Seminars in Cell & Developmental Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Shaping a fruit: Developmental pathways that impact growth patterns

Esther van der Knaap[a,*], Lars Østergaard[b,*]

[a] Institute of Plant Breeding, Genetics & Genomics, University of Georgia, Athens, GA, 30602, USA
[b] Department of Crop Genetics, John Innes Centre, Norwich Research Park, Norwich, NR4 7UH, United Kingdom

ARTICLE INFO

Article history:
Received 5 July 2017
Received in revised form 20 October 2017
Accepted 26 October 2017
Available online xxx

Keywords:
Tomato
Brassicaceae
Fruit growth
Fruit shape
Fruit size
Hormonal and genetic interactions

ABSTRACT

Angiosperms produce seeds as their progeny enclosed in maternally-derived structures called fruits. Evolutionarily, fruits have contributed enormously to the success of the Angiosperms phylum by providing protection and nutrition to the developing seeds, while ensuring the efficient dispersal upon maturity. Fruits vary massively in both size and shape and certain species have been targeted for domestication due to their nutritional value and delicious taste. Among the vast array of 3D fruit shapes that exist in nature, the mechanism by which growth is oriented and coordinated to generate this diversity of forms is unclear. In this review, we discuss the latest results in identifying components that control fruit morphology and their effect on isotropic and anisotropic growth. Moreover, we will compare the current knowledge on the mechanisms that control fruit growth, size and shape between the domesticated Solanaceae species, tomato and members of the large family of Brassicaceae.

Contents

* Corresponding authors.
E-mail address: EsthervanderKnaap@uga.edu (E. van der Knaap).

https://doi.org/10.1016/j.semcdb.2017.10.028
1084-9521/

1. Introduction

The Angiosperm phylum of flowering plants is the most successful plant phylum comprising >90% of all plants on Earth. They evolved during the Cretaceous Period 100–125 million years ago and their subsequent fast diversification in evolutionary terms remains an enigma and one, which Darwin famously referred to as 'an abominable mystery'. Flowering plants encase their seeds in a fruit or a vessel and from which the phylum name is derived (Greek: Angio = vessel; sperm = seed). Formation of flowers and fruits is indeed considered crucial for their success allowing attraction of pollinators for efficient fertilisation of the ovules and protection and nurturing of the developing seeds. The huge variety of fruit morphologies have led to ingenious ways for efficient seed dispersal. In addition to shape, size also varies significantly among fruits from different or even within species, ranging from the smallest known fruits from *Wolffia angusta* that are no larger than a grain of table salt to the giant pumpkins (*Curcurbita maxima*) that through intensive selection and breeding including highly specialised growth conditions can exceed 1000 kg. The latter case also highlights the result of domestication, a process that Darwin convincingly used to demonstrate evolution by natural selection [1,2]. Domestication of vegetable and fruit crops has often led to dramatic changes in fruit size and created a diversity of fruit shapes within the same species [3–5]. However, in the context of plant development, morphological diversity in crop plants is often underexplored.

Growth and shape of natural structures have been of interest to scientists at least since ancient Greece. From the early days of genetics, it was recognised that features controlling organ size and shape are inherited through generations [6–12]. In tomato, one of the earliest studies into the genetic inheritance of fruit morphology is that of elongated fruit and locule number, traits with a strong genetic inheritance [11,9]. Initially, the locus for elongated and pear-shaped fruit was called *pyriform* (*pr*) [11] but was renamed to *ovate* after *pr* was found to co-segregate with oblong and oval fruit shape [13]. Fruit cell number was the initial term for two related traits, namely *fasciated* (*f* or *fas*) and *locule number* (*lc*) reflecting flat-shaped tomatoes with many carpels as opposed to the wild-type carpel number of two [9,12]. The loci *fas* and *lc* control the same trait, the number of carpel primordia, but with a different degree of severity on the trait [14]. Linkage mapping placed several of the fruit shape loci together with other morphological traits and created one of the first linkage maps in plants [15,16]. In the Brassicaceae, George Harrison Shull crossed the tetraploid *Capsella bursa-pastoris* (heart-shaped fruits) with a natural variant of *C. bursa-pastoris*, named "*heegeri*", which has cylindrical fruits. Shull found a 15:1 segregation in the F_2 generation of heart-to-cylinder [17] leading him to suggest that two genetic loci contribute to the trait. This observation is in agreement with observations reported by the botanist Edmund W. Sinnott two decades later. Sinnott used pumpkin as a model system and his data suggested that it is possible to differentiate between gene activities that regulate shape and those that only affect size [18].

The quantitative nature of fruit weight initially hampered the discovery of genes controlling size traits in crop plants. However, with the advent of molecular genetic linkage maps and improvement in quantitative mapping tools, a large number of loci underlying quantitative traits have been identified including those for fruit and grain size [19–21,3]. This has led to supporting evidence from modern day's developmental genetics and the identification of key factors involved in determining shape and weight in domesticated vegetables and fruits [5,22]. In this review, we provide an overview of the current knowledge in fruit growth with a particular emphasis on examples from fleshy fruits (tomato) and dry dehiscent fruits (Brassicaceae).

2. Shape classifications in tomato and Brassicaceae species

Tomato varieties have traditionally been classified based on fruit morphology into shape categories described by the International Union for the Protection of New Varieties of Plants (UPOV) and the International Plant Genetic Resources Institute [23,24]. A revised tomato classification scheme was developed based on fruit shape analyses that were conducted on a large collection of cultivated accessions that included many heirloom varieties featuring the most diverse fruit shapes [14] (Fig. 1). Independent classification using contour morphometric data from scanned tomato fruit images in conjunction with elliptic Fourier shape modeling and Bayesian classification techniques led to similar results [25]. The latter classification is especially helpful to growers and breeders as it allows also an unbiased evaluation of uniformity of fruit shapes within a certain tomato variety [25]. In fruit and vegetable crops, shape and size uniformity is critical to the industry whereas for molecular geneticists uniformity suggests a strong genetic basis for the trait. Moreover, consumers recognize use type in tomatoes based on their morphology: from the small oval-shaped grape tomato for salads to the blocky and squared Roma tomato for soups and stews to the large and flat beefsteak tomato for slicing. The model plant *Arabidopsis thaliana* belongs to the large Brassicaceae family, which also contains the Brassica genus including important crop plants such as oilseed rape (*B. napus*) and broccoli (*B. oleracea*). Members of the Brassicaceae family exhibit an extraordinary diversity in fruit shape with different basic shape structures such as cylindrical, disc-formed, spherical as well as more complex structures including heart-shaped fruits or fruits that develop outgrowths [26] (Fig. 2). This wide variation among closely related and even within species provides an excellent resource for studying organ-shape formation. In many cases, it is not immediately evident what advantages the different shapes provide for fitness and dispersal. It is also unclear how such variation in form can evolve when coordination of tissue growth and specification is of pivotal importance for timely development and seed release.

3. General developmental principles of the female reproductive structure

Fruits represent the final stage of the life cycle of a plant. Whereas plant growth ensues through axillary shoot development or indeterminate above ground stems, tomato and Brassicaceae fruits classically represent the final growth stage of a terminating floral meristem. Fruits develop from carpels which originate from the fourth and final whorl in the floral meristem. Carpels comprise the female reproductive tissue that produce the female gametophytes. At anthesis, pollen grains land and germinate at the apical stigma and pollen tubes grow through the style and ovary to deliver the male gametophyte and fertilise the ovules. Fertilisation marks the beginning of fruit development and is in most species required for fruits to develop [5,27,28]. In the first phase after fertilisation, fruit growth occurs mainly via cell division, but subsequently enters a second phase of cell expansion, which continues until the fruit has reached its final size [28–32]. There are examples, however, such as avocado, where cells continue to divide throughout fruit development up until ripening [33]. Fruit development is finalized with the ripening and seed dispersal stage. The latter stage as well as fruit set following fertilisation are critical for proper fruit development. Despite the impact of poor fertilisation on shape and size of the affected fruits, this process is not associated with regulating the morphology of the organ in a consistent manner and will therefore not be discussed in this review. The processes of ripening and seed dispersal will also not be discussed because that stage in general does not affect fruit morphology. Readers interested in these

