



REVIEW PAPER

# Molecular and genetic bases of heat stress responses in crop plants and breeding for increased resilience and productivity

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## Abstract

To ensure the food security of future generations and to address the challenge of the ‘no hunger zone’ proposed by the FAO (Food and Agriculture Organization), crop production must be doubled by 2050, but environmental stresses are counteracting this goal. Heat stress in particular is affecting agricultural crops more frequently and more severely. Since the discovery of the physiological, molecular, and genetic bases of heat stress responses, cultivated plants have become the subject of intense research on how they may avoid or tolerate heat stress by either using natural genetic variation or creating new variation with DNA technologies, mutational breeding, or genome editing. This review reports current understanding of the genetic and molecular bases of heat stress in crops together with recent approaches to creating heat-tolerant varieties. Research is close to a breakthrough of global relevance, breeding plants fitter to face the biggest challenge of our time.

**Keywords:** Breeding, climate change, cultivated plants, food crops, food security, global warming, heat stress, omics, phenomics.

## Introduction

Current analysis conducted by scientific communities including NASA’s Goddard Institute for Space Studies (GISS) indicates that the average global temperature on Earth has increased by ~0.8 °C since 1880. Two-thirds of the warming has

occurred since 1975, at a rate of roughly 0.15–0.20 °C per decade (Lorenz *et al.*, 2019). Moreover, the Intergovernmental Panel on Climate Change (IPCC) in its last report assesses that even limiting global warming to just 1.5 °C would require

an unprecedented change in many aspects of society (<https://www.ipcc.ch/sr15/>).

For many years, scientists have studied the physiological mechanisms underlying heat stress response (HSR) and tolerance in plants (Fahad *et al.*, 2017; Prasad *et al.*, 2017; Govindaraj *et al.*, 2018). However, after the discovery of the molecular responses and regulation of heat shock proteins (HSPs) and the activation of other genes, understanding of the HSR process became more mechanistic (Key *et al.*, 1981; Altschuler and Mascarenhas, 1982). Major advances have been made in the molecular mechanisms of HSR (Ohama *et al.*, 2017) and identification of genes or quantitative trait loci (QTLs) associated with heat tolerance in plants.

The production of plants with new alleles in HS-responsive genes and the possibility of testing these plants on innovative phenotyping platforms offer the opportunity fully to establish the role of these genes in the HSR and to develop crop plants with an increased tolerance to heat (Comastri *et al.*, 2018).

## Temperature stress, crop yield, and food security

Temperature is one of the major environmental factors which affect plant growth, development, and yield. Temperatures persistently above optimal for plant growth may induce HS and reduce yields. At some threshold, they will be lethal. Extreme heat events can be measured in different ways: the maximum temperatures reached (intensity), how often the events occur (frequency), and how long they last (duration). HS has negative effects on crop physiology (e.g. decreased photosynthesis, increased respiration) and plant growth and yield (Prasad *et al.*, 2017). Another adverse effect of HS is the negative influence on the plant root system, which provides support, nutrient and water uptake, and transport to other plant organs (Valdés-López *et al.*, 2016), resulting in disrupted pollination, flowering, root development, and root growth stages (Sehgal *et al.*, 2017; Cho, 2018).

In many species, for both cool and warm seasons, yield reduction after HS is observed as a consequence of decreasing seed- or fruit-set percentage (Otero *et al.*, 2011; Shah *et al.*, 2011; Singh and Jwa, 2013; Jangid and Dwivedi, 2016; Fahad *et al.*, 2017; Sehgal *et al.*, 2017; Comastri *et al.*, 2018; Devasirvatham and Tan, 2018; Govindaraj *et al.*, 2018). In wheat, exposure to short episodes (2–5 d) of HS (>24 °C) at the reproductive stage (start of heading) resulted in substantial damage to floret fertility, while a mean daily temperature of 35 °C caused total failure. Increasing the duration of high temperature at this stage reduced the grain weight linearly (Maestri *et al.*, 2002; Prasad and Djanaguiraman, 2014); similarly for pea (Bhattacharya, 2019), lentil (Barghi *et al.*, 2012), and chickpea (Wang *et al.*, 2006). An extensive review on the threshold temperatures for several crop species was reported by Kaushal *et al.*, 2016. Table 1 shows threshold temperatures in vegetative and reproductive development for several crop species, together with literature indications about the losses (or gains) attributed to HS alone.

HS can impair several physiological processes linked to seed size and quality. HS during grain filling markedly decreased starch accumulation in wheat (Hurkman *et al.*, 2003), rice

(Yamakawa and Hakata, 2010), and maize (Yang *et al.*, 2018). The levels of sugars such as fructose, sugar nucleotides, and hexose phosphate also declined due to HS (Yang *et al.*, 2018). The decrease in sugars may be related to assimilate utilization for purposes other than edible component production (Asthir *et al.*, 2012). In maize, waxy grain starch content decreased, whereas protein content increased, resulting in a change of grain quality (Yang *et al.*, 2018). Moreover, increasing temperature and CO<sub>2</sub> reduced protein and micronutrient content in grain (Chakraborty and Newton, 2011) and soybean (Li *et al.*, 2018). In soybean under HS, the nutritional value of total free amino acids was reduced together with total protein concentration, while the oil concentration was significantly increased. As a general evaluation, reductions in total yield are mainly due to an alteration in balance of the source and sink activities that take place under HS.

The capacity of crop plants to overcome temperature stress has been interpreted in terms of avoidance, escape, or tolerance (Osmond *et al.*, 1987). Avoidance is any mechanism that permits the plant to be or to become non-susceptible to the stressor effect, annulling in this way most of its deleterious effects (Hasanuzzaman *et al.*, 2013). In escape, plants can alter their growth cycle before the stress hits hard, such as anticipating reproduction or shedding vegetative structures. From the agronomic point of view, tolerance is certainly more interesting; being based on the endurance of the plant in stress conditions, it does not involve substantial modification of the growth habit with potential deleterious effects on yield. A heat-tolerant plant is therefore inclined to continue its growth cycle quite independently of the stress (Barnabás *et al.*, 2008).

## The contributions of ‘omics’

Conventional plant breeding strategies based mainly on phenotype selection and qualitative genetics have led breeders, after the green revolution, to achieve continuous increases in seed yield and improved yield stability, independently of the environmental cost of achieving them (Setia and Setia, 2008). However, the growing worldwide demand for enhancing yields of major crops is placing pressure on breeding programs to provide elite cultivars more adaptable to the ongoing changes. The complexity of the information needed to meet this challenge has prompted advances in understanding the biochemical and molecular processes that underlie important metabolic, physiological, and developmental traits which affect the ability of plants to cope with the upcoming climate change. This has provided new insights into how plants function, and promoted the development of new scientific disciplines, mainly based on high-throughput approaches.

The progress of ‘omics’ technologies, in particular genomics, transcriptomics, proteomics, and metabolomics, has enabled direct and unbiased monitoring of the factors affecting crop growth and yield in response to environmental threats. Overall, omics constitute powerful tools to reveal the complex molecular mechanisms underlying plant growth and development, and their interactions with the environment, which ultimately determine yield, nutritional value (Setia and Setia, 2008; Soda and Wallace, 2015), and the required level of agricultural inputs.

**Table 1.** Yield losses due to heat stress in cool and warm season crops

Species	Threshold temperatures for the species <sup>a</sup>	World production in 2017 <sup>b</sup> (kg ha <sup>-1</sup> )	Average yield reduction (%)	Reference
<b>Cool-season crops</b>				
Barley ( <i>Hordeum vulgare</i> L.)	Not reported	3136	15	Weichert et al. (2017)
Chick pea ( <i>Cicer arietinum</i> L.)	15–30 °C for growth, 25 °C for reproductive growth	1015	19–50	Devasirvatham and Tan (2018)
Citrus ( <i>Citrus</i> spp.)	35 °C for vegetative growth	9600	N/A	N/A
Lentils ( <i>Lens culinaris</i> Medik.)	Not reported	1153	38–58	Sita et al. (2018)
Spinach ( <i>Spinacia oleracea</i> L.)	Not reported	29 993	50	Yan et al. (2016)
Wheat ( <i>Triticum</i> spp.)	20–30 °C for vegetative growth, 15 °C for reproductive growth	3531	6	Lobell et al. (2011); Zampieri et al. (2017); Comastri et al. (2018)
<b>Warm-season crops</b>				
Grapes ( <i>Vitis vinifera</i> L.)	Not reported	10 716	35–50	Greer and Weedon (2013)
Maize ( <i>Zea mays</i> L.)	33–38 °C for photosynthesis and pollen viability	5755	7–40	Valdés-López et al. (2016); Zhao et al. (2017); Meseka et al. (2018); Prasad et al. (2018)
Peanut ( <i>Arachis hypogaea</i> L.)	29–33 °C for vegetative growth, 39–40 °C for seed set and yield	1686	6	Prasad et al. (2001)
Potato ( <i>Solanum tuberosum</i> L.)	Not reported	20 111	18–23	Hancock et al. (2014)
Rapeseed ( <i>Brassica napus</i> L.)	About 30 °C for flowering	2195	Up to 85%	Koscielny et al. (2018); Sparks (2018)
Rice ( <i>Oryza sativa</i> L.)	33 °C for biomass, 35 °C limiting for grain formation and yield	4602	3	Zhao et al. (2017)
Sorghum [ <i>Sorghum bicolor</i> (L.) Moench]	26–34 °C for vegetative growth, 40 °C for reproductive growth and yield	1416	17–44	Tack et al. (2017)
Soybean [ <i>Glycine max</i> (L.) Merr.]	26–36 °C for reproductive development, 39 °C lethal	2854	3–7	Valdés-López et al., 2016; Zhao et al. (2017)
Sunflower ( <i>Helianthus annuus</i> L.)	Not reported	1804	10–70	Debaeke et al. (2017)
Tomato ( <i>Solanum lycopersicum</i> L.)	37 °C for vegetative growth, 28–30 °C for reproductive development	37 600	28	Snider et al. (2012); Lamaoui et al. (2018)

<sup>a</sup> Data from Luo (2011) and Kaushal et al. (2016).

