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Review

The Roles of Multidrug and Toxic Compound Extrusion (MATE) Transporters in Regulating Agronomic Traits

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Abstract: Multidrug and toxic compound extrusion (MATE) transporters are ancient proteins conserved among various kingdoms, from prokaryotes to eukaryotes. In plants, *MATE*s usually form a large family in the genome. Homologous MATE transporters have different subcellular localizations, substrate specificities, and responses to external stimuli for functional differentiations. The substrates of MATEs in plants include polyphenols, alkaloids, phytohormones, and ion chelators. The accumulation of these substrates is often associated with favorable agronomic traits such as seed and fruit colors, the balance between dormancy and germination, taste, and stress adaptability. In crops, wild germplasms and domesticated germplasms usually have contrasting agronomic traits such as seed color, seed taste, and stress tolerance. MATE transporters are involved in the regulations of these traits. In this review, we discuss the uniqueness and significance of there being such a large family of MATEs in plants, their substrate diversity that enables them to be involved in various agronomic traits, and the allelic forms and the expression patterns of *MATE* that are associated with favorable agronomic traits in domesticated crops. The understanding on the roles of MATEs in regulating favorable agronomic traits in crops will provide hints for the selection of genes for molecular breeding that improve desirable traits.

Keywords: ancient protein; gene family; multidrug and toxic compound extrusion (MATE) transporter; agronomic trait; domesticated crop; wild crop

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1. Introduction

Multidrug and toxic compound extrusion (MATE) transporters are ancient proteins conserved among the three domains of life: Bacteria, Archaea, and Eukarya. In plants, MATE transporters usually form large families with dozens to over a hundred family members [1–8]. For example, 117 *MATE* genes were identified in the *Glycine max* genome, 49 in *Zea mays* [2], 67 in *Solanum lycopersicum* [6], 71 *Populus trichocarpa* [3], 53 in *Oryza sativa* [7], 56 in *Arabidopsis thaliana* [8], 40 in *Medicago truncatula* [4], 65 in *Vitis vinifera* [5], 48 in *Solanum tuberosum* [9], and 33 in *Vaccinium corymbosum* [10]. Within the same species, the copy numbers of *MATE* genes have often expanded due to genome duplication events [3,11].

A typical MATE transporter consists of 12 transmembrane domains (TMDs) and is driven by a H^+ or Na^+ gradient across the biological membrane [12,13]. In plants, MATE transporters are involved in growth, stress responses, leaf senescence, and metabolite transport including the efflux of antibiotics, the transportation and compartmentalization of alkaloids and flavonoids, iron homeostasis, aluminum tolerance, and the transportation of phytohormones [14–17]. MATE proteins have been reported to transport substrates that are characteristic to particular groups of plants. For example, the characteristic colored skin of berry fruit is known to be resulted from the accumulation of anthocyanins, while VvMATE1 and VvMATE2 were reported to be putative proanthocyanidin transporters in

seed berries [18]. Another example is the rich content of isoflavone in soybean seeds [19]. GmMATE1, GmMATE2, and GmMATE4 were reported to mediate isoflavone transport into the vacuole [16,17]. As discussed in Section 1, genome-wide identification studies demonstrated that many plant species have a large family of MATE transporters. The multitasking abilities of MATE transporters in plants to mediate the transport of various substrates for the regulation of different biological processes, including xenobiotic detoxification, regulation of iron homeostasis, tolerance to aluminum, regulation of biotic stress, and phytohormone transport, have been reviewed [20]. The role of MATE transporter in exporting isoflavonoid for regulating nodulation was also reported [21]. The diversity of metabolites in different plant species and the capacities of MATEs to transport various substrates are the possible reasons behind the large MATE families in plants.

Most eukaryotic MATE transporters mediate substrate transports in exchange for H^+ from the other side of the biological membrane [13]. However, prokaryotic MATE transporters could utilize H^+ or Na^+ as the anti-porting agent [13]. Although MATE transporters are highly conserved in terms of the 12 typical MATE-type TMDs, they have different substrate specificities, such as ion chelators, phytohormones, alkaloids, and flavonoids [4,16,17,22–29]. Many agronomic traits, such as seed color, bitterness of seeds, stress tolerance, and the balance between dormancy and germination, are closely related to the functions of MATE transporters. Many of these agronomic traits regulated by MATE transporters display contrasting properties between wild crops and domesticated crops. For example, compared to wild germplasms, domesticated germplasms usually have less colored seeds, bitter seeds, and easier germination of seeds [30–32]. On the other hand, some domesticated germplasms contain higher levels of alkaloids compared to wild germplasms due to different cultivation purposes [33,34]. Some domesticated germplasms may also have improved stress tolerance compared to the wild germplasms [35]. Many of these favorable agronomic traits in domesticated germplasms are associated with metabolites transported by MATE transporters.