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

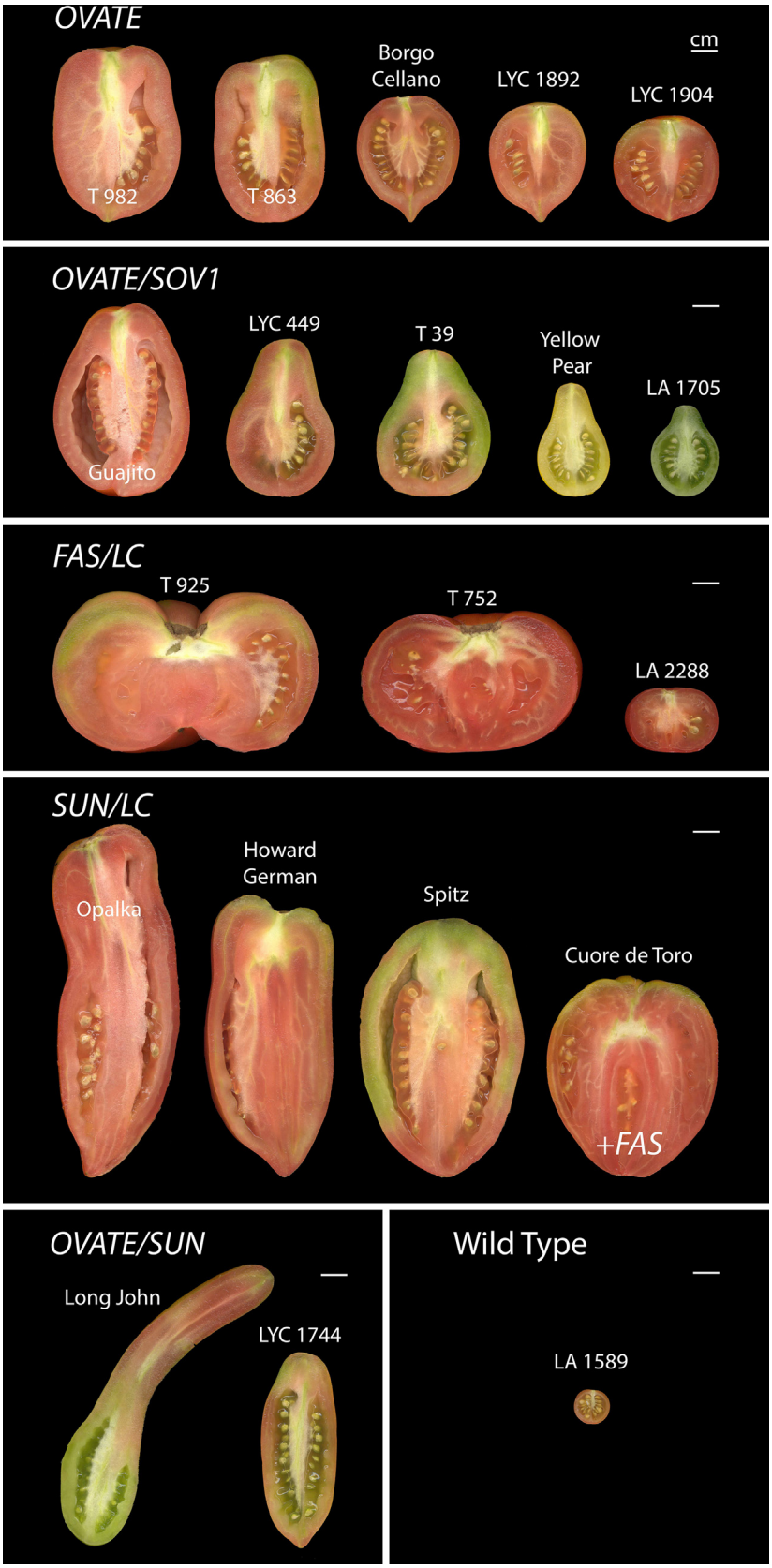

Fig 1. Tomato fruit shape variation. The effect of the fruit shape genes *SUN*, *OVATE*, *SOV1*, *LC* and *FAS* on tomato shapes. Size bar, 1 cm. The name of the varieties are shown in the graph. Image composition by Carmen Kraus, University of Georgia.

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

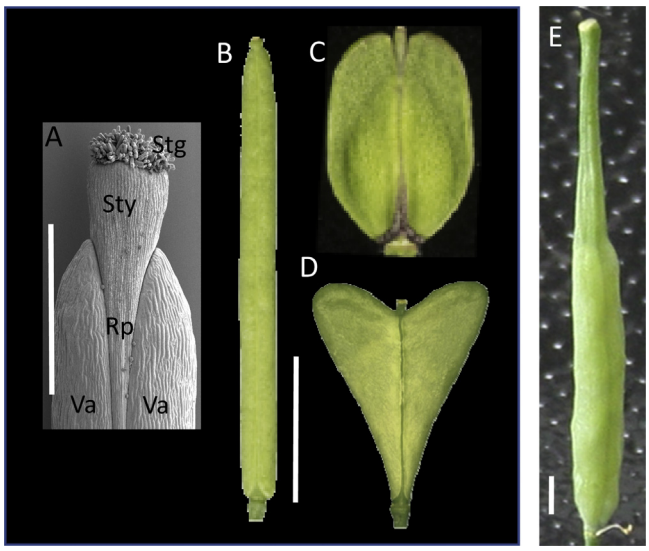

Fig. 2. Examples of fruit structure and shape in the Brassicaceae family. A. Scanning electron micrograph of mature fruit from *Arabidopsis thaliana* Col-0. B–D. Whole-mount images of mature fruits from *Arabidopsis thaliana* (B), *Lepidium campestre* (C) and *Capsella rubella* (D). E. Mature fruit from *Brassica rapa*.
Scale bars: 500 μm (A), 5 mm (B-E).
Stg, stigma; Sty, style; Va, valve; Rp, replum.

two topics are referred to the following comprehensive reviews [34–39].

By comparing growth of different fruit forms, it may be possible to obtain information of overall principles in growth control without identifying the specific genetic components underlying them. This was recently done by combining sector analysis and mathematical modelling in Capsella (heart-shaped fruit) and Arabidopsis (cylindrical fruit). This work demonstrated that the different shapes of fruits from Arabidopsis and Capsella arise through different patterns of anisotropic growth during three distinct phases [30]. These experimental data can be accounted for by tissue-level models in which specified growth rates vary in space and time and are oriented by a proximo-distal polarity field, which deforms as the tissue grows. By switching certain parameters of the model in specific tissues, it was possible to change overall structure of the fruit model. Interestingly, fruits with these new model fruit shapes exist among members of the Brassicaceae family thus showing that modulations of the model are able to at least broadly account for the growth dynamics of shapes of other Brassicaceae species. Such basic differences in growth patterns may therefore explain the multiple incidents of evolutionary switches between different shapes of fruits in the Brassicaceae [40].

In tomato, modelling fruits from a mutagenized population showed that weight was controlled by two growth processes: i) isotropic and proportional growth of all fruit tissues or ii) anisotropic growth of the pericarp only [41]. In another study, modelling of fruits during the cell expansion stage of growth (see below) showed that these later stages led to a differential patterning of vasculature and concomitant changes in water distribution in fruits that featured different shapes [42]. While these studies modelled growth at a relatively late stage in development (after anthesis) and may not address all growth patternings, they describe the consequences of overall fruit morphology on functioning of the tissues as well as their impact on fruit quality [42].

4. Principles of organ growth at the cellular level

The rate, duration and plane of cell division as well as the direction and degree of cell expansion are key parameters that contribute profoundly to the overall final size and shape of the fruit. These processes start as early as in the meristem by regulating the architecture and organization of this tissue and continues until the later stages of fruit development prior to ripening [28]. The initial processes are under tight control by meristem organization, organ identity, positioning and boundary genes [43–46]. Also critical are regulators of the cell cycle [47–51] hormone dynamics [52], cell wall biosynthesis and modification [53–55] and turgor pressure [56,57]. Moreover, cell size is affected by endoreduplication, a process that is common in higher plants. Maturing cells often sidestep the mitosis stage several times resulting in larger cells with higher nuclear ploidy levels, bypassing chromatid segregation and cytokinesis [58–60]. Endoreduplication is proposed to occur in many multicellular organisms as a mechanism for cell enlargement and differentiation, and is critical for the full development of tomato fruits [61]. However, cloning of natural tomato mutants that underlie domestication of fruit size and shape characters have so far not revealed any genes known to be directly involved in cell-cycle control, endoreduplication, or hormone, cell wall and turgor pressure pathways. In contrast, modifiers affecting fruit morphology have been identified in abundance [62–67] and most of these genes will be discussed later in this review. However, it is important to note that in line with previous theories [18], common principles are likely to underlie shape determination of all above-ground plant organs [68]. Tissue-level models of leaf and petal growth have led to the suggestion that shape depends on patterns of anisotropic growth oriented by a polarity field [69–71]. These studies have recently been extended by demonstrating that such models also can account for the growth patterns and diversity of three-dimensional fruit shapes [30].

