Triticeae CBF Gene Cluster for Frost Resistance

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The pivotal role of *CBF*/*DREB1* transcriptional factors in *Triticeae* crops involved in the abiotic stress response has been highlighted. The CBFs represent an important hub in the ICE-CBF-COR pathway, which is one of the most relevant mechanisms capable of activating the adaptive response to cold and drought in wheat, barley, and rye. Understanding the intricate mechanisms and regulation of the cluster of *CBF* genes harbored by the homoeologous chromosome group 5 entails significant potential for the genetic improvement of small grain cereals.

abiotic stress Triticeae CBF transcription factors cold acclimation frost tolerance drought tolerance

1. Triticeae as Staple Food and Adaptable Crops

The Green Revolution had been able to meet the demand for food, reducing world hunger among the growing population (from 2.519 billion in 1950 to 4.435 billion in 1980) thanks to an unprecedented increase in crop yield and agricultural production [1][2]. New irrigation techniques, massive use of fertilizers and plant protection products, mechanization, crop breeding, and adoption of improved varieties were the determining factors in the observed increase in productivity [3][4][5]. Cereal crops, in particular, saw significant improvement, with yields tripling despite a small increase in arable land [6][7]. However, besides the positive effects, the excessive agricultural intensification created the conditions for the rise of environmental problems such as pollution, soil degradation, and loss of genetic diversity [8][9]. For example, in many breeding programs, genotypes were selected for the high-input systems driving gene pool erosion, especially for the alleles responsible for adaptation to the environment [10][11][12]. However, new issues emerged: yield seems to have reached a plateau and a contraction of genetic diversity has been observed [13][14]; as a result, the adaptation to biotic and abiotic stresses of cereal crops has been reduced [15][16][17][18][19]. In a scenario where the population is still growing (based on UN estimations, planet Earth will be populated by 8.5, 9.7, and 10.9 billion people by 2030, 2050, and 2100, respectively [2]), one of the goals of the global food production system is to provide higher yields and food quality while reducing, however, environmental pollution [6]. Furthermore, extreme weather conditions, reduction of arable lands, and increasing demand of fertilizers and irrigation water are putting the crops cultivation in open fields under stress conditions, significantly affecting agricultural production on all continents [20]. A novel approach is required to cope with the climate issue. Crop breeding programs need to develop new genotypes with a higher adaptation to weather fluctuations [21][22] and contribute to global food security [23].

The *Triticeae* tribe, a grass tribe of the *Poaceae* family that includes cultivated wheats (durum wheat *Triticum turgidum* L. ssp. *durum* Desf., bread wheat *Triticum aestivum* L.), barley (*Hordeum vulgare* L.), and rye (*Secale cereale* L.), is by far the most important source of energy and nutrients worldwide [24][25]. For example, wheat and barley together were the most cultivated herbaceous crops in the world in 2021, with a harvested area of 220 and 48 million hectares and a total grain production of 770 and 145 million tons, respectively [26]. Rye is an important crop for Northern and Eastern European countries, with a harvested area of 3.5 million hectares and a total production of 11 million tons [26]. The *Triticeae* tribe comprises about 350 species, including the so-called minor cereals such as triticale, spelt emmer, and einkorn wheats, poulard, polish, and khorasan wheats [27].

