity gene (*Tsn1*) in the host (wheat) and the corresponding NE gene (*ToxA*) in the pathogen are known for wheat-SB pathosystem. The presence of the *Tsn1* gene is generally but not always associated with susceptibility to the pathogen carrying the *ToxA* gene, as shown in the material surveyed in Australia and India (McDonald et al., 2018; Navathe et al., 2020). It was reported that sometimes an isolate lacking *ToxA* is still highly virulent on cultivars from Australia and India lacking *Tsn1*. In contrast, a cultivar containing *Tsn1* can still be resistant to isolates carrying the *ToxA* gene. These results suggest that there are additional factors in the wheat genome, which control resistance; these factors may include R genes and QTLs controlling resistance to SB (Navathe et al., 2020).

BsToxA differs from *SnToxA* and *PtrToxA*

The gene *BsToxA* is embedded in the 12-kb AT-rich region of the pathogen genome (McDonald et al., 2013; McDonald et al., 2018). Decay near the gene edges has been reported and is attributed to repeat-induced polymorphism (RIP) (Supplementary Figure S5; McDonald et al., 2018). Small indels have also been reported in the gene's promoter region; the size of indel in *BsToxA* (148 bp) differs from that, in *SnToxA* (43 bp) and *PtrToxA* (238 bp) (McDonald et al., 2012; McDonald et al., 2018; also see Supplementary Figure S5). The haplotype organization of *ToxA* genes in three pathogens (*BsToxA*, *PtrToxA* and *SnToxA*) also differed (McDonald et al., 2018). The frequencies of pathogen isolates carrying *BsToxA* and the wheat genotypes carrying *Tsn1* also differ in different parts of the world (Friesen et al., 2018; McDonald et al., 2018; Navathe et al., 2020; Wu et al., 2021).

Sensitivity-related QTLs against *B. sorokiniana* have also been identified in barley, where recessive alleles of *Rcs5* and *Rcs6/Scs2* provided resistance to SB (Gupta et al., 2018a; Leng et al., 2018).

Two additional QTLs (*QSbs-1H-P1* and *QSbs-7H-P1h*) for susceptibility to SB were also identified in barley; of these two QTLs, *QSbs-7H-P1* mapped to the same region as the *Rcs5* gene, but *QSbs-1H-P1* was a novel QTL later reported by Leng et al. (2020).

Genetics of resistance

R genes

Resistance to SB is mainly associated with one or more of the four major R genes (*Sb1-Sb4*) that were identified using classical methods of genetics for Mendelian traits. The genetics of resistance to spot blotch has also been studied, taking the disease as a quantitative trait (reviewed by Gupta et al., 2018a).

QTLs/MTAs

Using interval mapping, ~70 QTLs were identified, which included 14 major QTLs with PVE >20% (Supplementary Table S2). Some of the QTLs were inherited in a Mendelian manner and overlapped the known major Sb genes (Lillemo et al., 2013; Kumar et al., 2015; Lu et al., 2016; Zhang et al., 2020). Such QTLs were later designated as *Sb1* (*QSb.bhu-7DS*) and *Sb2* (*QSb.bhu-5BL*) in two independent studies (Lillemo et al., 2013; Kumar et al., 2015). *Sb1* gene is also associated with *Lr34*, an important gene for leaf rust resistance in wheat (Lillemo et al., 2013). Using GWAS also, ~80 MTAs were identified (Gupta et al., 2018a; Chand et al., 2021; Supplementary Table S3). These interval mapping studies and GWAS were generally conducted only at the adult plant stages.

Resistance at seedling and adult stages

Resistance against SB in wheat has generally been examined only at the adult plant stage. Only in a recent study, resistance at seedling and adult plants stages and its association with biochemical profiling was examined (Mahapatra et al., 2021).

Phylogeography and genomics of *B. sorokiniana*

The phylogeographic pattern of *B. sorokiniana* isolates was examined in a recent study involving 254 isolates from different parts of the world with the goal to elucidate the demographic history. In this study, 162 ITS, 18 GAPDH and 74 TEF-1a gene sequences from *B. sorokiniana* obtained from GenBank were utilized and 40 haplotypes were identified (Sharma et al., 2022). It was inferred that human-mediated dispersal perhaps played a major role in shaping the distribution of *B. sorokiniana*.

Genomic studies of *B. sorokiniana* include generation of a draft genome sequence followed by a refined genome sequence of an Indian isolate, namely *B. sorokiniana* strain BS_112. These genome sequemces were reported in two independent publications by Aggarwal et al. (2019), Aggarwal et al. (2022) from Indian Council of Agriculture Research-Indian Agriculture Research Institute (ICAR-IARI) in India. The genome size was estimated to be 35.64 Mb, with an average G/C content of 50.20%. A total of 10,460 genes were predicted with an average gene density of 250 to 300 genes/Mb, which covers around 98% of predicted genes. The lengths of genes ranged from 50 bp to 8,506 bp with an average length of 435 to 545 bp per gene.