During domestication, specific alleles of domestication genes resulting in the desired agronomic traits were selected [36,37]. The artificial selection during domestication and breeding resulted in a drastic decrease of genetic diversity in certain regions of the genome, where the potentially beneficial alleles for domestication are located [38]. Examples of domestication genes include *TB1* (*Teosinte Branched 1*), which encodes a transcriptional regulator for regulating apical dominance and leads to short and ear-tipped branches of domesticated maize [39,40], *GmOLEO1*, which encodes a oleosin protein for enhancing the seed oil content in domesticated soybean [41], and *BH4* (*BLACK HULL4*), which encodes an amino acid transporter for the regulation of the hull color of rice [42]. The 22-bp deletion in the exon of *BH4* resulted in the white hull color of cultivated rice [42]. Details of domestication genes have been summarized in previous reviews [43,44]. Although *MATE* genes have not been characterized as domestication genes, they are involved in regulating favorable traits, which are selected during domestication. The nature of MATEs being transporters to directly transport metabolites that bring forth the desirable traits, such as color and taste, may suggest *MATE* genes as the suitable candidate genes for molecular breeding to shape a particular trait.

2. Favorable Agronomic Traits

During cultivation, plants have been selected for improvements in yield and harvestability [45]. Other traits, such as seed color and fruit color [30,31], the balance between dormancy and germination [32], taste profile [46,47], and adaptability to the environment [48], are also constantly under conscious selection by breeders and consumers. MATE transporters are involved in the regulation of these agronomic traits.

2.1. Color

Seed coat color is usually distinguishable between wild germplasms and domesticated germplasms. During domestication, seeds with lighter color were selected due to the

ease of sowing and religious reasons [30]. Common examples of such domesticated crop plants include legumes, rice, and sorghum. As reviewed previously, in legumes such as *Phaseolus vulgaris*, *Lablab purpureus*, *Arachis hypogaea*, soybean, *Pisum sativum*, lentil, and *Cicer arietinum*, the cultivars tend to have seed coats with lighter colors or less complex patterns compared to their wild relatives [46]. In rice, the change in grain color is one of the alterations due to domestication [49]. Wild rice grains usually have black hulls and red pericarps, while cultivated rice accessions usually have straw-white hulls. It was reported that such a change in hull color was due to a mutation in the gene *Bh4*, while the change in pericarp color was due to a mutation in the gene *Rc*. Various deletions in different regions of *Bh4* resulted in the same straw-white hull phenotype in different domesticated rice accessions [49]. In Amaranth, the change in seed color from dark to white is also a contrasting trait between wild germplasms and domesticated germplasms [50]. A MYB-like protein, homologous to the MYB-type transcription factors identified in other species for regulating seed coat color, was suggested to have soft selective sweep [50]. The maize homolog determining seed coat color is known as Anthocyanin Regulatory C1 [50]. Similarly, domesticated quinoa accessions tend to have seeds of lighter colors, such as white, yellow, red, and purple, while wild quinoa accessions tend to have black seeds [51].

Major plant pigments include anthocyanins, betalains, carotenoids, and chlorophylls [52]. Anthocyanins have been known to be associated with the black color of the seed coat [53]. In a study on the polyphenol composition of the colored seed coat of five pulses, including *Cicer arietinum* L., *Vicia faba* L., *Lens culinaris* Medik., *Pisum sativum* L., and *Phaseolus vulgaris* L., anthocyanins were only detected in the black seed coat of *Lens culinaris* Medik and *Phaseolus vulgaris* L. but not in the seed coat of other colors, such as white, green, brown, beige, grey, maple (patterned), and dun (brown) [54]. Although anthocyanins were not detected in the black seed coat of the chickpea and faba bean, another class of colored compound, procyanidins, was detected in the black seed coat of the faba bean [54]. However, it was not clear which compounds result in the black seed coat color of the chickpea [54].

MATE transporters have been known to mediate the accumulation of colored compounds in the seed coat. For example, in Arabidopsis, *TRANSPARENT TESTA12* (*TT12*), which encodes a MATE transporter, was reported to mediate the sequestration of proanthocyanidins (PAs) in the vacuole and thus enhance the accumulation of PAs in the seed coat [55,56]. In *Medicago truncatula*, MtMATE1 was reported to be functionally orthologous to Arabidopsis *TT12*, in mediating the vacuolar uptake of PAs and epicatechin *3′-O*-glucoside, which is the precursor for PA biosynthesis (Zhao and Dixon, 2009). The mutation of *MtMATE1* resulted in seeds with a lighter color compared to the wild type (Zhao and Dixon, 2009). In addition, the pale seed phenotype of the Arabidopsis *tt12* mutant could be complemented by the ectopic expression of *MtMATE1* (Zhao and Dixon, 2009). Later, it was found that Arabidopsis *TT12* is regulated by *TRANSPARENT TESTA GLABRA2* (*TTG2*), which encodes a WRKY-type transcription factor [22]. Compared to the wild type, the *ttg2* mutant produces seeds with a lighter color [22]. Such a phenotype is consistent with the pale seed color resulting from the *tt12* mutation (Zhao and Dixon, 2009).

