Sensitivity genes in wheat and corresponding effector genes in necrotrophs exhibiting inverse gene-for-gene relationship

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Abstract

In wheat, genes for resistance (R) as well as susceptibility (S) are now known for several diseases. The S genes also include sensitivity genes like Tsn1 in wheat. R genes follow a gene-for-gene (GFG) relationship and generally involve biotrophs and S genes particularly sensitivity genes, follow an inverse gene-for-gene relationship (IGFG), generally involving necrotroph or hemi-biotroph pathogens. The toxin (virulence factor) genes of the pathogen and the corresponding sensitivity genes have been described in some detail for the following three pathogens: (i) Paragonospora nodorum (causing Septoria nodorum blotch or SNB); (ii) Pyrenophora tritici-repentis (tan spot) and (iii) Bipolaris sorokiniana (spot blotch). These and some other pathogens produce several necrotrophic effectors (NEs), which interact directly or indirectly with the products of S genes in the host and produce disease symptoms like necrosis and/or chlorosis. In this article we present a critical review of all the relevant information about the interactions between NEs of the above three pathogens and the corresponding S genes in wheat. The gaps in knowledge and possibilities for future research are also discussed.

Introduction

Wheat (Triticum aestivum L.) is the third most important staple food crop worldwide (first two being maize and rice), sometimes also consumed as animal feed (Mauseth 2014). Among cereals, wheat has been estimated to occupy maximum cultivated land area, which was 215.2 million hectares in 2019, giving 22% of the total cereal grain production (FAO 2020). The total global production of wheat grain was 732 million tonnes during 2018-19 (FAO 2019) and ~763 million tonnes in 2019-20 (FAO Release May 7, 2020); in terms of global cereal production, this production level is next to only maize (FAO 2019).

Wheat production is significantly reduced by various biotic and abiotic stresses. The biotic stresses mainly include pathogens like fungi, viruses, bacteria, nematodes, etc., which cause a variety of diseases Among these pathogens, fungal pathogens are alone responsible for 15-20% losses in yield (Figueroa et al. 2018). The fungal diseases include rusts, mildew, blast, bunts, blights, etc. Among these diseases, the diseases caused by necrotrophs and hemi-biotrophs include Septoria nodorum blotch or SNB (Paragonospora nodorum), tan spot (Pyrenophora tritici-repentis) and spot blotch (Bipolaris sorokiniana) (Fig. 1). A summary of necrotrophs and hemi-biotrophs causing different diseases in wheat is presented in Table 1.

The genetics of disease resistance has been worked out in some detail, not only for diseases caused by biotrophs, but also for those caused by necrotrophs and hemi-biotrophs. In case of biotrophs, mainly R genes/QTLs in the host provide resistance, but in case of some necrotrophs, the disease is facilitated by the presence of one or more sensitivity (S) genes in the host, and corresponding virulence genes in the pathogen. The necrotrophic effectors (NEs) encoded by the virulence genes of the pathogen interact directly or indirectly with the product of the dominant sensitivity genes of the host leading to necrosis and/or chlorosis (Tan et al. 2010; Oliver et al. 2012). The biotrophs cause cell death leading to hypersensitive reaction (HR) that is responsible for resistance, due to non-availability of living tissue as food and thereby restricting the pathogen multiplication and growth in the plant (Faris et al. 2010; Liu et al. 2012). The necrotrophs, on the other hand, feed on the dead cells leading to the so-called NE-triggered susceptibility, so that resistance is generally (but not always) achieved through elimination of these dominant sensitivity genes or using their recessive resistant alleles. The differences between biotrophs and necrotrophs are listed in Table 2.

It has been shown that a gene-for-gene (GFG) relationship proposed by Flor (1942) holds good between a R gene of the host and a matching Avr gene in the pathogen, because in the absence of a matching Avr gene in the prevalent race of the pathogen, R gene can not function and provide resistance (Fig. 2a). In contrast, an inverse gene-for-gene (IGFG) relationship holds good for sensitivity genes in case of necrotrophs, because a virulence gene does not provide a
compatible interaction in the absence of a corresponding sensitive gene in the host (Fig. 2b; McDonald et al. 2018; Navathe et al. 2020).

In addition to R genes in case of biotrophs and S genes in case of necrotrophs, quantitative trait loci (QTLs) have also been identified for disease resistance against all pathogens including biotrophs, necrotrophs and hemi-biotrophs. These QTLs have been identified using interval mapping involving different types of mapping populations. Association panels for genome-wide association studies have also been used for identification of marker-trait associations (MTAs; Ruud et al. 2019; Francki et al. 2020). In some cases, a QTL identified through interval mapping may also overlap a resistance R gene as shown in case of Sb1-4 for resistance against B. sorokinina (Gupta et al. 2018). The relative roles of QTLs/R genes and the sensitivity genes has also been assessed and it was shown that QTLs/R genes are the major source of resistance against both biotrophs and necrotrophs, while individual sensitivity genes do not play a major role, particularly for the disease SNB (Cowger et al. 2020), although all sensitivity genes together might play a significant role.

The present review is intended to provide an overview of the dual system of resistance against necrotrophs in wheat, involving GFG for R genes and IGFG involving sensitivity genes, with major emphasis on IGFG. While doing so, we recognize that the work involving GFG is widely known and regularly reviewed. Therefore, in this review, we include a relatively detailed but only a brief account of available information on three pathosystems involving necrotrophs and hemi-biotrophs, where the disease is caused by an interaction between NEs encoded by virulence genes of the pathogens and the proteins encoded by the corresponding sensitivity genes in the host. A relatively detailed account is presented for two diseases, namely SNB and tan spot, where extensive work has been undertaken and a brief account of spot blotch, where only limited literature is available. The review may prove useful for both pathologists and geneticists/plant breeders.

**Sensitivity/susceptibility genes in wheat (e.g., ToxA-Tsn1 system)**

The identification of sensitivity genes in wheat (including Tsn1) as above, and the susceptibility (S) SWEET genes in rice and several other crops created a new area of plant immunity research, which is attracting increased attention of both breeders and pathologists world-over. SWEET genes are not covered in this review, but a summary on SWEET genes and disease resistance is available in a brief article recently published (Gupta 2020). Sensitivity genes, which are independent of dominant R genes, have been identified in wheat for several diseases. These genes are generally dominant in nature and are utilized by the pathogens for a compatible interaction. Recessive alleles or ‘loss of function’ alleles of these sensitivity genes impart resistance to the host. In the literature, the words sensitivity and susceptibility have sometimes been used interchangeably. For instance, the sensitivity gene Tsn1 located on wheat chromosome arm 5BL has sometimes been described as susceptibility gene (Friesen et al. 2008). Sensitivity, however, should not be confused with susceptibility, since sensitivity refers to response of the host against a specific NE, while susceptibility means compatible interaction between the host and the pathogen.

The major sensitivity genes in wheat include Tsn1, Tsc1, Tsc2 and seven Snn genes (Snn1 to Snn7), which render the host susceptible to a few diseases including SNB, tan spot and spot blotch (Effertz 2002; Friesen and Faris 2004; Faris et al. 2013; Francki 2013; Gao et al. 2015; Navathe et al. 2020). Therefore, resistance against diseases caused by sensitivity genes can be achieved either through elimination of the dominant sensitivity genes or replacing them by alternative recessive alleles. This situation provides for yet another system of disease resistance in addition to the two other systems of disease resistance available for diseases as above. Among these two other systems, one involves dominant R genes and the other involves quantitative resistance loci (QRLs) These two additional classes of genes may not be exclusive, as demonstrated through Mendelization of some QTLs (Kumar et al. 2015). The genes from the above three systems can be pyramided for developing durable and broad-spectrum resistance against diseases (Engler et al. 2005; Navathe et al. 2020).
As many as ~60 genes encoding NEs have been identified for different pathosystems involving necrotrophs (Sperschneider et al. 2018). At least 13 of these NEs in three different pathosystems (8 for SNB, 4 for tan spot and 1 for spot blotch) involving wheat as the host have already been identified and subjected to detailed studies (Friesen et al. 2006, 2008, 2009, 2012; Chu et al. 2010; Faris et al. 2011; Waters et al. 2011; Abeyesekara et al. 2012; Crook et al. 2012; Liu et al. 2012; Oliver et al. 2012; Shi et al. 2015; McDonald and Solomon 2018). Horizontal transfer of genes (HGT) encoding NEs from *P. nodorum* to other pathogens has also been demonstrated (Friesen et al. 2006; McDonald et al. 2019).

For wheat, NEs and sensitivity genes involved in the three different pathosystems have been studied in some detail (Fig. 3). The chemical nature of several NEs has also been worked out showing that all NEs are proteinaceous in nature, except ToxC associated with tan spot (*P. tritici*-repentis), which is a polar non-ionic metabolite with low molecular weight, although not fully characterized so far (Effertz et al. 2002; Wegulo 2011). Details of major host-pathogen interactions involving the three pathogens included in this review are summarized in Table 3.