<sup>b</sup> Data obtained by world production and world cultivated extension for each crop, from FAOSTAT 2017, <http://www.fao.org/faostat/en/#data/QC/visualize>.

The following sections provide some examples showing the successful application of omics in crop improvement.

### Genomics and transcriptomics

Molecular responses to HS have been investigated in many plant species to identify the complex processes and pathways regulated in acclimation and protection against temperature stress (Qu et al., 2013; Driedonks et al., 2016). Regulation of gene expression through transcriptional and post-transcriptional mechanisms is certainly linked to both stress recognition and stress response; this aspect has been investigated at different stress levels and comparing different genetic resources. The conventional transcriptomic approach has been applied to study gene expression changes under stress conditions in many crop species, such as rice (Sarkar et al., 2014; González-Schain et al., 2016; Mangrauthia et al., 2017), tomato (Frank et al., 2009; Bitá et al., 2011), barley (Mangelsen et al., 2011), maize (Frey et al., 2015; Shi et al., 2017b), wheat (Qin et al., 2008), soybean (Chung et al., 2013; Gillman et al., 2019), brassica (Dong et al., 2015), and grape (Liu et al., 2012a). More recently, application of advanced genome-wide transcriptome analyses has elucidated the roles of relevant genes from HS perception to signal transduction and stress response (Table 2). In general, most of the HS-responsive genes are involved in

primary and secondary metabolism, translation, transcription, regulation, and responses to processes such as calcium, phytohormone, sugar, and lipid signaling, or protein modifications including phosphorylation (Jha et al., 2014; Takahashi and Shinozaki, 2019). Up-regulation under HS conditions is confined mainly to transcription factors and HSPs.

The activation and production of heat shock factors (HSFs) and HSPs and the increase in reactive oxygen species (ROS)-scavenging activity play a key role in the responses and acclimation of plants to HS (Maestri et al., 2002; Driedonks et al., 2016; Comastri et al., 2018). ROS-related genes are within the main up-regulated category under HS in different plant species (Chao et al., 2008; Chou et al., 2012; Mittal et al., 2012; Suzuki et al., 2014) and have been associated with basal heat tolerance (Almeselmani et al., 2006, 2009; Kang et al., 2009; Bhattacharjee, 2012). Moreover, ROS play an important role as signal molecules involved in the transduction of intracellular and intercellular signals controlling gene expression and activity of anti-stress systems (Petrov and Van Breusegem, 2012), suggesting a role for ROS in the activation of HSFs during HS (Driedonks et al., 2016).

Both HSFs and HSPs are central to the HSR and in the acquisition of thermotolerance in plants (Scharf et al., 2012; Ohama et al., 2017). As a result of advances in whole-genome sequencing, additional information has been gathered for the

**Table 2.** Review of the transcriptomic, proteomic and metabolomic analyses performed to dissect the mechanisms involved in the heat stress response

Species	Primary stress	Secondary stresses	Tissue or development stage analyzed	Simulation conditions	Molecular techniques applied	References
Barley	Heat	N/A	Anthesis	42 °C	Transcriptomics (Affymetrix Barley1 GeneChips)	Mangelsen <i>et al.</i> (2011)
Barley	Heat	Drought	Plant leaf	26 °C	Metabolomics IC-MS/MS	Templer <i>et al.</i> , (2017)
Barley	Heat	Mild drought and combination	Flag leaves	30 °C+50% FC	Transcriptomics (RNA-seq)	Cantalapiedra <i>et al.</i> (2017)
Chickpea	Heat	N/A	Whole plant development	Up to 42 °C	Proteomics (LC-MS)	Parankusam <i>et al.</i> (2017)
Chickpea	Heat	General oxidative stress	Plant leaf	37 °C	Targeted metabolomics	Salvi <i>et al.</i> (2018)
Citrus	Heat	Drought	Plant leaf	40 °C	Metabolomics GC-MS LC-MS	Zandalinas <i>et al.</i> (2017)
Grape	Heat	Various temperatures	Leaves	35, 40, and 45 °C	Proteomics iTRAQ LC-MS/MS	Jiang <i>et al.</i> (2017)
Grape	Heat	Followed by recovery	Plant leaves	43 °C	Proteomics (iTRAQ LC-MS/MS)	Liu <i>et al.</i> (2014)
Grapes	Heat	N/A	Leaves	45 °C	Transcriptomics (Affymetrix gene chip)	Liu <i>et al.</i> (2012a)
Lentils	Heat	N/A	Pods	Up to 33 °C	Enzyme activities	Sita <i>et al.</i> (2018)
Lentils	Heat	N/A	Leaves and pods	30–50 °C	Enzyme activities	Chakraborty and Pradhan (2011)
Lentils	Heat	Drought, also combined	Leaves and pods	30 °C	Enzyme activities	Sehgal <i>et al.</i> (2017)
Maize	Heat	Drought	Leaves	42 °C	Proteomics (iTRAQ LC-MS/MS)	Hu <i>et al.</i> (2015); Zhao <i>et al.</i> (2016)
Maize	Heat	Drought	Chloroplasts	42 °C	Proteomics (MALDI TOF/TOF MS/MS)	Hu <i>et al.</i> (2015)
Maize	Heat	N/A	Seedlings	32–38 °C	Transcriptomics (RNA-seq)	Frey <i>et al.</i> (2015)
Maize	Heat	N/A	Seedlings	42 °C	Transcriptomics (RNA-seq)	Shi <i>et al.</i> (2017b)
Maize	Heat	High CO <sub>2</sub>	Plant leaf	32 °C	Metabolomics (GC-MS)	Qu <i>et al.</i> (2018)
Mung bean	Heat	Exogenous glutathione	Plant leaves	42°	Targeted lipidomics	Nahar <i>et al.</i> , 2015
Peanut	Heat	N/A	Seedlings	40 °C and 30 °C	Physiological measurements, metabolomics	Singh <i>et al.</i> (2016)
Peanut	Heat	N/A	Leaves	45 °C	Transcriptomics (qRT-PCR), physiological measurements	Chakraborty <i>et al.</i> (2018)
Potato	Heat	N/A	Leaves, tubers	Up to 30 °C	Metabolomic (GC/MS), physiological measurements, transcriptomic (microarray)	Hancock <i>et al.</i> (2014)
Potato	Heat, drought		Leaves	35 °C	Transcriptomics (RNAseq)	Tang <i>et al.</i> (2016)
Potato	Heat	<i>Potato virus Y</i> (PVY)	Leaves	28 °C	Transcriptomics (qRT-PCR)	Makarova <i>et al.</i> (2018)
Potato	Heat		Tubers, skin and phelloderm	33–35 °C	Transcriptomics (qRT-PCR)	Ginzberg <i>et al.</i> (2009)
Rapeseed	Heat	N/A	Flowering	Up to 35 °C	GWAs	Rahaman <i>et al.</i> (2018)
Rapeseed	Heat	N/A	Developing seed	Up to 35 °C	Transcriptomics (95k EST microarray)	Yu <i>et al.</i> (2014)
Rapeseed	Heat, drought	Combination of the two stresses		29±0.5 °C from the 38th day after sowing, 30% field capacity	Metabolomics, physiological measurements	Elferjani and Soolanayakanahally (2018)
Rice	Heat	N/A	Anthers	Up to 37 °C in	Proteomics (iTRAQ LC-MS/MS)	Mu <i>et al.</i> (2017)
Rice	Heat	N/A	Grain and Leaves	30 °C	Transcriptomics (qRT-PCR)	Phan <i>et al.</i> (2013)
Rice	Heat	Open field	Leaves, early milky stage of rice grains, spikelets	42/32, 38, 28 °C	Proteomics (MALDI TOF/TOF MS/MS)	Liao <i>et al.</i> (2014); Das <i>et al.</i> (2015)
Rice	Heat	Cold	Suspension cell	44 °C	Proteomics (label-free in-gel digestion together with LC-MS/MS)	Gammulla <i>et al.</i> (2010)
Rice	Heat	Various temperatures	Seedlings, anthesis	35 °C, 40 °C and 45 °C, 38 °C	Proteomics (MALDI TOF MS/MS)	Han <i>et al.</i> (2009); Jagadish <i>et al.</i> (2010)