Domesticated vegetables and fruits also have altered skin colors compared to the wild accessions. For example, wild carrots are usually white or off-white [57,58]. The edible part of carrot is the root, which grows underground. Having a colored root appears to offer no advantage to the plant's growth and survival [57]. However, many domesticated carrots are colored, with roots in yellow, orange, red, and purple [57–59]. It was suggested that the first event of domestication resulted in the popularity of yellow and purple carrots [58]. After that, the second domestication event led to the popularity of the orange carrot [58]. The orange color is due to the accumulation of carotenes [58]. Another example is the grapevine (*V. vinifera*). The white and red fruits of the grapevine are preferred on the market, while the dark-colored ones of the wild ancestor are not as popular [31]. The pale green skin color of the domesticated grapevine fruit was reported to be due to a retroelement insertion in *VvMybA1* and a mutation in *VvMybA2*, both of which encode

MYB-type transcription factors [60]. The dark skin color of grapevine fruit is largely due to the accumulation of anthocyanins [31]. *VvVHP1;2* (*V. vinifera vacuolar* H^+ *PPase 1;2*) was reported to be the transcriptional activation target of VvMYBA1 [61]. The overexpression of *VvVHP1;2* enhanced the accumulation of anthocyanins in transgenic berry fruit skins and transgenic Arabidopsis leaves [61]. The overexpression of *VvVHP1;2* also led to the increased expression of *VvMATE3* [61]. In *V. vinifera*, MATE transporters have been reported to mediate the accumulation of anthocyanins. anthoMATE1 and anthoMATE3 were reported to be tonoplast-localized MATE transporters that mediate the import of acylated anthocyanins in the vacuole [5]. In addition, VvMATE1 and VvMATE2, which localize in the membranes of the vacuole and Golgi, respectively, were reported to be associated with the transport of PAs [18].

Although *MATE* genes have not been regarded as domestication-related genes in crops, MATE transporters play important roles in regulating the color of seed and fruit, which have always been the agronomic traits selected. The link between the domesticated related genes, such as the *MYB* genes, and MATE transporters, which mediate the transport of colored compounds, has remained unclear. Nevertheless, MATE transporters that transport the colored compounds could be the possible candidates for molecular breeding when color is the agronomic trait of interest.

2.2. Dormancy

Seed dormancy is one of the contrasting traits between wild germplasms and domesticated germplasms [32]. Dormancy could prevent seeds from germinating under favorable conditions [62]. On the other hand, dormancy is critical for preventing preharvest sprouting when the humidity and temperature are favorable for germination [32,63]. Although a long dormancy is not desirable for cultivation, too short a dormancy causes problems such as preharvest sprouting and could result in low grain quality and quantity [63]. Therefore, an appropriate balance between seed dormancy and germination is a desirable trait selected during domestication. The equilibrium between ABA and GA levels regulates dormancy and the time for germination. Other phytohormones such as brassinosteroid, jasmonic acid, salicylic acid, cytokinin, strigolactone, and ethylene regulate the balance between ABA and GA [64,65]. In addition to ABA and GA, auxin is also recognized as a master regulator of dormancy for its role in regulating the expression of genes involved in dormancy and germination [65].

In Arabidopsis, the transport of ABA from maternal tissue to the embryo for dormancy regulation has been suggested [66]. In another report, it was shown that ABA is released from the endosperm to the embryo to regulate seed dormancy [67]. Later, ATP-binding cassette (ABC) transporters AtABCG25, AtABCG31, AtABCG30, and AtABCG40 were reported to be responsible for the transport of ABA from the endosperm to the embryo in Arabidopsis [68]. The mutation of *AtABCG31*, *AtABCG30*, or *AtABCG40* led to a faster germination compared to the wild type [68].

Besides the ABC transporters mentioned above, in Arabidopsis, AtDTX50, a MATE transporter, was also identified as an ABA transporter that regulates seed dormancy [26,69]. AtDTX50 was found to be localized at the plasma membrane [26]. Using ectopic expressions of *AtDTX50* in *Escherichia coli* cells and *Xenopus* oocytes, the ABA transportation activity of AtDTX50 was validated [26]. The Arabidopsis *dtx50* mutant exhibited a slower germination rate when compared to the wild type upon the ABA treatment. This ABA-sensitive phenotype of the *Atdtx50* mutant implies that this MATE transporter also plays a role in seed dormancy regulation [26].

2.3. Bitterness and Psychostimulant

2.3.1. Alkaloids

As reviewed previously, the taste of crops has been a character selected by breeders [46,47]. Domesticated crops tend to have reduced levels of alkaloids due to the bitter

taste of alkaloids and the absence of selection pressure exerted by biotic stresses during domestication [46,47].

In Arabidopsis, AtDTX1 (*Arabidopsis thaliana* Detoxification 1) was identified to be a MATE-type transporter that mediates the transport of berberine, which confers a bitter taste [8,70]. The expression of *AtDTX1* in *E. coli* mediated the efflux of berberine out of the bacterial cells [8]. A subcellular localization study demonstrated that AtDTX1 is localized in the plasma membrane [8]. Such exporter activity and plasma membrane localization of AtDTX1 are in line with a previous finding that alkaloids are transported between plant organs [71]. In *Coptis japonica*, which is a medicinal plant, the role of CjMATE1 in mediating berberine accumulation in vacuole was suggested [72]. CjMATE1 was found to localized at the tonoplast and preferably expressed in rhizomes, where berberine is accumulated [72]. Using yeast as a model, the berberine transport activity of CjMATE1 was shown [72]. Although berberine confers a bitter taste, which is an undesirable trait in most edible crops, it is of important pharmaceutical value in medicinal plants [73].