The basic outline of the mechanism involved in compatible/incompatible interactions involving IGFG is now known. Details for individual pathosystems have also been worked out in some cases. The degree of correlation between the level of NE proteins and expression of related sensitivity genes has also been worked out using a number of wheat cultivars; these correlations were also related with field resistance (Tan et al. 2014). In case of tan spot and spot blotch, it has been shown that a clear dominance of interaction between individual NE with corresponding sensitivity gene can cause a disease (e.g., ToxA/ *Tsn1*; Moffat et al. 2014). It has also been reported that all current cultivars grown in Western Australia are sensitive to at least one of the following three SNB NEs: SnToxA, SnTox1 and SnTox3 (Tan et al. 2015). IGFG relationship between sensitivity gene *Tsn1* of the host and *ToxA* gene in *B. sorokiniana* has also been demonstrated recently in several countries including Southern USA, Australia, India, and Mexico (Friesen et al. 2018; McDonald et al. 2018; Navathe et al. 2020; Wu et al. 2020).

**Pathosystems involving sensitivity genes in wheat**

The available literature on plant immunity largely deals with resistance R genes, such that thousands of R genes are now known for resistance against many diseases in plants. For instance, ~80 *Lr* genes are now known in wheat for resistance against leaf rust alone. With the availability of whole genome sequences for majority of crop plants (including wheat), we now also know that the number of R genes in a crop like wheat can be as large as >1300 (GrainGenes; [https://wheat.pw.usda.gov/GG3/](https://wheat.pw.usda.gov/GG3/)).

A number of sensitivity genes have been identified for several diseases caused by necrotrophs or hemi-biotrophs. Sometimes, the same sensitivity gene may function not only for different isolates of the same pathogen, but also for more than one disease. For instance, *Tsn1* functions as a sensitivity gene for at least three diseases, namely SNB, tan spot and spot blotch (Faris et al. 2010; McDonald et al. 2018; Navathe et al. 2020). A summary of interactions involving the above three necrotrophs/hemi-biotrophs causing diseases in wheat is provided in Table 3. However, sensitivity genes in wheat have been identified only for three of the ten necrotrophs/hemibiotrophs listed in Table 1. In future, sensitivity genes may also be discovered for other diseases caused by necrotrophs/hemibiotrophs, including Fusarium head blight (FHB), which is one of the most important diseases of wheat causing major losses in yield in wheat (Hales et al. 2020). For necrotrophs, where wheat sensitivity genes are already known, additional sensitivity genes may also be discovered in future.

In this section of the review, we first describe genes encoding different NEs and the corresponding sensitivity genes for each of the three pathosystems. The recessive alleles of these sensitivity genes provide resistance, but there are also R genes and QTLs which function independently of the sensitivity genes, so that the recessive alleles of sensitivity genes can be deployed along with R genes and QTLs in order to achieve improved resistance against diseases like SNB, tan spot, and spot blotch.
Effector-assisted breeding is also being recommended for disease resistance. This has become possible due to the availability of genome-wide catalogue of effectors (effectomics) for various pathogens, which can be utilized either through MAS-assisted classical resistance breeding or through transgenic approach. The available literature on effector-assisted breeding has been reviewed by Vleeshouwers and Oliver (2014). The details of sensitivity genes, which can be utilized for future wheat breeding, along with R genes and QTLs for resistance against different diseases are listed in Table 4.

**Parastagonophora nodorum-wheat pathosystem**

SNB occurs in warm and humid areas of the world causing yield losses of up to 30% (Bhathal et al. 2003); the disease includes both leaf blotch and glume blotch (Fig. 1a). Currently, no cultivar is available with complete resistance/immune reaction to SNB. Therefore, tillage, crop rotation and chemical control are still utilised as disease management practices for control of this disease. *P. nodorum*-wheat pathosystem is also the most extensively studied pathosystem involving necrotrophs, such that *P. nodorum* is also used as a model necrotroph for the study of host-pathogen interactions involving sensitivity genes.

*P. nodorum* genome is 37 Mb in size with 23 chromosomes. Whole genome sequencing of pathogen has been undertaken for a number of isolates of this pathogen, which include the following: (i) one isolate (SN15) (Hane et al. 2007); (ii) three other isolates, (SN4, SN2000, SN79-1087) (Richards et al. 2018) and (iii) 197 isolates collected from spring, durum, and winter wheat producing regions of USA. The number of genes in this pathogen was initially reported to be 10,762 (Hane et al. 2007), but later revised in two different studies to be 13,569 (Syme et al. 2013, 2016) and 13,379 (Richards et al. 2018). A pan-genome for *Parastagonospora spp* was also developed using genome sequences of 33 different isolates (including 21 isolates of *P. nodorum*), showing wide range of structural variations (SVs), thus providing a resource for the prediction of novel NEs (Syme et al. 2018). It was also shown that different isolates carry genes encoding different NEs. Isolates like SN79-1087 with no known gene encoding NE have also been reported (Richards et al. 2018).

In a more extensive recent study, Richards et al. (2019) conducted whole genome sequencing for 119 isolates to examine effector diversity and to identify genomic regions that are subject to selection pressure specific to populations defined by geographical regions.

**NE genes, sensitivity genes and interactions:** Following nine interactions involving nine wheat sensitivity genes and eight *P. nodorum* NEs are known (Haugrud et al. 2019). (i) *Tsn1*-SnToxA (Friesen et al. 2006, 2009; Liu et al. 2006; Faris and Friesen 2009; Zhang et al. 2009; Faris et al. 2010, 2011), (ii) *Snn1*-SnTox1 (Liu et al. 2004a, b, Liu et al. 2012; Reddy et al. 2008; Shi et al. 2016b), (iii) *Snn2*-SnTox2 (Friesen et al. 2007, 2009; Zhang et al. 2009), (iv) *Snn3*-B1-SnTox3 (Friesen et al. 2008; Liu et al. 2009; Shi et al. 2016a), (v) *Snn3*-D1-SnTox3 (Zhang et al. 2011), (vi) *Snn4*-SnTox4 (Abeysekara et al. 2009, 2012), (vii) *Snn5*-SnTox5 (Friesen et al. 2012), (viii) *Snn6*-SnTox6 (Gao et al. 2015) and (ix) *Snn7*-SnTox7 (Shi et al. 2015). Among these nine interactions, the first, second and fourth (*Tsn1*-SnToxA, *Snn1*-SnTox1, *Snn3*-B1-SnTox3) have been subjected to relatively detailed studies, because the sensitivity genes and the NE genes involved in these interactions have all been cloned and characterized. A possibility of another unconfirmed interaction (*Snn8*-SnTox8) has also been suggested (Faris et al. 2008).

The interaction of each NE with the product of a specific sensitivity gene, as above, leads to programmed cell death, which allows the corresponding necrotroph to gain nutrients, sporulate and cause the disease (See et al. 2019). The interactions have also been shown to be additive in nature, sometimes also exhibiting epistatic interactions, particularly in the following three interactions: (i) *Snn2*-SnTox2 (Friesen et al. 2007), (ii) *Snn3*-SnTox3 (Friesen et al. 2008; Phan et al. 2016) and (iii) *Snn5*-SnTox5 (Friesen et al. 2012). However, the role of epistatic interactions in the expression of these interactions is rather limited (Phan et al. 2016).
It has also been shown that, several QTLs also occur in addition to major sensitivity genes. However, the absence of one or more sensitivity genes or presence of their recessive alleles provide disease resistance. The importance of the absence of sensitivity gene in providing resistance relative to that due presence of R genes and QTLs has been shown to be rather limited (see review by Cowger et al. 2020; also see later in this review).

**Distribution of NE genes in the pathogen.** The distribution of each of the eight NE genes and nine sensitivity genes differs in different wheat growing regions of the world, although data is available mainly from USA, Europe (including UK and Norway) and Australia. Distribution of three NE genes, namely SnToxA, SnTox1 and SnTox3 has been examined in several studies. Some details of the distribution reported in these studies are summarized in Table 5, which suggest that the gene SnTox1 is the predominant gene, which is reported to occur in 95.4% of natural populations in USA (as above) and 84% isolates worldwide; these frequencies are not very different from the frequencies of the occurrence of the corresponding sensitivity gene Snn1 gene in wheat, which has also been reported to be 85% (McDonald et al. 2013).

The predominance of SnTox1 as above, was not universal, as apparent from the following two reports on SnToxA, where isolates were screened for NE genes. (i) Among Australian isolates, 71 (97%) of 73 isolates (collected from only one field) carried SnToxA (Stukenbrock and McDonald 2007; McDonald et al. 2013). This was attributed to the biased sample from a single field and may not represent the situation in whole of Australia (Oliver et al. 2009). (ii) In a diverse sample of 165 P. nodorum isolates, from Norway and 9 isolates from other countries, SnToxA was found to occur with high frequency in Norwegian P. nodorum isolates relative to other parts of Europe, suggesting that SnToxA gene is the major virulence factor in Norway (Lin et al. 2020). The disease reaction in interaction Snn1-SnTox1 has been observed to range from 0 to 58% and seems to depend on both, the genetic background of the host and that of the pathogen (Liu et al. 2004a; Chu et al. 2010; Phan et al. 2016).