Temperate grass species are characterized by winter growth habits (WH) in their natural environments [28][29]. The two key traits of WH genotypes are the vernalization requirement and the cold acclimation. Vernalization is defined as the induction of flowering after prolonged exposure to cold. Moreover, *Triticeae* are usually classified as long-day (LD) plants because most varieties flower earlier when exposed to longer days. This mechanism synchronizes plants to flower after cold, harmful temperatures in the wintertime [30][31]. The cold acclimation is the ability of the crop to adapt to cold temperatures and then survive frost events [32]. The winter habit (WH) genotypes are usually sown in winter due to their higher productivity. In Mediterranean climates, sowing is performed in the autumn to take advantage of the rainiest seasons, and the plants are harvested during the drier summer. Winter habit is a limiting factor in the widespread cultivation of *Triticeae* in environments where winter is too cold to survive or too warm to satisfy the vernalization requirement [33]. To overcome this limit, spring habit (SH) and facultative habit (FH) genotypes were selected for their lack of vernalization requirements [34][35]. SH genotypes are sown in spring, whereas FH genotypes can be alternatively sown either in autumn or spring. Most SH cultivars are frost-prone and, due to a shorter crop cycle, may be exposed to drought. For these reasons, in the last few years, FH genotypes are gaining more and more interest since they show a high level of frost tolerance (FT) and do not require vernalization [36][37]. The *Triticeae* crops are thus adaptable to several environments, ranging from sub-arctic to tropical climates, allowing their cultivation across a wide geographical area [38][39], even if the highest yields are achieved in temperate regions [40].

2. C-Repeat Binding Factors and Cluster Organization in Triticeae

C-repeat binding factors, or dehydration responsive element (*CBF*/*DREB1*), are a larger subfamily of transcription factors that belong to the APETALA2/ethylene-responsive element binding factor (AP2/ERF) protein family and are induced/activated in response to osmotic stresses such as cold or drought. The AP2/ERF domain binds to the C-repeat/dehydration responsive elements (CRT/DRE) in the promoter region of a variety of genes involved in the abiotic stress response, also known as “CBF’s regulon.” These genes protect against the adverse effects of losing water caused by frost and drought with the biosynthesis of osmoprotectant proteins, carbohydrate metabolism-related activity, and sugar transport [41][42][43]. Among these, cold-regulated genes (*COR*) are the most important family, including late embryo abundant proteins (*LEA*), low-temperature-induced (*LTI*), cold-inducible (*KIN*), responsive to desiccation (*RD*), early dehydration-inducible (*ERD*), and the dehydrin (*DHN*) genes [44][45][46][47]. The distinctive element of *CBFs* within the AP2/ERF family is the specific “CBF signature” flanking the AP2 domain [42][48].

CBF1 was the first *CBF* gene isolated and characterized by Stockinger and colleagues in *Arabidopsis thaliana* [49]. Subsequently, other important works discovered the *CBF* family and its role in the model plant [50][51] and then in other 54 genera: 31 dicotyledons, 23 monocotyledons, and 13 woody species [52][53][54][55][56]. In *Poaceae*, multiple elements of the family were isolated and characterized, either in chilling-sensitive (e.g., rice and maize) or frost-tolerant species (e.g., wheat, barley, and rye) [52][57][58][59]. The *CBF* genes are characterized by short, mono-exon coding sequences (average length 700 bp) with no introns [52][60][61]. Interestingly, Shi et al. [47] performed a phylogenetic analysis and found that the *CBF* gene structure is remarkably conserved across various species (monocots/dicots), independently of their degree of frost tolerance. As reported by Campoli et al. and Badawi et al. [62][63], *CBF* genes are classified into four phylogenetic groups, each with two or more sub-groups. Some elements of the *CBF* gene family are scattered along the genome, while others, more frequently, are organized in clusters of tandemly duplicated genes on the long arm of homoeologous chromosome group 5 of *Triticeae* [64][65][66][67]. The cluster of *CBF* genes has been shown to coincide with a QTL for frost tolerance, namely *Frost Resistance 2* (*FR-2*) in barley (*FR-H2*), diploid (*FR-A^{m}2*) and polyploid wheats (*FR-A2* and *FR-B2*), and rye (*FR-R2*) [64][67][68]. In *Triticeae* crops, beside *FR-2*, part of the phenotypic variation for frost tolerance is attributed to another QTL located about 25–30 cM apart from *FR-2* on the long arm of homoeologous chromosome group 5: *Frost Resistance 1* (*FR-1*). This locus was identified by Hayes et al. in 1993 and Galiba et al. in 1995 [66][69] in barley and wheat, respectively, and reported to co-segregate with *VRN-1*, the vernalization requirement gene [64], whose expression leads the plant to become competent for flowering [70].