4.1. Early growth and differentiation in angiosperm flowers - termination of meristematic activities in the centre of flowers

The earliest stages of fruit development commence when the remaining stem cells in the floral system turn into carpel primordia, effectively terminating growth of the floral meristem. Thus, the size and organization within each floral meristem provides the foundation of the fruit that will arise after several stages of development including pollination and fertilization. The CLAVATA and WUSCHEL signaling pathway functions in parallel with other pathways to control meristem organization. The CLV-WUS pathway is highly conserved in the higher plant kingdom with a central role played by WUS [72]. The CLV receptor-ligand system comprises a receptor-like kinase (CLV1), an LRR receptor (CLV2) and a ligand peptide (CLV3). The role of the CLV-WUS pathway is to control the boundary between the central (meristematic stem cells) and peripheral (towards organ initiation) zones in the meristem [73,74]. WUS encodes a homeodomain transcription factor and it enhances stem cell activity while repressing differentiation. It directly increases the expression of *CLV3*. *CLV3,* on the other hand, encodes a small peptide that is required to limit cell division in the central zone. Interaction of CLV3 with its receptor CLV1 restricts the domain of the central zone and indirectly limits *WUS* expression [75]. These two genes function in a negative feedback loop mechanism regulating meristem size and floral organ number [76,77]. In Arabidopsis, loss-of-function mutations in any of the *CLV* genes leads to enlarged meristems due to excess undifferentiated cells in the central zone [78]. In the shoot apical meristem, this results in a fasciated stem, whereas the larger floral meristem leads to an increased number of carpels and hence wider fruits with more locules [79–81]. In tomato, two natural mutations named *fasciated* (*fas*) and *locule number* (*lc*) exhibit a synergistic effect on meristem size and the number of locules, the seed compartments in the tomato fruit [82,83] (Fig. 1). Mutations in these genes greatly increases locule number from two in wild progenitors and small cultivated toma-

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

toes up to 10–15 in the very large fruited types [14]. Initially, the gene underlying *fas* was thought to be *Yabby2*, a transcription factor belonging to the family that is known to regulate abaxial-adaxial development of lateral organs [84]. Later studies discovered that the underlying cause of the mutation was a 296-kb inversion at the *fas* locus, possibly impacting the promoter of *SlCLV3* [85]. This structural variant mutation was strongly correlated to locule number and flat fruit shape, implying that it could be the cause of the mutation at *fas* [14,46]. Transformations using a genomic 10 kb construct carrying 6 kb of the wild type *CLV3* promoter rescued the high locule phenotype in mutant tomatoes, effectively demonstrating that *SlCLV3* underlies *fas* [45]. Expression of *SlCLV3* is likely reduced as a result of the promoter mutation leading to increased locule number [45]. The effect of reduced expression of *SlCLV3* on floral organ number is similar to the defect observed in *clv3* mutants in Arabidopsis demonstrating the conserved nature of this gene in regulating meristem architecture in different plant species. *Yabby2* is abolished as a result of the 296-kb inversion; however, its role in controlling locule number in tomato is predicted to be minor if any.

The other natural mutation in tomato that affects locule number is at the *lc* locus [82]. The locus was fine-mapped to a 1.6 kb region 3′ of the likely tomato ortholog of *WUS* [46]. Association mapping led to the identification of two SNPs that are 1 kb downstream of *WUS* [46]. Closer inspection of these two mutations showed that they were located in a putative CArG box known to regulate WUS expression in Arabidopsis [22]. *WUS* expression is required to maintain stem cell identity and restriction of cellular differentiation which is needed for organogenesis. As cells move out of the central zone into the peripheral zone to initiate organ formation, the expression of *WUS* would need to be reduced in the differentiating cells. In Arabidopsis, *WUS* expression is reduced by the transcriptional repressor KNUCKLES (KNU) [86]. In parallel, *WUS* expression is directly repressed by the floral identity protein AGAMOUS (AG), a MADS box transcription factor critical for carpel identity and development [87]. AG has been shown to bind to the *WUS* CArG box that is 3′ of the gene [88]. The role of AG's binding to the CArG box is to recruit Polycomb Group proteins leading to the repressive histone H3 Lys-27 methylation at the locus [89]. In tomato, it has been hypothesized that the two SNP mutations in *lc* lead to reduced or abolished binding of AG to the *WUS* 3′ regulatory region, effectively reducing the ability of AG to turn off *WUS* expression [22]. Delayed downregulation of *WUS* would lead to an expansion of the *SlCLV3* expression zone. However, since SlCLV3 and CLV1 together result in downregulation of *WUS* expression, the phenotypic consequences of delayed termination of *WUS* expression is expected to be small. Indeed, in tomato the *lc* mutation alone has a minor effect on increasing locule number [14,82]. On the other hand, when the delayed downregulation of *SlWUS* is coupled with the reduced expression of *SlCLV3* leading to the weaker control of the *WUS* expression zone, the synergistic effect of both mutations on locule number is relatively high. Indeed, tomato varieties with the highest number of locules are nearly always carrying mutations in both *lc* and *fas* [46,14].

The tomato gene, *FASCIATED AND BRANCHED* (*FAB*), is the ortholog of the Arabidopsis *CLV1* gene with *fab* mutants having very similar developmental defects [45] indicating that other components of the CLV-WUS pathway are functionally conserved as well between tomato and Arabidopsis. Recently, other key components of the CLV-WUS pathway were identified in tomato, including *FASCIATED INFLORESCENCE* (*FIN*), *FAB2* and *SlRRA3a* which encode different enzymes regulating the arabinosylation of SlCLV3 and other CLE peptides [45]. The arabinosyl modifications are essential for the biological activity of the CLEs and application of a chemically produced glycosylated CLV3 peptide will rescue *clv3* mutant meristems [90].

4.2. Organ initiation and patterning

The floral meristem terminates with the initiation of the female reproductive structure, the gynoecium. *AG* encodes a MADS box transcription factor that is critically required for the specification of cells in the terminating floral meristem to form the gynoecium primordium [87]. As described above, AG initiates gynoecium development by recruiting PcG proteins to the *WUS* promoter resulting in downregulation of its expression [88]. This in part determines the termination of stem cell activity in the central zone as these cells become subsumed by the emerging gynoecium. Brassicaceae gynoecia are roughly cylindrical in shape (Fig. 2B) where the lateral parts develop into valves (seed pod walls) that are fused to a medial replum (Fig. 2A). Between the valves and the replum, narrow strips of tissue made up of a few cell files form the valve margins where fruit dehiscence will take place to allow the seeds to be released upon maturity [44,39]. Differences in gynoecia morphology are apparent within the Brassicaceae family. For example, whereas the style in Arabidopsis fruits is relatively short (Fig. 2A,B), it can span more than a third of the *Brassica* fruit length (Fig. 2B). Also, while Arabidopsis has a replum of 8–10 cell rows, the replum of *Brassica* fruits generally only have one row of cells [91].

For Brassicaceae species, the gynoecia develop similarly and the mechanism for its formation may therefore be highly conserved. In Arabidopsis, detailed knowledge of the hormonal and genetic interactions required for proper gynoecium development is emerging [92,93]. It is known that the plant hormone auxin plays a pivotal part both in terms of biosynthesis and distribution. For example, basal-to-apical transport of auxin is important to allow growth along the proximo-distal axis, whereas biosynthesis at the apical region as well as lateral auxin transport is required to mediate formation of a radial style that will facilitate efficient fertilisation [94–96]. In the medial region of the gynoecium, another hormone, cytokinin, interacts with auxin dynamics to ensure meristematic activity and formation of the ovules [97]. Some of the key regulators of gynoecium patterning in *Arabidopsis* have been identified in other Brassicaceae species and genetic interactions between them established. *FRUITFULL* (*FUL*) and *REPLUMLESS* (*RPL*) genes specify valve and replum formation, respectively, and they do so at least partly by restricting the expression of valve-margin identity genes, such as *SHATTERPROOF1* (*SHP1*), *SHP2*, *INDEHISCENT* (*IND*) and *ALCATRAZ* (*ALC*) [44,98–103]. Whereas *Brassica FUL* and *IND* genes have conserved functions in fruit tissue development [104,105], *Brassica RPL* genes have lost their ability to specify replum tissue [91].

The dynamic activities of auxin and cytokinin are tightly regulated via intricate transcription factor networks [106,97]. A major regulator of gynoecium patterning and polarity is the auxin response factor, ETTIN (ETT) [107,108]. ETT interacts directly with a basic helix-loop-helix (bHLH) protein, INDEHISCENT (IND) to regulate auxin distribution. Their activity is feedback-regulated such that the interaction between ETT and IND is sensitive to auxin itself [106]. IND interacts with another bHLH protein, SPATULA (SPT) and this interaction is required to mediate formation of auxin maxima in the medial region of the apex allowing the apex to undergo a bilateral-to-radial symmetry change [94]. SPT also promotes formation of the medial region by facilitating cytokinin signalling necessary for the formation of placenta and ovules [97].

In tomato, the role of many orthologs of the Arabidopsis genes that are involved in gynoecium patterning are not well understood. The most likely tomato ortholog of *AG* is *TAG1*. RNAi suppression of *TAG1* leads to defects in carpel development and determinacy by producing fruits within fruits [109–111]. However, carpel identity

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

was not changed similarly as in the *ag* mutant in Arabidopsis. On the other hand, different genes that modify the morphology of the fruit have been found to function during the earliest stages of gynoecium development. For example, a knock-out of *ENHANCER OF J2* (*EJ2*) leads to a slightly elongated shape of the fruit in addition to several pleiotropic effects such as jointless fruit stems and enhanced inflorescence branching [112]. *EJ2* encodes a MADS box protein that is a paralog of *SEP4* in Arabidopsis. Another gene with a large effect on fruit shape is *OVATE*. Initially identified as the founding member of the Ovate Family Proteins (OFP) class in plants [62,113] and described as early as 1908 [9], the *ovate* mutation only controls fruit shape with no apparent changes in leaf and other floral organ shapes or any other developmental defects [114] (Fig. 1). *OVATE* is expressed in floral meristems and initiating floral primordia [66]. The null mutation leads to changes in gynoecium shapes due to changes in cell division patterns in the proximal part of the fruit. Compared to wild type, the number of cells in the proximo-distal direction is increased whereas the number of cells in the mediolateral direction are decreased in *ovate* mutants [66]. This effect is particularly enhanced in the presence of a locus that modifies the effect of *ovate* [115] (Fig. 1). Overexpression of Arabidopsis OFP members often lead to reduced organ length such as siliques, leaves and cotyledons [116,117,113]. Moreover, in pepper, a paralog of *ovate* has also been implicated in regulating fruit shape suggesting that this family may control organ shape in other plants as well [118]. The molecular functions of OVATE are not well understood. However, it has been shown to interact with proteins associated with microtubules [22] suggesting a role in cell division patterns by its interaction with the cytoskeleton.

