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LARGE FRUIT OF TOMATO *Solanum lycopersicum* L.: GENETIC DETERMINANTS, ORGANOGENESIS AND FRUIT DEVELOPMENT
(review)

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Abstract

Large fruit in *Solanum lycopersicum* L. is the result of domestication. We were interested in the appearance of large fruits in tomato in connection with the practice task to get new tomato forms with large fruits for multi-tiered hydroponic and aeroponic installations for vertical fruit production in greenhouses. Using the technology of target tomato breeding we obtained the first special dwarf tomato varieties Natasha and Timosha with small fruits for multi-tiered hydroponic installations. Obtaining of large fruit in tomato is connected with genetic and epigenetic control of the trait (An. Frary et al., 2000; B. Cong et al., 2006; Z. Huang et al., 2011; S. Wang, et al., 2011; A.J. Monforte et al., 2014; L. Azzi et al., 2015). The goal of this review is to summarize data on genetic determinants the trait of "size/weight of the fruit", analysis processes of organogenesis, hormone and metabolic regulation of fruit development. Analysis of papers dedicated to fruit weight increasing during domestication shows the availability of 37 loci involved in regulation of cell division and enlargement at four different stages of fruit development, starting from the phases of ovary development and fruit set to the phases of cell development and enlargement of cells which form the mature fruit. Some of these loci are connected with processes of hormonal plant development at the phase of anthesis, fertilization, formation of fruits and seeds, and so, they are involved in auxin (*SlPIN4*, *SlTIR1*, *SlARF7*, *SlARF8*, *SlIAA9*) and gibberellin (*SlGA20ox1*, *SlDELLA1*) signaling pathways. Others control cell enlargement during fruit development and maturing, and so, they are involved in regulation of primary (*HXK1*, *SuSY*, *LIN5*, *TIV1*, *mMDH*, *cpFBP*, *SPA*) and secondary (*NOTABILIS/NCED1*, *FLACCA*, *Gal-LDH*, *GME*) metabolism. Individual group of loci controls cell cycle at the period of ovary development (*TAGL1*, *FAS*, *LC*, *SlWUS*, *SlIMA*) and fruit growth (*SlCDKA1*, *SlCDCB1*, *SlCDKB2* and *SlCCS52A*, *SlWEE1*, *SlKRP1*) (L. Azzi et al., 2015). The *fw2.2* is the first locus which has been described in detail (An. Frary et al., 2000). Locus *fw2.2* controls the small fruit size in *S. lycopersicum* and is semidominant to allele *FW2.2* of large fruit size. With transgenic lines, it had been established, that locus *fw2.2* is carried by cos50. Sequence analysis of the cos50 had identified two open reading frames. One of them contain a single recombinant event, which delimited "the rightmost" end of the *fw2.2* (XO33). Because genetic mutation(s) causing change in fruit size must be to the left of XO33, cDNA44 cannot be involved and open reading frame is the likely cause of the small-fruit phenotype. Next studies indicated that *fw2.2* acts as a negative regulator of cell division during the very early stages of fruit development following pollination. Thus, *fw2.2* is one of regulatory QTLs, such as *achaete-scute*, *scabrous and Delta* QTLs in fruit flies, *teosinte-branched 1*(*tb1*) in maize and *Hox* genes in animals (cited by B. Cong et al., 2006). Possible, locus *FW2.*2 is positive regulator of cell division, which is involved in interaction with cytoplasmic membranes mediated by the regulatory (beta)-subunits of CKII kinase, that is well known in yeast and animals where it forms part of cell cycle related with signaling pathway (B. Cong et al., 2006).

Keywords: *Solanum lycopersicum* L., tomato, breeding, heritability, large fruits, average fruit weight, dwarfism, regulatory QTLs, fruit development

The main modern trend in greenhouse vegetable growing is multi-tier narrow-shelving hydroponic and aeroponic installations (vertical vegetable growing)

which produce greenery yield 530 times as much as in field conditions [1, 2]. To fill the capacious [1] and fast-growing [2] vertical vegetable growing market with the main crops (tomato, cucumber, sweet pepper), new plant breeding technologies are required. Knowing the peculiarities of the phenotypic manifestation of genes that control the key trait (dwarfism) allowed us to developed a target technology to select forms of vegetable crops for vertical vegetable growing [3, 4] and to produce the world's first small-fruited tomato varieties Natasha and Timosha for multi-tiered narrow-shelled hydroponics [5]. Application of genetic analysis [6] and targeted hybridization with large-fruited maternal forms almost doubled the average weight of fruits in the F_3 generation [7]. But the tomato fruit size is a complex quantitative trait. Consequently, to effectively produce large-fruited varieties, it is necessary to know not only the genetic determinants of the trait, but also the mechanisms that modulate phenotypic manifestation of these genes. In our review, we focused on the analysis of data on genes involved in the control of fruit weight in tomato, and the possibilities to regulate their expression, which, in our opinion, are of primary interest for breeding.