Z. tritici-wheat pathosystem

Z. tritici (syn. *Septoria tritici*, *Mycosphaerella graminicola*) is an important apoplastic fungal pathogen causing STB, which is responsible for major yield losses, sometimes approaching 50% under severe epidemic conditions (Eyal, 1973; Eyal et al., 1987). The fungus has been shown to be a hemibiotroph (Fones and Gurr, 2015), with the following two main phases: (i) the initial symptomless biotrophic latent phase (typically lasting for about 10 to 12 days), during which the hyphae enter the leaves through stomata and colonize the leaf tissues (Kema et al., 1996), and (ii) the later necrotrophic phase (Hehir et al., 2018), when the host tissue begins to die, and the fungus feeds on dead tissue (Keon et al., 2007).

In wheat-*Z. tritici* pathosystem, the host secretes β-1,3-glucanase into the apoplast, which cleaves β-1,3-glucan in the pathogen's cell wall and prevents colonization of the pathogen (Shetty et al., 2009). The major R genes and QTLs for the STB disease have been listed by Brown et al. (2015) and are also available on the Komugi database (https://shigen.nig.ac.jp/wheat/komugi/).

NEs, ZtNIP1/2, MgNLP and ZtSSPs

Hundreds of *Z. tritici* candidate effector genes have been identified through comparative genomics and transcriptomics (Gohari, 2015; Rudd et al., 2015; Kettles et al., 2017; Palma-Guerrero et al., 2017; Plissonneau et al., 2018). Three well characterized LysM effector genes (NE genes), namely *Mg3LysM*, *Mg1LysM* and *Mgx1LysM* have also been identified (Marshall et al., 2011; Tian et al., 2021). Initially, only two LysM effectors, namely Mg1LysM and Mg3LysM, were known. Among these two effectors, Mg3LysM, but not Mg1LysM, was shown to suppress the response of the host immune system at the level of pattern triggered immunity (PTI) (Figure 3).

The host's immune system involves synthesis of chitinases, which destroy fungal cell wall chitin that causes virulence. A third LysM gene, which was initially believed to be a pseudogene, was later shown to encode a LysM effector, named Mgx1LysM, also named Zt3LysM (Zhang, 2022). Later Zt3LysM effector was also shown to contribute to *Z. tritici* virulence, and to protect fungal hyphae against hydrolysis by chitinases of the host. All three LysM effectors display partial functional redundancy (Tian et al., 2021).

In addition to three LysMs as above, *Z. tritici* also secretes many rapidly evolving, small secreted proteins (ZtSSPs), which function as effectors and help the pathogen to colonize plant tissue. In a recent study, while working with the pathogen's SSPs, ZtSSP2 was found to express throughout *Z. tritici* infection phase in wheat, with

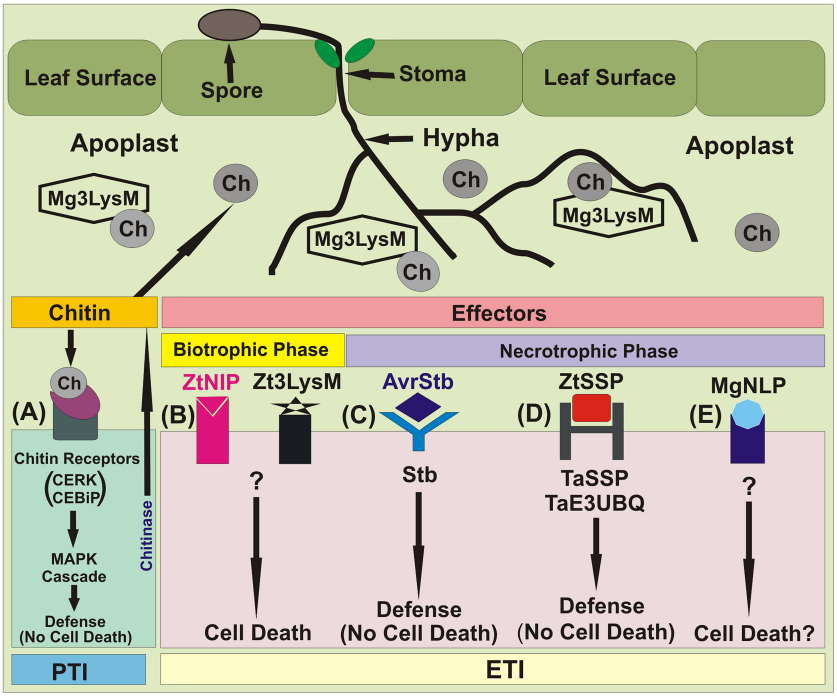

FIGURE 3
Major molecular events during *Z. tritici*–wheat interactions. **(A)** Fungal PAMP chitin is recognized by the host receptors Chitin Elicitor Binding Protein (CEBiP) and Chitin Elicitor Receptor Kinase 1 (CERK1), triggering MAP kinase cascades and immune activation. Multi-functional LysM-domain containing effector Mg3LysM scavenges chitin to suppress immunity and protects fungal hyphae from wheat chitinases. **(B)** 'Necrotrophic' effectors (NEs), Necrosis-Inducing Protein 1/2 (ZtNIP1/2) and and LysM effector (Zt3LysM) induce host cell death. **(C)** *Stb* gene-specified resistance, presumably triggered following recognition of cognate fungal effectors (AvrStb) secreted into the apoplast. This results in arrest of pathogen growth *via* an unknown mechanism that does not involve HR. **(D)** The NEP1-like effector protein MgNLP (unknown *Z. triticini* effector, predicted by bioinformatics analysis) has an unknown function(s) during wheat infection, but triggers cell death in dicots. **(E)** Small secreted proteins (ZtSSPs) of *Z. tritici*, which act as an effector. The TaE3UBQ synthesize in the wheat and interacts with the ZtSSPs resulting inhibition of the growth of *Z. tritici* pathogen.

the highest levels observed early during infection. A study of the interaction between ZtSSP2 and wheat E3 ubiquitin ligase (TaE3UBQ) further confirmed that down-regulation of the gene encoding TaE3UBQ using virus-induced gene silencing increased the susceptibility of wheat to STB, suggesting that ZtSSPs also function as effectors. These results also suggested that the wheat TaE3UBQ plays a role in plant immunity and helps the host to achieve defense against *Z. tritici*.