4.3. Fruit development after successful fertilisation of the ovules

Induction of post-fertilization fruit growth depends on the hormonal activities of both auxin, cytokinin and gibberellin [28]. Fertilization-induced fruit growth follows an auxin-signal produced in the fertilized ovules, which induces gibberellin biosynthesis required to degrade the growth-repressing DELLA proteins, thereby facilitating growth [119,120]. How or if these activities regulate fruit shape is unknown, we describe the effects of auxin dynamics in tomato during fruit growth below.

Immediately following fertilisation, cell division reinitiates in the growing fruit tissues. This initial phase of cell division is followed by the prolonged phase of cell enlargement. Changes in division rates and direction could profoundly impact fruit morphology after fertilisation has occurred. Whereas gynoecium development appears highly conserved among the different Brassicaceae species, morphology establishment which occurs after fertilisation may be controlled in very different ways [30,26]. For example, the valves of mature *Capsella* fruits are extended and flattened at the distal end resulting in a heart-shaped appearance of the organ (Fig. 2D). The role of Arabidopsis patterning genes have been investigated in other Brassicaceae species as well. When the *FUL* gene encoding a MADS box protein is knocked out in species that develop highly diverse fruit shapes, such as *Arabidopsis*, *Capsella* and *Lepidium*, fruits fail to elongate after fertilisation and the valves become dramatically reduced [44,26]. The similarity in the *ful* mutant phenotype in these species suggests that the diversity of shapes originates primarily from the differential activities of factors during post-fertilisation growth. The phenotype of the *Capsella ful* mutant and indeed the *Arabidopsis ful* mutant is intriguingly similar to the *heegeri* mutant described by Shull [17]. The wild-type background of the *heegeri* variant is the tetraploid *Capsella bursa-pastoris*. The genome sequence for *C. bursa-pastoris* was recently published revealing two copies of the *FUL* gene [121] and it is therefore possible that mutations in these two *FUL* genes are responsible for the *heegeri* fruit phenotype. Unfortunately, *heegeri* seeds are no longer available so we may never be able to assess if this is indeed the case. However, with respect to the function of *FUL*, it will be interesting to study whether the *Capsella FUL* gene is sufficient to create the shoulders of the *Capsella* fruit. This could be achieved either by a difference in expression pattern in comparison to Arabidopsis through changes in *cis*-regulatory elements or by changes to the amino acid sequence potentially leading to alternative downstream targets. In this context, it is interesting to note that *FUL* in *Arabidopsis* has recently been found to influence differential growth in stem and inflorescence branches through direct control of the *SAUR10* gene [122]. An alternative possibility is that FUL does not control shape formation *per se*, but acts upstream of species-specific shape programs to simply promote growth. This latter scenario would agree with Sinnott's hypothesis in which *FUL* would promote tissue growth whereas other factors are responsible for determining the species-specific fruit shape [18].

The role of *FUL* homologs, *SlFUL1* and *SlFUL2* in tomato development are to control the fruit ripening process via its interactions with *RIN*, encoding another MADS box protein that controls fruit ripening [123–125,38]. So far, a role for FUL in fruit patterning and expansion has not been found in tomato. Instead, the fruit shape gene *SUN* impacts fruit shape most noticeably immediately following fertilisation in tomato [126,31] (Fig. 1). The shape change mediated by *SUN* coincides with the cell division stage and is completed 7–10 days post pollination. This change is due to increased cell division along the proximo-distal axis as well as increased cell elongation [127]. *SUN* encodes a protein that is a member of the IQ67-domain (IQD) family [65] and members of this family have been shown to bind calmodulin in a calcium-dependent manner [128]. Mechanistically, how *SUN* mediates cell division patterns is not known. A role for auxin has been implied from overexpression studies that showed a dramatic auxin-like effect on fruit and leaf shape as well as nearly abolished seed development in tomato [127]. Moreover, promoters of several Arabidopsis members of the IQD family are targets of the Auxin Response Factor 5 (ARF5 also known as MONOPTEROS) [129], implying that a role for auxin signalling underlies the changes in tomato shape mediated by SUN. Insights into the function of members of the IQD family have come from studies in Arabidopsis. AtIQD1 interacts with a kinesin-light chain-related protein and proposed to be involved in cellular trafficking by its association with microtubules [130]. More recently, the entire IQD family has been shown to localize in distinct subcellular compartments and are most often associated with microtubules. Overexpression of several IQD genes indeed showed changes in cell shape and organ morphology that is associated with altered microtubule structure in the cells [131]. These results start shedding important insights into how SUN and other IQD family proteins may alter cell division patterns and cell shape in tomato and other plants. Downstream effects of *SUN* expression in tomato were identified in gene expression studies which showed that the central role is to control calcium-regulated processes [132]. Moreover, the co-differential expression studies showed that *SUN* results in profound shifts of gene expression in the different parts of elongating fruit tissues compared to wild type control samples. These shifts occur in genes that are involved in key processes such as cell division, cell wall, and patterning [132]. Supporting a role for *SUN-like* genes in other crops, a homolog of SUN in cucumber may also underlie shape variation in this vegetable [133].

The gene *KLUH/PLASTOCHRON1* regulates organ size and initiation in Arabidopsis and rice respectively [134,135]. In tomato, this gene was found to underlie the *fw3.2* QTL [64,136]. Notably, not only fruit size was increased but also seed size whereas fruit ripening time was delayed. The gene encodes a CYP450 of the 78A class and is highly expressed in meristems and young tissues [22,64]. The most likely mutation is a single SNP in the promoter leading to increased gene expression and larger fruit. Even though *SlKLUH*

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

is differentially expressed in young flower buds, the increase in fruit weight in the mutant becomes only apparent after fertilisation. The increase in fruit weight results from increased number of cell layers in the pericarp of the developing fruit after anthesis. The delay in ripening that is associated with the larger fruit weights has been hypothesized to be the result of the extension of the cell proliferation stage [64]. KLUH has been found to regulate seed size in rice, wheat and soybean [137–139] as well as biomass in maize [140]. Moreover, CaKLUH is associated with fruit weight in pepper suggesting that domestication-driven increases in fruit weight are in part through the KLUH signalling pathway [64]. It has been hypothesized that KLUH generates a mobile growth promoting signal different from the known phytohormones. However, the exact molecular and biochemical nature of the "mobile" signal remains elusive and the substrate for this subfamily of P450 enzymes is also yet to be deciphered [141,134].

The increase in size from a 1–2-mm wide gynoecium to a 5–10-cm wide tomato fruit is predominantly the result of a dramatic increase in cell size in the pericarp [28,31]. In the developing gynoecium and fruit, the transition to and maintenance of cell enlargement in pericarps has been described [142], but is not well understood at the molecular genetic level. The tomato gene *Cell Size Regulator* (*CSR*) controls cell size in the pericarp and underlies the *fw11.3* QTL [67,85]. *CSR* encodes a protein of unknown function that is homologous to the FAF-like protein in Arabidopsis [143]. Its expression is undetectable in meristems, young floral buds, anthesis-stage flowers and gynoecia or very young developing fruit. Only in fruits starting about 5 days post pollination, *CSR* is expressed to detectable levels peaking at 25–33 days post pollination and declining rapidly at the onset of ripening [67]. In addition to increasing cell size, coexpression analyses suggest a role in shoot development and phloem/xylem histogenesis. Moreover, these studies also suggested a potential link between auxin and cytokinin signalling that is critical for the transition of the cell division to cell expansion phase fruit growth [67].

5. How knowledge on fruit growth can lead to crop improvement

The largest challenge facing agriculture today is the secure supply of food for an ever-increasing human population. This challenge is exacerbated with the reduction in land suitable for growing crops due to urbanization and the effects of climate change. It is therefore more important than ever to develop innovative ways for improving crop performance. The final shape and size of produce are critical aspects for all vegetable and fruit crops. Therefore, the knowledge of the genes and the developmental pathways that impact morphology will provide crucial insights into processes of economic importance. Whereas shape and weight of a vegetable like tomato dictate the market class and its culinary purpose, Brassicaceae fruits provide different functions. For example, oilseed rape (*Brassica napus*) is the third largest source of vegetable oil for human consumption. In addition, the residues from oil extraction provide the second largest source of protein meal for animal fodder. Pod (*i.e.* fruit) architecture holds great potential as a trait that could lead to significant yield gain for oilseed rape. Several crop physiological studies have demonstrated that seed filling in oilseed rape critically depends on photosynthesis in the pod walls and observations indicate that photosynthesis in the pods contributes >50% of the assimilates for seed filling, most of which is derived from photosynthesis [144]. Thus, strategies based on knowledge of fruit formation in closely related model species such as Arabidopsis and Capsella may allow increasing the photosynthetically active pod surface and lead to more assimilates being available for pod filling, thereby increasing seed size and yield.