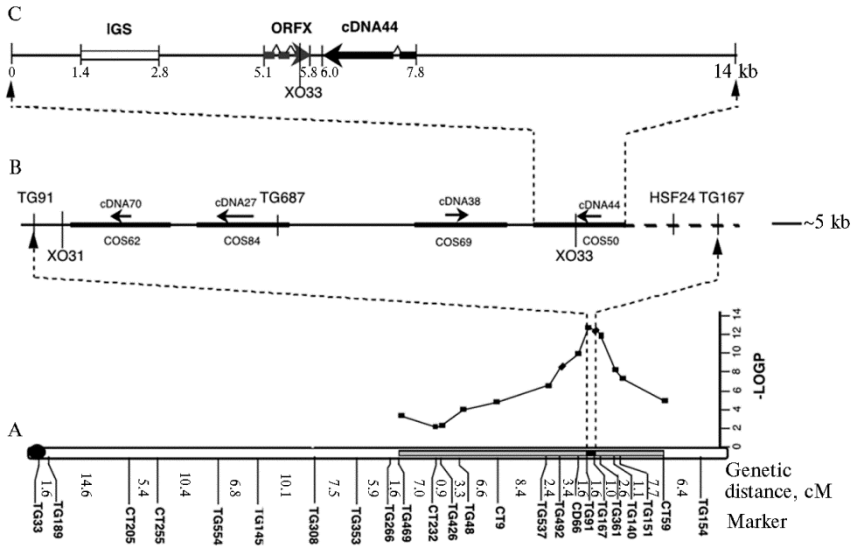
This review aims to summarize information on the genetic determinants of fruit weight in tomato and their relationship with organogenesis, hormonal and metabolic regulation of fruit development.

The tomato (*Solanum lycopersicum* Mill.) fruit is a multilocular berry widely used as a model of a juicy fruit in both agronomic and basic research [8-10]. The ancestral form of the domestic tomato had fruits less than 1 cm in diameter and weighing several grams. Changes in tomato fruit size are associated with domestication. We recorded a tomato fruit weight of 780 g (2018) [2], but in modern tomatoes it can reach 1000 g with a diameter of more than 15 cm [11].

Loci controlling fruit size. In tomato, fruit size is a polygenic trait. Most of the 37 loci involved in the evolution and domestication of tomato from small-fruited forms to larger-fruited ones are genetically mapped [12, 13].

The first mapped locus for tomato fruit size was *fw2.2*. Determining small fruit size, this locus behaves as semi-dominant vs. the semi-recessive large-fruit allele *FW2.2* [11]. All studied wild species of *S. lycopersicum* carry small-fruit alleles *fw2.2*, while modern varieties carry large-fruit alleles *FW2.2*. An international group of researchers cloned and sequenced a 19 kb segment containing *fw2.2* locus, and also identified the genes responsible for the effect of this locus [11]. The same authors constructed a high-resolution genetic map for the *fw2.2* locus using four unique transcripts identified in 3472 plants of the F_2 generation derived from crossing of two near-isogenic lines (NILs) different in *fw2.2* alleles (Fig.) [11]. Four cDNAs corresponding to these transcripts were used to screen a library of cosmids carrying fragments of *S. pennellii* genomic DNA. As a result, four positive non-overlapping cosmids were identified, the cos50, cos62, cos69 and cos84, each corresponding to one of the unique transcripts. Using transgenic lines, *fw2.2* was detected in cos50. Sequencing of this cosmid revealed two open reading frames (see Fig.). The first ORF corresponded to cDNA44 (one of the four unique cDNAs by which cos50 was identified), for the second ORF (663 nt), corresponding transcripts were not initially found in the library. The insertion contained a highly repetitive AT-rich (80%) 1.4 kbp region (see Fig., C). Previous mapping of *fw2.2* revealed a single recombination event [XO33] that delimited the "rightmost" end of the *fw2.2*. Comparison of the genomic DNA sequence in this recombinant plant with that in the two parental lines showed the localization of XO33 between the 43rd and 80th nucleotides from the 5′-end of the open reading frame X (ORFX) (see Fig., A). Since the genetic mutation(s) causing fruit size change can only be to the left of XO33, cDNA44 cannot be involved in the fruit size increase, and the ORFX or an upstream region is the likely cause of a standard small-fruited

fw2.2 phenotype.