Table 2. Continued

Species	Primary stress	Secondary stresses	Tissue or development stage analyzed	Simulation conditions	Molecular techniques applied	References
Rice	Heat	N/A	Anthers	38 °C	Proteomics (label-free in-gel digestion together with LC-MS/MS)	Kim <i>et al.</i> (2015)
Rice	Heat	N/A	Plants at flowering	38 °C for 1 d	Transcriptomics (RNAseq, large-scale qRT-PCR)	González-Schain <i>et al.</i> (2016)
Rice	Heat	N/A	Seeds	Germination at 30 °C (control) and 42 °C (stress)	Transcriptomics (RNA-seq, qRT-PCR)	Mangrauthia <i>et al.</i> (2016)
Rice	Heat and drought	Sugar starvation	Floral organs		Metabolomic and Transcriptomics	Li <i>et al.</i> (2015)
Rice	Heat	Oxidative stress	10-day-old seedlings	42±1 °C for 30 min with 10 mM H <sub>2</sub> O <sub>2</sub>	Transcriptomics (60mer rice 44k array, qRT-PCR)	Mittal <i>et al.</i> (2012)
Rice	Heat	N/A	Pollen	37 °C	Targeted metabolomics	Feng <i>et al.</i> (2018)
Rice	Heat	N/A	Leaves	45 °C	Transcriptomics (RNA-seq)	Fang <i>et al.</i> (2018)
Rice	Heat	N/A	Grains	38 °C	Transcriptomics (RNA-seq)	Liao <i>et al.</i> (2015)
Rice	Heat	Drought exogenous IAA	Plant leaf	40 °C	Target lipidomics	Sharma <i>et al.</i> (2018)
Rice	Heat	Exogenous brassinosteroids	Plant leaf	47 °C	Target lipidomics	Thussagunpanit <i>et al.</i> (2015)
Sorghum	Heat	Drought	Seedlings	28 °C and 50 °C, water withholding, Combination of the stress	Transcriptomics (microarray)	Johnson <i>et al.</i> (2014)
Soybean	Heat	High humidity	Pre-harvest seed	40 °C	Proteomics (MALDI TOF/TOF MS/MS)	Wang <i>et al.</i> (2012)
Soybean	Heat	N/A	3- to 4-week-old plants	45 °C for 3, 6, 24 h	Transcriptomics (qRT-PCR)	Chung <i>et al.</i> (2013)
Soybean	Heat	High CO <sub>2</sub>	Plant leaf	36 °C	Metabolomics (GC-MS)	Xu <i>et al.</i> (2016)
Soybean	Heat	N/A	Roots	40 °C	Proteomics (LC-MS/MS); Transcriptomics (RNA-seq)	Valdés-López <i>et al.</i> (2016)
Soybean	Heat	N/A	Dry, imbibed, or germinated seeds from heat-tolerant and heat-sensitive cultivars	Field conditions with heat stress	Transcriptomics (RNA-seq)	Gillman <i>et al.</i> (2019)
Spinach	Heat	N/A	Leaves	37 °C, 35 °C	Physiological, enzyme activity, proteomic (trypsin digestion and iTRAQ labeling), transcriptomics (NGS)	Yan <i>et al.</i> (2016); Zhao <i>et al.</i> (2018)
Sunflower	Heat	Light	Leaves and immature seed	37 °C	Transcriptomics	Hewezi <i>et al.</i> (2008)
Tomato	Heat	Melatonin		Up to 42 °C	Metabolomics	Xu <i>et al.</i> (2016)
Tomato	Heat	Oxidative stress	Flower buds	36 °C\25 °C for 3 months	Proteomics (SDS-PAGE followed by LC-MS/MS)	Mazzeo <i>et al.</i> (2018)
Tomato	Heat	Lipid antioxidant and galactolipid remodeling	5- to 6-week-old plants	38 °C	Metabolomics (MS)	Spicher <i>et al.</i> (2016)
Tomato	Heat	N/A	Different developmental stages of tomato pollen	38 °C	Proteomics (mass accuracy precursor alignment (MAPA) plus LC/MS)	Chaturvedi <i>et al.</i> (2015)
Tomato	Heat	Waterlogging in open field	Leaves	39 °C	Proteomics (MALDI TOF/TOF MS/MS)	Lin <i>et al.</i> (2016)
Tomato	Heat	N/A	Anthers	32 °C for 2, 6, 16 or 30 h	Transcriptomics (cDNA-AFLP; 90 K Custom TomatoArray 1.0)	Bitá <i>et al.</i> (2011)
Tomato	Heat	N/A	Flower buds	43–45 °C for 2h	Transcriptomics (Affymetrix GeneChip® Tomato Genome Array)	Frank <i>et al.</i> (2009)
Tomato	Heat	N/A	week-old tomato plants	1 h at 39 °C	Transcriptomics (massive analysis of cDNA ends (MACE))	Fragkostefanakis <i>et al.</i> (2015)
Tomato	Heat	N/A	Pollen	38 °C	Metabolomics (LC-QTOF-MS plus LTQ Orbitrap XL, mass spectrometer)	Paupière <i>et al.</i> (2017)

Table 2. Continued

Species	Primary stress	Secondary stresses	Tissue or development stage analyzed	Simulation conditions	Molecular techniques applied	References
Tomato	Heat	N/A	Pollen tubes	37 °C	Targeted metabolomics	Muhlemann <i>et al.</i> (2018)
Tomato	Heat	Cold	Plant leaves	38, 20, 10 °C	Untargeted lipidomics LC/MS	Spicher <i>et al.</i> (2016)
Wheat	Heat	N/A	Seeds in filling stage	37 °C for 4 h	Metabolomics, transcriptomics	Wang <i>et al.</i> (2015)
Wheat	Heat	Lipid alteration	Flowering	Up to 35 °C	Metabolomics	Narayanan <i>et al.</i> (2016)
Wheat	Heat	N/A	Seedlings	Up to 42 °C	Transcriptomics	Comastri <i>et al.</i> (2018)
Wheat	Heat	N/A	Seedlings	35 °C	Proteomics (MALDI TOF/TOF MS/MS)	Gupta <i>et al.</i> (2015)
Wheat	Heat	N/A	Leaves, stems, and spikes, flag leaf	38 °C, 37 °C	Proteomics (iTRAQ LC-MS/MS)	Lu <i>et al.</i> (2017); Kumar <i>et al.</i> (2019)
Wheat	Heat	Open field	Grain	40 °C	Proteomics (MALDI TOF/TOF MS/MS)	Wang <i>et al.</i> (2018)
Wheat	Heat	Low nitrogen	Plant leaf	32 °C	Proteomics (MALDI TOF/TOF MS/MS)	Yousuf <i>et al.</i> (2017)
Wheat	Heat	Drought	Post-anthesis	35 °C	Proteomics (MALDI TOF/TOF MS/MS)	Zhang <i>et al.</i> (2018)
Wheat	Heat	N/A	Flag leaf	35 °C	Proteomics	Wang <i>et al.</i> (2015)
Wheat	Heat	N/A	Leaf of heat-susceptible 'Chinese Spring' (CS) and heat-tolerant 'TAM107' (TAM)	40 °C for 1 h with and without heat acclimation (34 °C, 3 h)	Transcriptomics (wheat genome array)	Qin <i>et al.</i> (2008)
Wheat	Heat	N/A	Flag leaf, seedlings	37/17 °C for 3 days in anthesis stage	Proteomics	Lu <i>et al.</i> (2017)
Wheat	Heat	N/A	Spikelet post-anthesis	35 °C	Metabolomics (LC/HRMS)	Thomason <i>et al.</i> (2018)
Wheat	Heat	Drought	Seedlings	40 °C, 20 % (w/v) PEG-6000	Transcriptomics (RNA-seq)	Liu <i>et al.</i> (2015)
Wheat	Heat	N/A	Plant leaf	35 °C	Lipidomics ICP-MS	Narayanan <i>et al.</i> (2016)
Wheat	Heat	N/A	Pollen	35 °C	Lipidomics ICP-MS	Narayanan <i>et al.</i> (2018)
Wheat	Heat	N/A	Plant leaf	35 °C	Lipidomics ICP-MS/MS	Djanaguiraman <i>et al.</i> (2018)

Abbreviations: cDNA-AFLP, cDNA-amplified fragment length polymorphism; GWAS, genome-wide association study; IAA, indole-3-acetic acid; IC-MS/MS, ion chromatography tandem MS; ICP-MS, inductively coupled plasma MS; iTRAQ, isobaric tags for relative and absolute quantitation; LC/HRMS, liquid chromatography-high resolution MS; MACE, massive analysis of cDNA ends; MALDI TOF/TOF MS/MS, matrix assisted laser desorption/ionization-time of flight tandem MS; MAPA, mass accuracy precursor alignment; N/A, not applicable; NGS, next-generation sequencing; qRT-PCR, quantitative reverse transcription-PCR; QTOF, quadrupole time of flight; RNA-seq, RNA sequencing.

*Hsp* gene family (Chen *et al.*, 2018). HS transcription factors (TFs) involved in heat sensing and signaling are highly conserved both structurally and functionally throughout the eukaryotic kingdom and are key players for the expression of *Hsp* genes (Scharf *et al.*, 2012). The *HSF* gene family has been identified and characterized in several crop species such as grape (Liu *et al.*, 2012b), soybean (Scharf *et al.*, 2012; Chung *et al.*, 2013), maize (Lin *et al.*, 2011), wheat (Xue *et al.*, 2014), rice (Mittal *et al.*, 2009; Jin *et al.*, 2013; Lavania *et al.*, 2018), and tomato (Yang *et al.*, 2016). Progress in genome annotation has led to the development of the specialized HEATSTER database (<http://www.cibiv.at/services/hsf/info#anfang>) which can identify and correctly annotate new *HSF* genes in plant species (Berz *et al.*, 2019).

The involvement of HSPs in the defense response following HS has been extensively reported in several plant species (Park and Seo, 2015; Comastri *et al.*, 2018). Gene expression analysis was performed in tomato leaves applying MACE (massive analysis of cDNA ends), which showed that 2203 genes (9.6% of the total) had enhanced transcript abundance in response to HS (Fragkostefanakis *et al.*, 2015). Those encoding small HSP

(sHSP) family members showed the strongest induction, with nine out of 100 *Hsp40* genes up-regulated in response to heat. *HSF* genes showed basal and stable expression in non-stressed conditions and, for some, a strong induction in response to HS. These studies also reported the importance of TFs in the regulation of HSR, since 92 of the genes up-regulated upon HS are TF genes (*bHLH*, *bZIP*, *ERF*, *MYB*, and *WRKY* families). These are well-known major elements in HSR and thermotolerance, highlighting the complex regulatory networks activated beyond those directly controlled by HSFs. The tomato HsfA1a TF seems to have a unique function as a master regulator for acquired thermotolerance and cannot be replaced by any other HSF (Scharf *et al.*, 2012).

In wheat, 6560 probe sets displayed changes in expression after heat treatment at 40 °C, with or without acclimation at 34 °C; representing *Hsp* genes, *HSF* genes, and genes encoding proteins involved in phytohormone biosynthesis/signaling, calcium and sugar signal pathways, RNA metabolism and ribosomes, as well as primary and secondary metabolism (Kotak *et al.*, 2007; Qin *et al.*, 2008). In barley, the effects of a short-term HS on central developmental functions of the caryopsis

were studied at the transcriptional level (Mangelsen *et al.*, 2011). Over 2000 differentially expressed genes were identified, equally divided between up- and down-regulation. The core HSR includes some conserved processes such as abscisic acid- (ABA) responsive gene activation, HSP-mediated protein folding, calcium signaling, ROS scavenging, and the biosynthesis of compatible solutes, which are rapidly induced. Within the down-regulated genes, it is noticeable that those involved in carbon and nitrogen metabolism and cellular growth, which determine long-term negative effects, differ significantly depending on the plant developmental stage at the time of the stress.