6. Concluding remarks

Multicellular organisms develop organs with specialized functions that are vital for survival. The morphology that these organs adopt is shaped through evolution and selection to facilitate their optimal performance. Fruits from members of the angiosperm phylum exhibit enormous variation in size and shape and therefore provide excellent systems to understand the genetic control of the mechanisms underlying organ shape establishment. Although our focus has been on the fruit of specific model systems such as tomato, Arabidopsis and Capsella, it is likely that principles such as those that guide anisotropic growth are conserved in other organs in all plant species. Given the tight control that must be in place to govern organ growth in all multicellular organisms, such principles are expected go beyond fruit growth and understanding the mechanisms underlying fruit-shape determination therefore has implication for highly diverse disciplines ranging from medicine to crop improvement.

Developmental genetics and mathematical modelling have been pivotal disciplines in allowing the recent advance in our understanding of fruit formation and the resulting shape and size of the organ. Although, we are only beginning to identify the specific genetic components involved in the process and the interactions between them, it is now possible to identify precise and subtle genetic changes that can be used to predictively modify fruit development and facilitate increased crop production. Increasing yield through intelligent crop design will enable more efficient agricultural practices, thus reducing inputs and land use with obvious benefits for the environment.

Acknowledgements

The research in the Van der Knaap laboratory is supported by NSF IOS1564366 and AFRI competitive grant 2017-67013-26199 of USDA-NIFA. Research in the Østergaard laboratory is supported by the Biotechnological and Biological Sciences Research Council through Institute Strategic Programme grants [BB/J004553/1 and BB/P013511/1].

References

[1] C. Darwin, On the Origin of Species by Means of Natural Selection, 1859.
[2] J. Murray London, C. Darwin, The Variation of Animals and Plants Under Domestication, 1868.
[3] I. Paran, E. van der Knaap, Genetic and molecular regulation of fruit and plant domestication traits in tomato and pepper, J. Exp. Bot. 58 (2007) 3841–3852.
[4] B. Pickersgill, Domestication of plants in the Americas: insights from mendelian and molecular genetics, Ann. Bot. 100 (5) (2007) 925–940.
[5] A.J. Monforte, A.I. Diaz, A. Cano-Delgado, E. van der Knaap, The genetic basis of fruit morphology in horticultural crops: lessons from tomato and melon, J. Exp. Bot. 65 (2014) 4625–4637.
[6] E.E. Dale, Inheritance of fruit length in Capsicum, Michigan Acad. Sci. Arts Lett. 9 (1925) 89–110.
[7] R.A. Emerson, E.M. East, The inheritance of quantitative characters in maize, Nebraska Agric. Exp. Stat. Res. Bull. 2 (1913) 1–120.
[8] G.F. Freeman, The heredity of quantitative characters in wheat, Genetics 4 (1) (1919) 1–93.
[9] H.L. Price, A.W. Drinkard, Inheritance in tomato hybrids, in: H.L. Price, A.W. Drinkard (Eds.), Bulletin/Virginia Agricultural Experiment Station, 177, Virginia Agricultural Experiment Station, Blacksburg,Va, 1908, p. 1908 (p 19).
[10] E.W. Sinnott, S. Kaiser, Two types of genetic control over the development of shape, Bull Torrey Bot. Club 61 (1934) 1–7.
[11] U.P. Hedrick, N.O. Booth, Mendelian characters in tomatoes, Proc. Am. Soc. Hortic. Sci. 5 (1907) 19–24.
[12] A.F. Yeager, Studies on the inheritance and development of fruit size and shape in the tomato, J. Agric. Res. 55 (1937) 141–152.
[13] E.W. Lindstrom, The inheritance of ovate and related shapes of tomato fruits, J. Agric. Res. 34 (1927) 961–985.
[14] G.R. Rodriguez, S. Munos, C. Anderson, S.C. Sim, A. Michel, M. Causse, B.B. McSpadden Gardener, D. Francis, E. van der Knaap, Distribution of SUN, OVATE, LC, and FAS in the tomato germplasm and the relationship to fruit shape diversity, Plant Physiol. 156 (1) (2011) 275–285.