No S gene for STB

Despite major search and extensive studies in wheat–*Z. tritici* pathosystem, no S gene for compatible interaction between wheat and *Z. tritici* has been discovered so far. Earlier, till a few years ago, the same was true for *B. sorokiniana*, till McDonald et al. (2018) discovered the occurrence of *Tsn1* gene interacting with ToxA of the pathogen *B. sorokiniana*. It is, therefore, possible that a S gene for STB may also be discovered in the future, although it seems unlikely in view of the relatively extensive studies already conducted on wheat–*Z. tritici* pathosystem.

Genetics of resistance

TaSSPs and TaE3UBQ genes for resistance

As in the case of many other pathogens, in addition to LysM effectors, *Z. tritici* also secretes many SSPs, which can block plant defense and permit pathogens to colonize plant tissue (Zhou et al., 2020). It has also been shown that there are also independent TaSSP loci in the host associated with resistance to STB at seedling as well as at the adult plant stages.

In a recent study involving wheat genomics, an SSP-discovery pipeline was developed and 6,998 TaSSPs (each with <250 AA) were identified, which included 141 *Z. tritici* – responsive TaSSPs. A subset of these TaSSPs also had a functional signal peptide, which could interact with *Z. tritici* SSPs. It was also shown that the synthesis of TaSSPs was induced during pathogen attack. In a wheat cultivar named Stigg, two of these TaSSPs, namely *TaSSP6* and *TaSSP7*, when silenced using virus induced gene silencing (VIGS) led to susceptibility, thus confirming the role of TaSSPs in defense against *Z. tritici* (Zhou et al., 2020). ZtSSP2 was also shown to interact with wheat E3 ubiquitin ligase (TaE3UBQ) thus confirming that down-regulation of this wheat E3 ligase using

VIGS increased the susceptibility of wheat to STB. These results suggested that perhaps TaE3UBQ gene also plays a role in providing resistance against *Z. tritici* (Karki et al., 2021).

R (Stb) genes for resistance

In the germplasm of wheat, which included landraces, wild wheat species, and synthetic hexaploid wheat, 22 major R genes (named Stb genes) have been identified and characterised (Saintenac et al., 2021; Supplementary Table S1). Most of these Stb genes are genotype-specific, each providing short-term resistance against only a few *Z. tritici* isolates. Among these 22 Stb genes, *Stb6* and *Stb16q* are the two major genes, which exhibit GFG relationship, each providing broad spectrum resistance against a majority of *Z. tritici* isolates; both these genes have been cloned and characterized. *Stb6* gene was shown to code for a wall-associated kinase (WAK), which represents a subfamily of receptor-like kinases (RLKs), which are involved in GFG of resistance against isolates carrying the matching *AvrStb6* gene (Saintenac et al., 2018). Similarly, the gene *Stb16q* encodes a plasma membrane cysteine-rich receptor like kinase (CRK, also a member of the RLK family of kinases). There is evidence that this gene (*Stb16q)* is derived from *Ae. tauschii via* synthetic wheat and has now become a part of wheat genome. This origin of *Stb16q*, also suggested the importance of wild relatives of wheat in the improvement of disease resistance in wheat cultivars (Saintenac et al., 2021).

AvrStb6–Stb6 interaction provides early defense

An avirulence locus called *AvrStb6* was also identified using diverse *Z. tritici* populations. The corresponding wheat locus *TaStb6* was also shown to be associated with qualitative resistance on multiple wheat cultivars (Kema et al., 2000; Brading et al., 2002; Chartrain et al., 2005c). The *AvrStb6* gene confers a GFG interaction with the *TaStb6* gene of wheat (Zhong et al., 2017; Kema et al., 2018). No direct interaction between the *AvrStb6* and *Stb6* proteins has been reported, and no typical hypersensitive resistance (HR) was noticed during the resistance response, indicating that programmed cell death (PCD) was not the mode of resistance in this case (Friesen and Faris, 2021).

Stb7 is another important R gene, which is recognised by the *Avr3D1* gene of the pathogen, triggering a strong defence response, but without preventing pathogen infection. In an important study, *Avr3D1* gene was found to be present in all 132 strains of *Z. tritici* that were used in the study and provided a strong fitness advantage (Meile et al., 2018). Allelic differences at the locus of *Avr3D1* are responsible for maintaining the gene but still evading recognition by the host harbouring *Stb7* (Friesen and Faris, 2021). The *Avr3D1* gene is upregulated during biotrophic phase but downregulated in the necrotrophic phase, thus permitting early colonisation (Meile et al., 2018).