High-resolution genetic mapping of *fw2.2* locus [11].

A. Location of *fw2.2* on chromosome 2 in crosses between *Solanum lycopersicum* and an isogenic line containing small introgression from *S. pennellii.*

B. A contig form the candidate region *fw2.2* delimited by recombination events at XO31 and XO33. Arrows mark four original candidate cDNA (cDNA70, cDNA27, cDNA38, and cDNA44), bold horizontal lines indicate four cosmids (cos62, cos84, cos69, cos50) isolated with these cDNAs as probes.

C. The sequence of cos50 spanning XO33 recombination event.

The same authors [11] found an open reading frame (ORFX) in flower organs (petals, carpels, sepals, and stamens) before flowering. Since ORFX is transcribed at a level too low to be detected using standard Northern hybridization protocols, the authors used reverse transcription polymerase chain reaction (RT-PCR) and revealed the highest level of ORFX expression in carpels. The study of the relative expression levels of ORFX transcripts in carpels in different isogenic lines showed a significantly higher level of expression of ORFX transcripts in carpels in small-fruited isogenic lines as compared to large-fruited ones. The study of ORFX transcription in carpels before flowering confirms that *fw2.2* is enhanced in the early stages of plant development. In order to test this hypothesis, the authors compared the masses of flower organs in small-fruited and large-fruited isogenic lines [11). Carpels which later develop into fruits, pistils and sepals before flowering were always heavier in large-fruited isogenic lines than in small-fruited lines. The cell size before flowering was similar in both types of isogenic lines, which means that carpels of large-fruited genotypes contain more cells. Analysis of allelic differences between *fw2.2* and *FW2.2* by comparing the 830 bp fragment containing ORFX in *S. pennellii* and *S. lycopersicum* led to the conclusion that, in the case of *fw2.2*, the phenotype is due to one or more upstream changes in the ORFX promoter region. The reduction in cell division in carpels of small-fruited isogenic lines correlates with the general increase in levels of the ORFX transcripts, confirming that ORFX can be a negative regulator of cell division [11]. Convincing evidence of this was obtained in later works carried out in the same laboratory [14]. It was found that *fw2.2* acts as a negative regulator of cell division in the earliest stages of fruit development, i.e., after pollination. Thus, the *fw2.2* is one of the regulatory quantitate trait loci (QTL) for an increase in fruit size, similar, for example, to the *achaete-scute*, *scabrous*, and *Delta* loci in fruity-cultures,

teosinte-branched 1 (*tb1*) in maize and *Hox* genes of animals, in which morphological changes reflect variations in gene regulation rather than modification of protein functions [cited from 14]. As for the *FW2.2* locus, it most likely plays the role of a positive regulator, direct or indirect, of cell division. Interaction occurs between the *FW2.2* locus and cytoplasmic membranes via the regulatory β-subunit of CKII kinase. CKII kinases are well studied in yeast and animals, in which theses kinases are involved in the cell cycle and are associated with signaling pathways. Thus, although *FW2.2* is a specific plant protein [11] and regulates cell division in a specialized organ (fruit), it appears to be involved in the cellular control of signal transduction [14].

The locus *FW2.2* belongs to the multigene family which in the tomato plants is comprised of 17 homologues. The family is usually referred to as the *FW2.2-like* or *FWL* genes. FW2.2 and FWL proteins contain an uncharacterized Placenta-specific 8 (PLAC8) motif which was originally found in the mammalian placental proteins [15]. The PLAC8 motif contains two cysteine-rich conservative domains separating the variable region that precedes the transmembrane segments. In tomato, the original FW2.2 proteins possess two transmembrane domains which fix the protein on the plasmalemma [14]. The earlier reports have shown that cysteine-rich domains may be involved in the transmembrane transfer of heavy metals such as cadmium and zinc. This was first established in proteins of cadmium-resistant *Arabidopsis* plants. This type of proteins can multimerize into a homopentamer to form a transmembrane pore, which makes it possible to transport metal cations [16].