**Distribution of sensitivity genes in the host** Surveys were also conducted for distribution of different sensitivity genes in wheat cultivars. Some of the available data for distribution of three major sensitivity genes is summarized in Table 6. These results suggest that Snn1 is not an important sensitivity gene for US wheat programs; instead, Tsn1 is important for hard winter wheats only, while Snn3 is important for both soft and hard wheats.

Sensitivity of individual resistant and susceptible cultivars against specific NEs was also examined. For this purpose, NEs were obtained from transgenic E. coli and Pichia pastoris. (i) In a study conducted in USA, 25 susceptible wheat cultivars (many from SE USA) and a resistant cultivar (NC-Neuse) were tested against different NEs isolated from 37 isolates from different regions of SE USA. It was found that all susceptible cultivars were sensitive to at least one NE, and that the resistant cultivar (NC-Neuse) was sensitive to none. Among susceptible cultivars, 32% contained sensitivity gene Tsn1 and 64% contained sensitivity gene Snn3. None was sensitive to SnTox1. (ii) In a panel of 480 northwest European varieties (~330 were from the U.K.), sensitivity to SnTox3 (presence of Snn3) was higher than that to SnTox1, while sensitivity to SnToxA (presence of Tsn1) was rare (Downie et al. 2018). (iii) In 157 Scandinavian spring wheats (including Norwegian, Swedish and CIMMYT lines), sensitivity to SnToxA (presence of Snn1) was present in 45% wheats (Ruud et al. 2018).

**Use of multiple sensitivity genes.** Wheat genotypes with multiple sensitivity genes were also identified. These genotypes produce significantly higher disease reactions relative to those harbouring only a single sensitivity gene (Friesen et al. 2007). Such studies with multiple sensitivity genes need to be conducted for characterization of wheat cultivars in different parts of the world, so that we know the identity of sensitivity genes present in wheat cultivars. Results of these studies can be used to discard out parents harbouring sensitivity genes when breeding for resistance to SNB.

**Use of multiple isolates.** In a recent study, multiple isolates of the pathogen were used to evaluate the effects of the following three host gene-NE interactions individually and in various combinations: (i) Tsn1-SnToxA, (ii) Snn1-SnTox1, and (iii) Snn3-B1-SnTox3. These results suggested that the IGFG interactions leading to ‘NE-triggered susceptibility’ in wheat-P.
*nodorum* pathosystem vary in their effects depending on the genetic backgrounds of the pathogen and the host, and that the interplay among the interactions is complex and intricately regulated (Mebrate and Cooke 2001).

Some information is also available regarding distribution of sensitivity genes in wheat genotypes used for cultivation in UK and Europe. It was shown that the host may carry one or more sensitivity genes along with R genes, the latter with a major effect. In wheat, one or more sensitivity genes (present along with R genes and QTLs) produce disease phenotype ranging in severity from 22 to 95% (Sharma 2016). *SnToxA* gene seems to resemble *PtrToxA* gene in its interaction with the sensitivity gene *Tsn1*, which is involved in all the three diseases including tan spot, SNB and spot blotch (Faris et al. 1996; Haen et al. 2004; Liu et al. 2006).

**Transcription factors regulating sensitivity gene-NE interactions.** Three interactions mentioned above, namely *Tsn1*-SnToxA, *Snn1*-SnTox1 and *Snn3-B1*-SnTox3 have also been shown, each to be positively regulated by the transcription factor Zn2Cys6 of PnPf2 zinc finger family (Tan et al. 2019). Another transcription factor is SnStudA that regulates the central carbon metabolism, mycotoxin production and effector gene expression in *Snn3-B1*-SnTox3 interaction (IpCho et al. 2010). The target of this transcription factor is WMGGVCCGAA motif and the associated genes were shown to be involved in downregulation for plant cell wall degradation and proteolysis; the genes associated with redox control, nutrient and ion transport were also up-regulated. TFs of the PnPf2 zinc finger family were also shown to regulate positively as many as 12 genes that encode effector-like proteins (Jones et al. 2019).

**High resolution mapping and cloning of sensitivity genes.** Following are some details about these three sensitivity genes, where the description for *Tsn1* will apply for all the three pathogens:

(i) Sensitivity gene *Tsn1*. The *Tsn1* gene is located on chromosome 5BL and is 10,581 bp in length with 4,473 bp covering eight exons, a 161 bp long 5’ UTR and a 391 bp long 3’ UTR (Fig. 4). The predicted protein is 1,490 amino acids long consisting of of N-terminal serine/threonine protein kinase (S/TPK) domain with ATP binding site, substrate binding site and an activation site and a C-terminal NB-LRR domain, which indicates similarity to the common product of R genes (Friesen et al. 2006; Faris et al. 2010). All domains of *Tsn1* are required for ToxA sensitivity (Manning and Ciuffetti 2005).

*Tsn1-ToxA* interaction is common among all the three pathosystems involving wheat with SNB, tan spot and spot blotch (Liu et al. 2006). It has been shown that at the transcription level, ToxA can activate wall associated kinases (WAKs) as a defense response (He et al. 1998). It is also possible that ToxA may utilise WAKs for recognition of the product of *Tsn1* (Pandelova et al. 2009). The potential targets of ToxA is the binding protein, ToxABP1 with vitronectin-like sequence (Manning et al. 2007).

(ii) Sensitivity gene *Snn1*. This gene is located on chromosome arm 1BS and was earlier fine-mapped using F2 population derived from a cross between Chinese Spring (CS) and its disomic substitution line carrying 1B chromosome from either *T. dicocoides* (Reddy et al. 2008) or from wheat cultivar Hope, leading to cloning (Shi et al. 2016b). Later, it was also fine mapped as a QTL through QTL interval mapping using a Multi-parent Advanced Generation InterCross (MAGIC) population involving eight or 1 (Cockram et al. 2019). The gene *Snn1* was shown to encode a member of the wall-associated kinase (WAK) class of plant receptor kinases and was therefore referred to as *TaWAK*. The gene is 3,045 base pairs (bp) long with three exons and a coding sequence of 2,145 bp with 5’ and 3’ untranslated regions (UTRs) of 164 and 102 bp, respectively. The deduced amino acid sequence indicated that the protein contains conserved wall-associated receptor kinase galacturonan binding (GUB_WAK), epidermal growth factor–calciubindin (EGF_CA), transmembrane, and serine/threonine protein ki-nase (S/TPK) domains, with the S/TPK domain predicted to be intracellular and the GUB_WAK and EGF_CA binding domains predicted to be extracellular.

*Snn1* gene encodes a protein with a structure like that of PRRs (pattern recognition receptors), which recognize pathogen-associated molecular patterns (PAMPs). The PRR like protein encoded by *Snn1* often resembles a wall-associated kinase
(WAK) protein with domains like PK transmembrane, galacturonan binding and calcium binding domains; this allows early recognition of SnTox1 effector protein and upregulate the PTI pathway (Haugrud et al. 2019; Faris et al. 2019).

(iii) Sensitivity genes Snn3-B1 and Snn3-D1. Snn1-B1 gene was fine-mapped on the chromosome arm 5BS initially using two F2 populations derived from crosses involving SnTox3 sensitive line Sumai3 and two different insensitive lines (Shi et al. 2015) and later using GWAS and composite interval mapping involving a MAGIC population derived from 8 founder parents (Downie et al. 2018). The cloning of Snn3-D1 (located on 5DS) was reported by Faris et al. (2019) at the 1st International Wheat Congress, held at Saskatoon in July 2019. The gene Snn3-D1 differed from the two other cloned sensitivity genes (Tsn1 and Snn1). Like the other two cloned sensitivity genes (Tsn1 and Snn1), Snn3-D1 also carries a S/TPK domain, but it also have some other domains related to the receptor-like kinase and MAP kinase (Winterberg et al. 2014). Snn3-D1 also differed from Tsn1 and Snn1 in its light regulated and circadian expression patterns. This and other characteristics of Snn3-D1 and how it compares to Tsn1 and Snn1 will be known when results of cloning Snn3-D1 are published. However, one common feature of the above three cloned sensitivity genes is the presence of a PK domain, which indicates that signaling is necessary from the pathogen to exploit programmed cell death in the host.