During grain development, the main negative effects of HS are related to the decreased accumulation of storage compounds, which can have a detrimental effect on both seed quality and final yield (Mangelsen *et al.*, 2011; Hurkman *et al.*, 2013). In wheat, HSPs can play a crucial role in gluten formation as a 'glue' between the reserve proteins (glutenins and gliadins) and starch (Maestri *et al.*, 2002). During flowering, a significant reduction in the expression of non-essential photosynthetic genes may constitute an energy-saving strategy to facilitate other key stress responses with the aim of maintaining sugar metabolism and consequently protecting pollen viability (X. Li *et al.*, 2015). Unraveling the complexity of high temperature tolerance may benefit from a systems biology approach (see Fig. 1).

### Proteomics

Protein profiling under HS conditions helps to identify stress-responsive proteins, and the detailed investigation of these proteins reveals their function in stress tolerance mechanisms (Priya *et al.*, 2019). The synthesis and accumulation of HSPs is a prompt response after exposure to high temperature and it is considered one of the most important adaptive strategies to overcome the deleterious effects of HS (Wahid *et al.*, 2007; Keller and Simm, 2018). The majority of HSPs are molecular chaperones involved in protein stabilization and signal transduction during HS (Sung *et al.*, 2001; Arce *et al.*, 2018). HSPs prevent accumulation of proteins with anomalous conformations and eliminate non-native aggregations formed during stress, with ubiquitin-mediated degradation of these proteins (Kotak *et al.*, 2007).

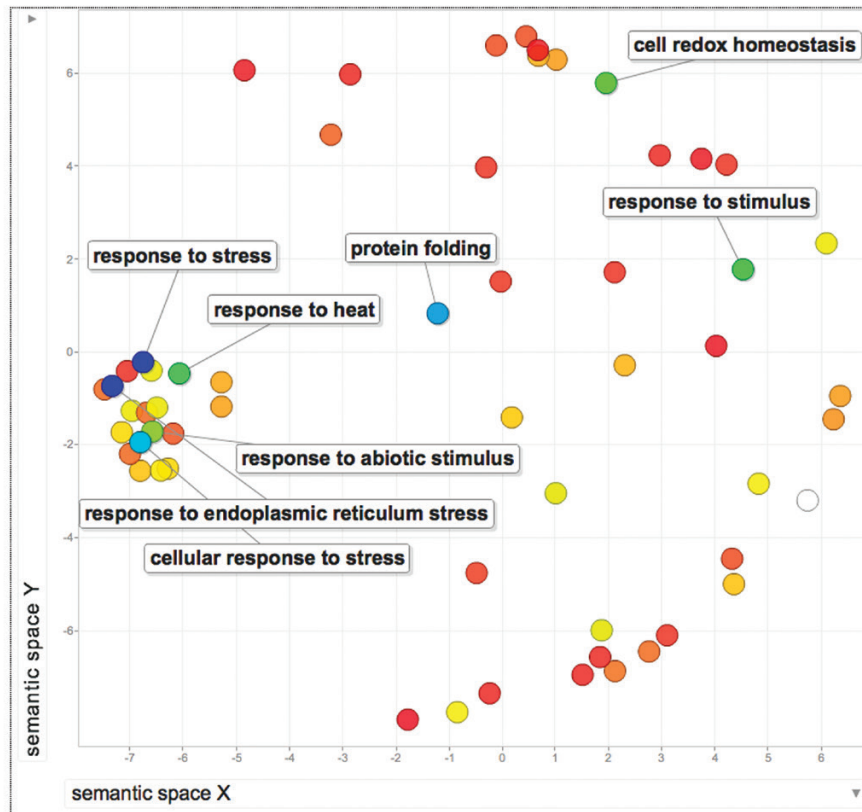
Proteomics allows the study of the direct gene products, which often differ with the level of gene regulation. This technique has been applied to investigate heat responses in rice, wheat, tomato, maize, soybean, grape, and chickpea (for references, see Table 2). The types of technique utilized for these studies have been mostly 2D gel electrophoresis (SDS-PAGE) for protein separation, followed by MS: MALDI-TOF (matrix-assisted laser desorption/ionization-time of flight), MS, or TOF/TOF MS/MS for protein isolation, and iTRAQ (isobaric tags for relative and absolute quantitation) with LC-MS/MS for relative quantification (Zhang *et al.*, 2006; Wiese *et al.*, 2007). Other techniques have been deployed including label-free in-gel digestion together with LC-MS/MS or Orbitrap; SDS-PAGE followed by LC-MS/MS; and mass accuracy precursor alignment (MAPA) plus LC-MS (Chaturvedi *et al.*,

2015). Many successful examples of proteomics applied to the study of HSPs and other HS-induced proteins have been reported (Malcevski and Marmiroli, 2012; Table 2).

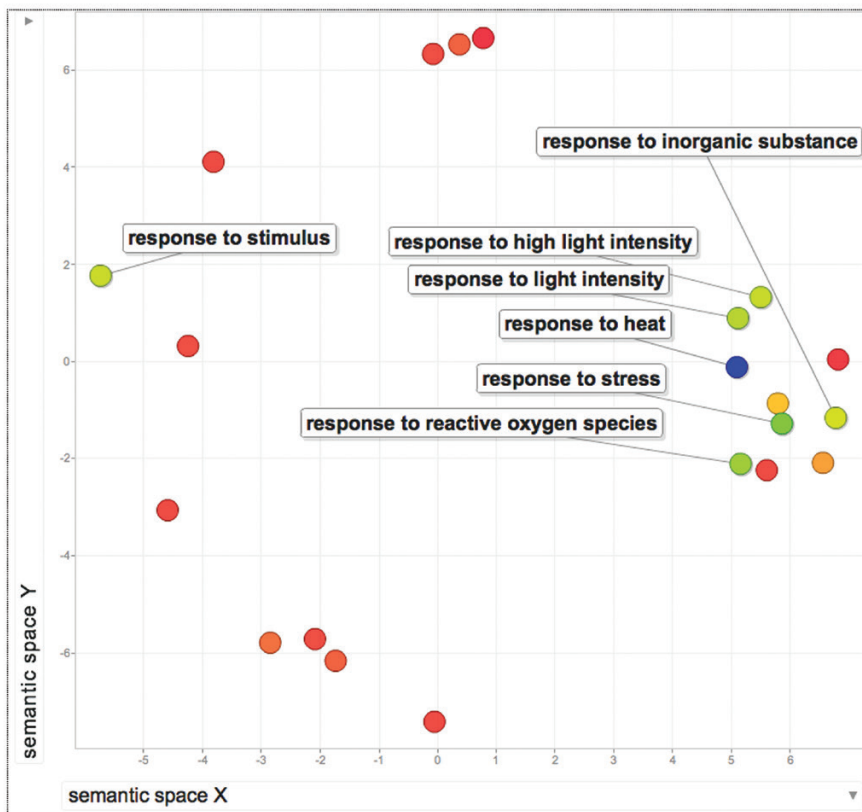
Different stages of plant development have been investigated using proteomics, from seedling, to flower (anthers and pollen especially in rice and tomato), to fruit, but also spikelet and grain maturation. In rice, where HS has been studied in isolation, all classes of HSPs (high and low molecular weight) have been found among the predominant protein categories, although other protein types and Gene Ontology (GO) classes varied extensively according to the part of the plant investigated. For instance, in pollen and anthers, late embryogenesis abundant (LEA) proteins were present in high numbers. Interestingly, proteins related to oxidative stress were identified in most of the studies on high HS, alone or in combination with other stresses. ROS are produced during HSR, which results in an oxidative imbalance within the cell. Furthermore, chloroplast function and photosynthesis are both strongly affected by ROS generated during HS, and it seems that HSPs can prevent ROS damage to the photosystems or the organelle structure. As an example, in maize, it was found that sHSP26 protects chloroplasts under HS (Hu *et al.*, 2015). Other GO categories involved were sugar metabolism, the tricarboxylic acid (TCA) cycle, regulatory proteins, and proteins that function in energy metabolism.

More information on stress-associated active proteins (SAAPs) in wheat has recently been reported (Kumar *et al.*, 2019). This study identified ~4272 SAAPs in wheat using absolute quantification methods. Some of the differentially abundant SAAPs identified were Rubisco, Rubisco activase (RCA), oxygen-evolving extrinsic protein (OEEP), HSP17, superoxide dismutase (SOD), catalase (CAT), and calcium-dependent protein kinase (CDPK). Pathway analysis showed the carbon assimilation pathway, followed by starch metabolism, to be most perturbed under HS in wheat. A positive correlation was established between the expression of SAAPs at transcript and protein levels in wheat under HS (Kumar *et al.*, 2019).

Adaptive responses to HS also involve various post-translational modifications (PTMs) of proteins. There is a detailed literature on the effects of HS on PTMs such as protein phosphorylation in rice and wheat (Chen *et al.*, 2011; Wu *et al.*, 2014). Currently, >300 PTMs have been detected and partly characterized, and the numbers are increasing (Wu *et al.*, 2016). HS has also been shown to enhance the small ubiquitin-like modification (SUMOylation) of particular proteins (Miller and Vierstra, 2011). SUMOylation of accessible lysines on target proteins is mediated in plants by a sequential three enzyme conjugation pathway: the E1 activating enzyme heterodimer (SAE1a or b combined with SAE2), a single E2 conjugating enzyme (SCE1), and at least two E3 ligases (SIZ1 and MMS21/HPY2). In *Arabidopsis thaliana* L. (Heynh), the activity of the HS TF HSFA2 was shown to be regulated by SUMOylation (Cohen-Peer *et al.*, 2010). Moreover, in potato, rapid changes in protein SUMOylation and serine phosphorylation were observed in response to HS (Colignon *et al.*, 2019). In addition, the overexpression of SIZ1 E3 ligase was shown to enhance heat tolerance in tomato (Zhang *et al.*, 2018).



A)



B)

**Fig. 1.** Scatterplots obtained by multidimensional scaling of the matrix of biological process Gene Ontology (GO) terms across transcriptomic data obtained from heat-stressed tomato (A) and maize (B). The color of each spot indicates the level of enrichment from red (lowest p) to blue (highest p). The labels refer only to the most frequent GO terms. (A) Tomato transcripts identified by *Fragkostefanakis et al. (2015)* are analyzed through their Arabidopsis orthologs, 67 genes in total; (B) maize transcripts have been identified in *Frey et al. (2015)* as significantly induced, 454 genes in total. Enriched GO classes have been identified with AgriGO v.2 (<http://systemsbiology.cau.edu.cn/agriGOv2/>; *Du et al., 2010*) and the results visualized with ReviGO (<http://revigo.irb.hr>; *Supek et al., 2011*).



