Fruit Development and Ripening

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Abstract
Fruiting structures in the angiosperms range from completely dry to highly fleshy organs and provide many of our major crop products, including grains. In the model plant Arabidopsis, which has dry fruits, a high-level regulatory network of transcription factors controlling fruit development has been revealed. Studies on rare nonripening mutations in tomato, a model for fleshy fruits, have provided new insights into the networks responsible for the control of ripening. It is apparent that there are strong similarities between dry and fleshy fruits in the molecular circuits governing development and maturation. Translation of information from tomato to other fleshy-fruited species indicates that regulatory networks are conserved across a wide spectrum of angiosperm fruit morphologies. Fruits are an essential part of the human diet, and recent developments in the sequencing of angiosperm genomes have provided the foundation for a step change in crop improvement through the understanding and harnessing of genome-wide genetic and epigenetic variation.
INTRODUCTION

True fruits are found only in the angiosperms, or flowering plants; the name angiosperm means hidden seed. Flowering plants comprise some 250,000–400,000 species in four major clades (10) that are the dominant component of vegetation in most tropical, subtropical, and temperate zones worldwide. The angiosperms comprise tiny herbs to large canopy trees, occupy terrestrial and aquatic (including marine) habitats, and are the source of all major crop plants. As such, humans have a long and intimate association with angiosperms, particularly with their fruits and seeds.

Fruits are often defined as structures derived from a mature ovary containing seeds (48), but many structures we might define as fruit are in fact composed of a variety of tissue types (Figure 1). Van der Pijl (155) used the concept of the dispersal unit as his definition of a fruit; this links fruits to their role in the ecology of the plant life cycle as the mechanism by which seeds are dispersed. Dispersal units also occur in land plants other than angiosperms; some Carboniferous seed ferns had fleshy structures that are thought to have been eaten by reptiles (148), and the seed of the “living fossil” Ginkgo biloba is enveloped in a soft fleshy covering called the sarcotesta. These propagules are not considered true fruits despite their functional similarities. True fruits are derived from the flower gynoecium (see Fruit Development and Ripening, below).

NOMENCLATURE, EVOLUTION, DIVERSITY

The myriad of fruit types recognized in angiosperms can be simplified using combinations of the following characteristics: dehiscence or indehiscence, dry or fleshy exterior, and free (apocarpous) or fused (syncarpous) carpels. Capsules (Figure 1c) and the siliques of Arabidopsis relatives (Figure 1a) are dehiscent, dry, and syncarpous; achenes and nuts (Figure 1e,g,b) are indehiscent, dry, and unicarpellate; and berries (Figure 1b,d) are indehiscent, fleshy, and syncarpous. A drupe is an indehiscent, fleshy, single-seeded fruit where the seed is enclosed in a hard endocarp, like a peach pit (Figure 1f). Syncarpy occurs in 83% of extant angiosperm species and has been interpreted as facilitating pollen tube competition and thus fitness (36); it has arisen independently in both the monocots and the eudicots (37). Apocarpy is rarer but can be seen in the fruits of magnolias, with clusters of separate carpels termed follicles. Endress (36) has suggested that syncarpy might facilitate adaptive radiation in fruit type by increasing the possibility of developing fleshiness and/or dehiscence mechanisms.

Darwin thought that the recent origin and rapid diversification of the angiosperms was “an abominable mystery” (44). The angiosperm fossil record extends back to the Early Cretaceous period, and the earliest unambiguous fossils (65) are dated conservatively to approximately 132 Mya. Angiosperms were common and diverse by the mid-Cretaceous, indicating either that their first major diversification and
Figure 1
Fruit diversity. (a) *Lunaria annua* L. (Brassicaceae), cultivated, United Kingdom: dehiscent siliques that dry and shatter irregularly with age, releasing the seeds. (b) *Mandragora officinarum* L. (Solanaceae), Andalucía, Spain: indehiscent berries with fleshy, brightly colored mesocarp and many seeds. (c) *Nicotiana sylvestris* Spec. & Comes (Solanaceae), Apurimac, Peru: dehiscent capsules opening along suture lines. The seed-bearing placenta are visible as columns in the center of the capsule. (d) *Ribes cereum* Douglas (Grossulariaceae), New Mexico, United States: indehiscent berries from an inferior gynoecium. The remnants of the flower are clearly visible. (e) *Corylus* sp. (Betulaceae), cultivated, United Kingdom: indehiscent, single-seeded nuts. (f) *Rhus trilobata* Nutt. (Anacardiaceae), New Mexico, United States: indehiscent, single-seeded drupes with fleshy mesocarp. (g) *Fallugia paradoxa* (D. Don) Endl. (Rosaceae), New Mexico, United States: indehiscent, single-seeded achenes with long plumes to aid dispersal. (h) *Fragaria × ananassa* Duchesne ex Rozier (Rosaceae), cultivated, United Kingdom: tiny, single-seeded achenes on the surface of an expanded, brightly colored receptacle. All photos by Sandra Knapp.