**Cloned NE genes for SNB.** Three of the eight NE genes (SnToxA, SnTox1 and SnTox3) have also been cloned and characterized (Friesen et al. 2006; Liu et al. 2009, 2012). Following are some details:

(i) SnToxA gene has two introns, which included a 55 bp intron located in the leader sequence and the other 50 bp intron located at the C-terminal coding region. The gene encodes a 13.2 kDa mature protein, which targets the protein PR-1-5 causing necrosis in the presence of Tsn1 gene during ToxA-Tsn1 interaction. The target protein PR-1-5 is present in both ToxA-sensitive and ToxA-insensitive wheat lines; it is only the level of expression that differs (Lu et al. 2009, 2011, 2014).

(ii) SnTox1 gene lies in a 7.6 kb genomic region and has three exons (180 bp, 162 bp and 12 bp) associated with 58 bp long 5'UTR and 164 bp long 3' UTR (Fig 5a). The gene is associated with one downstream gene (SNOG_07153) and three upstream genes (SNOG_07154, SNOG_07155, SNOG_7156; SNOG stands for S nodorum gene) (Fig. 5b; Liu et al. 2012). The gene encodes a cysteine-rich protein carrying a conserved and functional chitin-binding (CB) motif at its C-terminal (Liu et al. 2012; Liu et al. 2016). This CB motif occurs in all necrotrophs and plays a role in the protection of fungus at the time of its initial penetration in the plant tissues (Liu et al. 2016). Some other domains such as two myristoylation sites, N-terminal pyroglutamate, six phosphorylation sites, an RGD cell attachment motif and C domain also occur in mature ToxA proteins (Manning et al. 2004).

(iii) SnTox3 gene is 693 bp long and carries no introns. It encodes a 25.8 kD protein with 20 amino acid signal sequence and a possible pro-sequence (Liu et al. 2009). Six cysteine residues were also predicted to form disulfide bonds, which were shown to be important for SnTox3 activity. This gene also encodes a 230 aa long pre-pro protein. SnTox3 protein also contains a 20 aa signal peptide along with disulfide bonds formed by the six cysteine residues, which help in stabilization of mature protein and its protein activity (Liu et al. 2009). The genomic location and structure of the gene SnTox3 is shown in Fig. 6. An experiment was also conducted for the identification of the interaction between the P. nodorum NE protein SnTox3 and PR-1-1 in wheat using yeast-two-hybrid library approach, which indicated that the interaction was associated with the necrosis on the leaves of wheat (Breen et al. 2016).

**Mechanism of action of NEs.** The mechanism of action for different NEs may also differ and is known for at least two NEs. For instance, SnTox1 functions in the apoplast and directly recognizes Snn1 protein, thus facilitating infection by overcoming the barrier due to wheat chitinases (Liu et al. 2016). SnToxA, on the other hand, is internalized into the cytoplasm and interacts directly or indirectly with the product of gene Tsn1. In both cases the NE-Sn interactions activate MAPK signalling, which upregulates defense pathways and leads to release of reactive oxygen species (ROS), which results in cell death (Shi et al. 2016b; Fig. 7).
QTLs for SNB resistance (leaf blotch and glume blotch). P. nodorum pathogen is responsible for the development of two SNB diseases in wheat i.e., leaf blotch and glume blotch (including flag leaf and spike blotch). The pattern of inheritance for resistance against the two diseases differ (Shankar et al. 2008; Chu et al. 2010; Wicki et al. 1999; Xu et al. 2004). However, in a number of genetic studies, no distinction was made between leaf blotch and glume blotch. QTLs for resistance against SNB have been identified following both linkage based interval mapping and LD-based GWAS. The QTL analysis for the resistance to this disease was undertaken at two different stages [seedling (leaf blotch) and adult plant stages (flag leaf and spike)], but most of the association mapping studies were conducted at the seedling stage (Supplementary Tables 1 and 2). QTLs for seedling resistance (leaf blotch) have been identified on chromosomes 1A, 1B, 2B, 2D, 3A, 4A, 4B, 4D, 5A, 5B, 5D, 6A, 6D, 7A, 7B and 7D. Similarly, QTLs for adult plant resistance (glume blotch) have been identified on chromosomes 1A, 1B, 2A, 2D, 3A, 3B, 4B, 5A, 5B, 7A and 7B.

As many as ~90 QTLs for SNB have so far been identified through several studies using linkage-based interval mapping involving both bi-parental and multi-parental MAGIC mapping populations (Friesen et al. 2007; Ruud et al. 2017; Lin et al. 2020). Of the 90 QTLs, as many as 24 QTLs had major effects, each explaining >20 percent phenotypic variation (Supplementary Table 1). Similarly, GWAS resulted in identification of 46 MTAs (Gupta et al. 2014; Korte and Farlow 2013; Pascual et al. 2016; Ruud et al. 2019; Halder et al. 2019; Supplementary Table 2). After due validation, the markers associated with QTLs and MTAs can be utilized for MAS for resistance breeding.

In a recent major detailed study conducted by Lin et al. (2020), QTLs were also identified using a MAGIC population (643 RILs). Sixteen QTLs were detected using IM/CIM, being located on chromosomes 2A, 2D, 5B, 6A and 7D. A QTL (QSnb.niab-5B.2) overlapping Tsn1 was also identified on the long arm of chromosome 5B.

High resolution fine mapping has also been undertaken for sensitivity genes for SNB. A high-density genetic linkage map was developed for the region of chromosome 2D, 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 Snn2 gene (Zhang et al. 2009). Phenotypic variation (PV) for disease was 47% for the interaction Snn2-SnTox2, 20% for the interaction Tsn1-SnToxA, and 66% for both interactions taken together, suggesting the utility of these interactions in breeding (Friesen et al. 2007). Saturated gnetic map was also prepared for the region carrying the gene Snn3 using two crosses between sensitive line Sumai3 and the corresponmding insensitive genotypes (Downie et al. 2918).

Pyrenophora tritici-repentis-wheat pathosystem

Tan spot caused by P. tritici-repentis (Ptr) causes a mean yield loss of 5-10% in different parts of the world, which may approach 50% under conditions favorable for the pathogen (DeWolf et al. 1998; Faris et al. 2013). The disease 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). The wide adoption of minimum tillage practices and unconscious widespread cultivation of Tsn1-carrying wheats perhaps caused a rise in the incidence of tan spot and its severity throughout the world (Lamari et al. 2005). Tan spot is characterized by two distinct and independent symptoms in the form of necrosis and chlorosis (Fig. 1, b1, b2). It has also been shown that resistance against necrosis and chlorosis are controlled by two independent recessive factors.

Necrotrophic effectors (NEs). Three different NEs secreted by Ptr include ToxA, ToxB and ToxC. The presence of a fourth NE (Ptr ToxD) has also been suggested, but no corresponding sensitivity gene for this NE is known (Meinhardt et al. 2003; Ciuffetti et al. 2003). The genes encoding these three NEs were also identified in different isolates of the pathogen and are involved in the following three interactions: Tsn1-ToxA, Tsc1-ToxC and Tsc2-ToxB (Table 3; Faris et al. 2013). Among these three interactions, Tsn1-ToxA interaction is common with wheat-P. nodorum and wheat-B. sorokiniana pathosystem.

Among the three NEs, PtrToxA and PtrToxB are characterized as small effector proteins; ToxA produces necrosis, while ToxB produces chlorosis. ToxC, which also causes chlorosis, has not been characterized and may be the product of a
secondary metabolite gene cluster. There is strong evidence that _P. tritici-repentis_ acquired the gene _ToxA_ from _P. nodorum_ through horizontal gene transfer (Friesen et al. 2006).

In addition to the above three toxins, as many as 38 novel toxins called triticones have been identified (Rawlinson et al. 2019), although only triticone A and triticone B have been purified from _Ptr_ and shown to cause necrosis/chlorosis. A biosynthesis gene cluster _TtcA_ has also been identified. A deletion of _TtcA_ abolished the production of all triticones, but the pathogenicity of mutant _ttcA_ was not visibly affected. Triticone A/B gave visible necrotic symptoms but inhibited the growth of some bacteria like _Bacillus subtilis_ and _Rhodococcus erythropolis_, when tested using disk diffusion method, suggesting their antimicrobial activity. No inhibition was observed for gram negative bacteria, like _P. pastoris_ (Rawlinson et al. 2019).

A detailed study of the _Ptr_ genome has also been undertaken by R.P. Oliver and his group from Western Australia (Moolhuijzen et al. 2018a, b). The genome is 40.9 Mb in size and has already been fully sequenced, using eight new _Ptr_ isolates representing races 1, 2 and 5, and a new race (for races 1-8, see later). As much as 98% of the genome has been mapped on 10 or more chromosomes, which carry 13,797 annotated genes. Comparative analysis of the whole genome also revealed major chromosomal segmental rearrangements and fusions, highlighting intraspecific genome plasticity (Moolhuijzen et al. 2018a).