QTLs/GWAS for resistance

Quantitative resistance against STB is controlled by QTLs, each with a small to moderate effect, thus providing relatively durable resistance. Relative to Stb genes, these QTLs have weak specificity. According to a review by Brown et al. (2015), till 2015, 89 genomic regions carrying quantitative trait loci (QTLs) or meta-QTLs were known. Some of these QTLs have also been mapped at or near Stb genes like *Stb6* and *Stm16q*, which are each present in many genotypes.

Many interval mapping studies involving identification of QTLs have already been conducted (Adhikari et al., 2015; Stadlmeier et al., 2019; Tamburic-Ilincic and Rosa, 2019; Riaz et al., 2020). These studies suggested that host-pathogen interaction is complex and can-not be explained by simple R–Avr interactions. Additive epistatic interactions were also reported for more minor and significant qualitative effects that govern virulence for *Z. tritici* (Jones and Dangl, 2006; Meile et al., 2018; Stewart et al., 2018). The role of necrosis inducing protein 1 (ZtNIP1) of *Z. tritici* has been shown to trigger PCD. This protein is also expressed during 8 and 12 dpi and correlates with necrotic phase symptoms (Ben M'Barek et al., 2015). The 'Necrosis and Ethylene-Inducing Peptide 1' (NEP1) is also involved in causing necrosis (Kettles and Kanyuka, 2016).

A number of GWA studies for identification of MTAs (QTLs) for resistance against STB have also been conducted. The results of four such studies are summarized in Supplementary Table S3.

Seedling vs adult plant resistance

Majority of the 22 Stb genes contribute to STB resistance independently of the plant growth stage, although resistance can also be effective only in seedlings or only in adult plants. In a recent QTL mapping study on seedling and adult plant resistance, Piaskowska et al. (2021) reviewed the literature on this subject and reported identification of a new QTL (*QStb.ihar-2B.4*) for resistance at the seedling stage (PV upto 70.0%), thus proving its utility in breeding programs. In another recent study, Yang et al. (2022) reported identification of new QTLs for seedling resistance and APR, also described as multi-stage resistance (MSR) QTLs. Two of these new QTLs included *QStb.wai.6A.2* for APR and *QStb.wai.7A.2* for MSR.

Genetics and genomics of *Z. tritici*

Population genetics of *Z. tritici* from northern France, Iran, UK, Canada, and Ethiopia was also examined using molecular markers (generally SSR markers). Significant genetic diversity was reported in all these studies; the latest of these studies by Mekonnen et al. (2020) described an average of 2.5 alleles per SSR locus, although in some earlier reports a higher level of diversity was also reported.

The genome of *Z. tritici* carries 21 chromosomes, which include 13 core chromosomes and 8 dispensable/accessory chromosomes (Croll and McDonald, 2012). The genome size varies from 32 to 40 Mb, and the pangenome carries a core set of 9,149 genes (McDonald and Martinez, 1991; Mehrabi et al., 2007; Romdhane, 2011). Genome sequences of *Z. tritici* indicated the following important features (Stukenbrock et al., 2010); (i) The essential and dispensable chromosomes evolved differently and

independently, the former being syntenic, while the latter carrying many structural rearrangements. (ii) The average synonymous substitution rate in dispensable chromosomes is considerably lower than in essential chromosomes, whereas the average non-synonymous substitution rate is three times higher. (iii) As many as 43 candidate genes showed evidence of positive selection, one of these genes encoding a potential pathogen effector protein.

Similarities and differences among four pathosystems

The four pathosystems involved in four leaf spot diseases of wheat discussed above have several similarities and differences. Among similarities, the pathogens involved in these four pathosystems are all fungal pathogens belonging to the phylum Ascomycota, and all are either necrotrophs or hemibiotrophs, there being a thin cryptic line of distinction between necrotrophs and hemibiotrophs (Rajarammohan, 2021). The hemibiotrophic nature of *Z. tritici* has also been questioned (Sanchez-Vallet et al., 2015). Following are some other similarities: (i) occurrence of both GFG relationship involving R genes of the host and Avr genes of the pathogen and IGFG relationship, involving sensitivity (Tsn/Snn) genes of the host and NE genes of the pathogen. In this respect, the pathosystem involved in STB is the only exception. The pathogens also exhibit similar modes of reproduction involving asexual reproduction through conidia and sexual reproduction involving a mating system and producing ascospores. In this respect, *B. sorokiniana* is an exception being an anamoporph (its sexual form being teleomorph, described as *Cochliobolus sativus*). Another major difference includes homothallic nature of sexual forms: *P. nodorum* and *P. tritici-repentis* are homothallic, as against heterothallic nature of *B. sorokiniana* and *Z. tritici*. The availability of sexual reproduction also has a bearing on the diversity of the pathogen, the frequent sexual reproduction leading to higher level of diversity. Other differences include the number of known sensitivity (S) genes, R genes and QTL/QRL in the host and NE/Avr genes in the pathogen, there being nine S genes in the host and eight NE genes in the pathogen for SNB involved in nine interactions, three S genes and three NE genes for TS, only one S gene (*Tsn1*) and one NE gene (*ToxA*) for SB, and there being no known S gene for STB. The pathosystem involving STB also differs for the occurrence of a relatively large number of R genes (22 Stb genes) in the host and ZtSSP genes in the pathogen for virulence and the TaSSP genes for resistance/defence in the host.