Thirteen *TmCBF* were described in *Triticum monococcum* L.; eleven of them were mapped on *FR-A^{m}2*, while *TmCBF15* and *TmCBF18* were mapped on chromosomes 7A^m and 6A^m, respectively [71]. Vágújfalvi et al. [67] attributed the locus for FT to chromosome 5A, and subsequently Knox and colleagues [72] divided the *FR-A2* locus into: proximal (*CBF 2*, *4*, *9*, and *17*), central (*CBF 12*, *14*, and *15*), and distal (*CBF 3*, *10*, *13*, and *16*).

The genome of hexaploid wheat encodes 65 *TaCBF*s [73], 27 of which are paralogs with 1–3 homoeologous A, B, and D copies [73]. As reported by The International Wheat Genome Sequencing Consortium (IWGSC) [74], 54 *TaCBF*s are located on chromosome Group 5: 17 genes on 5A, 19 on 5B, and 18 on 5D chromosomes. Other *TaCBF*s are located on homoloegous chromosomes 6 (A, B, and D).

3. Role of the ICE-CBF-COR Pathway in Cold Acclimation

In winter cereals, cold acclimation, also known as “hardening”, has the vital function of protecting the crown and young leaves from ice damage [75]. Even after a severe stress episode, if the crown and young leaves survive, the plant maintains the potential to restore from tillering nodes [76]. This peculiarity is linked to the ability of the meristematic tissue to survive thanks to the physiological phenomenon of cold acclimation [77]. Phenolic compounds, sugars, soluble proteins, new enzyme isoforms, proline and organic acids, modification of the fatty acid composition in the phospholipid membrane, and higher levels of antioxidants are all proactive compounds connected to the reduction of frost damage [43][75][78][79].

In winter barley, wheat, and rye, cold acclimation occurs only in the vegetative phase, and it has two different signaling pathways: abscisic acid or ABA-dependent (ABA pathway) and ABA-independent (also known as the ICE-CBF-COR pathway) [80]. Although the ABA and CBF signal transmissions were considered distinct from each other, recent studies suggest a cross-talk between these two pathways [81].

In short-day conditions, the ICE-CBF-COR pathway is promptly activated after a brief exposure to low, non-harmful temperatures [82][83], and the *CBF* gene has a pivotal role in the coordination of the acclimation processes [84]. In Arabidopsis, a marked increase in *CBF* transcript levels was observed 15 min after cold exposure, followed by up-regulation of the effector genes about 2 h later [32][85]. On the other hand, in wheat and barley, an increase in *CBF* transcript levels was observed 4–12 h later after the cold exposure [86][87][88]. The gene induction relies on a temperature threshold dependent on the species and occurs in a 10 °C to 12 °C range in winter barley, wheat, and rye [89][90]. The result of the ICE-CBF-COR pathway cascade is the activation of the effector genes that modify the plant metabolism, conferring frost tolerance [91]. The temperature must be below 10 °C for 4–6 weeks in short-day conditions to complete the adaptive response in *Triticeae* [92][93]; once the process is completed, crops can withstand freezing at −7/12 °C for barley, −9/18 °C for wheat, and −18/−30 °C for rye [82][94].

Interestingly, no receptors receiving the low temperature signal have been identified so far [78]. The ICE-CBF-COR pathway is activated by an increase in intracellular Ca^{2+} concentration by either rigidification of the plasma membrane or ligand-activated channels. After calcium influx into the cytosol and its binding by Ca-sensors (such as calmodulins), a signal cascade based on calcium-binding proteins (CBPs) is initiated to target the *ICE* (inducers of *CBF*-gene expression) transcription factors that up-regulate the *CBF* genes [95][96]. *ICE* transcription factors belong to the MYC family and MYC subfamily of bHLH (basic helix–loop–helix) [97] and are known as positive *CBF* expression regulators, considered to act upstream of the low-temperature signaling pathway [97][98][99].