ecological radiation occurred over a relatively short time frame or that they originated and diversified earlier than was previously thought. The reproductive structures of these Early Cretaaceous angiosperms were mostly very small (45), with fruit volumes between 0.1 and 8.3 mm³ (the size of a small cherry) and seed volumes between 0.02 and 6.9 mm³ (39). Diverse
fruit types are represented in Early Cretaceous fossils; the vast majority are either indehiscent, single-seeded nuts or drupes with one or a few seeds, but some dehiscent, apocarpous fruits have been found, as have many fruits with fleshy outer layers (45). One-quarter of all fruits found at one site were fleshy drupes or berries (40).

Lorts et al. (91) mapped crude fruit type categories (dry dehiscent, dry indehiscent, and fleshy) onto the orders of extant angiosperms and found no association (assessed visually) between fruit type and major clade. This suggests that there is no phylogenetic constraint on fruit type evolution across the major lineages (orders) of angiosperms, with most orders having all three broadly defined fruit types (see figure 1 of Reference 91). Fruit and seed size both increased in the Tertiary (39), with a drastic change at the Cretaceous–Tertiary boundary (147, 162). It has been suggested that the origin of fleshiness was initially related to defense against pathogens and only later co-opted for biotic dispersal (93, 149).

Size change in both fruits and seeds through the fossil record has been attributed to co-evolution with seed-dispersing animals (147), with this mutualistic relationship then driving the development of closed, forested habitats (large seeds are characteristic of closed plant communities). An alternative hypothesis is that changes in habitat through climate change, perhaps coupled with the demise of large herbivores (e.g., dinosaurs), drove the evolution of larger fruits and seeds, and the availability of seed dispersers reinforced this trend (39). Dispersers thus tracked, rather than led, changes in fruit size and morphology. Distinguishing between these two hypotheses is difficult owing to bias in the fossil record (39) and uncertainty over ecological dynamics in the past (149), but a series of studies using both extant and fossil fruits have strongly supported the latter hypothesis. The significant correlations between fruit type and habitat conditions in a broad set of extant flowering plants (8) suggest that the evolution of fleshiness is related to changes in vegetation from open to closed habitats.

It is tempting to assume that fruit diversity is the result of adaptation to frugivores; adaptationist scenarios about tight obligate relationships between fruits and their dispersers abound in the literature, but they have been shown to be less compelling than originally thought. The strong role of habitat and climate in the origin and evolution of fruit characteristics such as fleshiness (39) has been clearly demonstrated in both the fossil record and through correlation studies with extant angiosperms. Syncarpy may represent a key innovation for angiosperm fruits in that it facilitated pollen competition and pollen tube protection (37). Fruit color is another characteristic that on its face seems to be adaptive for frugivore attraction, but studies examining color as a signal have demonstrated that, like the evolution of other fruit characteristics, the evolution of fruit color is mediated through diffuse interactions between plants, antagonists (such as microbial predators), and mutualists (128). Fleshy-fruit evolution has clearly been an important and continually recurring theme throughout flowering plant evolution, and assumptions with respect to the adaptive value of particular fruit traits must be carefully examined.