Based on the occurrence of R/SSP genes and QTLs/QRLs for resistance and S genes for susceptibility in the wheat genome and the corresponding Avr/NE/SSP genes in the pathogen, one can perhaps try to study the interactions among these genes and plan strategies for developing resistance involving each of the four pathosystems. One such project for SB has already been planned by the authors of this review.

Breeding strategies

S genes, R genes and QTLs for resistance

The sensitivity (S) genes in bread wheat as the host are the most important source of susceptibility involving compatible interaction between the host and the pathogen, so that apparently the loss of these genes or use of their recessive alleles or mutant alleles should be the major sources of resistance. The interactions between S genes of the host and the NE genes of the pathogens for four diseases are summarised earlier in this review. All these cases represent examples of IGFG, where the pathogen can-not cause the disease, unless the host carries the corresponding S gene, which is recognized by the pathogen-derived effector.

There are examples, where a loss-of function mutations in S genes may either occur naturally, or else may be induced through mutagenesis. The most important example of such a loss of function mutations is the loss-of function of the *Mlo* gene in barley and many important cereals (including wheat and rice), vegetables (tomato, pepper, cucumber, and melon), legumes (peas and lentils), fruit trees and shrubs (apples, grapevines, peaches, and strawberries), and flowers (petunia and roses) providing resistance to powdery mildew disease. It is still unknown whether all these Mlo homologs can act as susceptibility genes in their respective hosts (for details of References, see Phd Thesis of Pavan, S. 2011). However, the susceptibility gene *Mlo* differs from the S genes like *Tsn1* involved in diseases like SNB and TS and SB in wheat, although this difference is not apparent. Examples of actual use of recessive alleles or mutants of S genes for breeding wheat cultivars with resistance against a necrotroph are limited. In a recent review involving evaluation of the role of NE-S genes in development of resistant cultivars, it was shown that most of the wheat cultivars in Eastern USA, carried durable quantitative SNB resistance and that *Snn*–NE interactions had very little role in providing resistance (Cowger et al., 2020).

If S genes did not play any major role in resistance breeding, it is apparent that either classical R genes or QTLs must be the source of resistance as shown in several studies cited earlier in this review. These resistant cultivars apparently resulted by an unconscious selection of specific R genes or QTLs. Since R genes and QTLs are now known for each of the four necrotrophs under review, one may plan a strategy, where specific R genes or QTLs may be used for developing resistant cultivars. This should be possible because molecular markers associated with these R genes and QTLs are now available.

QTLs using interval mapping and MTAs associated with QTLs using association mapping have also been discovered for almost all nerotrophs and hemi-biotrophs. A list of known S genes, R genes and QTLs for the four diseases under review are listed in Supplementary Tables S1–S3 suggesting that all the three systems operate in necrotrophs as well as hemibiotrophs and can be exploited for imparting resistance against the corresponding diseases.

The distribution of different S genes in wheat cultivars and that of NE genes in the isolates of the pathogen *P. nodorum* causing SNB has also been examined in multiple locations in different parts of the world. The relative frequencies of S genes in wheat cultivars and those of races with three different Tox genes in the pathogen are summarized in Table 3. In some cases, races could be classified based on NE constitution. For instance, eight races for the TS pathogen have been characterized based on their NE constitution (Table 5). A holistic view of the management of four foliar diseases through genetic tools is also given in Figure 4.

Identification of effectors and effector-assisted breeding

It is widely known now that effectors that are produced by a variety of pathogens, targeing host cells causing diseases. Development of tools for identification and utilization of these effectors has consequently been recognized as a new resistance breeding strategy. During the last two decades, hundreds of these effectors have already been identified and genome-wide catalogues of effectors have become available, such that effectoromics has emerged as a new area for research. Effector-assisted breeding has also been shown to be successful for some crops (for a review, see Vleeshouwers and Oliver, 2014). The question therefore is, whether or not the disease resistance of new cultivars can be accurately predicted from the response to effectors of the input germplasm. Genetic analysis of the response to purified effectors allowed the identification of several wheat genetic loci that correspond to regions conferring susceptibility to the disease.

Methods are also available for the identification of effectors in the secretome using conserved domains, which are common among effector families. One such example is the presence of RXLR (Arg-X-Leu-Arg) motif. Other effector motifs, located in the C-terminal and N-terminal regions, include CRN, LysM, RGD, DELD, EAR, RYWT, Y/F/WXC or CFEM. Rapid identification of effectors using RXLR motif allowed development of a catalogue of effectors for *Phytophthora infestans*, which later enabled identification of R genes in potato, Arabidopsis, and lettuce. More recently, WAxR motif has been found in different effectors in races of *Puccinia striiformis* (yellow rust) and other rust races through screening of secretomes. The tool EffectorP 3.0 has also been utilized for the identification of effectors (Sperschneider and Dodds, 2022).