In addition, temperature variation is not the only environmental stimulus influencing the expression of the *CBFs*; also, circadian rhythms and light characteristics (i.e., quality and quantity) have been reported to be involved in cold acclimation [83]. For example, recent studies showed that the expression of some barley *HvCBF* genes (*HvCBF2A*, *HvCBF4B*, *HvCBF6*, and *HvCBF14*) is regulated by the circadian rhythm and day length [83][100][101]. In warm conditions, *CBF* genes show high expression late in the afternoon and continue to decrease early in the night [100]. The peak of expression is 8–12 h after the dawn, either in short- or long-day conditions. However, the amplitude of the peaks is wider in short-day compared to long-day conditions [102]. This peak does not coincide with the coolest period of the day, but it may be functional for the preparation of the cell for the subsequent cold of the night [63]. The circadian clock regulates the expression of several genes. The G-Box-like motifs are necessary for transcriptional regulation by the circadian pseudo-response regulators binding basic helix–loop–helix transcription factors [103]. Other environmental stimuli are the light spectra and intensity; several works have elucidated that the variation of light spectra and light intensity might modulate the expression of *CBF* genes and also increase frost tolerance [46][104][105][106][107][108].

The vernalization process is controlled by three major genes: *VRN-1*, *VRN-2*, and *VRN-3* [109][110]. *VRN-1* is a flowering promoter that was shown to be an AP1-like MADS-box transcription factor, whose expression leads the plant to the transition from the vegetative to the reproductive phase [111][112]. Moreover, it was also proven to be involved in cold acclimation and frost tolerance [113]. *VRN-2* is a dominant flowering repressor down-regulated by vernalization treatment and includes two tandem zinc finger-CCT domain genes (ZCCT1 and ZCCT2) [31][114]. *VRN-3*, the main integrator of the photoperiod and vernalization signals that lead to the transition of the apical meristem [115], is homologous to the flowering integrator FLOWERING LOCUS T gene in Arabidopsis [116][117]. Due to their diploid nature, WH barleys can be considered a model for vernalization in Triticeae crops [24]. *VRN-H2* is expressed in long and neutral day conditions [118]. In autumn, when plants are still in the seedling stages, *VRN-H2* is highly expressed and represses the *VRN-H3*, which is the flowering induction gene [115][119]. The repression of *VRN-H3* also limits the expression of *VRN-H1* [111][112]. Exposure to cold temperatures activates *VRN-H1* and results in the down-regulation of *VRN-H2* and, consequently, the release of *VRN-H3* from repression [31][109]. After prolonged cold exposure, the expression level of *VRN-H1* reaches a threshold necessary to induce the transition phase, up-regulating *VRN-H3*, and initiating the flowering process [119]. Exposure to long-day conditions mediated by the photoperiod genes *PPD-H1* and *PPD-H2* is also necessary [120].

The expression of *VRN-H1* changes in function of the plant growth habit; as mentioned above, in winter genotypes, the expression of the recessive *vrn-h1* allele is induced by prolonged periods of cold [121][122]. The quantity of time under cold and short-day conditions necessary to satisfy the vernalization requirements varies with the geographical origin of the genotype and the environmental condition, changing from 6 to 10 weeks of temperatures in a range between 6 °C and 2 °C under short-day conditions [31][92][93][123]. In spring genotype, the dominant *Vrn-h1* allele has a constitutive high expression that rapidly induces the transition [124]. The vernalization in wheat is more complex compared to barley due to the presence of three homoeologous *VRN-A1*, *VRN-B1*, and *VRN-D1* loci mapped on the long arm of chromosome group 5 [125], with the major effect of *VRN-A1* in determining the growth habit [126].

The interaction between *VRN-1/FR-1* and *FR-2* (*CBFs*) has also been demonstrated [127]; *VRN-H1* can bind promoter regions of the *CBF* genes, inducing a reduction of their transcription levels; nevertheless, the mechanism is still not fully understood [128][129].