*Metabolomics and lipidomics*

Major environmental stresses cause metabolic reorganization towards homeostasis, maintaining essential metabolism and synthesizing metabolites with stress-protective and signaling characteristics. In plants such as tomato (Paupière *et al.*, 2017), maize (Qu *et al.*, 2018), barley (Templer *et al.*, 2017), wheat (Thomason *et al.*, 2018), soybean (Xu *et al.*, 2016), and citrus (Zandalinas *et al.*, 2017), metabolism reprogramming under HS has been studied by untargeted metabolomics. For example, in maize, under CO<sub>2</sub> stress and a sudden HS, malate, valine, isoleucine, glucose, starch, sucrose, proline, glycine, and serine were successfully found as key players in the combined stress response (Qu *et al.*, 2018). Under both heat and drought stress, amounts of amino acids, and antioxidants such as glutathione and  $\alpha$ -tocopherol, were highly affected in two cultivars of barley (Templer *et al.*, 2017); in particular, this combination of stresses led to accumulation of free amino acids in the leaf. In post-anthesis wheat, the amounts of some amino acids increased, while others decreased [L-arginine, L-histidine, L-tryptophan, L-threonine, 4-aminobutanoate (GABA), L-aspartate, and L-phenylalanine]; sugars, sugar alcohols, and other organic compounds were among the major groups of metabolites whose concentration decreased in tissue due to HS.

Thomason *et al.* (2018) identified the metabolites that exhibited the greatest decreases during HS in wheat: drummondol, anthranilate, dimethylmaleate, galactoglycerol, guanine, and also glycerone. Soybean subjected to both HS and excess CO<sub>2</sub> had decreased starch, fructose, glucose, sucrose, and maltose concentrations, whereas pinitol increased with temperature (Xu *et al.*, 2016). Zandalinas *et al.* (2017) found in citrus that water stress and HS, and their combination, altered metabolite levels related to glycolysis and the TCA cycle, the chloroplastic phase of the glyoxylate/dicarboxylate cycle, and the quantity of polar metabolites participating in the phenylpropanoid pathway arising from shikimic acid, depending on the level of stress. In tomato pollen, under HS, most of the putatively identified secondary metabolites belonged to three major groups: flavonoids, polyamines, and alkaloids (Paupière *et al.*, 2017). Other examples come from untargeted metabolomics experiments where it was found that salicylic acid, ascorbic acid, sulfur-containing molecules (glutathione), phenolic secondary metabolites, and in general all antioxidant molecules can reduce HS symptoms in many plant species (Mobin *et al.*, 2017; Feng *et al.*, 2018; Muhlemann *et al.*, 2018; Niu and Xiang, 2018; Salvi *et al.*, 2018; Ihsan *et al.*, 2019). Other major aspects of high temperature stress are cell signaling, molecular transport, and the changes in lipid metabolism as a basic mechanism to regulate membrane fluidity.

Lipids, which are major components of the membranes of cells and organelles, are among the first targets of ROS produced during HS and directly by high temperatures (Narayanan *et al.*, 2016, 2018). Stress-induced lipid peroxidation of unsaturated fatty acids and other changes in membrane lipid profiles can lead to membrane damage, electrolyte leakage, and cell death (Liu and Huang, 2000). Under severe HS and long-term HS conditions, both chloroplastic and extra-plastidial glycerolipids are oxidized, yielding oxylipin-containing glycerolipids and

other cytotoxic molecules such as acrolein and methyl vinyl ketone (MVK), derived from peroxidation of trienoic  $\omega$ -3 fatty acids (Vu *et al.*, 2012).

Accumulation of highly saturated fatty acids helps confer HS tolerance by reducing structural membrane fluidity, which is increased at high temperatures (Escandón *et al.*, 2018). There is an interesting correlation between the type of metabolites involved and the need to protect specific cellular functions or cell compartments from the adverse effects of stress. In addition to acyl oxidation, plants regulate other aspects of membrane lipid composition in response to changes in temperature; in particular, the chloroplast membranes that host the photosynthetic apparatus are thought to be highly vulnerable to damage caused by HS (Welti *et al.*, 2007; Zheng *et al.*, 2011). Severe HS results in increasing frequency of membrane phase separation of non-bilayer-forming glycerolipids. Moderate HS (30–45 °C) results in thylakoid grana membrane destacking (Higashi and Saito, 2019). During HS, the endoplasmic reticulum (ER) is the major site for membrane phosphatidylcholine (PC) synthesis in plants (Jessen *et al.*, 2015). Free fatty acids are exported from chloroplasts and re-esterified to CoA in the cytosol. PC synthesis in the ER utilizes a mixed pool of acyl-CoA substrates via the Kennedy pathway and the PC acyl editing pathway (Lands cycle) (Wang *et al.*, 2012a). Fatty acid desaturase 2 (FAD2) converts PC-bound 18:1 to 18:2 in the ER and, during HS, FAD2 mediates polyunsaturation of ER glycerolipids and plays a role in the plant ER stress response to HS (Martinière *et al.*, 2011). Chloroplastic galactolipid biosynthesis through the eukaryotic pathway needs a transfer of glycerolipids from the ER to chloroplasts by phospholipid flippase ALA10 which interacts with FAD2 affecting the degree of PC saturation. LACS4/9 proteins are also involved in this mechanism (Botella *et al.*, 2016).

At the chloroplastic outer and inner membranes, five trigalactosyldiacylglycerols (TGDs) and proteins TGD1, 2, 3, 4, and 5 form a transporter complex that mediates ER to plastid lipid trafficking (Xu *et al.*, 2008). However, there is no concerted induction of these membrane proteins at the transcriptional level under HS in Arabidopsis (Higashi *et al.*, 2015). In chloroplasts, long-term HS (>1 d) decreases the levels of glycerolipids containing 16:3 and/or 18:3, and reduces the activity of all FAD enzymes (Higashi and Saito, 2019). In general, during HS and other environmental stresses, conversion of monogalactosyldiacylglycerol (MGDG) into digalactosyldiacylglycerol (DGDG) increases through the action of DGDG synthases, encoded by DGD1 and DGD2. Terrestrial plants increase the ratio of DGDG to MGDG to improve thylakoid membrane stability under various abiotic stresses (Higashi *et al.*, 2018). MGDGs are also decreased through the action of specific lipases (DAD1; PLIP1, 2, and 3; and HIL1). These recent studies suggest that lipases which are localized in chloroplasts have an important role in the lipid remodeling process under HS (Higashi and Saito, 2019).

Glycerolipids and phospholipids are converted to triacylglycerol (TAG) in the form of oil bodies, as a transient storage depot for acyl groups prior to membrane lipid recycling/degradation: phospholipid:diacylglycerol acyltransferase 1 (PDAT1) transfers an acyl group from PC to diacylglycerol

(DAG), and produces TAG. Mutant *pdatt1* seedlings are more sensitive to HS than the wild type; therefore, PDAT1 contributes to HS-induced TAG accumulation, and plays a role in HS response in Arabidopsis seedlings (Mueller *et al.*, 2017). Other chloroplast-localized enzymes that maintain the structure of the thylakoid membranes during HS are FAX 1, 2, and 3, and VIPP1 (Zhang *et al.*, 2012; N. Li *et al.*, 2015). HS also changes the lipid composition of the plasma membrane and of the ER; PC and PE (phosphatidylethanolamine) phospholipids are major components of extra-plastidial membranes. A decrease in the PE polyunsaturation level is likely to improve membrane stability under HS (Narayanan *et al.*, 2016). Long-term HS increases phosphatidylserine (PS) content in the leaves of wheat (Narayanan *et al.*, 2016).

Most of the lipidomics investigations of the response to HS have been performed on Arabidopsis, with only a few studies on crops such as wheat and rice. One example of lipidomics applied to HS in wheat found that the decrease in the photosynthetic rate under HS is due to lipid desaturation, oxidation, acylation, and consequent damage to organelles (Djanaguiraman *et al.*, 2018). The membrane protein–lipid associations are of great importance for the maintenance of membrane fluidity; in this context, overexpression of the gene *OsFBN1* (coding for a fibrillin) facilitates the import of lipids to the chloroplast during HS and the consequent grain filling (Djanaguiraman *et al.*, 2018).

It has been suggested that diminishing the ROS pool directly has positive consequences on the state of the lipids. For example, modulating antioxidant defenses and the detoxification of methylglyoxal (MG) through the application of exogenous glutathione to mung bean [*Vigna radiata* (L.) R. Wilczek] increased the tolerance of the plants to HS in the short term (48 h) (Nahar *et al.*, 2015). The increase in certain plant hormones can also be beneficial to the lipid status in rice during HS (Lim *et al.*, 2017). For example, high concentrations of indole-3-acetic acid (IAA) or brassinosteroids can successfully initiate a mechanism for the decrease of primary ROS caused by HS that attack lipid membranes (MGDGs and sulfoquinovosyldiacylglycerols) and thylakoids (Thussagunpanit *et al.*, 2015; Sharma *et al.*, 2018). In a non-targeted lipidomics experiment in rice under both HS and water stress, 298 lipids responded to the changes in conditions; of these, 128 were identified. Interestingly, in the case of HS, a decrease in the unsaturation of lipids was predominant and can be linked to an increase in the cell membranes' rigidity (Navarro-Reig *et al.*, 2019). In a lipidome-wide study of tomato leaf under HS, changes in 791 molecules were detected between 20 °C and 38 °C. These results indicate that the most important changes at the lipidome-wide level occur in tocopherols, plastoquinone/plastoquinol (and their metabolites), and in the degree of fatty acid saturation of galactolipids (Spicher *et al.*, 2016).