FW3.2 is the second major QTL for tomato fruit size/weight that has been mapped and cloned [17]. The genes of this locus encode the P450 enzyme from the CYP78A5 subfamily, previously identified as KLUH [18]. The effect of *SlKLUH* is to increase the fruit volume through an increase in the cell number in the pericarp and septum tissues. *SlKLUH* function suppression using RNA interference strategy led to a decrease in fruit and seed sizes [17].

FW11.3 is another important QTL responsible for tomato fruit weight [19]. Genetic mapping revealed an overlap of *FW11.3* with the *fasciated* (*fas*) locus which determines the fruit shape and is located on chromosome 11, but *FW11.3* and *fas* are not alleles [20]. The large-fruit allele *FW11.3*, in contrast to *FW2.2* and *fas*, is partially dominant [19].

The complex family of loci that control the tomato fruit size/weight often overlaps with the loci responsible for the fruit shape, which, according to the opinion of some authors, was the result of domestication and is closely related to the regulatory functions of these loci [21]. Therefore, we will consider QTLs for fruit shape in *S. lycopersicum*. In contrast to the ancestral round shape, modern tomatoes are round, flat, ellipsoidal, pear-shaped, heart-shaped, oval and elongated in shape. But all the diversity of these forms is controlled by only four mutant genes, the *OVATE, SUN*, *FASCIATED* (*FAS*), and *LOCULE NUMDER* (*LC*) [22].

OVATE is the first gene for fruit shape identified by positional cloning [23]. *OVATE* is a platform for the ovate family of proteins, the functions of which are not fully understood [23, 24]. The *ovate* mutation is expressed in the appearance of elongated, pear-shaped, and ellipsoidal fruits, depending on the genotypic background of the plant carrying the *ovate* mutation [25]. This diversity confirms that *OVATE* is not the only gene responsible for the observed phenotype, but interacts epistatically with other genes [23]. It is assumed that the *OVATE* mutation is associated with the lost function of a negative plant growth regulator, the role of which remains to be clarified. For example, in *Arabidopsis*, proteins of the

OVATE family act as transcriptional repressors of the expression of AtGA20ox1, a key factor in the biosynthesis of gibberellic acid, which reduces cell elongation and, therefore, can affect fruit size [24, 26, 27].

Elongated fruit shape is associated with the *SUN* gene. The retrotransposon, which places this gene under the control of the *DEFL1* defensin gene promoter, provides duplication of this gene, which leads to its high expression in tomato fruits [28, 29]. Overexpression of the *SUN* gene increases the cell number in the direction of fruit elongation, which ultimately forms a phenotype with an elongated fruit [30].

The number of locules (gene *LOCULE NUMDER*, LC) is determined by the number of carpels within the flower. Wild tomato species have fruits with 2-4 locules, while modern varieties and hybrids can have more than 15 locules per fruit. As a result, not only the shape, but also the size/weight of the fruit changes, sometimes by more than 50% [9].

QTL *FASCIATED* (*FAS*) has been identified as a locus that regulates tomato fruit size via an increased number of locules, from 2 to 7 or more, while the *lc* mutation has a weaker effect [31, 32]. *FAS* encodes a YABBY-like transcription factor [33], and *LC* is located in a non-coding region between two potential candidate genes, the *WUSCHEL* which is a member of a plant-specific transcription factor gene family *WUS* (*WOX*), and a gene encoding a protein carrying a WD40 repeat [34]. The functions of most *WOX* genes have been known for a very long time [35]. More specific *WUS* genes are involved in maintaining stem thickness and meristem size, and therefore *WUSCHEL* can influence the number of locules. *FAS* and *LC* are able to epistatically interact and produce fruits with a very large number of locules [36]. Both of these loci control the size of the floral meristem; therefore, the development of a large number of carpels (locules) is possible, leading to the appearance of enormous fruits [33, 34].

Functional analysis using *TOMATO AGAMOUS-LIKE1* (*TAGL1*), an ortholog of the duplicated *SHATTERPROOF* (*SHP*) *MADS* box gene of *Arabidopsis thaliana*, showed the involvement of this transcription factor in the regulation of fruit development [37]. Tomato plants in which *TAGL1* expression was suppressed produced small fruits with a thin pericarp consisting of several layers of cells, and the pigmentation of the fruits also changed during ripening, which indicated the participation of *TAGL1* in the regulation of these processes.