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

[15] J.W. MacArthur, Linkage studies with the tomato, Genetics 11 (1926) 387–405.
[16] E.W. Lindstrom, Inheritance in tomato, Science 60 (1924) 182–183.
[17] G.H. Shull, Duplicate genes for capsule-form in Capsella bursa-pastoris, Z Abst u Vererbl 12 (1914) 97–149.
[18] E.W. Sinnott, Evidence for the existence of genes controlling shape, Genetics 20 (1) (1935) 12–21.
[19] S.D. Tanksley, Mapping polygenes, Annu. Rev. Genet. 27 (1993) 205–233.
[20] J. Zuo, J. Li, Molecular genetic dissection of quantitative trait loci regulating rice grain size, Annu. Rev. Genet. 48 (2014) 99–118.
[21] S.D. Tanksley, The genetic, developmental, and molecular bases of fruit size and shape variation in tomato, Plant Cell 16 (Suppl) (2004) S181–S189.
[22] E. Van der Knaap, M. Chakrabarti, Y.H. Chu, J.P. Clevenger, E. Illa-Berenguer, Z. Huang, N. Keyhaninejad, Q. Mu, L. Sun, Y. Wang, S. Wu, What lies beyond the eye: the molecular mechanisms regulating tomato fruit weight and shape, Front. Plant Sci. 5 (2014) 227.
[23] IPGRI, Descriptors for Tomato (Lycopersicon spp.), International Plant Genetic Resources Institute, Rome, 1996.
[24] UPOV, Guidelines for the Conduct of Tests for Distinctness, Uniformity and Stability (Tomato) TOMATO (Lycopersicon Lycopersicum (L.) Karsten Ex Farw.), Switzerland International Union for the Protection of New Varieties and Plants, Geneva, 2001.
[25] S. Visa, C.X. Cao, B.M. Gardener, E. van der Knaap, Modeling of tomato fruits into nine shape categories using elliptic fourier shape modeling and Bayesian classification of contour morphometric data, Euphytica 200 (3) (2014) 429–439.
[26] L. Langowski, N. Stacey, L. Ostergaard, Diversification of fruit shape in the Brassicaceae family, Plant Reprod. 29 (1–2) (2016) 149–163.
[27] A.H. Roeder, M.F. Yanofsky, Fruit development in arabidopsis, Arabidopsis Book/Am. Soc. Plant Biol. 4 (2006) e0075.
[28] G. Gillaspy, H. Ben-David, W. Gruissem, Fruits: a developmental perspective, Plant Cell 5 (10) (1993) 1439–1451.
[29] L. Azzi, C. Deluche, F. Gevaudant, N. Frangne, F. Delmas, M. Hernould, C. Chevalier, Fruit growth-related genes in tomato, J. Exp. Bot. 66 (4) (2015) 1075–1086.
[30] T. Eldridge, L. Langowski, N. Stacey, F. Jantzen, L. Moubayidin, A. Sicard, P. Southam, R. Kennaway, M. Lenhard, E.S. Coen, L. Ostergaard, Fruit shape diversity in the Brassicaceae is generated by varying patterns of anisotropy, Development 143 (18) (2016) 3394–3406.
[31] H. Xiao, C. Radovich, N. Welty, J. Hsu, D. Li, T. Meulia, E. van der Knaap, Integration of tomato reproductive developmental landmarks and expression profiles, and the effect of SUN on fruit shape, BMC Plant Biol. 9 (2009) 49.
[32] A. Vivian-Smith, A.M. Koltunow, Genetic analysis of growth-regulator-induced parthenocarpy in Arabidopsis, Plant Physiol. 121 (2) (1999) 437–451.
[33] C.A. Schroeder, Growth and development of the fuerte avocado fruit, Proc. Am. Soc. Hortic. Sci. 61 (1953) 103–109.
[34] Y.L. Ruan, J.W. Patrick, M. Bouzayen, S. Osorio, A.R. Fernie, Molecular regulation of seed and fruit set, Trends Plant Sci. 17 (11) (2012) 656–665.
[35] H.J. Klee, J.J. Giovannoni, Genetics and control of tomato fruit ripening and quality attributes, Annu. Rev. Genet. 45 (2011) 41–59.
[36] M. Liu, J. Pirrello, C. Chervin, J.P. Roustan, M. Bouzayen, Ethylene control of fruit ripening: revisiting the complex network of transcriptional regulation, Plant Physiol. 169 (4) (2015) 2380–2390.
[37] P. Pesaresi, C. Mizzotti, M. Colombo, S. Masiero, Genetic regulation and structural changes during tomato fruit development and ripening, Front. Plant Sci. 5 (2014) 124.
[38] R. Karlova, N. Chapman, K. David, G.C. Angenent, G.B. Seymour, R.A. de Maagd, Transcriptional control of fleshy fruit development and ripening, J. Exp. Bot. 65 (16) (2014) 4527–4541.
[39] G.B. Seymour, L. Ostergaard, N.H. Chapman, S. Knapp, C. Martin, Fruit development and ripening, Annu. Rev. Plant Biol. 64 (2013) 219–241.
[40] K. Mummenhoff, I.A. Al-Shehbaz, F.T. Bakker, H.P. Linder, A. Muhlhausen, Phylogeny, morphological evolution, and speciation of endemic brassicaceae genera in the cape flora of southern africa, Ann. Missouri Bot. Garden 92 (2005) 400–424.
[41] C. Musseau, D. Just, J. Jorly, F. Gévaudant, A. Moing, C. Chevalier, M. Lemaire-Chamley, C. Rothan, L. Fernandez, Identification of two new mechanisms that regulate fruit growth by cell expansion in tomato, Front. Plant Sci. 8 (988) (2017).
[42] M. Cieslak, I. Cheddadi, F. Boudon, V. Baldazzi, M. Génard, C. Godin, N. Bertin, Integrating physiology and architecture in models of fruit expansion, Front. Plant Sci. 7 (1739) (2016).
[43] J.L. Bowman, D.R. Smyth, CRABS CLAW, a gene that regulates carpel and nectary development in Arabidopsis, encodes a novel protein with zinc finger and helix-loop-helix domains, Development 126 (11) (1999) 2387–2396.
[44] C. Ferrandiz, S.J. Liljegren, M.F. Yanofsky, Negative regulation of the SHATTERPROOF genes by FRUITFULL during Arabidopsis fruit development, Science 289 (5478) (2000) 436–438.
[45] C. Xu, K.L. Liberatore, C.A. MacAlister, Z. Huang, Y.H. Chu, K. Jiang, C. Brooks, M. Ogawa-Ohnishi, G. Xiong, M. Pauly, J. Van Eck, Y. Matsubayashi, E. van der Knaap, Z.B. Lippman, A cascade of arabinosyltransferases controls shoot meristem size in tomato, Nat. Genet. 47 (7) (2015) 784–792.
[46] S. Munos, N. Ranc, E. Botton, A. Berard, S. Rolland, P. Duffe, Y. Carretero, M.C. Le Paslier, C. Delalande, M. Bouzayen, D. Brunel, M. Causse, Increase in tomato locule number is controlled by two single-nucleotide polymorphisms located near WUSCHEL, Plant Physiol. 156 (4) (2011) 2244–2254.
[47] W. Dewitte, J.A. Murray, The plant cell cycle, Annu. Rev. Plant Biol. 54 (2003) 235–264.
[48] L. De Veylder, T. Beeckman, G.T. Beemster, J. de Almeida Engler, S. Ormenese, S. Maes, M. Naudts, E. Van Der Schueren, A. Jacqmard, G. Engler, D. Inze, Control of proliferation, endoreduplication and differentiation by the Arabidopsis E2Fa-DPa transcription factor, EMBO J. 21 (6) (2002) 1360–1368.
[49] K. Sugimoto-Shirasu, N.J. Stacey, J. Corsar, K. Roberts, M.C. McCann, DNA topoisomerase VI is essential for endoreduplication in Arabidopsis, Curr. Biol. 12 (20) (2002) 1782–1786.
[50] L. De Veylder, T. Beeckman, G.T. Beemster, L. Krols, F. Terras, I. Landrieu, E. van der Schueren, S. Maes, M. Naudts, D. Inze, Functional analysis of cyclin-dependent kinase inhibitors of Arabidopsis, Plant Cell 13 (7) (2001) 1653–1668.
[51] A. Hemerly, A. Engler Jde, C. Bergounioux, M. Van Montagu, G. Engler, D. Inze, P. Ferreira, Dominant negative mutants of the Cdc2 kinase uncouple cell division from iterative plant development, EMBO J. 14 (16) (1995) 3925–3936.
[52] H. Tsukaya, Organ shape and size: a lesson from studies of leaf morphogenesis, Curr. Opin. Plant Biol. 6 (1) (2003) 57–62.
[53] D.J. Cosgrove, Growth of the plant cell wall, Nat. Rev. Mol. Cell Biol. 6 (11) (2005) 850–861.
[54] Y. Wu, D.J. Cosgrove, Adaptation of roots to low water potentials by changes in cell wall extensibility and cell wall proteins, J. Exp. Bot. 51 (350) (2000) 1543–1553.
[55] F. Nicol, H. Hofte, Plant cell expansion: scaling the wall, Curr. Opin. Plant Biol. 1 (1) (1998) 12–17.
[56] R.P. Elumalai, P. Nagpal, J.W. Reed, A mutation in the Arabidopsis KT2/KUP2 potassium transporter gene affects shoot cell expansion, Plant Cell 14 (1) (2002) 119–131.
[57] K.L. Dennison, W.R. Robertson, B.D. Lewis, R.E. Hirsch, M.R. Sussman, E.P. Spalding, Functions of AKT1 and AKT2 potassium channels determined by studies of single and double mutants of Arabidopsis, Plant Physiol. 127 (3) (2001) 1012–1019.
[58] K. Sugimoto-Shirasu, K. Roberts, Big it up: endoreduplication and cell-size control in plants, Curr. Opin. Plant Biol. 6 (6) (2003) 544–553.
[59] C. Breuer, L. Braidwood, K. Sugimoto, Endocycling in the path of plant development, Curr. Opin. Plant Biol. 17 (2014) 78–85.
[60] B.A. Edgar, N. Zielke, C. Gutierrez, Endocycles: a recurrent evolutionary innovation for post-mitotic cell growth, Nat. Rev. Mol. Cell Biol. 15 (3) (2014) 197–210.
[61] C. Cheniclet, W.Y. Rong, M. Causse, N. Frangne, L. Bolling, J.P. Carde, J.P. Renaudin, Cell expansion and endoreduplication show a large genetic variability in pericarp and contribute strongly to tomato fruit growth, Plant Physiol. 139 (4) (2005) 1984–1994.
[62] J. Liu, J. Van Eck, B. Cong, S.D. Tanksley, A new class of regulatory genes underlying the cause of pear-shaped tomato fruit, Proc. Natl. Acad. Sci. U. S. A. 99 (20) (2002) 13302–13306.
[63] A. Frary, T.C. Nesbitt, S. Grandillo, E. van der Knaap, B. Cong, J. Liu, J. Meller, R. Elber, K.B. Alpert, S.D. Tanksley, fw2.2: a quantitative trait locus key to the evolution of tomato fruit size, Science 289 (5476) (2000) 85–88.
[64] M. Chakrabarti, N. Zhang, C. Sauvage, S. Munos, J. Blanca, J. Canizares, M.J. Diez, R. Schneider, J. McClead, M. Mazurek, M. Causse, E. van der Knaap, A cytochrome P450 CYP78A regulates a domestication trait in tomato (Solanum lycopersicum), Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 17125–17130.
[65] H. Xiao, N. Jiang, E.K. Schaffner, E.J. Stockinger, E. Van der Knaap, A retrotransposon-mediated gene duplication underlies morphological variation of tomato fruit, Science 319 (2008) 1527–1530.
[66] S. Wu, The Roles of OVATE and Other Elongation Genes in Regulating Proximal-distal Patterning of Tomato Fruit, The Ohio State University, 2015.
[67] Q. Mu, Z. Huang, M. Chakrabarti, E. Berenguer, X. Liu, Y. Wang, A. Ramos, E. van der Knaap, Fruit weight is controlled by Cell Size Regulator encoding a novel protein that is expressed in maturing tomato fruits, PLoS Genet. 13 (2017) e1006930.
[68] A. Sluis, S. Hake, Organogenesis in plants: initiation and elaboration of leaves, Trends Genet. 31 (6) (2015) 300–306.
[69] A.A. Green, J.R. Kennaway, A.I. Hanna, J.A. Bangham, E. Coen, Genetic control of organ shape and tissue polarity, PLoS Biol. 8 (11) (2010) e1000537.
[70] E.E. Kuchen, S. Fox, P.B. de Reuille, R. Kennaway, S. Bensmihen, J. Avondo, G.M. Calder, P. Southam, S. Robinson, A. Bangham, E. Coen, Generation of leaf shape through early patterns of growth and tissue polarity, Science 335 (6072) (2012) 1092–1096.
[71] S. Sauret-Gueto, K. Schiessl, A. Bangham, R. Sablowski, E. Coen, JAGGED controls Arabidopsis petal growth and shape by interacting with a divergent polarity field, PLoS Biol. 11 (4) (2013) e1001550.
[72] M. Galli, A. Gallavotti, Expanding the regulatory network for meristem size in plants, Trends Genet. 32 (6) (2016) 372–383.
[73] M. Perales, K. Rodriguez, S. Snipes, R.K. Yadav, M. Diaz-Mendoza, G.V. Reddy, Threshold-dependent transcriptional discrimination underlies stem cell homeostasis, Proc. Natl. Acad. Sci. U. S. A. 113 (41) (2016) E6298–E6306.