### Epigenetic modifications

The epigenetic changes that occur at the DNA level through methylation of cytosine residues or at the level of chromatin by post-translational modifications of histones can result in altered gene transcription, and are an important mechanism

in regulating gene expression during development and in response to environmental stimuli (Zhang and Hsieh, 2013). The persistence of a memory of temperature stress is dependent not only on the persistence of HSPs and their TFs but also on the expression of certain genes relevant for epigenetic signatures (Liu *et al.*, 2015). A primary stress episode can sensitize plants for acclimation to subsequent stresses, resulting in faster or stronger changes in gene expression upon repeated exposure (Vriet *et al.*, 2015), constituting a physiological priming mechanism. This primary event is fundamental in the acquisition of thermotolerance (Sanyal *et al.*, 2018). A comprehensive RNA-Seq (RNA sequencing) analysis of gene expression and splicing events in HS-primed and non-primed plants has been carried out (Ling *et al.*, 2018). This study showed alternative splicing as a novel and significant part of HS priming-induced memory and that this is critical for enhanced stress tolerance. However, most studies have been carried out in Arabidopsis, and in cultivated plants the understanding of the molecular mechanisms involved still represents a challenge (Friedrich *et al.*, 2019).

Further epigenetic control is due to miRNAs, which are emerging as factors involved in transcriptional regulation and HS memory. miRNAs are involved directly in HS adaptation by acting as post-transcriptional regulators. Plant miRNAs bind their target transcripts and cleave and/or degrade the target mRNA molecule (Budak and Akpinar, 2015; Alptekin *et al.*, 2017). The regulation of stress-responsive genes through activation of miRNAs is particularly important under abiotic stress conditions (Liu *et al.*, 2017; Gahlaut *et al.*, 2018).

Experimental validation of miRNA targets is still a challenge in polyploid crops including wheat. Recently, HS-responsive miRNAs have been reported from several susceptible and tolerant cultivars, with responses primarily being invoked within 24 h of treatment (Qin *et al.*, 2008; Kumar *et al.*, 2015). Furthermore, Ravichandran *et al.* (2019) performed a detailed miRNA and isomiR (miRNA isoforms) annotation and validated the HS-regulated miRNA target genes associated with thermotolerance. They confirmed a high degree of conservation between dicots and monocots for miR156 regulation of squamosa promoter-binding-like protein (Stief *et al.*, 2014), miR159 regulation of MYB transcription factor (Wang *et al.*, 2012b), miR166 regulation of homeobox leucine-zipper protein (Arikiti *et al.*, 2014), and miR398 regulation of SOD (Jagadeeswaran *et al.*, 2009). New miRNA targets were also identified for organelle-specific transcripts such as pentatricopeptide repeat-containing proteins and mitochondrial transcription termination factor-like proteins.

Interestingly, several miRNAs showed altered expression patterns under heat and cold stresses in wheat, including miR164 (targeting HSP17) and miR319 (targeting a MYB transcription factor). These are up-regulated during a cold stress response but down-regulated in response to HS. On the contrary, miR160 and miR164 were down-regulated in response to heat, resulting in the induction of HSP expression, and up-regulated under cold stress. Regulating mechanisms triggered by high temperature can be reversed by cold stress, although the underlying mechanisms may be similar (Alptekin *et al.*, 2017).

## Breeding for heat tolerance

To ensure food security for future generations, agriculture must double the current crop production rate despite the predicted threats, which include climate change (Sedek *et al.*, 2019), decrease in arable land and desertification, salinization, and emerging diseases. Plant breeders need affordable and scalable solutions to achieve a more sustainable production. Approaches to reach the essential goal of producing more with less include (i) harnessing natural and artificial mutations; (ii) exploiting the available genetic resources to produce new genetic material more tolerant to HS and related secondary stresses; (iii) improving the ability to screen and identify the available sources of resilience; and (iv) developing new breeding techniques.

### Conventional breeding approach

The effects of HS and prolonged heat waves on food production are heightened by a greater genetic uniformity in crop plants resulting from the narrowing of the varieties used in developed countries (Fu, 2015; Lopes *et al.*, 2015). This has prompted increased efforts to identify new genetic resources and useful traits to mitigate or counteract the effects of climate change on crop productivity (Pignone *et al.*, 2015; Janni *et al.*, 2018) (Table 3).

It is well established that responses in crop species to abiotic stress, including HS, form a complex quantitative trait whose inheritance is controlled by a synergy between genes identified as QTLs, distributed throughout the genome. Traditionally QTL mapping has been used to identify new genetic variability and new sources of tolerance for introduction to breeding programs. However, QTL regions can be quite large and may contain many genes to be investigated as potential candidate genes, and many QTL studies had limited value for breeding because of low marker density. More recently, genotyping-by-sequencing (GBS) has allowed an increase in the number of markers, in particular SNPs (single nuclear polymorphisms),

evenly distributed throughout the genome (Spindel and Iwata, 2018). In this way, it is now possible to obtain genetic maps with high resolution and precise mapping of QTLs, and in some cases identifying candidate genes controlling associated quantitative traits (Bhat *et al.*, 2016). The application of genome-wide association studies (GWAS) permits narrowing down the candidate regions to explore specific haplotypes in natural populations and even wild species (George and Cavanagh, 2015; Verdeprado *et al.*, 2018).

In wheat, several genomic regions associated with heat tolerance have been mapped using QTL analysis, often combined with GWAS and GBS. Major QTL clusters associated with drought and heat tolerance have been mapped on several chromosomes (Vijayalakshmi *et al.*, 2010; Paliwal *et al.*, 2012; Talukder *et al.*, 2014; Acuña-Galindo *et al.*, 2015; Shirdelmoghanloo *et al.*, 2016; Sharma *et al.*, 2017; Maulana *et al.*, 2018). GWAS of sorghum seedlings under HS has identified associated key genomic regions, and specific alleles from these regions can be used to develop heat-tolerant sorghum cultivars (Chopra *et al.*, 2017). Through inheritance studies, Marfo and Hall (1992) reported two dominant genes controlling most of the heritable tolerance to heat at pod set in cowpea. Four QTLs were identified in cowpea as associated with pod set number per peduncle under HS, and markers were utilized in breeding applications (Lucas *et al.*, 2013; Pottorff *et al.*, 2014). Syntenic analysis of the closely related soybean genome identified HSPs and HSFs in these QTL regions (Liu *et al.*, 2019). In rice, heat tolerance at the flowering stage is controlled by several QTLs that have been used in breeding programs based on gene pyramiding (Ye *et al.*, 2012, 2015; Kilasi *et al.*, 2018).

A major QTL for thermotolerance was successfully identified and cloned in African rice (*Oryza glaberrima* Steud.); *thermo-tolerance 1 (TT1)* encodes an  $\alpha 2$  subunit of the 26S proteasome involved in the degradation of ubiquitinated proteins. The allele *OgTT1* of the thermotolerant accession permitted increased thermotolerance through a more efficient elimination of cytotoxic denatured proteins and effective maintenance of

**Table 3.** Harnessing plant genetic resources for heat stress breeding

Species	Countries of origin	Number of accessions	Source	Type of study	Reference
Barley	Spain and Germany	N/A	Saatzucht Breun GmbH	Gene expression studies	Cantalapiedra <i>et al.</i> (2017)
Chickpea	Several countries	300	N/A	GWAS	Thudi <i>et al.</i> (2014)
Chickpea	India	280	ICRISAT	Identification of heat tolerance superior lines	Krishnamurthy <i>et al.</i> (2011)
Maize	N/A	100 inbred lines	N/A	Field trial	Naveed <i>et al.</i> (2016)
Rice	Several countries	455	N/A	QTL identification	Ye <i>et al.</i> (2015)
Rice	Several countries	511	IRRI	Identification of heat tolerance superior lines	Tenorio <i>et al.</i> (2013)
Tomato	Several countries	81	University of Naples (Italy)	GWAS	Ruggieri <i>et al.</i> (2019)
Tomato	N/A	44	TGRC, University of California, Davis	Identification of heat tolerance superior lines	Alsamir <i>et al.</i> (2017)
Wheat	Several countries	1711	CYMMIT	GWAS	Singh <i>et al.</i> (2018)
Wheat	Mexico	2255	CYMMIT	Identification of heat tolerance superior lines	Hede <i>et al.</i> (1999)

CYMMIT, International Maize and Wheat Improvement Center; GWAS, genome-wide association study; ICRISAT, International Crops Research Institute for the Semi-Arid Tropics; IRRI, International Rice Research Institute; N/A not applicable; QTL, quantitative trait locus; TGRC, Tomato Genetics Resource Center

heat response processes than the non-tolerant cultivar carrying the *OsTT1* allele. Overexpression of *OgTT1* was associated with enhanced thermotolerance in rice, Arabidopsis, and *Festuca elata* Keng f. ex E.B.Alexeev (X.M. Li *et al.*, 2015).

In tomato, several QTLs involved in heat tolerance have been identified (Xu *et al.*, 2017), while two QTL hot spots for heat tolerance with respect to grain yield were found in maize (Jha *et al.*, 2014; Frey *et al.*, 2016).

Screening for genotypic differences, and effective selection techniques, are crucial for identifying heat-tolerant parental sources and for inheritance studies, and also for crop improvement by combining other traits which are influenced by heat tolerance (Marfo and Hall, 1992; Hall, 2004). Since photosynthesis and reproductive development processes are directly adversely affected by HS (Prasad *et al.*, 2008), desired characteristics of a heat-tolerant variety will be higher photosynthetic rates (e.g. stay-green leaves), enhanced membrane thermostability, and stable pod set or grain production under high temperature conditions (Bita and Gerats, 2013). Methods for breeding for heat tolerance in cowpea involved selection for abundant flower production and greater pod set under higher night temperatures and long-day growing conditions (Marfo and Hall, 1992). These efforts resulted in release of the HStolerant cowpea variety California Blackeye 27 (CB27) with better yield (Ehlers *et al.*, 2000). This variety was crossed with Pima (a Nigerian heat-tolerant germplasm) giving Apagbaala, a cowpea variety intended for Ghana (Padi *et al.*, 2004). However, this was not heat tolerant in Ghana even though it performed well under Californian growing conditions.