FRUIT DEVELOPMENT AND RIPENING

The Fruiting Structure

The gynoecium is derived from the fusion of carpels and forms in the center of the flower. Many regulators of carpel development identified in Arabidopsis also have roles during leaf development, thereby confirming the evolutionary origin of carpels as modified leaves (41, 129). The main patterning events of the Arabidopsis gynoecium take place before fertilization and occur along three axes: apical-basal, mediolateral, and abaxial-adaxial (dorsoventral). Stigmatic tissue (Figure 2) that mediates pollen germination develops at the apical (distal) end. After germination, the pollen tube grows down through the transmitting tract and enters the ovules through the micropyle, a small opening
in the integument layers (90). A solid style with radial symmetry supports the segment of the transmitting tract just below the stigma and is required for efficient fertilization (Figure 2). The ovary is formed from the carpels as a longitudinal cylinder with mediolateral symmetry that reflects its origin as two fused leaflike organs (Figure 2). It is composed of two compartments divided by a septum and placenta from which ovules arise. The carpel walls exhibit abaxial-adaxial asymmetry with an exocarp layer of large cells interspersed with stomata, three or four layers of mesocarp cells, and two innermost layers of endocarp cell layers. The Arabidopsis gynoecium is connected at its base to the pedicel and the rest of the plant via a gynophore.

Hormonal and Genetic Regulation

The plant hormone auxin has been established as an important component for patterning along the different axes of polarity in the Arabidopsis gynoecium. In the apical-basal orientation, auxin synthesis at the apex is required for specification of the style and stigma (137). Auxin biosynthesis at the apex is promoted through the activity of transcription factors such as STYLISH1 (STY1), STY2, and NGATHA3, which induce expression of YUCCA auxin biosynthesis genes (2, 15, 34, 137, 153). Exogenous application of auxin rescues the split style of the sty1/2 mutant (141).

The basic helix-loop-helix (bHLH) proteins are a large family of transcription factors found in all eukaryotic organisms (99, 115). Several members of this family have functions during gynoecium development or later in fruit development. For example, mutations in the SPATULA (SPT) gene lead to early defects in the development of carpel marginal tissues such as the stigma, style, septum, and transmitting tract (3, 61). SPT activity promoting carpel development was recruited during the evolution of flowering plants from light-regulated processes such as those involved in shade-avoidance responses in vegetative organs (120). Phenotypic defects similar to those observed in spt mutant gynoecia were observed in multiple combinations of mutations in the bHLH-encoding HECATE (HEC) genes, and protein-protein interactions between SPT and HEC proteins in yeast two-hybrid experiments suggest that these factors may jointly regulate downstream targets (55). Loss-of-function mutations in the ETTIN (ETT) gene, which encodes AUXIN RESPONSE FACTOR3 (ARF3), exhibit enlarged apical and basal regions at the expense of the ovary (132). Because ETT negatively regulates SPT/HEC genes in the ovary, it has been suggested that ETT regulates ovary size, perhaps in response to local auxin dynamics (61, 108, 144).

Further connections between gynoecium patterning and auxin were made when it appeared that mutations in another bHLH-factor-encoding gene, INDEHISCENT (IND), strongly enhanced the phenotype of the spt single mutant (51) (Figure 2d). IND and SPT
Parthenocarpic: producing fruit without fertilization; the resulting fruits are seedless

heterodimerize in plant cells and regulate a common set of target genes (51, 139), and a number of their direct targets are involved in controlling the direction of auxin transport (51, 139). IND belongs to the same clade in the Arabidopsis bHLH family as the three HEC genes (115). Loss of all three HEC genes gives rise to a split-style phenotype with no stigmatic tissue, identical to the ind spt mutant gynoecium (55), and it is therefore likely that HEC proteins also interact with SPT in planta.

Tissue identity factor activity and auxin dynamics are at the center of gynoecium patterning control. With the development of tools to study auxin transport and signaling in Arabidopsis, data are now emerging to provide an overview of how auxin is distributed during gynoecium development. For example, the auxin signaling reporter DR5::GFP shows a strong green fluorescent protein (GFP) signal accumulating in a ring at the distal end of the gynoecium prior to stigma formation (51). In the spt single mutant and the ind spt double mutant, this ring is not formed; instead, the GFP signal accumulates in two foci at the distal end. Because both IND and SPT are expressed in this distal region, it is likely that they are responsible for lateral auxin distribution to create a continuous ring and ensure proper development.