However, a question remains: how does the ICE-CBF-COR pathway confer frost tolerance?

4. FR-2 in Barley—A Synergistic Action of CNV and HvCBF14?

The efforts to identify the molecular mechanisms underlying *FR-2* in *Triticeae* crops were based on integration studies on structural and functional aspects of the locus. Several barley genotypes have been sequenced, and a pan-genome has been assembled [130]. Thanks to this data, *FR-H2* was studied in different frost-prone and tolerant genotypes to evaluate the *CBFs* position in the cluster, the variability in the structure, the *CBF* coding sequences, and the promoter regions [24][131][132][133][134].

Initially, four *HvCBF* genes (*HvCBF3*, *HvCBF6*, *HvCBF9*, and *HvCBF14*) have been selected as candidate genes due to the presence of homologs in other *Triticeae* already reported to be involved in cold resistance [63][135]. Then, *HvCBF14* has emerged as the major candidate for the frost tolerance in barley in several works [46][52][107][128][135][136][137]. Two SNP linked to *HvCBF14*, associated with frost tolerance, were identified by Fricano and colleagues [135] in an association analysis of a panel of European cultivars, landraces, and *H. spontaneum* accessions. Later on, a correlation between frost tolerance and the same *HvCBF14* gene in spring haplotypes was demonstrated by Guerra et al. [136], who investigated a panel of 403 accessions with exome sequencing-based allele mining.

Structural variation is recognized as a common feature and evolutionary force of genomes, where copy number variations (CNV) and resulting gene dosage effects determine a number of traits/phenotypes in plants [138][139][140][141][142]. One of the first clear associations between CNV and phenotype was reported for the boron-toxicity tolerance in barley [143]. The first indication of the involvement of CNV at the *FR-H2* locus and frost tolerance in *Triticeae* was reported by Knox et al. [144]. Two *HvCBF2* paralogs (*HvCBF2A* and *HvCBF2B*) and multiple copies of the *HvCBF2A-HvCBF4B* genomic segment were identified in the frost-tolerant genotypes ‘Dicktoo’ and ‘Nure’. On the other hand, genomic clones of ‘Morex’ and ‘Tremois’ showed only single paralogs of *HvCBF4* and *HvCBF2.* Results on CNV were confirmed by sequencing the same physical region in the tolerant ‘Nure’ [128] and susceptible ‘Morex’ [131] genotypes, in successive, independent experiments. Francia et al. [145] and Rizza et al. [120] confirmed that frost-resistant varieties of barley were characterized by a high number of copies for the *HvCBF2* and *HvCBF4* genes and maintained two distinct *HvCBF2* paralogs (*HvCBF2A* and *HvCBF2B*). In summary, the influence of structural variation on determining the *FR-2* effect remains a long-standing conundrum and leaves an open question: is the phenotype influenced by the expression of the *HvCBF14* gene alone, or are multiple copies of other *CBFs* involved? Is the number of copies at the *HvCBF2A–HvCBF4B* segment relevant for the modulation of the *HvCBF14* expression level and the resulting phenotype?

The influence of the gene dosage (i.e., the pool of transcripts) of a specific *CBF* on the expression of other elements of the ICE-CBF-COR pathway was tested/evaluated in two elegant experiments. The overexpression of *HvCBF2* in the spring susceptible cultivar ‘Golden Promise’ resulted in higher transcript levels of *COR* genes; *HvCOR14B* and *HvDHN5*, already at warm temperatures, were raised strongly at cold temperatures. Moreover, higher transcription levels of *HvCBF12*, *HvCBF15*, and *HvCBF16* and greater frost tolerance were observed in overexpressed lines [146]. According to authors, *HvCBF2* may activate target genes at warm temperatures, and transcript accumulation for some of them is greatly enhanced by cold temperatures.