2.3.2. Cyanogenic Glucosides

Cyanogenic glucosides are plant metabolites that are related to defense mechanisms [74]. An example is domesticated sorghum (*Sorghum bicolor*), which produces high levels of cyanogenic glucosides when compared to its wild ancestors [34]. *Sorghum bicolor* contains a high level of cyanogenic compounds, which are bitter, and thus has been cultivated for forage crop and animal feed because of the bitter taste [34,75]. Young seedlings of domesticated *Sorghum bicolor* harbor high concentrations of cyanogenic glucosides, when compared to its wild relatives, including *Sorghum brachypodum* Lazarides, *Sorghum bulbosum* Lazarides, *Sorghum ecarinatum* Lazarides, *Sorghum intrans* F. Muell ex. Benth, *Sorghum macrospermum* E.D. Garber, and *Sorghum matarankense* E.D. Garber & L.A. Snyder [34]. Cyanogenic glucosides are derived from amino acids, such as L-valine, L-isoleucine, L-leucine, L-phenylalanine, and L-tyrosine, and synthesized by membrane-bound cytochrome P450s and UDP-glucosyl-transferase [74]. The synthesized cyanogenic glucosides would then be hydrolyzed by β-glucosidase into cyanohydrin, which is unstable, and would further dissociate to form hydrogen cyanide and ketone via a process known as cyanogenesis [74]. Cyanogenic glucosides are toxic to herbivores. During ingestion and chewing, cyanogenic glucosides confer a bitter taste with the release of toxic hydrogen cyanide, which leads to tissue disruption [74]. Young seedlings of sorghum plants are highly toxic [76]. Therefore, sorghum plants are usually grazed when the plants have reached the five-leaf stage where the toxicity is reduced [76]. Although toxic to herbivores, cyanogenic glucosides are beneficial to plants. They scavenge hydrogen peroxide, which is a reactive oxygen species, by the Radziszweski process to alleviate the oxidative stress caused by biotic and abiotic stresses [77]. In addition, cyanogenic glucosides, which are derived from amino acids, also serve as a primary means of nitrogen storage and transport, and as a nitrogen reservoir under adverse conditions [78]. During their domestication as a forage crop and animal feed, sorghum plants have been mainly grown under sub-optimal conditions such as in the dry tropics under high temperatures, in regions such as Africa and Australia [75]. Such adverse growth conditions probably drove the selection for high cyanogenic glucoside levels in domesticated sorghum. It was reported that the biosynthetic genes of cyanogenic glucosides are organized in a gene cluster to enhance the co-inheritance of alleles in the same biosynthetic pathway [79].

SbMATE2 was one of the genes found within the gene cluster encoding cyanogenic glucoside biosynthetic enzymes in the *Sorghum bicolor* genome [79]. It was found to be co-expressed with other cyanogenic glucoside biosynthetic genes [79]. A subcellular localization study demonstrated that SbMATE2 transporters localize at the vacuolar membrane [79]. The ability of SbMATE2 to transport cyanogenic glucosides, such as dhurrin and other hydroxynitrile glucosides, was demonstrated in the *Xenopus laevis* oocyte model [79]. The SbMATE2-mediated influx of cyanogenic glucosides into the vacuole was enhanced by a lower pH in the medium [79]. As MATE transporters utilize the proton gradient as a

driving force, it was hypothesized that the direction of transport of cyanogenic glucosides by SbMATE2 is from the cytoplasm, where cyanogenic glucosides are synthesized, to the acidic vacuole [79]. Such storage of cyanogenic glucosides has been suggested as a strategy to reduce self-toxicity to the plant [79].

2.3.3. Nicotine

Besides food crops, tobacco (*Nicotiana* sp.), which is usually consumed as a psychostimulant, is also a popular plant known to have been domesticated. Unlike the general effort to reduce the levels of alkaloids in other food plants, human selection actually drives the increase in nicotine levels in tobacco. The use of tobacco by humans was estimated to have begun 12,300 years ago [80]. It was suggested that hunter-gatherers in western North America first cultivated wild tobacco [33]. Compared to wild tobacco plants, domesticated tobacco plants usually have larger leaves and higher levels of nicotine [33]. In *Nicotiana tabacum*, NtJAT1 (*Nicotiana tabacum* jasmonate-inducible alkaloid transporter 1), which is expressed in the leaf, stem, and root, mediates the efflux of nicotine out of the vacuole [29]. NtJAT2, which is also expressed in the leaf, was shown to have a similar nicotine export function to NtJAT1 when ectopically expressed in yeast [81]. Furthermore, NtMATE1 and NtMATE2 were reported to be localized in the tonoplast for the sequestration of nicotine from the vacuoles of root cells [82]. Nicotine is synthesized in the root and transported to the leaf [29]. Although the nicotine level in leaves could be enhanced by overexpressing transcription factors such as *NtMYC2a* and *NtMYC2b*, most nicotine synthetic genes, including NtPMT (*Nicotiana tabacum* putrescine N-methyltransferase), NtQPT (*Nicotiana tabacum* quinolinic acid phosphoribosyltransferase), NtMPO (*Nicotiana tabacum* N-methylputrescine oxidase), NtA622 (orphan oxidoreductase), NtBBL (*Nicotiana tabacum* berberine bridge enzyme-like), NtADC (*Nicotiana tabacum* arginine decarboxylase), and NtODC (*Nicotiana tabacum* ornithine decarboxylase), in NtMYC2a overexpressors were down-regulated [83]. Similar phenomena were reported in another study. The expression of NtMYC2a under constitutive promoters (GmUBI3 promoter/2XCaMV35S promoter) or a JA-inducible promoter (4XGAG) in tobacco plants led to the upregulation of nicotine level in the leaves [84]. Methyl-JA treatment further increased the nicotine level in transgenic plants expressing NtMYC2a under either one of these promoters [84]. It was also demonstrated that nicotine application at the root of tobacco seedlings repressed the expression levels of the nicotine synthetic genes regulated [83]. NtMYC2a and NtMYC2b form nuclear complexes with NtJAZ1, which is a transcriptional repressor of JA inducible genes, for the down-regulation of nicotine biosynthesis-related genes [85]. Considering that the whole profile of transcriptional regulatory targets of NtMYC2a and NtMYC2b are unclear, NtMYC2a- and NtMYC2b-mediated gene regulation involves JA signaling, which is associated with various physiological responses; the phenomenon that the nicotine level negatively regulates nicotine synthetic genes means MATE transporters that ultimately mediate the transport of nicotine in leaves may be the more direct candidates for altering the nicotine level.