Fertilization

The developmental switch that turns a gynoecium into a growing fruit depends on the fertilization of ovules that form along the placenta. In most angiosperms, the gynoecium senesces and dies if not fertilized. The fruit initiation process has traditionally been thought to involve phytohormone activities (49). Upon fertilization, a seed-originating auxin signal is generated (32, 104, 126) that is thought to upregulate biosynthesis of another hormone, gibberellin (GA). This leads to activation of GA signaling in the ovules and valves, thereby stimulating fruit growth (32, 111, 131, 156).

Degradation of the growth-repressing DELLA proteins is central to GA signaling. DELLA proteins are characterized by a conserved DELLA motif in the N-terminal domain and a SCARECROW-like C-terminal domain (113, 136). According to the “relief of restraint” model (58), GA-mediated DELLA degradation is required to overcome the growth-repressing DELLA activity. In agreement with their function as growth repressors, reduction in DELLA activity can promote parthenocarpic fruit growth in both dry dehiscent fruits and fleshy fruits (32, 97). GA treatment of gynoecia in a della loss-of-function mutant has revealed the existence of a GA-dependent but DELLA-independent pathway that contributes to fruit growth in Arabidopsis (46). This newly identified DELLA-independent pathway provides additional opportunities for fine-tuning fruit growth.

ARFs and Aux/IAA proteins also function during fruit initiation. In Arabidopsis and tomato, expression of aberrant forms of ARF8 results in parthenocarpic fruit development (53, 54), as does silencing of IAA9 in tomato (160). It is not clear by what mechanism ARF8 regulation occurs, but based on the model for auxin signal transduction, it has been suggested that ARF8 and the Aux/IAA protein IAA9 may form a transcriptional repressor complex that is destabilized by the aberrant forms of ARF8 to allow transcription of auxin-responsive genes (53).

In tomato, pollination causes upregulation of ARF9 and downregulation of ARF7. Silencing of the SLARF7 gene in transgenic plants (cv. Moneymaker) results in parthenocarpic fruit development (32, 111, 131, 156). This leads to activation of GA signaling in the ovules and valves, thereby stimulating fruit growth (32, 111, 131, 156).

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tomato that early photosynthesis is important for proper seed set (92).

**Fruit Development**

Upon fertilization, *Arabidopsis* fruit enters a stage in which ovary growth and maturation are tightly coordinated with seed development. During this process, a number of fruit tissues develop, including valves (derived from the carpel walls), a central replum, a false septum, and valve margins that form at the valve/replum borders. Late in development, the valve margins differentiate into dehiscence zones, where fruit opening will take place. Although these individual tissues were specified prior to fertilization, their distinct appearance becomes more striking after fertilization, forming sharp boundaries, particularly along the valve margin (125).

As described above, the valves (carpel walls) exhibit abaxial-adaxial asymmetry and are composed of an outermost (abaxial) epidermal layer with long, broad cells interspersed with guard cells (stomata). Underneath the epidermal layer, three to six layers of mesophyll cells follow (Figure 3). Two specialized adaxial cell layers form in the valves: The innermost endocarp A layer (valve margins) is composed of large cells that undergo cell death before the fruit has completely matured, whereas cells in the endocarp B layer remain small and develop lignified cell walls (Figure 3) whose rigidity may assist in the process of fruit opening by providing significant tension in the mature fruit (140). The replum is connected to the septum and contains the main vascular bundles. At the valve margin, a narrow file of dehiscence zone cells differentiates along the entire length of the fruit late in development, allowing the valves to detach from the replum, which causes seed dispersal to occur by a shattering mechanism. The valve margins consist of two distinct cell layers: a separation layer, where cell separation will take place, and a layer of lignified cells, whose rigidity may promote the opening process (140).

Development of fleshy fruit such as tomato involves cell division and expansion of the ovary tissues, but without the lignification phase found in dry fruit. In the miniature tomato (cv. Micro-Tom) (112), cell division starts at 2 DPA, when the ovary is 1 mm in diameter with 10 cell layers (Figure 3). Cell divisions are both periclinal and anticlinal, and by 4 DPA the fruit is 1.5 mm in diameter and has 30 cell layers. Cell division continues at 7–8 DPA, but then cell expansion becomes apparent and the cell layer number increases to 35 at the apex of the fruit and 20 at the equator. Cell division stops by 10–13 DPA, and cell expansion progresses at a dramatic rate until approximately 30 DPA, when the fruit reaches a diameter of 1.5–2 cm (Figure 3). The layers of cells that undergo division after anthesis are the mesocarp colenchyma. Cell expansion is responsible for the increase in fleshy-fruit size (Figure 3), with cell sizes in tomato reaching 0.5 mm in diameter in the pericarps of some varieties (16).