_PtrToxA_ is a single copy gene and is characterized by 900 nucleotides long cDNA (PtrNEC) producing a 19.7 kD protein precursor. _Ptr ToxB_, on the other hand, is a multi-copy gene (1-3 Kb in length) producing a protein with a mass of 6.6 kD (Martinez et al. 2001, 2004). The number of copies of _ToxB_ in a race has a correlation with the level of virulence. A total of ten identical _ToxB_ gene copies were identified, with nine loci associated with chromosome 10 and a single copy with chromosome 5. Multiple _ToxB_ gene loci on chromosome 10 were separated by large segments of 31-66 kb long, and exhibit an alternating pattern involving forward and reverse DNA strands, and flanked by transposable elements (Moolhuijzen et al. 2020; Fig. 8). The sequence variability of _PtrToxB_ gene among _Ptr_ races of the pathogen has also been reported. Homologues of _PtrToxB_ have also been reported from several other pathogens including _Pyrenophora bromi_, suggesting its common origin in early ancestors of the Ascomycota (Andrie et al. 2008).

**Genetics of sensitivity.** A genetic analysis of ToxB sensitivity was conducted using an association mapping panel (n = 480) and a MAGIC population (n founders = 8, n progeny = 643) that were genotyped with a 90K SNP array. ToxB sensitivity was found to be highly heritable (h² ≥ 0.9) and was controlled predominantly by _Tsc2_ locus on chromosome 2B in a 1921 kb long interval that contains 104 genes in the reference genome of ToxB-insensitive variety ‘Chinese Spring’ (Corsi et al. 2020). A minor ToxB sensitivity QTL was also identified on chromosome 2A. These resources can be used for deployment of recessive allele of _Tsc2_ using MAS.

As a result of extensive studies on tan spot during the last 40 years, we now have the following resources for conducting research on this disease: (i) a wheat differential set for tan spot, which included Salamouni (universal resistant), Glenlea (sensitive to _Ptr ToxA_), 6B365 (sensitive to _Ptr ToxC_), and 6B662 (sensitive to _Ptr ToxB_). The hard spring wheat line ND495 was included in the differentials set as a susceptible control; (ii) a rating scale for lesion type disease; (iii) basic race classification system involving eight races (Table 7); the four differential genotypes can differentiate between the known eight races of the pathogen. Details about three NEs-sensitivity combinations are summarized in Table 3 (Faris et al. 1997, 1999; Effertz et al. 2001, 2002).

**Distribution of _Ptr_ NE genes.** The pathogen _Ptr_ is known to have 8 races (race 1-8), representing all possible combinations of _ToxA_, _ToxB_ and _ToxC_ (Table 7). Isolates belonging to each race were collected both from bread wheat and durum wheat, although race 1 in hexaploid wheat is believed to have originated from durum wheat. Three isolates, namely Ascl (race 1), D308 (race 3) and Alg3–24 (race 5) were found to carry genes _Ptr ToxA_, _Ptr ToxC_, and _Ptr ToxB_ respectively. The distribution of the genes encoding three different NEs differs widely not only in different parts of the world, but also in the
area occupied by the same set of wheat genotypes. Of these, ToxA is the most widely distributed, being present in ~80% of the world's isolates (Friesen et al. 2006); this is a small protein that induces a strong necrotic response in wheat lines carrying the gene Tsn1 (Faris et al. 2010) on chromosome 5BL.

**Distribution of races 1-8 among isolates.** The distribution of eight Ptr races in different isolates from a particular geographical region or from different geographical regions have also been examined. Following are some examples: (i) In Tunisia, using four wheat differential genotypes (mentioned above), virulence was examined for 73 single-spore isolates, and the results indicated that 68 isolates belonged to race 7; 3 belonged to race 5 and one each to race 2 and 4, suggesting that race 7 is the predominant race in Tunisia. PCR was also performed to examine the frequencies of each of the three genes (ToxA, ToxB and toxB), but not for ToxC, which has not been cloned and sequenced, so that primers could not be designed for this gene. ToxA was present in 37 (51%) isolates, ToxB was present in 71 (97%) isolates with its homolog toxB present in 68 (93%) isolates (Kamel et al. 2019). A subset of 22 isolates was also subjected to sequencing resolving sequence polymorphism in ToxA and ToxB/toxB (Kamel et al. 2019). (ii) In Australia, races 1 and 2 are the most predominant races, although races 5-8 are also common, which were rarely found in the Americas. (iii) In Algeria, among 55 isolates, races 1, 4, 5, 6, 7 and 8 were found and a new virulence pattern was identified. Isolates with this pattern induced necrosis in durum wheat but not in the common wheat genotypes. A majority of the isolates represented races 1 (41%) and 7 (40%), while races 4, 5, 6, and 8 were rare; race 1 occurred in all regions (Benslimane et al. 2011). (iv) In Morocco, majority of isolates were classified as races 5 and 6, both carrying P. triticina (Gamba et al. 2017). (v) In the centre of origin of wheat (Middle East, North Africa, and the Caucasus regions), the situation was rather complex, with the occurrence of all the eight races and all the three effectors. (vi) In Western Canada, race composition varied, when distribution of 144 Ptr isolates was examined in durum wheat, bread wheat and grasses; R1 and R2 were common in wheat and occurred in equal frequencies in durum wheat; R1 was twice as frequent as R2 on winter bread wheat; R3 was recovered only from durum wheat and R4 was the only race recovered from grasses (Wet et al. 2021) (for a Review and References, see Kamel et al. 2019).

**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 give the expected symptoms. When wild type and toxA mutant isolates were used for infection, majority of Tsn1 varieties exhibited lower disease scores with toxA mutants (as expected), but several varieties exhibited no distinct differences between wild-type and toxA mutant. This pattern suggested that ToxA is not the sole major cause of tan spot disease, and that the appearance of the disease partly also depends on the background of the host. It is thus suggested that ToxA may need additional factors to cause infection (See et al. 2018).

**Cloned sensitivity genes for tan spot.** Among the sensitivity genes, Tsn1 (common among three necrotrophs) has already been cloned and characterized (Fig. 4). The details of this genes were already described earlier, while describing cloned sensitivity gene for P. nodorum. The other two sensitivity genes Tsc1 and Tsc2 are yet to be cloned and characterized, but markers have been developed for these two other sensitivity genes. A variety ‘Maris Dove’ was also identified to be the historic source of Tsc2 alleles in the wheat germplasm. A minor sensitivity QTL was also identified on chromosome 2A. The marker developed in this study can be used for MAS aimed at selection of insensitive genotypes exhibiting disease resistance (Corsi et al. 2020).

**Cloned NE genes for tan spot.** Among products of cloned NE genes, PtrToxB (6.6 kD) is a polar and low-molecular-mass molecule (Effertz et al. 2002) encoded by the multiple-copies of the gene, which carries a 261-bp open reading frame (ORF) within its sequence (Strelkov et al. 2002). The protein PtrToxB is recognised by the sensitivity gene Tsc2 (located on chromosome arm 2BL) and produces chlorosis on the leaf surface of wheat (Orolaza et al. 1995; Friesen and Faris 2004). Ptr ToxC has not been fully characterized and purified; mode of action of this NE is also not known. However, its partial characterization and purification has been reported (Lamari and Bernier 1991; Gamba et al. 1998; Effertz et al. 2002).
**Interactions between sensitivity genes and NEs.** Among the three interactions, namely $Tsn1$-$ToxA$, $Tsc1$-$ToxC$ and $Tsc2$-$ToxB$, the interaction between $Tsn1$ and $ToxA$ has been shown to be negatively affected when mutation occurs at different motifs of the Tsn protein (Manning et al. 2004). The interaction $Tsc2$-$ToxB$ is unique to tan spot and leads to upregulation of several wheat genes encoding proteins like RLKs, pathogenicity related proteins, components of jasmonic acid, and phenyl propanoid pathways and WRKY transcription factors (Pandelova et al. 2012). Some physiological changes have also been observed, which decrease chlorophyll a and b and overlap with the symptom development and ROS accumulation (Pandelova et al. 2012; Ciuffetti et al. 2010). Other details of this interaction are given in Table 3.

An additive interaction of sensitivity gene $Tsn1$ with $Tsc1$ and $Tsc2$ has also been reported for tan spot in bread wheat (Liu et al. 2017) but not in durum wheat (Virdi et al. 2016). It is therefore apparent that elimination of one or more sensitivity genes along with introgression of R genes/QTLs should be a good strategy for developing resistant cultivars.

**NEs regulating transcription factors and other proteins.** ToxA and ToxB both induce upregulation of WRKY transcription factors, PR proteins and receptor-like kinases (RLKs) (Adhikari et al. 2009; Pandelova et al. 2009, 2012). The responses also include activation of phenylpropanoid and JA pathways and accumulation of ROS and disruption of photosystem (Adhikari et al. 2009; Pandelova et al. 2009, 2012). However, the response of the host to ToxB differs in host genotypes with a single dominant R gene (Singh et al. 2008a, b) and those with a single recessive gene (Singh et al. 2010).