3. Other Stress Tolerance-Related Compounds

In field pumpkin (*Cucurbita pepo*), the cotyledon cucurbitacin accumulation was reported to be controlled by a single locus, *Bi-4*, with a causal gene encoding a MATE transporter involved in the transportation and accumulation of cucurbitacin [86]. It was reported that the cucurbitacin level in the cotyledon served as a predictor of the preference for cotyledons by the striped cucumber beetle, *Acalymma vittatum*, suggesting MATE transporters to be one of the selection factors during independent domestication events in the cultivation of *C. pepo* subspecies, such as *C. pepo* ssp. *Pepo*, and *C. pepo* ssp. *ovifera* [86]. In persimmon (*Diospyros* spp.), MATE transporters underwent positive selection during the domestication event [87]. Although the actual functions of the MATE transporters during *Diospyros* domestication is unclear, it was hypothesized that the positively selected genes

might aid in reducing/removing the astringency of persimmon fruits via reducing the accumulation of soluble proanthocyanidins [87].

Aluminum (Al) toxicity is one of the root growth-limiting factors in acidic soil. The concentration of soluble Al cations increases in the acidic environment and are predominantly in the form of the trivalent cation Al^{3+}, which is toxic to the root. Plants have evolved sophisticated counter-measures by releasing organic anions from root apices, such as citrate and malate, to chelate the soluble Al^{3+} ion to form non-toxic complexes [88]. MATE transporters have been reported to mediate Al tolerance by mediating citrate efflux from the roots of various plant species, such as barley, rice, wheat, and sorghum [89–99].

3.1. The Regulation of MATE Expression Levels by Transposable Element (TE) Insertion to Regulate Malate Transport Efficiency

In relation to the MATE transporter-assisted Al tolerance, transposable elements (TEs) in the coding sequences or flanking regions of MATE-encoding genes often underwent a positive selection during domestication or cultivation. Some of the TE-induced genetic variations improve Al resistance by modifying the spatial and temporal expression patterns of *MATE* genes, eventually enhancing the efflux of organic anions from the root.

Barley (*Hordeum vulgare*) is an important crop plant that is highly sensitive to Al. A positive correlation between citrate secretion and Al resistance was found by comparing the Al resistance levels among various barley varieties [100]. In barley, *HvAACT1* (*Hordeum vulgare Al-activated citrate transporter 1*) encodes a MATE transporter that serves the dual function of the Al-activated citrate secretion for enhanced Al^{3+} tolerance and Fe ion translocation from the root pericycle cells to the xylem [89,90]. A positive correlation among the expression of *HvAACT1*, the amount of citrate secreted, and the level of Al resistance in different barley cultivars was established [89]. In the Al-tolerant barley cultivars, a 1-kb transposable element-like insertion was found upstream of the coding region of *HvAACT1* [90]. It was further validated that the inserted sequence regulates the expression pattern of *HvAACT1*. The insertion enhances the expression of *HvAACT1* in the whole root and specifically in the root tips. The insertion had a single origin during the expansion of barley cultivation into areas with acidic soil. Only the Al-tolerant cultivars from Japan, Korea, and China carry the insertion, suggesting the insertion was responsible for helping the plant adapt to the acid soils in these areas [90]. In addition, different allelic forms of *HvAACT1* exist in different barley cultivars. The Chinese barley genotype CXHKSL, moderately tolerant of Al, carries another allele of *HvAACT1* that does not have the typical insertion that was found associated with Al tolerance [92]. Although barley having the CXHKSL genotype demonstrated a similar Al tolerance mechanism to other Al-tolerant barley lines, the actual mechanism of how different promoter variants affect the expression of *HvAACT1* remains unclear [92].