The influence of CNV at *HvCBF2A-HvCBF4B* on the expression levels of *HvCBF12*, *HvCBF14*, and *HvCBF16* was investigated using the high frost-tolerant variety ‘Admire’ and different descendent genotypes (namely, Missouri barley—MO B lines) by Dhillon and colleagues [101]. MO B lines harboring a higher number of copies of *HvCBF2A-HvCBF4B* had higher expression levels of all three genes under normal growth conditions.

5. FR-2 in Wheats—CBF Cluster Ploidy

While barley has a diploid genome (2n = 2x = 14, HH) of 5 giga base pairs (Gbp) [147], tetraploid durum wheat (2n = 4x = 28, AABB) has 12 Gbp [148], and hexaploid wheat (2n = 6x = 42, AABBDD) has approximately 17 Gbp [149]. Thereby, *FR-2* organization in wheat is more complex compared to barley due to the contribution of one/multiple homoeologous chromosome regions and redundancy caused by the ploidy level [150][151][152]. Wheat exhibits high variability in frost tolerance traits, given that hexaploid wheat genotypes (AABBDD) exhibit greater frost tolerance than diploid (AA) and tetraploid genotypes (AABB) [153][154].

The first works on *CBF/FR-2* in wheat were carried out in mapping populations of einkorn diploid wheat (*Triticum monococcum* L.), which is the ancestor of the A genome in hexaploid wheat and is considered a practical model for the functional genetics of wheat [67][71][72][86][125][155][156]. First expression studies showed the association of *CBF* genes at the *FR-A*^{m}*2* with the expression of *COR* genes and frost tolerance [67][86].

TmCBF12, *TmCBF14*, *TmCBF15*, and *TmCBF16* (central cluster) expression levels were significantly associated with frost tolerance, measured as regrowth capacity after stress. Moreover, a high-density mapping study confirmed that *TmCBF12*, *TmCBF14*, and *TmCBF15* were the candidates for the observed differences [72].

Thanks to the works carried out on *T. monococcum*, the number and position of *CBF* genes in bread wheat were identified in different works. While in barley, a CNV has never been associated with a central cluster at *FR-H2* (see above), in diploid and polyploid wheat, a lower copy number of *CBF14* in the B genome compared to the A and D genomes was reported [157].

TaCBF14 and *TaCBF15* were associated with increased frost tolerance in doubled haploid (DH) mapping populations of ‘Norstar’ × ‘Winter Manitou’ and ‘Norstar’ × ‘Cappelle-Desprez’ (all WH genotypes) [155]. Higher levels of *TaCBF14* induced by temperature shift and blue light were reported in winter wheat ‘Cheyenne’ [137].

Recent studies expanded the investigation of ICE-CBF-COR interconnection with other environmental stimuli with high-throughput functional analysis [97][152][158][159][160][161]. Guo et al. [97] carried out RNAseq and qPCR analysis in wheat tissues under different stress conditions, observing the expression of 53 genes belonging to the ICE-CBF-COR signaling cascade that revealed tissue-specific expression patterns of the *ICE*, *CBF*, and *COR* genes under different stress conditions. Six genes related to the ICE-CBF-COR pathway (*TaCBF11a*, *TaCBF16b*, *TaICE1a*, *TaICE1d*, *TaCOR5a*, and *TaCOR6d.1*) were induced by all treatments (drought, heat, drought, and cold). Three genes, two *CBFs* and one *COR* (*TaCBF1b*, *TaCBF4a*, and *TaCOR3b*), were induced specifically by cold.

Zheng et al. [161] carried out an isoform sequencing experiment at four leaf stages under frost stress (at −6 °C), and expression levels of *TaCBF8a* and *TaCBF14a* decreased, while *TaCBF6a, TaCBF9a*, *TaCBF10a*, *TaCBF13a*, and *TaCBF15a* expression levels increased. Recently, Wang et al. [158] performed a transcriptome analysis during the vernalization (4 °C) time-course with sampling from one to six weeks. Six *CBF* genes of the III subgroup were highly expressed exclusively before vernalization (“steady state” at 22 °C), while 10 *CBFs*, mainly from the IV subgroup, were not expressed before and were highly induced by vernalization, reaching the highest level of expression after three weeks and decreasing after five/six weeks of treatment. Two different homologs of the MYC-like bHLH transcription factor *ICE* were identified in wheat as *TaICE41* and *TaICE87* [98], and their overexpression in Arabidopsis enhanced frost tolerance after hardening. The recent availability of the wheat genome allowed us to locate three *TaICE1* genes on the long arm of homoeologous chromosome group 3; these genes were shown to be induced by drought and cold treatment [97]. In addition, Wang et al. [158] reported that *TaICE41* was expressed at extremely high levels after five weeks of vernalization.