**Insertion element PtrHp1 in ToxA gene.** A novel 166 bp insertion element (PtrHp1) was also detected in ToxA gene from isolates from many regions of the world (Australia, Europe, North and South America and the Middle East, Denmark, Germany, and New Zealand). PtrHp1 perfectly matched 59 bp inverted repeat hairpin structure located downstream of the ToxA coding sequence in the 3’ UTR exon. Further examination revealed that PtrHp1 elements were distributed throughout the genome. Analysis of genomes of isolates from Australia and North America had 50–112 perfect copies of PtrHp1 that often overlap other genes. The hairpin element appears to be unique to Ptr and the lack of ancient origins in other species suggests that PtrHp1 emerged after speciation of Ptr (Moolhuijzen et al. 2018b).

**R genes and QTLs for tan spot resistance.** Resistance genes (R genes or major QTLs) providing resistance against tan spot have also been identified. Among these 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. Durum cultivar Langdon, which is susceptible to tan spot became resistant with the substitution of chromosome 3B from the wild emmer accession IsraelA (Faris et al. 2020). $Tsr7$ locus in tetraploid wheat was later found to be the same as the race-nonspecific QTL previously identified in the hexaploid wheat cultivars BR34 and Penawawa. Four user-friendly SNP-based semi-thermal asymmetric reverse PCR (STARP) markers co-segregated with $Tsr7$ and should be useful for MAS (Faris et al. 2020).

More than 20 QTL studies were also conducted in hexaploid and tetraploid wheats for identification of QTLs for resistance against tan spot in wheat. These QTL studies resulted in identification of as many as >160 QTLs, a number of these QTLs explained >20% phenotypic variation (Supplementary Table 1). Utilizing the results of QTL studies, a meta-QTL analysis was also conducted leading to identification of 19 meta-QTLs that were derived from 104 QTLs (Liu et al. 2020a, b for details of all QTL studies and for meta-QTL analysis). 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 in both bread and durum wheats.

GWA studies were also conducted leading to identification of 242 significant MTAs (Supplementary Table 2), although a large number of these could be false positives. Most QTLs and MTAs were associated with seedling resistance and very few studies have been conducted for the identification of QTLs associated with adult plant resistance (Supplementary Table 1 and 2). The markers associated with the above meta-QTLs and those involved in MTAs can be utilized for MAS in wheat breeding programmes after due validation.
Candidate genes were also identified for 16 of the above 19 meta-QTL; the number of candidate genes for individual meta-QTL ranged from 2 to 85, many of these located on chromosome 2B. A number of these candidate genes encoded NBS- and/or LRR-like proteins and co-localised with sensitivity gene Tsc2. However, none of these candidate genes could be Tsc2, because genome sequence utilized for identification of candidate genes belonged to CS, which is insensitive to Ptr ToxB.

**PR genes.** The level of the expression of most PR genes has also been shown to be up-regulated due to effector protein ToxA during infection and increases over time (Pandelova et al. 2009). Glucanases (PR-2) and chitinases (PR-4) represent the largest group of PR genes displaying differential expression in which majority of glucanases belong to the family of β-1,3-glucanases (glucan endo-1,3-β-glucosidases). A downregulation of the expression of some genes of glucanases such as (1–3,1–4)-β-glucanases has also been reported (Pandelova et al. 2009).

**Bioplaris sorokiniana-wheat pathosystem: BsToxA-Tsn1 system**

*Bioplaris sorokiniana* is a hemi-biotroph and is the causal organism for wheat diseases including spot blotch (Fig. 1a) and common root rot (CRR), which are responsible for major yield losses in several parts of the world (Gupta et al. 2018a, b). The gene ToxA, initially reported to be present in *P. nodorum* and *P. tritici repentis* (Friesen et al. 2018) 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 sensitivity gene) is more virulent on wheat lines carrying the sensitivity gene Tsn1 (McDonald et al. 2018; Navathe et al. 2020).

The gene ToxA is embedded in 12-kb AT-rich genomic region of each of the three pathogens. Near the edges of the gene, a decay has been reported, which has been attributed to repeat-induced polymorphism (RIP) (Fig. 9). Small indels, which differ in size in the three pathogens have also been reported in the promoter region of the gene; this indel is 148-bp in *BsToxA*, 238-bp in *PtrToxA* and 43 bp in *SnToxA* (McDonald et al. 2012, 2018; also see Fig. 9). The haplotype organization of three ToxA genes (*BsToxA*, *PtrToxA* and *SnToxA*) also differed.

The frequencies of pathogen isolates carrying *BsToxA* and the wheat genotypes carrying Tsn1 also differ in different parts of the world. In Australia, 12 (34%) of the 35 isolates of *B. sorokiniana* isolates carried ToxA, while in India 77 (70%) of the 110 *B. sorokiniana* isolates carried ToxA. In a solitary report of the frequency of *Tsn1* gene from India, the sensitivity gene was present in 81 (36.8%) of 220 Indian wheat cultivars screened (Navathe et al. 2020). However, presence of *Tsn1* gene does not always guarantee susceptibility to the pathogen carrying ToxA gene, as shown in the material surveyed in Australia and India. In Australia and India, it was reported that sometimes an isolate lacking ToxA is still highly virulent on non-Tsn1 cultivars, while a cultivar containing Tsn1 can still be resistant to isolates carrying ToxA gene. These results suggest that there are additional factors in the wheat genome, which control resistance; these additional factors may include R genes and QTLs controlling resistance to spot blotch (Navathe et al. 2020; see later).

Sensitivity-related QTLs against *B. sorokiniana* have also been identified in barley, where recessive alleles of Rcs5 and Rcs6/Scs2 provided resistance to spot blotch (Leng et al. 2018; Gupta et al. 2018a). Two additional QTLs (QSbs-1H-P1 and QSbs-7H-P1h) for susceptibility to spot blotch were also identified in barley (Leng et al. 2020); of these two QTLs, QSbs-7H-P1 mapped to the same region as Rcs5 gene, but QSbs-1H-P1 was a new QTL.

**QTLs for spot blotch resistance.** Resistance to spot blotch is mainly associated with the major R genes (*Sb1-Sb4*) as well as QTLs, which may or may not overlap the known major genes (Lillemo et al. 2013, Kumar et al. 2015; Lu et al. 2016; Zhang et al. 2020). The genetics of resistance to spot blotch has also been studied taking the disease as a quantitative trait (Gupta et al. 2018). It has been shown that some major QTL identified through QTL mapping found to be inherited in a Mendelian manner, so that these later designated as *Sb1* (flanking markers Xgwm1220–Xgwm295 on chromosome arm 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*, which is an important gene for leaf rust resistance (Lillemo et al. 2013).
Using bulked segregant analysis (BSA), Sb3 gene was also fine-mapped on chromosome arm 3BS near two other QTLs (QSb.bhu-3B and QSb.cim-3B; Lu et al. 2016). The fourth resistance gene Sb4 was recently identified and mapped on chromosome arm 4BL using segregant RNA-Seq (BSR-Seq) analysis and SNP mapping (Zhang et al. 2020). The locus with Sb4 carried 21 genes.

In addition to the four major genes as above, 38 QTLs (including 12 QTLs with >20% PVE) using QTL interval mapping (Supplementary Table 1) and 79 MTAs using GWAS were also identified (Supplementary Table 2). These QTL analysis and association studies were conducted at seedling as well as at adult plant stages (Supplementary Table 1 and 2).

**Conclusions And Future Perspectives**

Disease resistance in plants including wheat can be race-specific or race non-specific, the latter sometimes also described as adult plant resistance (APR). Both these types of disease resistance are generally controlled by R genes, which have been subjects of detailed studies. The plant immunity involving these R genes has also been subjected to detailed studies at the molecular level, leading to the development of zig-zag model involving PTI, ETS and ETI (Jones and Dangl 2006). During the last > 25 years, > 300 R genes and a number of Avr genes have also 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). In majority of examples of R genes, gene-for-gene (GFG) relationship proposed by Flor (1942, 1956) holds good. However, disease resistance controlled by susceptibility genes like SWEET genes for bacterial blight (BB) in rice (Gupta 2020) and sensitivity genes like Tsn1 in wheat follow an inverse gene-for-gene (IGFG) relationship with corresponding Avr 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, a number of sensitivity genes in wheat for three important diseases (SNB, Tan Spot and Spot Blotch) and the corresponding Avr (NE) genes in the form of toxin producing genes (Tox genes) in the pathogens (P. nodorum, P. tritici-repentis and B. sorokiniana) have been identified. Some of these genes (both sensitivity 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 pathosystem. In this review, a comparison has first been made between the general molecular mechanisms involved in resistance against biotrophs and necrotrophs. This was followed by a brief review of information on the above three pathosystems. In summary, perhaps only about a dozen NE genes and an equal number of corresponding sensitivity genes are now known, which have been described in this review. In future more sensitivity genes in wheat and other corps and the corresponding Tox genes in the pathogens exhibiting IGFG may be discovered.