Fruit size in tomato is controlled by nearly 30 quantitative trait loci. The *Fw2.2* gene is responsible for approximately 30% of the variation, and encodes a plant-specific and fruit-specific protein that negatively regulates mitosis and is possibly part of the cell cycle signal transduction pathway (20). Pericarp cell number in tomato is also linked to the expression of the MADS-box gene TOMATO AGAMOUS (TAG)–LIKE1 (TAGL1), which is an ortholog of the *Arabidopsis* SHATTER-PROOF (SHP) genes (158). *TAGL1* is expressed in floral organs and young tomato fruit as well as during ripening. It is one of the most abundant MADS-box genes expressed in tissues of young fruits (100), and in RNAi::TAGL1 tomato fruits there is a reduction in pericarp thickness from 25 to 15 layers measured at 28 and 38 DPA, respectively, and the inner pericarp appears to be absent.

Four genes that control shape in tomato have been cloned: *SUN* and *OVATE*, which control fruit elongation shape; *FASCIATED*, which is associated with flat-shaped fruit; and *LOCULE NUMBER*, which is associated with floral development and ripening. *SUN* encodes an IQD family protein that is thought to alter hormone or secondary metabolite levels (164), whereas...
Figure 3
Changes in fruit anatomy during development. (a) Pericarp layers characteristic of dry fruits (e.g., capsules). (b) Pericarp layers characteristic of fleshy fruits. (c) Transverse section of entire mature Brassica pod. (d) Transverse section of Brassica pod valve wall. (e) Transverse section of Solanum lycopersicum cv. Micro-Tom fruit at different days postanthesis (DPA), showing pericarp layers and illustrating cell division and cell expansion phases. Panels a, b, and e courtesy of Pabón-Mora & Litt (112).

OVATE encodes a negative growth regulator, presumably by acting as a repressor of transcription and thereby reducing fruit length. FASCIATED encodes a YABBY transcription factor (19). LOCULE NUMBER was recently linked to two single-nucleotide polymorphisms (SNPs) located approximately 1,200 base pairs downstream of the stop codon of a gene encoding a WUSCHEL homeodomain protein, members of which regulate plant stem
cell fate. Alleles of these genes appear to have played a critical role in forging the shape of domesticated tomato fruits (123).

**Hormonal and Genetic Regulation of Maturation and Dehiscence in Dry Fruits**

Formation of the valve margin region depends on several transcription factor activities. Upstream in the hierarchy, two closely related MADS-box transcription factor–encoding genes, SHP1 and SHP2, positively regulate the IND gene described above as well as ALCATRAZ (ALC), which encodes another bHLH transcription factor (83, 84, 118). Although none of the shp single mutants have any detectable phenotype on their own, the combined shp1 shp2 double mutant produces indehiscent fruit devoid of valve margin differentiation (83). Despite the role of IND in gynoecium formation, the most pronounced phenotypic defect of ind mutants and loss of IND function is a loss of valve margin identity that affects both the lignified and separation layers (84). In contrast, fruits from alc mutants produce lignified cells at the valve margin, but the separation layer cells fail to develop (118).

The FRUITFULL (FUL) gene encodes a MADS-box transcription factor that is required for maintaining valve identity (57). The valves developed in ful mutant fruits adopt a partial change of identity into valve margin cells with ectopic lignification. In these mutant valves, SHP1, SHP2, and IND become ectopically expressed, and the phenotype can be almost entirely rescued by combining the ful mutant with mutations in valve margin identity genes. FUL thus specifies valve cell fate at least in part by repressing the expression of valve margin identity genes in valve tissue (42, 84).