A high-throughput screening procedure for evaluating wheat genotypes through the infiltration of effectors like ToxA into wheat leaves has also been developed and used in Australia (Tan et al., 2014; Vleeshouwers and Oliver, 2014). This method helped in the quick elimination of *Tsn1* from commercial cultivars. As a result, the area sown with ToxA sensitive cultivars was reduced from 30.4% to 16.9% during the three-year period following the use of this screening system (Vleeshouwers and Oliver, 2014; Cockram et al., 2015). However, the application of this method to other pathogens could be more complicated because all three homoeologues of the susceptibility/sensitivity gene must be eliminated to achieve resistance. In addition, undiscovered effectors that can differ between different regional populations may occur in the pathogen. Notwithstanding this, effector-assisted selection can be an effective way for determining weak and environment-dependent QTL (Vleeshouwers and Oliver, 2014; Downie et al., 2018). Moreover, this method enables to dissect components of quantitative resistance, develop diagnostic markers and fine-map susceptibility genes. Such markers can be converted into Kompetitive Allele-Specific PCR (KASP) markers for the rapid selection of desirable alleles. Thus, using effector-assisted selection for developing diagnostic markers can increase the pace of resistance breeding in wheat against necrotrophs (Cockram et al., 2015; Downie et al., 2018).

Necrotrophic effectors from *P. nodorum* (Pn) and toxic proteins from *Z. tritici* have also been utilized to detect R genes/QTLs in wheat (Lebrun et al., 2016). These effector/toxin proteins were first produced in yeast and purified proteins were obtained. These proteins were then delivered to wheat leaves through syringe infiltration. Disease symptoms were then scored after a few days. Screening of 220 elite French wheat cultivars with Pn ToxA 1 and Pn ToxaA3 allowed the identification of cultivars that were insensitive to the three necrotrophic effectors, and only a few were sensitive, suggesting that breeding for field resistance against Pn during 1960-1980 led to the accumulation of insensitive alleles (recessive alleles). The insensitive genotypes can be tested against Pn isolates producing Tox1 and Tox3 effectors, and insensitivity loci

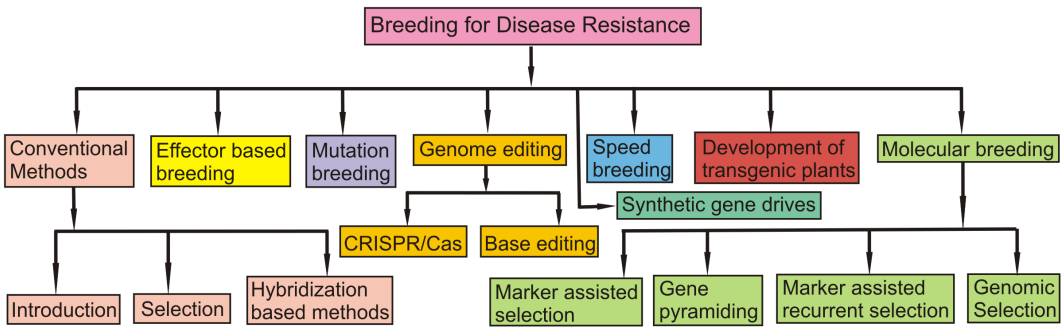

FIGURE 4
A schematic figure which shows a holistic view of the management of four foliar diseases through genetic tools.

can be mapped using GWAS and associated markers can be identified. This type of work will facilitate resistance breeding through MAS (For a review, see Li Q. et al., 2021).

In case of TS in Western Australia also, the elimination of a single effector, PtrToxA and the corresponding S gene *Tsn1*, has a dominating impact in breeding for disease resistance. The availability of ToxA to breeders has had a major impact on cultivar choice and breeding strategies. For *P. nodorum*, three effectors (SnToxA, SnTox1, and SnTox3) have been well characterized. Unlike TS, no one effector has a dominating role. Genetic analysis of various mapping populations and pathogen isolates has shown that different effectors have varying impact, and that epistatic interactions also occur. As a result of these factors, the deployment of these effectors for SNB resistance breeding is complex.

Tan et al. (2015) deleted genes encoding the three effectors in a strain of *P. nodorum* and measured effector activity and disease potential of a triple knockout mutant. The culture filtrate caused necrosis in several cultivars and the strain caused disease, albeit the overall levels are less than in the wild type. Modeling of the field disease resistance scores of cultivars from their reactions to the microbially expressed effectors SnToxA, SnTox1, and SnTox3 is significantly improved by including the response to the triple knockout mutant culture filtrate. This indicated that an additional one or more effectors are secreted into the culture filtrate. It was concluded that the *in vitro*-secreted necrotrophic effectors explain a very large part of the disease response of wheat germplasm and that this method of resistance breeding promises to reduce further the impact of these globally significant diseases. Thus, elimination of genotypes carrying *Tsn1* gene, inducing knockout mutants and introgression of QRLs are the three approaches that can be used for resistance breeding.

QTLs for resistance breeding

For diseases like SNB and TS, generally R genes are not known for breeding. In these cases, resistance is mainly quantitative in nature, governed by QTLs. Most QTLs had a limited effect that was hard to measure precisely and varied significantly from site to site and season to season.