Organogenesis: development of the tomato fruit. Fruits usually develop from anterior organs, for example, from carpels inside a flower. In tomato, carpels are formed during 17-20 cycles of cell division which occurs before flowering inside the L3 layer of the floral meristem not involved in cell expansion [38, 39]. Obviously, the number of cells formed before flowering is critical for the final size of the fruit, and such a positive correlation is often observed [9]. From the beginning of flowering to double fertilization that occurs in the ovules [8, 40], the morphogenesis and growth of carpel and ovules require the synthesis of auxins, cytokinins, and gibberellins, which act as a complex organized spatially and temporally. In order to protect the ovule and keep it dormant for a certain time, the abscisic acid and ethylene inside the ovary inhibit the growth of the ovule for a short period before flowering until it is ripe [41]. Only after successful pollination and fertilization of the ovules the process is completed with the involvement of fruit set triggers, the auxins and gibberellins synthesized by the ovary [42].

An increase in the tomato fruit size is the first and longest phase of a fruit development, it takes 5-8 weeks, depending on the genotype. Growth is due to the first period of intense mitotic activity in accordance with the spatial and temporal organization of cell division. Active cell division within the pericarp is usually limited to an initial period of 1-2 weeks after fruit setting. Remarkably, cell

division begins within discrete cell layers according to a certain scenario: two subepidermal layers of the pericarp undergo several cycles of periclinal division, thus leading to an increase in the number of periclinal cell layers, while two epidermal cell layers in response undergo anticlinal divisions, which leads to an increase in fruit volume [43]. These different types of cell division are regulated differentially, because cell division promotes the formation of cell layers that arise only within 5-8 days after flowering, while cell division less pronounced orientation occurs within 10-18 days after flowering [43]. Cell division in growing fruits covers about 80-97% of newly formed cells that arise after flowering and successful pollination.

During the second phase of growth, cell expansion occurs independently, but concomitant with cell division [8]. In fact, cell expansion begins a few days after fruit set [43] and continues during the entire period of fruit growth. At the end of the cell expansion phase, individual cells in the fleshy part of the fruit (mesocarp tissue) increase in volume by more than 30,000 times, which leads to an increase in the cell diameter by more than 0.5 mm [43). The increase in cell volume occurs mainly due to a significant increase in the volume of the vacuolar compartment and the vacuolar index of the cell. This expected cell hypertrophy is due to an increase in the amount of nuclear DNA as a result of endopolyploidization. Endopolyploidy means the appearance of different ploidy levels within the organism. In plants, it occurs as a result of endoreduplication, which is observed in 90% of angiosperms according to various estimates [44, 45]. Endoreduplication leads to the emergence of chromosomes with 2*n* chromatids or occurs without any changes in the number of chromosomes. Then hypertrophied nuclei arise from the successive cycles of DNA replication without separation of sister chromatids, which ultimately leads to the formation of polytene chromosomes [46]. The physiological relevance of endoreduplication is still a matter of debate. However, it is often noted that cell size and ploidy correlate highly and positively with each other in many plant species, in different organs, and in different cell types [47]. At each stage of organogenesis, certain groups of regulatory polygenic loci, associated with a change in the tomato fruit size in one way or another, are active [13]. The loci *TAGL1*, *FAS*, *LC*, *SlWUS*, and *SlIMA* are involved in the development of the ovule cell. During the flowering period, the genes *SlPIN4*, *SlTIR1*, *SlARF7*, *SlARF8*, and *SlIAA9* are involved in auxin signaling, and the *SlGA20ox1* and *SlDELLA1* participate in gibberellin signaling. During fruit growth, *SlCDKA1*, *SlCDCB1*, *SlCDKB2* (cell cycle control), *FW2.2*, *SlKLUH/FW3.2*, *FW11.3*, *OVATE*, *SUN*, *SlIMA* (cell division control), and *SlPIN4* (auxin signaling) are active. *SlCCS52A*, *SlWEE1*, *SlKRP1* (cell cycle control), *HXK1*, *SuSY*, *LIN5*, *TIV1*, *mMDH*, *cpFBP* (primary metabolism), *SlIAA17* (auxin signaling), *SPA* (regulation of primary metabolism), *NOTABILIS/NCED1*, *FLACCA* (biosynthesis of abscisic acid), *Gal-LDH*, *GME* (biosynthesis of ascorbates) are involved in increasing fruit volume (cell expansion) [13].