The homeodomain-containing transcription factor REPLUMLESS (RPL) is a key regulator of the replum tissue on the medial side of the valve margins. As the name implies, rpl loss-of-function mutants fail to develop a replum. Similar to the activity of FUL, RPL represses valve margin identity gene expression in the replum, and combining rpl mutants with, for example, the shp double or ind single mutant rescues the replum defect (122, 124). Species of *Brassica* produce fruits that are morphologically very similar to those of *Arabidopsis*, but they lack an outer replum, suggesting that brassicas have lost the RPL function in the fruit. Replum tissue was, however, produced in *Brassica rapa* with a strong ind mutant allele (52). Lack of RPL activity in *Brassica* fruits was demonstrated to result from reduced RPL gene expression due to a SNP in a cis-element located ∼3 kb upstream from the RPL-encoding region (5). In rice, the same SNP in the same cis-element in an RPL homolog is responsible for preventing seed shattering in domesticated rice (76), revealing a remarkable example in which the same nucleotide position in a regulatory element explains developmental variation in seed dispersal structures in widely diverged species (5).

In recent years more elements of the core genetic network of *Arabidopsis* fruit patterning have been identified, including genes involved in leaf development, such as ASYMMETRIC LEAVES1, ASYMMETRIC LEAVES2, and BREVIPEDICELLUS (1). The network has also expanded upstream to include a combination of genes, including JAGGED, NUBBIN, FILAMENTOUS FLOWER, and YABBY3 (29, 30).

The floral homeotic gene APETALA2 (AP2) has been demonstrated to repress replum development (122). A thorough description of all these interactions is not the purpose of this review and can be obtained at least partly elsewhere (6, 110, 125). Therefore, here we concentrate on the core network and its interaction with hormonal activities.

The core and extended genetic network of *Arabidopsis* fruit development consists entirely of interactions among transcription factors. The three genes encoding polygalacturonases (PGs) required for dehiscence downstream of IND are functionally redundant (109). This makes sense, as PGs have cell wall–degrading activities and secretion of PGs from dehiscence zone cells has been demonstrated (114).

Hormonal distribution and biosynthesis are emerging as immediate downstream outputs
from the core genetic network. In *Brassica napus*, direct measurements of auxin levels in valve margin tissue revealed an abrupt decrease in the auxin content of these cells immediately prior to fruit opening. This drop correlated exactly with an increase in the activity of cell wall–degrading enzymes (14), raising the possibility that auxin depletion from the valve margin tissue is a requirement for dehiscence. Work in *Arabidopsis* confirmed this hypothesis, demonstrating that IND ensures formation of an auxin minimum in the valve margins at maturity by regulating the direction of auxin transport (139); a subsequent study showed that IND most likely interacts with SPT to mediate this process (51).

As described earlier, GA promotes fruit growth in *Arabidopsis* following fertilization. This is in line with the general perception of GA as a growth-promoting hormone, which functions by promoting degradation of the growth-repressing DELLA proteins (58). GA has now also been identified as having a role in tissue specification during *Arabidopsis* fruit development. The *GA4* gene is a direct target of IND, and the *ga4* mutant has a defect in specifying the separation layer of the valve margin similar to that seen in *alc* mutants (4). *GA4* encodes a GA3 oxidase, which mediates the last step in the biosynthesis of active GAs (17, 145). Genetic analysis demonstrated that GA production at the valve margin is required to degrade DELLA proteins. In the absence of GA, DELLA proteins would otherwise interact with ALC proteins to inhibit ALC from regulating its target genes (4).

**Hormonal and Genetic Regulation of Maturation and Ripening in Fleshy Fruits**

In tomato and grape, levels of free IAA, the most abundant auxin, decline prior to the onset of ripening, and at the same time levels of the “inactive” IAA–amido acid conjugate IAA-Asp increase substantially. Similar profiles of free IAA and IAA conjugates have also been reported in pepper, banana, muskmelon, and strawberry (9). The IAA-Asp is generated from IAA by IAA–amido synthetase, and this enzyme is encoded by the *GH3* gene. Two *GH3* genes associated with the onset of ripening in tomato are upregulated (77), and tomato fruits over-expressing the pepper *GH3* gene ripen early (88). These observations are consistent with a role for endogenous IAA in controlling the onset of ripening and modulation of its levels by amino acid conjugation (9). *GH3* expression may be partially under the control of abscisic acid (ABA), another plant hormone that promotes ripening (9).