The common bean (*Phaseolus vulgaris* L.) has also been investigated. Initial screening at CIAT (Centro Internacional de Agricultura Tropical) of a germplasm core set for HS tolerance identified 30 resistant lines. Breeding programs utilizing these genetic resources helped to develop heat-tolerant bush (CIAT, 2006) and climbing bean lines (Blair *et al.*, 2006). Moreover, introgression of Tepary bean (*Phaseolus acutifolius* A.Gray) genes into *P. vulgaris* gave an interspecific line that was used as a parent for breeding heat-tolerant lines (Polania *et al.*, 2017). Recent screening of chickpea genotypes indicated the existence of extensive genotypic variation for reproductive stage heat tolerance; further studies led to the release of heat-tolerant breeding line ICCV 92944 for late-sown conditions (Gaur *et al.*, 2019).

Targeted breeding efforts will help to build heat tolerance in crops (Reynolds *et al.*, 2011). A conceptual model to improve heat tolerance in wheat was proposed involving genetically determined physiological traits such as light interception, radiation use efficiency, and partitioning of total assimilates. The physiological breeding approach combines all these traits towards generating a cumulative genetic effect on yield (Cossani and Reynolds, 2012). Data sets from three different spring bread wheat nurseries at CIMMYT (International Maize and Wheat Improvement Center) with different breeding goals were extensively analyzed, and the results showed that spring wheat breeding targeted against abiotic stress delivers better genetic gains in warmer environments (Gourdji *et al.*, 2013). The performance of yield traits under heat and non-stressed environments has been used to identify heat-tolerant

genotypes for breeding programs (Ni *et al.*, 2018; Gaur *et al.*, 2019). The identification of critical genes controlling heat tolerance in common wheat led to the release of new cultivars of bread wheat and durum wheat capable of withstanding severe heat (Tadesse *et al.*, 2019), for example the cultivar Faraj, which is able to maintain yield under heat and drought conditions El Hassouni *et al.* (2019).

It has been shown that compared with direct selection for grain yield, indirect selection through secondary traits with high heritability and significant association with grain yield under stress is a more effective approach in stress tolerance breeding (Bänziger and Lafitte, 1997; Bänziger *et al.*, 2000; Bheemanahalli *et al.*, 2017). In maize, traits associated with reproductive success under heat stress (anthesis-silking interval, pollen viability, stigma receptivity, tassel blast, tassel sterility, and seed set percentage under open pollinated conditions) and other morpho-physiological traits (leaf firing, senescence, and chlorophyll content) were studied along with grain yield for the selection of HS-tolerant germplasms (Alam *et al.*, 2017). As a result, two maize genotypes, VL05728 and VL05799, with better seed setting due to reproductive success under stress were identified as tolerant lines for heat stress (Alam *et al.*, 2017). Several maize breeding programs have successfully increased yields in HS conditions (Cairns and Prasanna, 2018). The identification of suitable donors, highly tolerant to HS and to the combination of HS and drought stress, was successfully achieved by evaluating 300 (Cairns *et al.*, 2013) or 29 (CIMMYT) maize inbred lines (Dinesh *et al.*, 2018). These studies are the best examples to show the significant molecular diversity among maize inbred lines selected for heat tolerance.

Reproductive stage HS in rice causes substantial yield loss. Delayed flowering, reduced pollen dispersal, low pollen production, spikelet sterility due to poor anther dehiscence, and impaired starch synthesis during grain development are the major problem areas (Jagadish *et al.*, 2016; Arshad *et al.*, 2017). Natural genetic variation for HS tolerance exists in rice, and significant genetic components controlling these variations have been identified. Several QTLs and genes associated with HS tolerance have been reported (Ye *et al.*, 2015; Shanmugavadeivel *et al.*, 2017; Kilasi *et al.*, 2018), and some have been characterized (Krishnan *et al.*, 2011), but more translational research is needed in this area. Guodao 6 and Xieyou 46 are heat-tolerant hybrids developed with stable high rates of grain setting and spikelet fertility under HS (Tao *et al.*, 2008). Other varieties including Fusaotome (tolerant), Hanahikari, Koshijiwase, and Tentakaku (moderately tolerant) were used in breeding for grain quality under heat stress (Ishizaki, 2006). In rice, HS-tolerant traits from line N22 (Jagadish *et al.*, 2008) have been used for introgression into other varieties for developing climate change-ready rice (Ye *et al.*, 2015). QTLs for HS tolerance during the reproductive stage were identified using a recombinant inbred population between N22 and IR64 (Ye *et al.*, 2012).

In tomatoes, reproduction is particularly sensitive to continuous mild heat, which mainly affects pollen viability. The Asian Vegetable Research and Development Center (AVRDC) has identified 39 tolerant lines after several years of natural genetic variation studies. Some of these were used in their tomato breeding programs which produced HS-tolerant lines,

such as Equinox (Scott *et al.*, 1995) and Sun Leaper (Gardner, 2000). Another example is the development of ‘Amelia’, a heat-tolerant tomato cultivar for tropical conditions (Gil *et al.*, 2004). Identification of more QTLs associated with heat tolerance in tomatoes (Wen *et al.*, 2019) could enhance breeding efforts for development of stress-tolerant tomato varieties.

The development of molecular tools to accelerate breeding is crucial for the identification of useful traits and their application in breeding programs. In particular, marker-assisted selection (MAS) to improve breeding efficiency has become commonplace. Many MAS strategies have been developed, including marker-assisted backcrossing with foreground and background selection, enrichment of favorable alleles in early generations, and selection for quantitative traits using markers at multiple loci and across multiple cycles of selection (Bassi *et al.*, 2016). MAS requires the use of markers flanking the target locus, and is considered one of the most efficient methods when working on complex traits having a quantitative hereditary characteristic, such as HS tolerance (Tayade *et al.*, 2018). MAS can be used in forward breeding to enrich the allelic frequency for a few desired traits with strong additive QTLs in early selection cycles, to introgress favorable alleles into an elite background, and for integration of (native) traits into a breeding pipeline. This approach has been used in maize to develop improved lines for stress-prone environments (Beyene *et al.*, 2016).

The exploitation of GWAS has led to the approach called genomic selection (GS) a promising tool to design novel breeding programs and to develop new marker-based models for genetic evaluation. The most important factor for its successful and effective implementation in crop species is the availability of genome-wide high-throughput, cost-effective, and flexible molecular markers, having low ascertainment bias, suitable for large population sizes, as well as for both model and non-model crop species with or without the reference genome sequence (Bhat *et al.*, 2016). As a pre-breeding tool, it can serve to identify genetic materials with beneficial variation for complex traits (Wang *et al.*, 2018), predicting the breeding value of an individual within a breeding population. It also provides new opportunities to increase genetic gain of complex traits efficiently. GS has been applied to active breeding programs in several crop species including wheat (Song *et al.*, 2017), rice (Spindel and Iwata, 2018), soybean (Duhnen *et al.*, 2017; Matei *et al.*, 2018), sunflower (Dimitrijevic and Horn, 2017), maize (Cerrudo *et al.*, 2018), chickpea (Roorkiwal *et al.*, 2016), and grapes (Fodor *et al.*, 2014; Viana *et al.*, 2016).

GS and marker-assisted recurrent selection (MARS), widely used in the private sector, are proving efficient for the development of novel cultivars in many crops (Tayade *et al.*, 2018). The major advantage of GS with respect to MAS/MARS is that alleles with minor effects can be captured and used in selection (Cairns and Prasanna, 2018). For both approaches, success depends on excellent phenotypic characterization during the discovery or training phase, respectively.

### *New breeding techniques to increase heat tolerance*

Genetic modification through biotechnology and other new breeding techniques (NBTs) is a powerful strategy that offers

novel opportunities to improve crop adaptability. However, general public concerns and complex legislation are limiting the application of NBTs. Encouraging data collected from genetics can be exploited to significantly increase tolerance to both biotic stresses and abiotic stresses such as salinity, drought, heat, and cold (Zou *et al.*, 2011; Raza *et al.*, 2019). Several studies have used TF genes and other genes associated with abiotic stress tolerance as targets for development of new varieties (Lamaoui *et al.*, 2018). Crops including wheat, maize, tomato, and rice have been genetically modified to enhance thermotolerance, targeting mainly HSPs and HSFs (Fu *et al.*, 2008; Qi *et al.*, 2011; Xue *et al.*, 2015; Casaretto *et al.*, 2016; Wang *et al.*, 2016; Trapero-Mozos *et al.*, 2018). Transgenic cotton plants developed to overexpress an HSP, AtHSP101, in pollen had improved pollen germination and pollen tube growth under high temperature. This significantly enhanced the overall heat tolerance of reproductive tissues and reduced yield losses due to high temperature, supported by both greenhouse and field evaluation of transgenic plants (Burke and Chen, 2015). A survey of the transgenic lines identified to enhance heat tolerance in several species is reported in Table 4.

The availability of genomic sequences for several crops together with genome editing techniques has opened up new breeding possibilities for almost any given desirable trait (Jaganathan *et al.*, 2018). The most common technique available for genome editing, clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), modifies a genome in a targeted manner, and has been used in nearly 20 crop species so far including rice, tomato, potato, cotton, soybean, maize, sorghum, and wheat (Table 5) (Ricroch *et al.*, 2017; Jaganathan *et al.*, 2018; Zaidi *et al.*, 2018). There are at least 13 different patents on new CRISPR/Cas9 approaches, which makes editing even more simple and secure, and new perspectives in the production of novel genetic variability are opened up by its application as an allelic-drive tool, engineering and repairing pathways, and introducing specific point mutations or insertions (Guichard *et al.*, 2019).

Currently, attempts exploiting genome editing to increase heat tolerance target several genes mainly involved in the ethylene response and TFs, with the final aim to increase yield under abiotic stresses including HS (Li *et al.*, 2016; Shi *et al.*, 2017a; Kim *et al.*, 2018). However, despite the abundance of novel genetic material generated through CRISPR, few field experiments have been conducted associated with breeding programs.