In *O. sativa*, it was reported that the MATE transporter OsFRDL4 at the plasma membrane of root cells mediated the transport of citrate and increased the Al tolerance [101]. It was demonstrated that the high expression level of *OsFRDL4* (*O. sativa* ferric reductase defective-like 4) was influential in conferring Al tolerance. Comparing the *OsFRDL4* gene structure between cultivated and wild rice accessions, the 1.2-kb single long terminal repeat of the retrotransposon-like insertion in the promoter region of *OsFRDL4* was found in 15 out of 16 *japonica* cultivars and five out of 52 *indica* cultivars, while none of the six wild accessions (*Oryza rufipogon*, *Oryza barthii*, *Oryza glumaepatula*, *Oryza meridionalis*, *Oryza australiensis*, and *Oryza punctata*) had the insertion [94]. The insertion event was suggested to occur around the time of the domestication of ancient *japonica* varieties [94]. In addition, it was proposed that the existence of the exceptional *indica* accessions having the insertion was likely due to the outcross between *indica* and ancient *japonica* [94]. The insertion enhances the overall expression level of *OsFRDL4* in rice without altering its spatial expression pattern or subcellular localization [94], unlike the case in barley where the insertion regulates the tissue-specificity of *HvAACT1* expression [90]. The sequence analyses revealed that the insertion in rice contains nine *cis*-acting elements for ALUMINUM

RESISTANCE TRANSCRIPTION FACTOR1 (ART1), a C2H2-type zinc finger transcription factor associated with Al tolerance. The ART1-regulated pathway contributed to the high promoter activity and expression level of *OsFRDL4* upon Al stress [95]. Besides OsFRDL4, OsFRDL2 is another citrate MATE transporter, which localizes in the mature region of the root, and is involved in Al tolerance via an unknown pathway in rice [93].

The involvement of transposable elements in affecting the expression levels of *MATE* genes was also observed in wheat (*Triticum aestivum*). *TaMATE1* encodes a citrate transporter localized on the plasma membrane. TaMATE1 was reported to be involved in citrate efflux for higher Al tolerance in wheat [91,96], and *TaMATE1* was constitutively expressed in the highly Al-resistant wheat cultivars [96]. A *Sukkula*-like transposable element (TE) was found in the promoter region of *TaMATE1-4B* in the Al-resistant cultivars [97]. In another study, the *Sukkula*-like TE was reported to be associated with the enhanced expression of *TaMATE1B* [91]. Between the genotype showing citrate efflux from root apices (cv Carazinho) and the genotype lacking citrate efflux (cv Egret), the coding regions of *TaMATE1B* are identical [91,97]. However, the sequences upstream of the coding region are different [91,97]. The 11.1-kb *Sukkula*-like transposable element was found in cv Carazinho but not in cv Egret [91]. In addition, a single-nucleotide polymorphism (SNP) was found at approximately 12 kb and 2 kb upstream from the start codon of *TaMATE1B* in cv Carazinho and cv Egret, respectively [91]. The SNP was suggested to further contribute to a 2-3-fold difference in the *TaMATE1B* expression and a 2-fold difference in citrate efflux [91,102]. The transposable element enables stress tolerance dynamics among different accessions.

In sorghum (*Sorghum bicolor*), *SbMATE* is an Al-activated citrate MATE transporter gene in the *Al tolerance locus* (*AltSB*). A tourist-like miniature inverted-repeat transposable element (MITE) was found in the promoter region of *SbMATE* and regulated the expression of *SbMATE* [98]. The MITE insertion region of the *SbMATE* gene was highly polymorphic in size, and such variations contributed to the different levels of Al tolerance in sorghum. Based on population structure analysis, the MITE insertion-mediated Al tolerance was not a random event, but was instead under a high level of positive selection, as the *AltSB* locus was genetically differentiated into subgroups featuring specific racial and geographical origins [99].

Besides TEs, the possible regulation of *MATE*s by miRNAs has also been reported. For example, in Tibetan hulless barley, by the RNA ligase-mediated 5′rapid amplification of cDNA ends (RLM 5′-RACE), the cleavage of a *MATE* gene by hvu-miR166a was reported [103]. In the ancient landrace Tibetan hulless barley accession *Lhasa goumang* (GM), the lower expression level of hvu-miR166a at germination stage than that in seedling stage was reported [103]. Based on the regulation of *MATE* by hvu-miR166a, such a pattern of hvu-miR166a expression was suggested to play a role in reducing H^+ accumulation in the seed during early germination [103]. In *Z. mays*, miR528s was identified in xylem sap and predicted to regulate a *MATE* gene related to metal handling, chelation, and storage (ZM2G148937) [104]. However, the miRNA targeting, and the functional significance of the regulation, have not yet been experimentally validated.

3.2. The Expansion of MATE Gene Copy Numbers and Functional Differentiation

Apart from the involvement of TE-like elements in regulating the expression of *MATE* genes, gene duplication events were also suggested to contribute to the enhancement of MATE-mediated stress tolerance. A recent gene duplication event in maize (*Z. mays*) resulted in the copy number variation in the citrate transporter gene, *ZmMATE1*. Based on quantitative trait locus (QTL) analyses, *ZmMATE1* underwent a tandem triplication, which served as the basis for phenotypic variations [11]. Such a copy number expansion in *ZmMATE1* originated from regions with acidic soil, resulting in higher *ZmMATE1* expression and better accommodation of Al toxicity. The structural variations in the maize genome suggests that rapid evolutionary responses might have contributed to local adaptations of maize to highly acidic soils [11]. A similar observation based on chromosome location and gene duplication analyses was reported in poplar (*Populus* spp.). It was revealed

that tandem repeats and duplication events contributed to the expansion of the MATE gene family in the *Populus* genome [3]. Functional differentiation after gene duplication in response to Al stress was observed in poplar, in which the *PtrMATE1* expression was induced at 12 h after exposure to Al stress, whereas the *PtrMATE2* expression was induced at 24 h [3].