We also believe that in the area dealing with sensitivity genes following IGFG model there are gaps, which need to be filled through future research. For instance, although much is known about the pathosystems dealing with SNB and Tan spot, the information dealing with spot blotch (caused by Bipolaris sorokiniana) has just started being generated and hardly any work is available on pathosystems involving necrotrophs causing the following diseases: (i) fusarium head blight (FHB) caused by F. graminearum; (ii) eye spot caused by Tapesia yallundae (syn Pseudocercosporella herpotrichoides, W-type anamorph); (iii) septoria tritici blotch (STB) caused by Zymoseptoria tritic. We also believe that for diseases like spot blotch caused by necrotrophs, both GFG and IGFG may operate in parallel. Further studies involving scoring of allelic states of genes involved in GFG and IGFG models need to be undertaken to resolve this issue. In a recent study on spot blotch involving analysis of Tsn1-ToxA system following IGFG, we ourselves discovered that the wheat genotypes carrying recessive allele of sensitivity gene (tsn1) can also be susceptible and vice versa; variation in the level of disease caused by ToxA positive isolates was also noticed (Navathe et al. 2020). This suggests that the relationship between a sensitivity gene in the host and the corresponding virulence gene in the pathogen is not so simple, suggesting further detailed investigations.

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Tables
### Table 1: Necrotrophs and hemibiotrophs causing diseases in wheat

| Pathogen (teleomorph) | Anamorph | Disease caused | Reference |
|-----------------------|----------|----------------|-----------|
| **Parastagonospora nodorum** (Berk.) | *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) | *Drechieslera tritici-repentis* (Died) | Tan spot | Drechsler 1923; Shoemaker 1959, 1962 |
| **Cochliobolus sativus** (S. Ito & Kurib.) Drechsler ex Dastur | *Bipolaris sorokiniana* | Spot Blotch (SB) | Dastur 1942; Shoemaker 1959 |
| **Phaeosphaeria avenaria f. sp. Tritici 1 (Pat 1)** | *Stagonospora avenae* f. sp. triticea | Septoria avenae blotch | Johnson 1947, 1952; Shoemaker and Babc 1989 |
| **Pyrenophora wirreganensis** | *Drechieslera wirreganensis* | Wirrega blotch | Wallwork et al. 1992 |
| **Pyrenophora semeniperda** | *Drechieslera campanulata* | Ring spot | Léveillé 1841; Sutton 1976 |
| **Zymoseptoria tritici** (Desm.) Quaedvlieg and Crous | *Mycosphaerella graminicola* (Fuckel) J. Schrot. in Cohn; *Septoria tritici* (Rob in Desm.) | Leaf Blotch (LB); *Septoria tritici* blotch (STB) | Quaedvlieg et al. 2011 |
| **Gibberella zeae** | *F. graminearum* | Fusarium head blight or scab | Mihuta-Grimm and Foster 1989; Reis 1985 |
| **Gibberella coronicola** | *F. culmorum* | Crown rot | Aoki and O’Donnell 1999 |
| **Magnaportha grisea** (Hebert) Barr | *Pyricularia grisea* (Saccardo), syn. *P. oryzae* (Cavara) | Wheat blast | Barr 1977; Yaegashi and Udagawa 1978 |

### Table 2: A comparison of characteristics of biotrophs and necrotrophs (http://www.davidmoore.org.uk/21st_Century_Guidebook_to_Fungi_PLATINUM/Ch14_10.htm).

| Biotrophs pathogen | Necrotrophs pathogen |
|--------------------|----------------------|
| Appressoria or haustoria produced | Appressoria/haustoria normally not produced |
| Resistance is controlled by SA-dependent host-defense pathways | Resistance controlled by JA and Et-dependent host-defense pathways |
| Gene-for-gene (GFG) relationship holds good | Generally quantitative resistance and/or Inverse gene-for-gène (IGFG) relationship |
| Difficult to culture | Easy to culture |
| Direct entry or through natural openings | Entry via wounds or natural openings |
| Survive on host or as dormant propagules | Survive as competitive saprotrophs |
| Survive on living tissues | Survive on living/dead tissues |
| Cells not killed rapidly; hypersensitive reaction (HR) in resistant genotype | Host cells killed rapidly |
| Few lytic enzymes/toxins are produced | Cell-wall-degrading (lytic) enzymestoxins |
| Often systemic | Seldom systemic |
| Attack vigorous; any stage | Attack weak, young/damaged plants |
| Narrow host range | Wide host range |
| Intercellular growth of pathogen | Intercellular/intracellular growth |
| Effectors: Avr proteins recognized by matching resistance (R) proteins. | Effectors: host-specific or host-selective toxins (HST). |
| Disease caused by suppressing PTI/ETI, | Disease due to interaction of HSTs (NEs) with products of sensitivity genes |
| HST sensitivity gene interaction | Pathotypes | Differential lines | Mass of HSTs | Experimental populations/Markers | Symptoms | Ref# |
|---------------------------------|------------|--------------------|-------------|----------------------------------|----------|------|
| **I. Wheat-*P. nodorum* interactions** | | | | | | |
| Tsn1-SnToxA                    | Sn2000, Sn6, Sn15, Sn1501 | BG261 | 13.2 kDa | RILs: BR34 × Grandin, 5BL*M1* | Necrosis chlorosis | 1 |
| Snn1-SnTox1                    | Sn4, Sn5, Sn6, Sn2000 | W-7984 | 10.3 kDa | RILs: W-7984 × Opata 85, 1BS*M2* | Necrosis | 2 |
| Snn2-SnTox2                    | Sn4, Sn5, Sn1501, Sn6 | BG223 | 7-10 kDa | RILs: BR34 × Grandin, 2DSM*3* | Extensive necrosis | 3 |
| Snn3B1-SnTox3                  | Sn4, Sn79+SnToxA, Sn1501, Sn15KO18, Sn79+SnTox3A, Sn79+SnTox3B | BG220 | 25.8 kDa | F2: TA2377 × BG220, 5BS*M4* | | 4 |
| Snn3D1-SnTox3                  | Sn4, Sn79+SnToxA, Sn1501, Sn15KO18, Sn79+SnTox3A, Sn79+SnTox3B | BG220 | 25.8 kDa | F2: TA2377 × AL8/78, 5DS*M5* | Necrosis chlorosis | 5 |
| Snn4-SnTox4                    | Sn99CH 1A7a | AF89, ITMI44 | 10.3 kDa | RILs: Arina × Forno, 1AS*M6* | Mottled necrosis | 6 |
| Snn5-SnTox5                    | Sn2000 Sn2000KO6-1, Sn1501 | LP29, ITMI44 | 10-30 kDa | RILs: Durum Lebslock × T. turgidum, Lebsock × PI 94749, 4BLM7* | Necrosis chlorosis | 7 |
| Snn6-SnTox6                    | Sn6 | ITMI37 | 12 kDa | RILs: Opata 85 × W-7984, 6AL*M8* | Necrosis chlorosis | 8 |
| Snn7-SnTox7                    | Sn6 | CTm208 | < 30 kDa | RILs: CS-Tm2D × CS, 2D*M9* | Necrosis chlorosis | 9 |
| **II. Wheat-*P. tritici repentin* interactions** | | | | | | |
| Tsn1-ToxA                      | Ptr Race 1, 2 | Glenlea | 13.2kDa (protein) | RILs: CS × CS-DIC 5B × F2: LDN × LDN-DIC 5B, 5BL*M1* | Necrosis chlorosis | 10 |
| Tsc1-ToxC                      | Ptr Races 1, 3 | Glenlea, 6B365 | Not a protein | RILs: Opata 85 × W-7984, 1AS*M10* | Chlorosis | 11 |
| Tsc2-ToxB                      | Ptr Race 5, 6, 7, 8 | 6B662, Coulter | 6.5 kDa (protein) | NIAB and BMW MAGIC population, 2BS*M11* | Chlorosis | 12 |
| **III. Wheat-*B. sorokiniana* interaction** | | | | | | |
| Tsn1-BsToxA                    | TecxD16B1s; other Aus/Ind pathotypes | BG261 | 13.2 kDa | RILs: Arina × Forno, 5BL*M1* | Necrosis | 13 |

* = Associated molecular markers; M1* = Xfog17, Xfog9, XBF483506, XBM138151.1, Xgwm260-Xbarc73, Xgwm1043, glk165, Xfcp623, Xfcp620, Xfcp394; M2* = XksuD14; Xmwg546, Xmwg546, Xcdo1312, XksuG12, Xksu912, Xcdo1508, Xbcd361, Xbcd758, and Xksu927, Xfcp618 and Xpsp3000, Xbcd183, Xbcd1030 (Tetraploid wheat), Xgwm33.1, Xfcp1, Xfcp394, Xfcp620, XBF293222, XBE422980, XBE637568, XBE605202, Xpsp3000; M3* = Xgwm614, Xbarc95, Xcfd56, Xcfd51, XTC253803, XTC240114, XBE489611; M4* = Xgwm234, Xfcp20, Xfcp306, XBE606637, XBF200555, Xcfd20, XBF293016, Xfcp306, Xmag705; Xfcp654, Snn3-B1, Xmag705, XTC266536, Xfcp654, Xfcp665, Xfcp652.
Table 4 Sensitivity genes, QTLs and R genes for three wheat diseases