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

[74] G.V. Reddy, E.M. Meyerowitz, Stem-cell homeostasis and growth dynamics can be uncoupled in the Arabidopsis shoot apex, Science 310 (5748) (2005) 663–667.
[75] M. Lenhard, T. Laux, Stem cell homeostasis in the Arabidopsis shoot meristem is regulated by intercellular movement of CLAVATA3 and its sequestration by CLAVATA1, Development 130 (14) (2003) 3163–3173.
[76] J.C. Fletcher, U. Brand, M.P. Running, R. Simon, E.M. Meyerowitz, Signaling of cell fate decisions by CLAVATA3 in Arabidopsis shoot meristems, Science 283 (5409) (1999) 1911–1914.
[77] U. Brand, M. Hobe, R. Simon, Functional domains in plant shoot meristems, Bioessays 23 (2) (2001) 134–141.
[78] S.J. Liljegren, M.F. Yanofsky, Genetic control of shoot and flower meristem behavior, Curr. Opin. Cell Biol. 8 (6) (1996) 865–869.
[79] M. Koornneef, L.W. Dellaert, J.H. van der Veen, EMS- and radiation-induced mutation frequencies at individual loci in Arabidopsis thaliana (L.) Heynh, Mutat. Res. 93 (1) (1982) 109–123.
[80] S.E. Clark, M.P. Running, E.M. Meyerowitz, CLAVATA1, a regulator of meristem and flower development in Arabidopsis, Development 119 (2) (1993) 397–418.
[81] J.M. Kayes, S.E. Clark, CLAVATA2, a regulator of meristem and organ development in Arabidopsis, Development 125 (19) (1998) 3843–3851.
[82] Z. Lippman, S.D. Tanksley, Dissecting the genetic pathway to extreme fruit size in tomato using a cross between the small-fruited wild species Lycopersicon pimpinellifolium and L. esculentum var. Giant Heirloom, Genetics 158 (1) (2001) 413–422.
[83] L.S. Barrero, S.D. Tanksley, Evaluating the genetic basis of multiple-locule fruit in a broad cross section of tomato cultivars, Theor. Appl. Genet. 109 (3) (2004) 669–679.
[84] B. Cong, L.S. Barrero, S.D. Tanksley, Regulatory change in YABBY-like transcription factor led to evolution of extreme fruit size during tomato domestication, Nat. Genet. 40 (6) (2008) 800–804.
[85] Z. Huang, E. van der Knaap, Tomato fruit weight 11.3 maps close to fasciated on the bottom of chromosome 11, Theor. Appl. Genet. 123 (3) (2011) 465–474.
[86] T. Payne, S.D. Johnson, A.M. Koltunow, KNUCKLES (KNU) encodes a C2H2 zinc-finger protein that regulates development of basal pattern elements of the Arabidopsis gynoecium, Development 131 (15) (2004) 3737–3749.
[87] M.F. Yanofsky, H. Ma, J.L. Bowman, G.N. Drews, K.A. Feldmann, E.M. Meyerowitz, The protein encoded by the Arabidopsis homeotic gene agamous resembles transcription factors, Nature 346 (6279) (1990) 35–39.
[88] X. Liu, Y.J. Kim, R. Muller, R.E. Yumul, C. Liu, Y. Pan, X. Cao, J. Goodrich, X. Chen, AGAMOUS terminates floral stem cell maintenance in Arabidopsis by directly repressing WUSCHEL through recruitment of Polycomb Group proteins, Plant Cell 23 (10) (2011) 3654–3670.
[89] X. Liu, L. Gao, T.T. Dinh, T. Shi, D. Li, R. Wang, L. Guo, L. Xiao, X. Chen, DNA topoisomerase I affects polycomb group protein-mediated epigenetic regulation and plant development by altering nucleosome distribution in Arabidopsis, Plant Cell 26 (7) (2014) 2803–2817.
[90] H. Shinohara, Y. Matsubayashi, Chemical synthesis of Arabidopsis CLV3 glycopeptide reveals the impact of hydroxyproline arabinosylation on peptide conformation and activity, Plant Cell Physiol. 54 (3) (2013) 369–374.
[91] N. Arnaud, T. Lawrenson, L. Ostergaard, R. Sablowski, The same regulatory point mutation changed seed-dispersal structures in evolution and domestication, Curr. Biol. 21 (14) (2011) 1215–1219.
[92] N. Marsch-Martinez, S. de Folter, Hormonal control of the development of the gynoecium, Curr. Opin. Plant Biol. 29 (2016) 104–114.
[93] L. Moubayidin, L. Ostergaard, Gynoecium formation: an intimate and complicated relationship, Curr. Opin. Genet. Dev. 45 (2017) 15–21.
[94] L. Moubayidin, L. Ostergaard, Dynamic control of auxin distribution imposes a bilateral-to-radial symmetry switch during gynoecium development, Curr. Biol. 24 (22) (2014) 2743–2748.
[95] S. Kuusk, J.J. Sohlberg, J.A. Long, I. Fridborg, E. Sundberg, STY1 and STY2 promote the formation of apical tissues during Arabidopsis gynoecium development, Development 129 (20) (2002) 4707–4717.
[96] V. Staldal, E. Sundberg, The role of auxin in style development and apical-basal patterning of the Arabidopsis thaliana gynoecium, Plant Signal. Behav. 4 (2) (2009) 83–85.
[97] J.I. Reyes-Olalde, V.M. Zuniga-Mayo, J. Serwatowska, R.A. Chavez Montes, P. Lozano-Sotomayor, H. Herrera-Ubaldo, K.L. Gonzalez-Aguilera, P. Ballester, J.J. Ripoll, I. Ezquer, D. Paolo, A. Heyl, L. Colombo, M.F. Yanofsky, C. Ferrandiz, N. Marsch-Martinez, S. de Folter, The bHLH transcription factor SPATULA enables cytokinin signaling, and both activate auxin biosynthesis and transport genes at the medial domain of the gynoecium, PLoS Genet. 13 (4) (2017) e1006726.
[98] Q. Gu, C. Ferrandiz, M.F. Yanofsky, R. Martienssen, The FRUITFULL MADS-box gene mediates cell differentiation during Arabidopsis fruit development, Development 125 (8) (1998) 1509–1517.
[99] S.J. Liljegren, G.S. Ditta, Y. Eshed, B. Savidge, J.L. Bowman, M.F. Yanofsky, SHATTERPROOF MADS-box genes control seed dispersal in Arabidopsis, Nature 404 (6779) (2000) 766–770.
[100] S. Rajani, V. Sundaresan, The Arabidopsis myc/bHLH gene ALCATRAZ enables cell separation in fruit dehiscence, Curr. Biol. 11 (24) (2001) 1914–1922.
[101] A.H. Roeder, C. Ferrandiz, M.F. Yanofsky, The role of the REPLUMLESS homeodomain protein in patterning the Arabidopsis fruit, Curr. Biol. 13 (18) (2003) 1630–1635.
[102] S.J. Liljegren, A.H. Roeder, S.A. Kempin, K. Gremski, L. Ostergaard, S. Guimil, D.K. Reyes, M.F. Yanofsky, Control of fruit patterning in Arabidopsis by INDEHISCENT, Cell 116 (6) (2004) 843–853.
[103] J.R. Dinneny, M.F. Yanofsky, Drawing lines and borders: how the dehiscent fruit of Arabidopsis is patterned, Bioessays 27 (1) (2005) 42–49.
[104] L. Ostergaard, S.A. Kempin, D. Bies, H.J. Klee, M.F. Yanofsky, Pod shatter-resistant Brassica fruit produced by ectopic expression of the FRUITFULL gene, Plant Biotechnol. J. 4 (1) (2006) 45–51.
[105] T. Girin, P. Stephenson, C.M. Goldsack, S.A. Kempin, A. Perez, N. Pires, P.A. Sparrow, T.A. Wood, M.F. Yanofsky, L. Ostergaard, Brassicaceae INDEHISCENT genes specify valve margin cell fate and repress replum formation, Plant J. 63 (2) (2010) 329–338.
[106] S. Simonini, J. Deb, L. Moubayidin, P. Stephenson, M. Valluru, A. Freire-Rios, K. Sorefan, D. Weijers, J. Friml, L. Ostergaard, A noncanonical auxin-sensing mechanism is required for organ morphogenesis in Arabidopsis, Genes Dev. 30 (20) (2016) 2286–2296.
[107] A. Sessions, J.L. Nemhauser, A. McColl, J.L. Roe, K.A. Feldmann, P.C. Zambryski, ETTIN patterns the Arabidopsis floral meristem and reproductive organs, Development 124 (22) (1997) 4481–4491.
[108] R.A. Sessions, P.C. Zambryski, Arabidopsis gynoecium structure in the wild and in ettin mutants, Development 121 (5) (1995) 1519–1532.
[109] L. Pnueli, D. Hareven, S.D. Rounsley, M.F. Yanofsky, E. Lifschitz, Isolation of the tomato AGAMOUS gene TAG1 and analysis of its homeotic role in transgenic plants, Plant Cell 6 (2) (1994) 163–173.
[110] I.L. Pan, R. McQuinn, J.J. Giovannoni, V.F. Irish, Functional diversification of AGAMOUS lineage genes in regulating tomato flower and fruit development, J. Exp. Bot. 61 (6) (2010) 1795–1806.
[111] E. Gimenez, L. Castaneda, B. Pineda, I.L. Pan, V. Moreno, T. Angosto, R. Lozano, TOMATO AGAMOUS1 and ARLEQUIN/TOMATO AGAMOUS-LIKE1 MADS-box genes have redundant and divergent functions required for tomato reproductive development, Plant Mol. Biol. 91 (4-5) (2016) 513–531.
[112] S. Soyk, Z.H. Lemmon, M. Oved, J. Fisher, K.L. Liberatore, S.J. Park, A. Goren, K. Jiang, A. Ramos, E. van der Knaap, J. Van Eck, D. Zamir, Y. Eshed, Z.B. Lippman, Bypassing negative epistasis on yield in tomato imposed by a domestication gene, Cell 169 (6) (2017) 1142–1155 (e1112).
[113] J. Hackbusch, K. Richter, J. Muller, F. Salamini, J.F. Uhrig, A central role of Arabidopsis thaliana ovate family proteins in networking and subcellular localization of 3-aa loop extension homeodomain proteins, Proc. Natl. Acad. Sci. U. S. A. 102 (13) (2005) 4908–4912.
[114] S. Wu, J.P. Clevenger, L. Sun, S. Visa, Y. Kamiya, Y. Jikumaru, J. Blakeslee, E. van der Knaap, The control of tomato fruit elongation orchestrated by sun, ovate and fs8. 1 in a wild relative of tomato, Plant Sci. 238 (2015) 95–104.
[115] G.R. Rodriguez, H.J. Kim, E. van der Knaap, Mapping of two suppressors of OVATE (sov) loci in tomato, Heredity 111 (2013) 256–264.
[116] S. Wang, Y. Chang, J. Guo, Q. Zeng, B.E. Ellis, J.G. Chen, Arabidopsis ovate family proteins, a novel transcriptional repressor family, control multiple aspects of plant growth and development, PLoS One 6 (8) (2011) 23.
[117] S. Wang, Y. Chang, J. Guo, J.G. Chen, Arabidopsis Ovate Family Protein 1 is a transcriptional repressor that suppresses cell elongation, Plant J. 50 (5) (2007) 858–872.
[118] A. Tsaballa, K. Pasentsis, N. Darzentas, A.S. Tsaftaris, Multiple evidence for the role of an Ovate-like gene in determining fruit shape in pepper, BMC Plant Biol. 11 (2011) 46.
[119] E. Dorcey, C. Urbez, M.A. Blazquez, J. Carbonell, M.A. Perez-Amador, Fertilization-dependent auxin response in ovules triggers fruit development through the modulation of gibberellin metabolism in Arabidopsis, Plant J. 58 (2) (2009) 318–332.
[120] S. Fuentes, K. Ljung, K. Sorefan, E. Alvey, N.P. Harberd, L. Ostergaard, Fruit growth in Arabidopsis occurs via DELLA-dependent and DELLA-independent gibberellin responses, Plant Cell 24 (10) (2012) 3982–3996.
[121] A.S. Kasianov, A.V. Klepikova, I.V. Kulakovskiy, E.S. Gerasimov, A.V. Fedotova, E.G. Besedina, A.S. Kondrashov, M.D. Logacheva, A.A. Penin, High-quality genome assembly of Capsella bursa-pastoris reveals asymmetry of regulatory elements at early stages of polyploid genome evolution, Plant J. (2017).
[122] M. Bemer, H. van Mourik, J.M. Muino, C. Ferrandiz, K. Kaufmann, G.C. Angenent, FRUITFULL controls SAUR10 expression and regulates Arabidopsis growth and architecture, J. Exp. Bot. 68 (13) (2017) 3391–3403.
[123] M. Bemer, R. Karlova, A.R. Ballester, Y.M. Tikunov, A.G. Bovy, M. Wolters-Arts, B. Rossetto Pde, G.C. Angenent, R.A. de Maagd, The tomato FRUITFULL homologs TDR4/FUL1 and MBP7/FUL2 regulate ethylene-independent aspects of fruit ripening, Plant Cell 24 (11) (2012) 4437–4451.
[124] Y. Shima, M. Kitagawa, M. Fujisawa, T. Nakano, H. Kato, J. Kimbara, T. Kasumi, Y. Ito, Tomato FRUITFULL homologues act in fruit ripening via forming MADS-box transcription factor complexes with RIN, Plant Mol. Biol. 82 (4–5) (2013) 427–438.
[125] M. Fujisawa, Y. Shima, H. Nakagawa, M. Kitagawa, J. Kimbara, T. Nakano, T. Kasumi, Y. Ito, Transcriptional regulation of fruit ripening by tomato FRUITFULL homologs and associated MADS box proteins, Plant Cell 26 (1) (2014) 89–101.
[126] E. Van der Knaap, S.D. Tanksley, Identification and characterization of a novel locus controlling early fruit development in tomato, Theor. Appl. Genet. 103 (2001) 353–358.