Hormonal regulation of fruit growth and development. After successful pollination of a flower and fertilization of an ovule and setting of fruits and seeds, the stage of ovary formation begins with the subsequent development of fruits and seeds, which occurs synchronously in accordance with a precise, genetically controlled process mediated by phytohormones [8]. Auxin and gibberellic acid seem to precede the phytohormones necessary for fruit set in response to pollination, since the exogenous use of these phytohormones leads to the formation of the ovary and the development of parthenocarpy [48]. The role of cytokinin, ethylene and abscisic acid was demonstrated later, but not well documented [49]. Early fruit development processes, controlled by auxins distributed in tissues and cells, initiate signal transduction pathways. Temporal and spatial distribution of *PIN* and *AUX/LAX* expression suggests that their coordinated action

regulates auxin transport during fruit development in tomato [50]. Silencing of the *SlPIN4* gene, which is first expressed in flower buds and young developing fruits, leads to the parthenocarpy of small fruits, which indicates the premature development of these fruits [51]. The auxin signaling pathway involves an auxin receptor, the transport inhibitor response protein (TIR1). In the presence of auxin, TIR1 involves the auxin-indolyl-3-butyric acid (Aux/IAA) transcription repressors in the process and induces their degradation by the 26S proteasomes. Degradation of the Aux/IAA protein repressor leads to the emergence of Aux/IAA-related auxin response factors (ARFs). The erroneous expression of the *TIR1* gene for the auxin receptor in tomato, as well as the erroneous expression of specific members of this gene family, the *Aux/IAA* and *ARF*, disrupts the flowering and formation of the ovary, as a result, normal pollination and fertilization does not occur, which increases the number of parthenocarpic fruits on a tomato plant [48, 52, 53]. In tomato, fruit setting is partly due to gibberellic acids in the complex of hormonal information exchange with auxin [54]. Auxin synthesized in the oocyte and apical shoots prevents the appearance of non-fertilized oocytes by reducing the transcription of genes encoding the biosynthesis of gibberellic acid enzymes, in particular, GA-20 oxidases [55]. Thus, phytohormones play the role of mediators in the signaling pathways of transport proteins and transcription factors during fruit setting and development in tomato. Phytohormones are involved in fruit size regulation with the participation of a number of genes organized into complex systems.

Metabolic control of fruit development. The early stages of fruit development are critical for the formation of economically valuable characteristics, for example, organoleptic composition, which ultimately determines fruit quality. Water, organic acids (primarily citrate and malate), and minerals accumulate inside the vacuoles of expanding cells [38], while starch is rapidly converted to simple sugars [56]. Fruit softness, color and taste are formed during ripening [57, 58]. The development and weight of the fruit is closely related to the content of primary and secondary metabolites [59, 60]. Consequently, modification of the expression of genes associated with metabolism can affect the organoleptic properties and weight of the tomato fruit. The development of the fruit as a succulent organ is more dependent on the accumulation of photoassimilates: a change in accumulation of assimilates significantly affects the development and size of the fruit through modulation of the number and size of cells [61, 62]. When a tomato plant is kept in the dark, fruit growth is significantly slowed down as a result of strong suppression of cell cycle genes in the fruit tissues [63]. On the contrary, an increase in the photoassimilation capacity of a fruit with a decrease in the number of fruits per plant led to an increase in the rate of flower formation and fruit growth. This is evidenced by an increase in the number of cells inside the carpel due to an increase in mitotic activity [64]. Thus, modification of carbohydrate and photoassimilate metabolism, driven partially by key enzymes involved in primary carbohydrate metabolism and photosynthesis, may affect fruit growth.

QTL *Lin5* has been identified as the main QTL controlling fruit weight and sugar content [65]. It was found that genes associated with it encode cell wall invertase [66]. When *Lin5* was silenced, fruit yield, fruit and seed size, and seed number were significantly reduced [67]. In transgenic plants, the changes affected the sugar metabolism, therefore, the sucrose content increased while the glucose and fructose content decreased at the full-ripening stage. Silencing of the vacuolar invertase gene (*TIR1*) in tomato led to generally similar results. The formation of small fruits was caused by a high rate of sucrose accumulation and a decrease in the amount of hexose at the final stage of fruit development [68]. Interestingly, changes in the concentration of osmotically active soluble sugars occurred during the expansion phase of the cell and affected the size of the fruit. This supports the

idea that the concentration of soluble sugars is associated with an increase in water volume, which is an important determinant of an increase in fruit size.