During domestication, the expression of *MATE*s was also reported to be altered by other events such as the insertion/deletion (InDel) removal by human selection. In tomato (*Solanum lycopersicum*) fruits, the high expression level of *Al-ACTIVATED MALATE TRANSPORTER9* (*ALMT9*) contributed to the accumulation of malate in the tomato fruit during ripening and in Al-stressed roots, improving both fruit flavor and Al stress resistance in cultivated tomato plants [35]. According to phylogenetic analyses, the high-malate phenotype, Sl-ALMT9HMH, originated through two evolutionary events, which were the insertion of LTR retrotransposon CopiaSL_37 into the second intron of the wild tomato followed by the removal of indel_3 by human selection [35]. As revealed by the RNA-seq analysis between the wild type and the *SlALMT9*-overexpressing line, potential alternative malate transporters from members of the *MATE* family were reported with altered expression levels [35].

Examples of contrasting agronomic traits between wild crops and domesticated crops associated with the transport of metabolites by MATE transporters are listed in Table 1. The agronomic traits regulated by MATE transporters are summarized in Figure 1.

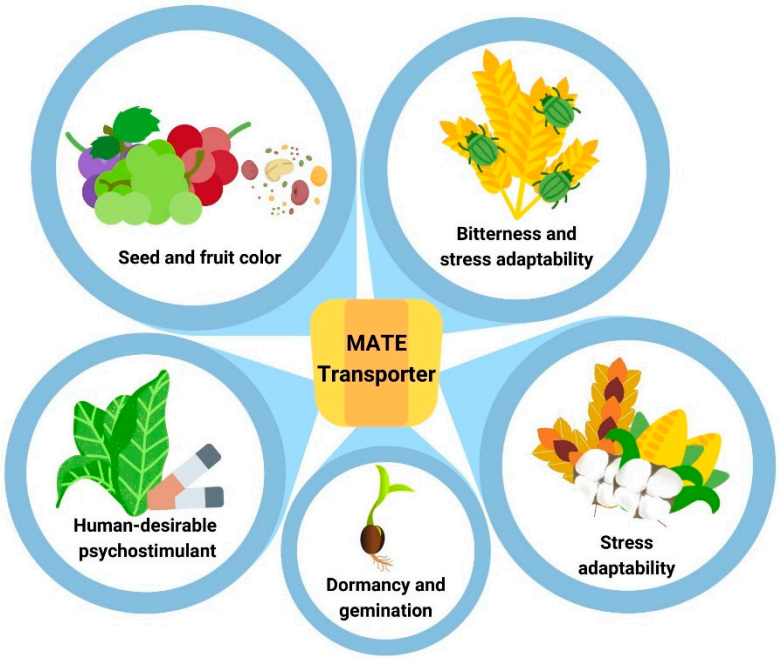

Figure 1. Agronomic traits of crops including seed and fruit color, seed dormancy and germination, the accumulation of psychostimulant, bitterness, and stress adaptability are regulated by MATE transporters.

Table 1. Examples of contrasting agronomic traits between wild crops and domesticated crops associated with the transport of metabolites by MATE transporters.

Agronomic Trait	Substrate	Species	MATE Transporter	Description	Reference
Seed and fruit color	Proanthocyanidins (PAs)	*Arabidopsis thaliana*	AtTT12	Enhances the accumulation of PAs in the seed coat; results in the darker seed coat color.	[4]
	Proanthocyanidins and epicatechin 3′-O-glucoside	*Medicago truncatula*	MtMATE1		[22]
	Anthocyanins	*Vitis vinifera*	VvMATE3	Mediates the accumulation of anthocyanins; results in the darker skin color of grapevine fruit.	[60]
Dormancy and gemination	Abscisic acid (ABA)	*Arabidopsis thaliana*	AtDTX50	Prevents seeds from germinating under unfavorable conditions; *Atdtx50* mutant exhibited slower germination rate compared to the wild type upon ABA treatment.	[26,69]
Human-desirable psychostimulant	Nicotine	*Nicotiana tabacum*	Nt-JAT1, Nt-JAT2 NtMATE1, NtMATE2	Enhance nicotine levels in the leaves of tobacco.	[29,81,82]
Bitterness and stress adaptability	Berberine	*Arabidopsis thaliana*	AtDTX1	Mediates the transport of berberine; associated with the transport of alkaloids between plant organs.	[8,46,47]
	Cyanogenic glucosides such as dhurrin and other hydroxynitrile glucosides	*Sorghum bicolor*	SbMATE2	Domesticated sorghum plants have higher cyanogenic glucoside contents than their wild relatives. Cyanogenic glucosides are toxic to herbivores and enhance the adaptability of the plant to adverse environments where sorghum plants are grown.	[34,74,77,79]
Stress adaptability	Malate	*Solanum lycopersicum*	Two potential members of MATE protein family	Altered expression levels of *MATE* in the high malate-content Sl-ALMT9HMH were related to domestication.	[35]
	Citrate	*Hordeum vulgare*	HvAACT1 CXHKSL	A 1-kb transposable element-like insertion at the *HvAACT1* promoter region enhances the expression and regulates the tissue specificity of the expression. The insertion is commonly found in the Al-tolerant barley cultivars from Japan, Korea, and China.	[90,92]
		Oryza sativa	OsFRDL4 OsFRDL2	A 1.2-kb retrotransposon-like insertion at the *OsFRDL4* promoter region enhances the expression of *OsFRDL4* for improved Al tolerance. The insertion is suggested to have occurred at the initial stage of domestication of the *japonica* subspecies.	[93,94,101]
		Triticum aestivum	TaMATE1	An 11.1-kb Sukkula-like transposable element insertion at the promoter region is associated with the constitutive expression of *TaMATE1* in both Al-resistant Brazilian and Portuguese wheat cultivars.	[91,96,97]
		Sorghum bicolor	SbMATE	Tourist-like miniature inverted-repeat transposable elements (MITEs) of different sizes are associated with the different levels of Al tolerance in sorghum.	[98,99]
		Zea mays	ZmMATE1	Gene duplication event resulted in the increase of *ZmMATE1* copy number for enhanced tolerance to Al toxicity.	[11]
		Populus trichocarpa	PtrMATE1 PtrMATE2	Gene duplication event resulted in the expansion of *MATE* gene family. *PtrMATE1* and *PtrMATE2* have different responses to stimuli to achieve functional coordination under Al toxicity.	[3]
	Cucurbitacin	*Cucurbita pepo*	Cp4.1LG05g02530	Cotyledon cucurbitacins might act as the predictor of *Acalymma vittatum* preference for cotyledon. Cp4.1LG05g02530 possibly mediates the accumulation of cucurbitacin in the cotyledon.	[86]