There is evidence that ABA acts as a promoter of ripening in tomato. Suppression of the *SINCED1* gene (encoding 9-*cis*-epoxycarotenoid dioxygenase), which catalyzes a key step in ABA biosynthesis, results in down-regulation in the transcription of several major ripening-related cell wall enzymes, including PG and pectin methylesterase; enhanced fruit shelf life; and slower softening (143). Retardation of ripening is also apparent in strawberry fruits with reduced levels of *NCED* (71). ABA is also a positive regulator of ripening in grape (9). The mechanism of ABA action is not known, but in grape it can increase *GH3* expression, and a promoter scan identified ABRE–like elements potentially involved in ABA signaling in the *GH3* promoter (9).

The role of ethylene in fruit ripening has been reviewed many times (most recently in References 74 and 56) and is therefore covered only briefly here. Fleshy fruits have historically been divided into two classes: climacteric (e.g., tomato, apples, and banana) and nonclimacteric (e.g., grape, strawberry, and citrus). Climacteric fruits show a burst of respiration at the onset of ripening along with a large rise in ethylene production. Ripening in climacteric fruits can also be initiated by exposure to exogenous ethylene. In nonclimacteric fruits, the respiratory increase is absent and ethylene does not appear to be critical for the ripening process. Direct evidence that ethylene is critical for the induction of ripening in climacteric fruit came from work with tomato, where antisense genes were used to suppress the expression of *ACO1* and *ACS2*, which encode ACC oxidase.
ripening process, including ripening inhibitor mutations that completely abolish the normal ripening process (86). The **MADS-RIN** gene is necessary for ripening in tomato (159) and the **rin** mutation impacts virtually all ripening pathways, which supports its role as a master regulator of the ripening process (96). Chromatin immunoprecipitation experiments indicate that MADS-RIN directly controls the expression of a wide range of other ripening-related genes, targeting the promoters of genes involved in (a) the biosynthesis and perception of ethylene, such as **LeACS2**, **LeACS4**, **NR**, and **E8**; (b) cell wall metabolism, such as polygalacturonase (**PG**), galactanase (**TBG4**), and expansins (**LeEXP1**); (c) carotenoid formation, such as phytoene synthase (**PSY1**); (d) aroma biosynthesis, such as lipoxygenase (**Tomlox C**), alcohol dehydrogenase (**ADH2**), and hydroperoxidelyase (**HPL**); and (e) the generation of ATP, such as phosphoglycerate kinase (**PGK**) and the promoter of **MADS-RIN** itself (47, 96, 117). MADS-RIN is also involved in suppressing the expression of most **ARF** genes (78) and therefore auxin-related gene expression.

In tomato, MADS-RIN is involved in switching on systemic ethylene through the induction of **LeACS2**, which encodes ACS (96). The conversion of ACC to ethylene, however, requires **ACO1**. The **ACO1** gene does not appear to be under the direct control of MADS-RIN, but its expression is governed by **MADS-RIN**, and the promoter of **MADS-RIN** itself. MADS-RIN is also involved in suppressing the expression of most **ARF** genes and therefore auxin-related gene expression.

Transcriptional regulators of ripening in tomato. A major breakthrough in dissecting the transcriptional control of tomato ripening was the identification of genes underlying rare mutations that completely abolish the normal ripening process, including ripening inhibitor (rin), nonripening (nor), and Colorless nonripening (Cnr). These mutant loci all harbor transcription factors. RIN is encoded by a member of the **SEPALLATA4** (SEP4) clade of MADS-box genes (159), NOR is a member of the NAC-domain transcription factor family (50), and Cnr is encoded by an SBP-box gene, targets of which are likely to include the promoters of the **SQUAMOSA** clade of MADS-box genes (95).

The **MADS-RIN** gene is necessary for ripening in tomato (159) and the **rin** mutation impacts virtually all ripening pathways, which supports its role as a master regulator of the ripening process (96). Chromatin immunoprecipitation experiments indicate that MADS-RIN directly controls the expression of a wide range of other ripening-related genes, targeting the promoters of genes involved in (a) the biosynthesis and perception of ethylene, such as **LeACS2**, **LeACS4**, **NR**, and **E8**; (b) cell wall metabolism, such as polygalacturonase (**PG**), galactanase (**TBG4**), and expansins (**LeEXP1**); (c) carotenoid formation, such as phytoene synthase (**PSY1**); (d) aroma biosynthesis, such as lipoxygenase (**Tomlox C**), alcohol dehydrogenase (**ADH2**), and hydroperoxidelyase (**HPL**); and (e) the generation of ATP, such as phosphoglycerate kinase (**PGK**) and the promoter of **MADS-RIN** itself (47, 96, 117). MADS-RIN is also involved in suppressing the expression of most **ARF** genes and therefore auxin-related gene expression.