When searching for genomic QTL regions associated with yield traits, Bermudez et al. [69)] identified 9 candidate genes located on chromosome 4. In particular, a gene encoding a protein similar to the DnaJ chaperone was identified, and an assumption was made about its connection with the primary metabolism in tomato during fruit development. Functional analysis of this gene, later named *SPA* (*sugar partitioning-affecting*) in planta using the silencing method, showed that the weight of the ripe fruit, the number of fruits per plant, and the harvesting index are significantly higher in transgenic plants than in wild plants [70]. A detailed analysis of metabolic and enzymatic activity showed that during silencing, intermediate metabolites (sugar phosphates) accumulated in the photosynthetic organs of plants, while the activity of phosphoglucomutase, sugar kinases, and invertases decreased. The SPA protein of tomatoes interacts with the thylakoid membranes of chloroplasts, plays an important role in metabolism, affects the redistribution of carbohydrates and, as a result, changes the harvest index [70].

In recent studies of QTLs that determine the size and shape of the tomato fruit, emphasis is placed on the complex nature of the alleles. Chu et al. [71] quite definitely state that the number of locules and fruit size in tomato are controlled by natural alleles *lc* and *fas*. *LC* encodes the WUSCHEL tomato ortholog (WUS), while the *FAS* encodes the CLAVATA3 tomato ortholog (CLV3). The leading role of the WUS-CLV3 in the organization of the meristem was demonstrated in several plant species. The authors of this work showed that mutation of both loci in tomato leads to an increase in the *SlWUS* expression level in flower buds 2-3 days after initiation. Single and double mutant alleles *lc* and *fas* retain a high level of *SlWUS* expression during the development of carpel in a flower bud [71]. Other authors, combining the sequence mapping technique and the CRISPR-Cas9 genome editing method, identified the AP2/ERF transcription factor locus which regulates the activity of the flower meristem [72]. They named this locus *EXCESSIVE NUMBER OF FLORAL ORGANS* (*ENO*) [72]. Mutation of the *ENO* gene leads to an increase in the number of multilocular fruits per plant as a result of the proliferation of the flower meristem. Genetic analysis revealed a synergistic effect of *LOCULE NUMDER* (*SlWUS* locus) and *FASCIATED* (*SlCLV3* locus) mutations, the two key mutations in the evolution of tomato fruit size upon domestication [72]. As a result of extensive research carried out by traditional (Tomato Analyzer) and modern (EcoTILLING) methods, a group of Indian scientists found that a population of one tomato variety with a low level of polymorphism detected by EcoTILLING, nevertheless, showed a wide phenotypic diversity. The authors explain the obtained results by the fact that phenotypic diversity is the result of interaction between the genome, transcriptome, proteome, and metabolome [73]. In the context of the studied topic, this means that not so much single genes control the size and weight of the tomato fruit, but regulatory QTLs which was mentioned above [71, 72]. Of particular interest are works devoted to the influence of regulatory QTLs involved in the metabolic pathways of auxin and gibberellin on the setting and regulation of fruit size in tomato [74, 75], but we believe that these aspects should be the subject of special review.

So, summarizing data on the genetic determinants of the fruit size in tomato, led us to the following conclusions. The fruit size in *Solanum lycopersicum* L. is controlled by a group of loci that regulate the processes of cell division and expansion during four stages of fruit development, from the development of the ovule and the ovary formation after fertilization to cell division and expansion of cells that form a mature fruit. To date, 37 such loci are known. These loci can

overlap with loci that control the fruit shape in *S. lycopersicum* and are likely involved in phytohormone signaling pathways and processes of primary and secondary metabolism. Genetic determinants of cell division and expansion are involved in the signaling pathways of auxin and gibberellin, and therefore changing fruit size through these phytohormones is quite likely. The development and weight of the tomato fruit is closely related to the amount of primary and secondary metabolites. Modification of the expression of genes associated with primary and secondary metabolism can change the organoleptic composition and weight of tomato fruits by adjusting the harvest index and distribution of carbohydrates, which will ultimately improve the biochemical composition of tomato fruits.

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