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028

[127] S. Wu, H. Xiao, A. Cabrera, T. Meulia, E. van der Knaap, SUN regulates vegetative and reproductive organ shape by changing cell division patterns, Plant Physiol. 157 (3) (2011) 1175–1186.
[128] M. Levy, Q. Wang, R. Kaspi, M.P. Parrella, S. Abel, Arabidopsis IQD1, a novel calmodulin-binding nuclear protein, stimulates glucosinolate accumulation and plant defense, Plant J. 43 (1) (2005) 79–96.
[129] B.K. Moller, C.A. Ten Hove, D. Xiang, N. Williams, L.G. Lopez, S. Yoshida, M. Smit, R. Datla, D. Weijers, Auxin response cell-autonomously controls ground tissue initiation in the early Arabidopsis embryo, Proc. Natl. Acad. Sci. U. S. A. 114 (12) (2017) E2533–E2539.
[130] K. Burstenbinder, T. Savchenko, J. Muller, A.W. Adamson, G. Stamm, R. Kwong, B.J. Zipp, D.C. Dinesh, S. Abel, Arabidopsis calmodulin-binding protein IQ67-domain 1 localizes to microtubules and interacts with kinesin light chain-related protein-1, J. Biol. Chem. 288 (3) (2013) 1871–1882.
[131] K. Burstenbinder, B. Moller, R. Plotner, G. Stamm, G. Hause, D. Mitra, S. Abel, The IQD family of calmodulin-binding proteins links calcium signaling to microtubules, membrane subdomains, and the nucleus, Plant Physiol. 173 (3) (2017) 1692–1708.
[132] J.P. Clevenger, J. Van Houten, M. Blackwood, G.R. Rodriguez, Y. Jikumaru, Y. Kamiya, M. Kusano, K. Saito, S. Visa, E. van der Knaap, Network analyses reveal shifts in transcript profiles and metabolites that accompany the expression of SUN and an elongated tomato fruit, Plant Physiol. 168 (3) (2015) 1164–1178.
[133] Y. Pan, X. Liang, M. Gao, H. Liu, H. Meng, Y. Weng, Z. Cheng, Round fruit shape in WI7239 cucumber is controlled by two interacting quantitative trait loci with one putatively encoding a tomato SUN homolog, Theor. Appl. Genet. 130 (3) (2017) 573–586.
[134] E. Anastasiou, S. Kenz, M. Gerstung, D. MacLean, J. Timmer, C. Fleck, M. Lenhard, Control of plant organ size by KLUH/CYP78A5-dependent intercellular signaling, Dev. Cell 13 (6) (2007) 843–856.
[135] K. Miyoshi, B.O. Ahn, T. Kawakatsu, Y. Ito, J. Itoh, Y. Nagato, N. Kurata, PLASTOCHRON1, a timekeeper of leaf initiation in rice, encodes cytochrome P450, Proc. Natl. Acad. Sci. U. S. A. 101 (3) (2004) 875–880.
[136] N. Zhang, M.T. Brewer, E. van der Knaap, Fine mapping of fw3.2 controlling fruit weight in tomato, Theor. Appl. Genet. 125 (2) (2012) 273–284.
[137] M. Ma, H. Zhao, Z. Li, S. Hu, W. Song, X. Liu, TaCYP78A5 regulates seed size in wheat (Triticum aestivum), J. Exp. Bot. 67 (5) (2016) 1397–1410.
[138] F. Xu, J. Fang, S. Ou, S. Gao, F. Zhang, L. Du, Y. Xiao, H. Wang, X. Sun, J. Chu, G. Wang, C. Chu, Variations in CYP78A13 coding region influence grain size and yield in rice, Plant Cell Environ. 38 (4) (2015) 800–811.
[139] B. Zhao, A. Dai, H. Wei, S. Yang, B. Wang, N. Jiang, X. Feng, Arabidopsis KLU homologue GmCYP78A72 regulates seed size in soybean, Plant Mol. Biol. 90 (1-2) (2016) 33–47.
[140] X. Sun, J. Cahill, T. Van Hautegem, K. Feys, C. Whipple, O. Novák, S. Delbare, C. Versteele, K. Demuynck, J. De Block, V. Storme, H. Claeys, M. Van Lijsebettens, G. Coussens, K. Ljung, A. De Vliegher, M. Muszynski, D. Inzé, H. Nelissen, Altered expression of maize PLASTOCHRON1 enhances biomass and seed yield by extending cell division duration, Nat. Commun. 8 (2017) 14752.
[141] N.M. Adamski, E. Anastasiou, S. Eriksson, C.M. O'Neill, M. Lenhard, Local maternal control of seed size by KLUH/CYP78A5-dependent growth signaling, Proc. Natl. Acad. Sci. U. S. A. 106 (47) (2009) 20115–20120.
[142] J.P. Renaudin, C. Deluche, C. Cheniclet, C. Chevalier, N. Frangne, Cell layer-specific patterns of cell division and cell expansion during fruit set and fruit growth in tomato pericarp, J. Exp. Bot. 68 (7) (2017) 1613–1623.
[143] V. Wahl, L.H. Brand, Y.L. Guo, M. Schmid, The FANTASTIC FOUR proteins influence shoot meristem size in Arabidopsis thaliana, BMC Plant Biol. 10 (2010) 285.
[144] E.J. Allen, D.G. Morgan, W.J. Ridgman, A physiological analysis of the growth of oilseed rape, J. Agric. Sci. 77 (1971) 339–341.

Please cite this article in press as: E. van der Knaap, L. Østergaard, Shaping a fruit: Developmental pathways that impact growth patterns, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.028