I. Septoria Nodorum Blotch (SNB) caused by *Parastagonospora nodorum*

* Sensitivity genes/QTLs: Tsn1, Snn1 (Qsnb.fcu-1BS, Qsnn.niab-5A), Snn2, Snn3 (Qsnn.fcu-5BS), Snn4 (Qsnn.fcu-1A), Snn5, Snn6, Snn7, Qsng.pur-2DL.1, Qsnn.ndsu.1BL, Qsng.pur-2DL.2, Qsnn.fcu-5BL.1, Qsng.cur-4BL Qsnn.cur-2AS1, Qsng.cur-3AL, Qsnn.cur-6BS, Qsng.cur-2DS, Qsng.cur-2AS2 and Qsnn.cur2BS (1*)

* R genes: SnbTM, and SnbAes1, snn1, Snb1, Snb2 and Snb3 (1#)

II. Tan Spot (TS) caused by *Pyrenophora tritici-repentis*

* Sensitivity gene/QTLs: Tsn1, Tsc1, Tsc2, QTsc.niab-2A and QTsc.ndsu-1AS (2*)

* R genes: Tsr1, Tsr2, Tsr3, Tsr4, Tsr5, Tsr6, Tsr7, TsrHar, TsrAri and TsrAes1 (2#)

III. Spot Blotch (SB) caused by *Bipolaris sorokiniana*

* Sensitivity gene/QTLs: Tsn1 (3*)

* R genes: Sb1, Sb2, Sb3 and Sb4 (3#)

*, #= References: 1* (Faris et al. 2010; Cockram et al. 2015; Friesen et al. 2008, 2009, 2012; Abeysekara et al. 2012; Shi et al. 2015); 1# (Uphaus et al. 2007; Abeysekara et al. 2012; Schnurbusch et al. 2003; Arseniuk et al. 2004; Gonzalez-Hernandez et al. 2009; Aguilar et al. 2005; Lin et al. 2020); 2* (Faris et al. 1997, 1999, 2010, Effertz et al. 2001, 2002; Liu et al. 2017), 2# (Faris et al. 1996, 2013, 2020; Singh et al. 2006, 2008a,b, 2019; Tadesse et al. 2006a,b, 2007, 2010, Meinhardt et al. 2003; Touri et al. 1995; Friesen and Faris 2004; Faris and Friesen 2005; Zhang et al. 2019; Chu et al. 2008), 3# (Kumar et al. 2010; Lillemo et al. 2013; Kumar et al. 2015; Lu et al. 2016; Zhang et al. 2020); 4* (Hales et al. 2020).

Table 5 Distribution (%) of three Tox genes among isolates of *P. nodorum*

| Region                                | SnToxA | SnTox1 | SnTox3 | Reference        |
|---------------------------------------|--------|--------|--------|-----------------|
| Norwegian                             | 69     | 53     | 76     | Ruud et al. 2018|
| North Dakota, South Dakota and Minnesota | 96     | 100    | 62     | Richards et al. 2019|
| USA                                   | 4.0    | 88     | 52     | Richards et al. 2019|
| Eastern USA                           | 63.4   | 95.4   | 58.9   | Richards et al. 2019|
| Fertile Crescent                      | 95     | 97     | 72     | Ghaderi et al. 2020|
| Southeastern United States            | 15     | 74     | 39     | Crook et al. 2012|
| World-wide collection                 | 18     | 26     | 22     | McDonald et al. 2013|
| Europe                                | 12     | 89     | 67     | McDonald et al. 2013|
| Norwegian                             | 67.9   | 46.1   | 47.9   | Lin et al. 2020|
| Canada                                | 69.2   | 80.7   | 76.9   | Hafez et al. 2020|
Table 6 Distribution (%) of three major wheat sensitivity genes for SNB in wheat germplasm

| Region                          | Tsn1 | Snn1 | Snn3 | Reference            |
|---------------------------------|------|------|------|----------------------|
| Australia                       | 63   | 71.7 | 91.3 | Tan et al. 2014      |
| USA                             | 32   | 0    | 64   | Bertucci et al. 2014 |
| Canada                          | 59   | 32.9 | 56.9 | Hafez et al. 2020    |
| 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   | 42   | Downie et al. 2018   |

Table 7 Eight races of *P. tritici-repentis* and their NE constitution

| Race | NE Constitution                     |
|------|-------------------------------------|
| 1    | *Ptr ToxA +Ptr ToxC*                |
| 2    | *Ptr ToxA*                          |
| 3    | *Ptr ToxC*                          |
| 4    | No effector (non-pathogenic)        |
| 5    | *Ptr ToxB*                          |
| 6    | *Ptr ToxB +Ptr ToxC*                |
| 7    | *Ptr ToxA +Ptr ToxB*                |
| 8    | *Ptr ToxA +Ptr ToxB +Ptr ToxC*      |
Figure 1

The visual symptoms of three necrotrophic diseases. (a) Septoria nodorum blotch; (b) tan spot (b1 and b2 showing necrosis and chlorosis) and (c) spot blotch.
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.

A graphical representation of chromosomal locations of sensitivity/susceptibility related genes/QTLs of tan spot (green), SNB (blue) and their associated molecular markers.

Figure 2

Figure 3
Map-based cloning of the Tsn1 gene. (A) The Tsn1 gene, located on wheat chromosome 5BL in the genome, is shown in red. (B) Genetic linkage map indicate the Tsn1 gene region. (C) A physical map based on the BAC of the Tsn1 region that anchored to the genetic map. Old LDN BACs map described by Lu and Faris (2006) has been shown in gray. The 5B and 5A BACs reported by (Faris et al. 2010) are given in green and orange colour, respectively. (D) Ovals shape structure is showing the predicted genes (ovals with names in dark red) and markers (names beginning with an “X”). Markers given in blue colour were used for association mapping. The candidate genes regions are indicated by blue and red lines defined by recombination in the mapping population and association mapping, respectively. (E) Purple and Gray colour show the Exons and UTRs of Tsn1 respectively (based on Faris et al. 2010).
Figure 5

Genomic location and structure of SnTox1. a. The structure of SnTox1 gene containing both 5’ and 3’ untranslated regions (green bars) and three exons (purple bars) b. A graphical representation of SnTox1 gene and associated genomic region. SnTox1 gene is flanked by four other genes (boxed arrows, SNOG7153 to SNOG7156) and a short, truncated molly-type retrotransposon sequence (yellow rectangle). The sequences are located within the supercontig 10 of the assembled SN15 genome sequence. (Based on Liu et al. 2012)

Figure 6

Structure of super-contig 14, containing gene SnTox3, showing details of the structure of this gene including promoter region, open reading frame (ORF) and the two untranslated regions. (reproduced from Liu et al. 2009)
An overview of the Snn1-SnTox1 and Tsn1-SnToxA interactions and known downstream events that result in NETS in the wheat-P. nodorum pathosystem. The proteins SnTox1 (blue star) and SnToxA (blue hexagon) are secreted by the fungus. SnToxA is internalized into cytoplasm of the cell, but SnTox1 is not. Upon recognition of SnTox1 and SnToxA by the Snn1 and Tsn1 proteins, respectively, signaling leads to up-regulation of defense response pathways and events resulting in programmed cell death ultimately providing a means for the pathogen to gain nutrients and reproduce. Plants with either Tsn1 or Snn1 are susceptible, and plants with both genes experience even higher levels of disease. Elimination of both genes makes the plant resistant (from Shi et al. 2016b).
Figure 8

Five different contigs of *P. tritici-repentis* genome showing positions of 10 different ToxB loci on forward and reverse strands. Blue arrows represent Tox B loci in the forward strand and by green arrows show Tox B loci in the reverse strand. In each case, the coding sequence is shown in yellow.

Figure 9
Alignment of the ToxA containing region from P. tritici-repentis, P. nodorum and B. sorokiniana. (A) Total alignment of the 12kb homologous region between the three species. This view shows the differences in ATrichness (green line), large increases are denoted by red asterisks. The decay in identity near the edges of the region can be attributed to RIP. All annotated genes are shown using gene accession number from P. nodorum (green bars). (B) Differences in the promoter of ToxA due to the presence of small indels. In P. tritici-repentis there is a 238bp insertion, which has no homology to any other organism. In P. nodorum, a single 43bp indel is present, which is a simple repeat of the same 43bp preceding the indel (blue bars). In B. sorokiniana there is a 148bp indel, which forms a near-perfect DNA hairpin (from McDonald et al. 2018).

**Supplementary Files**

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