In the late 1920s, A. E. Watkins collected ~7000 landrace cultivars (LCs) of bread wheat (*Triticum aestivum* L.) from 32 different countries around the world. Among these LCs, 826 LCs were viable and could be a valuable source of superior/favorable alleles to enhance disease resistance in wheat. Halder et al. (2019) used a core set of 121 LCs carrying the entire genetic diversity of Watkins collection, and evaluated them for identification of novel sources of resistance against SNB, TS and Fusarium Head Blight (FHB). Response for the three diseases, however, differed in 121 LCs, most of them being either moderately susceptible or susceptible to TS Ptr race 1 (84%) and FHB (96%), whereas a large number of LCs were either resistant or moderately resistant against TS Ptr race 5 (95%) and SNB (54%). Thirteen LCs were identified, which could be a valuable source for multiple resistance to TS Ptr races 1 and 5, and SNB, and another five LCs could be a potential source for FHB resistance.

GWA studies using 118 LCs were also carried out using disease phenotyping score and genotyping data using 8,807 SNPs data leading to identification of 30 significant MTAs (Halder et al., 2019). Ten, five, and five genomic regions were also found to be associated with resistance to TS Ptr race 1, race 5, and SNB, respectively in this study. In addition to *Tsn1*, several novel genomic regions were also identified, which included the following: (i) *Q.Ts1.sdsu-4BS* and *Q.Ts1.sdsu5BS* (TS Ptr race 1) and (ii) *Q.Ts5.sdsu-1BL*, *Q.Ts5.sdsu-2DL*, *Q.Ts5.sdsu-3AL*, and *Q.Ts5.sdsu-6BL* (TS Ptr race 5). These results indicated that these putative genomic regions contain several genes that play an important role in plant defence mechanisms. It was concluded that SNP markers linked to QTLs for SNB and TS resistance along with LCs harboring multiple disease resistance could be useful for future wheat breeding.

From QTLs to genes (R-Genes on 1BS and 5BL)

QTLs controlling response to SNB were initially identified on chromosomes 1BS and 5BL (although QTLs on other chromosomes are also known now). Li D. et al. (2021) conducted a study involving alignment of the genetic map with QTLs on 1BS and 5BS with the reference sequence of wheat. This allowed the identification of R-genes associated with SNB response, although correspondence of R genes with QTL was not shown. Alignment of QTL intervals allowed identification of significant genome rearrangements on 1BS between parents of the DH population (EGA Blanco, Millewa) and the reference sequence of Chinese Spring with subtle rearrangements on 5BL. Nevertheless, annotation of genomic intervals in the reference sequence allowed identification and mapping of 13 R-genes on 1BS and 12 R-genes on 5BL. R-genes discriminated co-located QTL on 1BS into following two distinct but linked loci, both associated with SNB resistance but in one environment only: (i) NRC1a and TFIID mapped in one QTL on 1BS, whereas (ii) RGA and *Snn1* mapped to QTL on 1BS. Similarly, *Tsn1* and *WK35* were mapped in one QTL on 5BL, with NETWORKED 1A and resistance gene analogs (RGA) genes mapped to the linked QTL interval. This study provided new insights on possible biochemical, cellular, and molecular mechanisms responding to SNB infection in different environments and also addressed limitations of using the reference sequence to identify the full complement of functional R-genes in modern varieties.

Multiple disease resistance

Since genotypes with multiple resistance and association among more than one disease have now been reported, it is also possible to plan a breeding programme for transfer of resistance for more than one disease using a single donor, as recommended by Gurung et al. (2014).

Possible molecular breeding approaches

As shown above, resistance against leaf spot diseases caused by necrotrophs in wheat is controlled by three different systems including S genes, R genes and QTLs. The genes belonging to all these three categories are now known for at least three of the four diseases (except for STB, for which S genes are not known; instead SSP genes are known). Markers associated with all these three systems are also known now. The number of markers for desirable genes will certainly be large (at least >20), thus making simple backcross or forward breeding approaches not suitable. Therefore, we recommend the use of either marker assisted recurrent selection (MARS) or QTL-based genomic selection (GS). Other possible molecular approaches include the use of genome editing, base/prime editing, and gene drive. The utility of these molecular approaches has already been demonstrated; these strategies are briefly described in this section.

Marker-assisted recurrent selection

MARS involving more than 20 markers and two or more than two cycles of recombination may be used as a suitable breeding strategy. Such an approach has already been successfully utilized by Rahman et al. (2020) for disease resistance involving crown rot disease in wheat. In this study, 22 markers could be recombined using two recombination cycles.

GS using QTLs and MTAs

In two recent studies, one each in maize and wheat, it has been shown that the prediction accuracy of genomic selection can be improved by using only those markers, which are known to be associated with QTLs or MTAs (Liu et al., 2019; Zaim et al., 2020). This strategy may be used for improvement of resistance against the four pathogens under review. Since we already have a large number of disease-associated markers, a selected set of polymorphic markers may be used in training population for estimation of breeding values, which may then be used for selecting desirable plants in the segregating breeding population.

Genome/base editing and synthetic gene drives

Genome editing, base editing and gene drives are three new approaches, which can also be used for resistance breeding. Several examples are available, where susceptibility genes in the host have been modified using CRISPR/Cas technology (for a review, see Borrelli et al., 2018; Tyagi et al., 2020; Paul et al., 2021; Negi et al., 2022). In wheat also, resistance against powdery mildew has been successfully achieved using this technology (Wang et al., 2014; Zhang et al., 2017). Base editing and prime editing are two other more efficient recent approaches, which have already been used for crop improvement (for a review, see Azameti and Dauda, 2021) and will certainly be used in future for disease resistance in wheat.