6. FR-2 in Rye—Evidence of ICE1 Involvement in the Tolerance

Compared to other *Triticeae* crops, rye is uniquely tolerant to biotic and abiotic stresses, showing high yield potential under marginal conditions [162][163][164]. However, it received little attention in terms of breeding efforts and genomic research due to its limited distribution worldwide. Likewise barley and rye have a diploid genome (2n = 2x = 14, RR); however, it has not become a reference crop for genomic analysis in the *Triticeae* tribe due to its elevated level of allogamy and the fact that the first chromosome-scale assembly of its large 7.9 Gbp genome was released only recently, in 2021 [165], showing 92% of repetitive elements [162][166][167][168][169].

Investigation of rye genome evolution and chromosome synteny [169] revealed, as expected, that the chromosome 5R harboring *FR-2* and *FR-1* loci is entirely collinear with wheat homoeologous chromosome group 5. Initially, eleven *ScCBF* genes were isolated in a winter rye genome, and nine of them were mapped on chromosome 5R with a cluster organization (*FR-R2*) [62]. Subsequently, Jung and Seo [162] identified 12 new *CBF* genes and five new *CBF* gene alleles. The genome assembly [165] reported CNV for 4 members of CBF Group IV between tolerant and resistant varieties.

Concerning the structure of the locus, *FR-R2* haplotyped variation has been associated with different frost tolerance levels in different rye genotypes [165][170].

7. New Frontiers for CBF Genes? CBF Genes in the Drought Stress Adaptative Response

CBF genes are members of a large protein family of the C-repeat binding factor/Dehydration responsive element-binding 1 (*CBF/DREB1*), known to be involved in the growth and development processes and responses to different environmental stressors (cold, heat, drought, salt, etc.) [171]. *CBF* genes could thus have in *Triticeae* a role in a cross-talk between the cold and drought response pathways, as already reported for Arabidopsis [54][172].

The *CBF/DREB1* regulon modifies the plant metabolism in conditions of water deficiency, and their activation might also be triggered by drought conditions in the seedling phase [97][173]. In several drought-responsive genes, such as *AtRD29A* (responsive to desiccation), *HvDHN1*–*HvDHN11* (dehydrin), or *AtCOR6.6*, a DRE/CRT motif is present in the promoter regions. When drought conditions occur, the plant reduces its water uptake by closing the stomata, which also reduces its CO_2 uptake, which results in a reduction in the photosynthesis and physiological activities. To cope with drought stress, plants activate several morphological and physiological modifications to conserve water and reduce its loss. The molecular response to drought follows a similar pathway to cold acclimation due to the same trigger of water scarcity, which activates both responses. As already summarized, water deficit activates, like low temperature stress, two different signaling pathways: ABA-dependent and ABA-independent [81]. The interaction between *CBF* genes in hormone-mediated acid abscisic (ABA) pathways has been reported [174][175]. In *A. thaliana*, the ABA-independent pathway is regulated by *AtCBF4*, which increases the production of a class of small, highly expressed, and stress-inducible proteins called late embryogenesis abundant (LEA), protecting the cellular membranes and the cytoskeleton from desiccation [172][176]. Interestingly, it has been shown in *A. thaliana* that *ABA-responsive* genes contain in the promoter regions both the ABA-response cis-element ABRE/ABF and the CRT/DRE motif [177]. Overall, drought stress in barley and wheat can have a significant negative impact on plant growth, yield, and grain quality; however, plants have evolved mechanisms to cope with water scarcity and to survive in dry environments [178]. Nevertheless, which *CBF* genes and which pathways are activated have not been determined yet [44][100][171]. In a study of *A. thaliana* transgenic lines, the overexpression of *AtCBF1* and *AtCBF3* genes resulted in an increase in drought tolerance [179]. A review of the conservative role of *CBF* genes throughout the *Poaceae* family reported rice *OsDREB1A* localized in the cluster *OsDREB1H*, syntenic with the *FR-2* locus on chromosome 5 of *Triticeae* involved in chilling tolerance [52]. However, few examples of studies of the role of *CBF* genes in drought tolerance are available for barley and wheat.