### *Mutational breeding*

Mutational breeding strategies have been applied since the late 1990s to generate new variability in plants (Gilliam *et al.*, 2017; Uauy, 2017). An important breakthrough came with the development of the TILLING (targeting induced local lesions in genome) approach, which provides a relatively simple strategy to identify mutations (lesions) in a target sequence independently of their phenotypic effect (Uauy, 2017). TILLING approaches require a population of, typically, ethyl methanesulfonate- (EMS) induced mutants based on the capacity of the chemical agent to generate

**Table 4.** List of selected heat stress- (HS) tolerant transgenic plants

Crop	Target gene or protein/sources	Promoter	Stress or trait	Reference
Maize	<i>OsMYB55</i> /rice	Maize ubiquitin Ubi1 promoter/ overexpression	Increased drought and HS tolerance	Casaretto <i>et al.</i> (2016)
Maize	<i>ZmNF-YB2</i> /maize	Rice actin 1 constitutive promoter/ overexpression	Enhanced drought tolerance and photosynthetic capacity	Nelson <i>et al.</i> (2007)
Potato	<i>HSc70</i> allelic variant/ potato	HSc70 native promoter	Greater tolerance to HS as determined by improved yield	Trapero-Mozos <i>et al.</i> (2018)
Rice	<i>HSP70</i> /rice	CaMV 35S	Overexpression manifested enhanced tolerance to HS	Qi <i>et al.</i> (2011)
Rice	<i>Athsp101</i> /Arabidopsis	CaMV 35S promoter	Increased tolerance to high temperature	Katiyar-Agarwal <i>et al.</i> (2003)
Rice	<i>OsRab7</i>	CaMV 35S	Greater tolerance to HS as determined by improved yield	El-Esawi and Alayafi (2019)
Rice	<i>TaMBF1c</i> /wheat	Maize ubiquitin 1	Higher thermotolerance than control plants at both seedling and reproductive stages	Qin <i>et al.</i> (2015)
Soybean	<i>P5CR</i> /Arabidopsis		Enhanced HS tolerance	De Ronde <i>et al.</i> (2004)
Tobacco ( <i>Nicotiana tabacum</i> L.)	<i>HSP70-1</i> /tobacco	CaMV 35S	Transgenics possessed enhanced tolerance to HT stress	Montero-Barrientos <i>et al.</i> (2008)
Tobacco	<i>HSP70-1</i> /brassica		Enhanced tolerance to HT stress	Wang <i>et al.</i> (2016)
Tomato	<i>HSP21</i> /tomato	CaMV 35S	Overexpression protected PSII from temperature-dependent oxidative stress; early accumulation of carotenoids noted	Neta-Sharir <i>et al.</i> (2005)
Wheat	<i>Hsf6A</i> /wheat	Barley HVA1s promoter/ drought inducible, up-regulated	Improved thermotolerance	Xue <i>et al.</i> (2014)
Wheat	<i>EF-Tu</i> /maize	Maize ubiquitin 1 promoter/ overexpression	Improved thermotolerance	Fu <i>et al.</i> (2008)
Wheat	Sucrose transporter gene <i>HvSUT1</i> /barley	Hordein B1 promoter	Increased enhanced in sucrose transport and shows a superior performance for many yield-related traits compared with control	Weichert <i>et al.</i> (2017)
Wheat	<i>TaHsfA6f</i> /wheat	HVA1s	Improved thermotolerance	Xue <i>et al.</i> (2015)
Wheat	<i>TaFER-5B</i> /wheat	Maize ubiquitin 1	Enhance thermotolerance	Zang <i>et al.</i> (2017)
Wheat	<i>TaGASR1</i> /wheat	NA	Improved tolerance to HS and oxidative stress	Zhang <i>et al.</i> (2017)
Wheat	<i>TaHsfC2a</i> /wheat	NA	Improved thermotolerance	Hu <i>et al.</i> (2018)

**Table 5.** Genome editing approaches used for heat stress breeding

Crop	Target gene	Stress or trait	Reference
Maize	<i>ARGOS8</i>	Improved yield under drought stress condition	Shi <i>et al.</i> (2017a)
Rice	<i>OsPDS</i> , <i>OsMPK2</i> , <i>OsBADH2</i>	Abiotic stress tolerance	Shan <i>et al.</i> (2013)
Rice	<i>OsMPK2</i> , <i>OsDEP1</i>	Yield under stress	Shan <i>et al.</i> (2014)
Rice	<i>GS3</i> , <i>Gn1a</i>	Grain size and number increase	Shen <i>et al.</i> (2017)
Rice	<i>GW2</i> , <i>GW5</i> , <i>TGW6</i>	Grain weight increase	Xu <i>et al.</i> (2016)
Rice	<i>Gn1a</i> , <i>DEP1</i> , <i>GS3</i>	Grain size and number Increase in dense, erect panicles	Li <i>et al.</i> (2016)
Wheat	<i>TaDREB2</i> , <i>TaERF3</i>	Abiotic stress tolerance	Kim <i>et al.</i> (2018)

point mutations distributed randomly in the genome, and a screening method to identify individuals with mutations in the target gene (Wang *et al.*, 2010). TILLING and its updated form, established for polyploidy species through the use of exome capture and the development of the *in silico* TILLING database (Krasileva *et al.*, 2017), have been used extensively to investigate genetic variability in several species mainly targeting quality traits.

Although in TILLING approaches mutagenesis is untargeted and does not provide the versatility of genome editing, crops improved using chemical or radiation mutagenesis via TILLING are not regulated as transgenic organisms in most jurisdictions,

increasing their commercial competitiveness with the more precise genome editing approaches (Kumar *et al.*, 2017).

Recently, Comastri *et al.* (2018) identified a collection of four new small *Hsp26* (*sHsp26*) alleles suitable for enhancing heat tolerance in durum wheat using both *in silico* and *in vivo* TILLING approaches. Following application of TILLING, the ability of a mutated HSP to enhance heat tolerance in tomato has also been demonstrated (Marko *et al.*, 2019). In rice, a TILLING population has been screened for mutations in the HSP genes, and a number of lines showing preliminary enhanced tolerance to HS may be useful for future breeding programs (Yona, 2015; Table 6).

**Table 6.** Mutational breeding in crops

Species	Target trait /genes	Reference
Barley	Starch increases	Sparla <i>et al.</i> (2014)
Bread wheat ( <i>Triticum aestivum</i> L.)	Starch branching enzyme	Botticella <i>et al.</i> (2011)
Chickpea	Salt tolerance	Kaashyap <i>et al.</i> (2017)
Durum wheat ( <i>Triticum durum</i> Desf)	Heat stress	Comastri <i>et al.</i> , 2018
Durum wheat ( <i>Triticum durum</i> Desf)	Amylose content	Sestili <i>et al.</i> (2015)
Durum wheat( <i>Triticum durum</i> Desf), bread wheat ( <i>Triticum aestivum</i> L.)	High amylose	Slade <i>et al.</i> (2012)
Oat ( <i>Avena sativa</i> L.)	Improved $\beta$ -glucan, antioxidants and omega-3 fatty acid	Chawade <i>et al.</i> (2010)
Peanut	Allergen reduction	Knoll <i>et al.</i> (2011)
Peanut	LOX gene	Guo <i>et al.</i> (2015)
Potato	Waxy mutant	Muth <i>et al.</i> (2008)
Rapeseed	Erucic acid synthesis	Wang <i>et al.</i> (2008)
Rapeseed	Sinapine biosynthesis	Harloff <i>et al.</i> (2012)
Sorghum	Reduction of cyanogenic glucosides	Blomstedt <i>et al.</i> (2012)
Sunflower	Accumulation of fatty acids	Kumar <i>et al.</i> (2013)
Tobacco	Leaf yield	Reddy <i>et al.</i> (2012)
Tomato	Fruit biology and ripening	Okabe <i>et al.</i> (2011, 2013)
Tomato	Virus resistance	Piron <i>et al.</i> (2010)
Tomato	Increased pigment and nutrient content	Jones <i>et al.</i> (2012)
Tomato	Early flowering, a solitary flower	MacAlister <i>et al.</i> (2012)
Tomato	Reduced ethylene sensitivity, delayed fruit ripening, prolonged fruit shelf life	Okabe <i>et al.</i> (2011)
Tomato	Decreased ascorbate	Baldet <i>et al.</i> (2013)
Tomato	Decreased carotenoid content	Gady <i>et al.</i> (2012)
Tomato	Increased lycopene content	Silletti <i>et al.</i> (2013)
Tomato	Reduced phenolics content	Di Matteo <i>et al.</i> (2013)

## Conclusions

There are several examples of heat-tolerant varieties in major crops such as wheat, maize, rice, tomato, and legumes successfully developed through conventional breeding. These efforts can be fast-tracked using modern genomic and phenotyping tools. The first HS gene was identified and cloned in tobacco with the pioneering work of Barnett *et al.* (1979). This gene was shown to encode HSP70, which strongly accumulated in heat-stressed tissue.

Subsequent molecular studies revealed a more complex system with the discovery of HSFs (reviewed in Guo *et al.*, 2016), organelle-specific HSPs (Waters and Vierling, 1999; Waters, 2013), and linkage between HS and the induction of an alternative splicing system (Ling *et al.*, 2018) capable of directing *de novo* HSP synthesis in conditions where most proteins were either produced abnormally or were degraded (Vierling, 1991), remodeling the global protein machinery in cells. However, neither these discoveries nor the networking of all the known elements have produced a satisfying picture of the plant heat stress response. QTLs for heat tolerance offer a different, potentially complementary, interpretation with a stronger emphasis on physiology of reproduction in heat stress conditions.

Current data indicate that at least two different genetic systems can protect plants from the otherwise lethal effects of heat stress: (i) a series of Mendelian HS genes acting possibly in a dominant or semi-dominant way; and (ii) a small number of QTLs which allow plant growth and reproduction under different stress conditions. There has been little progress using transgenic approaches in studies of model plant to crop plant

translational genetics. Extensive knowledge has become available on physiological, biochemical, and molecular regulation through advanced phenotyping and multi-omics tools developed over the last decade. All of this suggests that significant advances in crop improvement will be achieved, resulting in the development of new high-yielding varieties with greater heat tolerance and adaptation to climate change.

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## Author contributions

The authors contributed equally to the preparation of the review. MJ took on the responsibility of connecting all the different tasks distributed as follows: EM, gene ontology and system biology; MM, protein and metabolites; MG, gene expression and epigenetic modification; BV, gene expression and breeding; and MJ, induction of HS response; NM and HTN coordinated the planning and the writing of the review.

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