More recently, synthetic gene drives are being tried for creating bias in the inheritance of a particular DNA sequence, such that it can be used for increasing the frequency of genes/alleles that may spread and reduce the pathogen populations with virulence genes causing the diseases. The introduced gene/allele puts the pathogen at a disadvantage, and can be made to spread the altered desired trait throughout the population. Many such systems occur naturally, and will facilitate the development of new gene drives using synthetic biology techniques. For resistance breeding, synthetic gene drives may be used to modify either the susceptibility gene of the host or the virulence gene of the pathogen, so that either the host will lose susceptibility or the pathogen will lose virulence. If synthetically modified populations of the pathogen are released in wheat fields, this will soon spread in the pathogen population, and render the wheat cultivar resistant.

Disease management

In integrated management, resistant cultivars may be used along with cultural practices and fungicide application. Since infected seed and straw serve as the primary source of inoculum, seed treatment, crop rotation, and residue management may also prove useful in avoiding an epidemic in disease-prone areas. Also, since SNB infection causes the greatest yield losses at the adult plant stage, resistance screening may also be useful (Francki, 2013).

Conclusions and future perspectives

Disease resistance in plants, including wheat, can be race-specific or race-nonspecific, the latter sometimes also described as adult plant resistance. Both these types of disease resistance are generally controlled by R genes, which have been the subjects of detailed studies. The plant immunity involving these R genes has also been subjected to detailed studies at the molecular level, developing a zig-zag model involving PTI, effector triggered susceptibility (ETS) and effector triggered immunity (ETI) (Jones and Dangl, 2006). During the last >25 years, >300 R genes and several Avr genes have been cloned, thus providing an opportunity to study the interaction between the products of R genes of the host and the corresponding Avr genes in the pathogen at the molecular level (for a review, see Kourelis and van der Hoorn, 2018). However, studies on Avr genes have yet to be undertaken on a war scale to become comparable to those on R genes. In most examples of R genes, the GFG relationship proposed by Flor (1942), Flor (1956) holds good, although gene-for-gene models involving multiple genes have also been suggested (Sasaki, 2000; Fenton et al., 2009). However, disease resistance controlled by the absence (or presence of recessive alleles) of susceptibility/sensitivity genes like SWEET genes for bacterial blight (BB) in rice (Gupta, 2020) and S genes like *Tsn1* in wheat follow an inverse IGFG relationship with corresponding NE genes in the pathogen (Navathe et al., 2020).

This is an area of research on disease resistance, which has witnessed immense activity in recent years. As a result, several S genes in wheat for three of the four important diseases covered in this review, namely SNB, TS and SB and the corresponding NE genes in the form of NE producing genes or *Tox* genes) in the pathogens have been identified. Some of these genes (both S genes in the host and NE genes in the pathogen) have also been cloned and characterized, generating information about the molecular mechanism involved in plant immunity involving these pathosystems. In summary, perhaps only about a dozen NE genes and an equal number of corresponding S genes are now known. In future, more S genes in wheat and other crops and the corresponding NE Tox genes in the pathogens exhibiting IGFG may be discovered; it will be interesting to find out if S genes occur for STB also, although there is little chance, because despite detailed studies already undertaken, no S genes for STB have been discovered so far. It will, therefore, be interesting to find out the reasons for the absence of S gene and the implications of the presence of as many as 22 R (Stb) genes and many SSP genes for STB, both in the host and the pathogen.

We also believe and hope that the subject dealing with S genes following the IGFG model will receive more attention in future. For instance, although much is known about the pathosystems dealing with SNB and TS, the information about IGFG dealing with SB has just started being generated and hardly any work is available on pathosystems involving NEs causing the following diseases: (i) FHB caused by *F. graminearum*; (ii) eyespot caused by *Tapesia yallundae* (syn *Pseudocercosporella herpotrichoides*, W-type anamorph); (iii) STB caused by *Z. tritici* and their corresponding S related gene in the host. We also believe that for diseases like SB caused by hemibiotrophs, GFG and IGFG may operate in parallel. Further studies involving the scoring of allelic states of genes involved in GFG and IGFG models need to be undertaken. In a recent study on spot blotch involving analysis of *Tsn1-ToxA* system following IGFG, we discovered that the wheat genotypes carrying recessive allele of S gene (*tsn1*) could also be susceptible and vice versa. Variation in the SB caused by *ToxA* positive isolates was also noticed (Navathe et al., 2020). This suggests that the relationship between a S gene in the host and the corresponding NE genes in the pathogen is not so simple, offering scope for further detailed investigations.

Another interesting area of future research is to examine interactions and cooperation between dominant R genes, recessive alleles of S genes and QTLs for providing disease resistance. One such study for SB has been planned by the authors of the present review, with the hope that useful information will be generated through such a study, which should prove useful in planning future strategies for breeding cultivars that would be resistant against the four-leaf spot diseases covered in the present review. Use of gene editing and base editing involving CRISPR/Cas for disease resistance will also certainly receive more attention in future.

Author contributions

The subject of this review was conceived by PKG; All authors PKG, NKV, SS and AKJ contributed equally to this review.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpls.2023.1023824/full#supplementary-material

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