A common phenotypic response observed in transgenic lines overexpressing *CBF* genes in different crops can be identified as an increased tolerance to frost and/or drought and modified growth and development, as originally reported for Arabidopsis [171][179]. Overexpression of two *CBF/DREBs* (*TaDREB3* and *TaCBF5L*) in wheat and barley was reported to lead to an increase in drought and frost tolerance in transgenic barley. Moreover, in transgenic wheat, the *TaCBF5L* gene significantly increased the grain yield under severe drought during flowering [180]. Javadi and colleagues mined available GeneChip microarray data [181] in order to detect key genes involved in drought tolerance in barley and identified hub genes from the AP2 and NAC families that might be among the key TFs that regulate drought-stress response in barley. What is interesting is that *HvCBF6* (distal cluster of *FR-H2*) was included among the hub genes. In rye, the PEG treatment (drought condition simulation) revealed that there is a specific type of response to stress among *ScCBF* genes; most of them were highly responsive to cold stress, whereas *ScCBF2* and *ScCBF7b* were induced by water deprivation and were almost insensitive to low temperature [162]. Guo and colleagues [97] characterized the expression profile of the *ICE-CBF-COR* pathway in different wheat tissues under different stress conditions. Authors showed that *TaCBF11a*, *TaCBF16b*, *TaICE1a*, *TaICE1d*, *TaCOR5a*, and *TaCOR6d.1* were induced by drought, and the induction level was higher in tolerant genotypes [160].

The overlapping of cold/frost and drought conditions is a relatively unexpected new form of combination of abiotic stress, and it usually happens during the late autumn, after sowing, when winter genotypes are in the seedling phase. The drought stress in the seedling phase induces root architecture modification that might act as a constitutive resistance mechanism, useful when the stress re-occurs in other phenological phases [182][183][184]. As observed in numerous studies in the past years, *CBF* overexpression in the model plant Arabidopsis enhances abiotic stress tolerance but, on the other hand, reduces growth. *CBF* genes are known to interact with plant hormones [81], and the current model of CBF-GA (gibberellic acid) interplay proposes that overexpression of *CBFs*, either via cold induction or by transgenic means, stimulates the accumulation of DELLAs. Those growth-repressing proteins act downstream in the GA signaling pathway, leading to stunted growth. As far as the underlying molecular mechanism is concerned, in warm temperatures, DELLAs interact with JAZs to prevent JAZs binding to *ICE1*, leading to its inactivation. In cold temperatures, *ICE1* is modified to gain the function for activation of *CBF* transcription [185]. Understanding the relationship between *CBF* genes, GA and DELLA proteins might help to get an overall picture of the role of *CBFs* in plant physiology. One of the new frontiers that regard *CBF* genes is to evaluate their contribution in the tillering phase, crucial in the growth and development of wheat and barley, as it directly influences the potential yield and overall productivity of cereal crops [186]. Moreover, in this phase, winter cereals reach the maximum of their stress tolerance [28][82][94]. The main actors in tillering formation are gibberellic and abscisic acids; moreover, the roles of *VRN-1* and *VRN-2* and the photoperiod response gene *PPD-1* have been described [187][188][189]. All these components interact with *CBF* genes; however, mechanisms of interaction are still not clear.

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