4. MATE Transporters Are Possible Candidates for Molecular Breeding

Desirable traits in domesticated crops include light seed color for the ease of sowing and religious reasons [30]. Moreover, domesticated vegetable and wild vegetable tend to have contrasting color, with the fruits of domesticated vegetables usually being lighter in color [31,57,58]. In addition, domesticated crops have a better balance of dormancy and germination efficiency compared to wild crops to favor cultivation [32,63]. Domesticated crops may have less alkaloid level compared to wild crops due to the absence of biotic stresses as selective pressures [46,47]. To produce psychostimulants, domesticated tobacco has higher nicotine levels than wild tobacco [33]. To achieve the various favorable traits, the transports of substrates including pigmented metabolites, phytohormone, and alkaloids are involved.

*MATE*s constitute big families in the genomes of various plants [1–8]. In terms of the protein structure, MATEs typically consist of 12 TMDs [13]. However, MATE proteins do not share conserved amino acid sequences in the core domain [6]. Such property enables the diverse substrate specificities. Many domestication genes are those encoding transcription factors [43,44]. It was suggested that domestication involves the regulation of transcriptional network [105]. The power of transcriptional control lies on the combinatorial effect of the interaction among transcriptional regulators to enable diverse outcomes of gene regulation [106]. However, such a characteristic of transcription factors may not be an advantage if the gene is selected for molecular breeding. Although transcription factors are able to regulate various agronomic traits [43,44], there may be additional regulations between the transcriptional control and the desired regulation of metabolites. For example, *NtMYC2a* and *NtMYC2b* could regulate the nicotine level in the tobacco leaf [83]. However, the genes involved in nicotine biosynthesis are also regulated by JA signaling [85]. The modulation of transcription factors in molecular breeding may thus involve unpredicted factors. On the contrary, MATE transporters are down-stream regulators that directly mediate the accumulation or export of specific substrates. MATE transporters are therefore possible candidates for molecular breeding to achieve a specific trait. In the soybean, it was demonstrated that the alteration of the expression level of *GmMATE1* could regulate seed isoflavone level. When *GmMATE1* was overexpressed, the soybean seeds increased the isoflavone level [16]. In contrast, when *GmMATE1* was knocked-down, the soybean seed isoflavone level was decreased [16]. Besides the alteration of the expression level by genetic engineering, the selection of naturally occurring allelic forms of *MATE* for molecular breeding is also possible. For example, in the Al-tolerant barley cultivars, the *HvAACT1* gene, with a 1-kb transposable element-like insertion upstream to the coding region, was suggested to be responsible for the Al tolerance [89,90]. The insertion enhances the expression level of *HvAACT1* in the whole root and specifically in the root tips [90]. The other allelic form of *HvAACT1* without the a 1-kb transposable element-like insertion was found in a less tolerant barley cultivar [92]. More examples of naturally occurring allelic forms of *MATE*s are discussed in Section 4.

5. Conclusions

MATE transporters are ancient proteins conserved among most species, from prokaryotes to eukaryotes. A special feature of *MATE*s is that they form a large gene family with many paralogous genes and/or large copy numbers in the same species. Such gene family member expansions were due to genome duplication events. The need to transport different substrates under different situations requires many homologous transporters and therefore results in a large gene family. MATEs mediate the transport of a wide variety of compounds, including those that give colors to various organs/tissues, flavor compounds, and phytohormones. As discussed above, many of these compounds had undergone selection during domestication. Although MATEs have seldom been discussed for their role in crop domestication, the involvement of MATEs in regulating domestication-related traits and the possibility of *MATE*s being candidates for molecular breeding should not be overlooked.

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