In tomato, MADS-RIN is involved in switching on systemic ethylene through the induction of **LeACS2**, which encodes ACS (96). The conversion of ACC to ethylene, however, requires **ACO1**. The **ACO1** gene does not appear to be under the direct control of MADS-RIN, but its expression is governed by **MADS-RIN**, and the promoter of **MADS-RIN** itself. MADS-RIN is also involved in suppressing the expression of most **ARF** genes and therefore auxin-related gene expression.
MADS-RIN binding to promoter targets occurs throughout ripening (96). The action of MADS-RIN to induce the transcription of ripening-related genes is also dependent on the presence of the CNR gene product or a CNR-regulated gene product (96). The promoters of the NOR, CNR, HB1, and TDR4 genes are also targets for MADS-RIN, and MADS-RIN can form heterodimers with other MADS-box transcription factors such as TAGL1 and TAG1 of the AGAMOUS (AG) clade and TDR4 of the SQUAMOSA clade (158). This indicates that MADS-RIN exerts its control over ripening in cooperation with a range of other regulatory factors. TAGL1 is upregulated during tomato ripening, and its suppression inhibits normal ripening. This occurs partly through inhibition of ethylene biosynthesis, and in TAGL1-silenced lines it appears to occur predominantly through direct ACS2 suppression. Indeed, transient promoter-binding studies indicate direct interactions with ACS2. TAGL1 needs RIN for lycopene accumulation, with Lyc-B and CYC-B upregulated in TAGL1 RNAi lines. Additionally, TAGL1 appears to regulate some cell wall activities in a RIN-independent manner. It also appears to be linked to the phenyl propanoid pathway and activates the flavonoid pathway. TAGL1 RNAi fruit also have thin pericarps, and upregulation produces fleshy ripening sepalis. This implicates TAGL1 in not only ripening but also the development of fleshiness in tomato (68, 158).

RNAi suppression of AP2—which belongs to the AP2/ETHYLENE RESPONSE FACTOR (ERF) family of transcription factors (18, 72) and acts downstream of RIN, NOR, and CNR—results in rapid softening and earlier ripening. Evidence indicates that AP2 is a negative regulator of ripening in tomato (18) that operates in a negative-feedback loop with CNR, as illustrated by the observation that in the pericarps of AP2 RNAi fruits, mRNA levels of CNR were elevated. In addition, it has been demonstrated that CNR can bind to the promoter of AP2 in vitro (72). Interestingly, AP2 RNAi fruits show enhanced GH3 gene expression (72), likely linking AP2 to auxin-related gene expression. A study of the expression of ARF genes during fruit development in the rin mutant and wild-type fruits indicated that MADS-RIN normally suppresses the expression of most ARFs (78). These data point to a control system involving the removal of auxin by conjugation and then repression of ARFs by the presence of MADS-RIN.

Unraveling the transcriptome network controlling fruit ripening in tomato has revealed some striking parallels with the regulatory circuits in dry fruit (Figure 4). Similar MADS-box transcription factors play a central role in both fruit types, and in some cases they seem to be directly orthologous (e.g., SHP1/2 and TAGL1). There are also some major differences between the molecular events. In dry fruits, lignification follows cell division, whereas in fleshy fruits, cell expansion is observed. Also, in Arabidopsis there does not appear to be a fruit-related MADS-RIN ortholog.

Control of color and texture changes. A systems biology approach to the tomato transcriptome and metabolome during ripening has led to the identification of a putative carotenoid modulator, SIERF6 (80). Reduced expression of SIERF6 by RNAi enhanced both carotenoid and ethylene levels during ripening. The majority of genes substantially influenced by SIERF6 repression were upregulated, indicating that the primary function of SIERF6 occurs via negative regulation. SIERF6 was responsive to ethylene and may be a component of a feedback restriction in ethylene production during ripening, similar to SIAP2 (80). A small number of fruit high-pigment mutants have been described in tomato, including high pigment1 (bp1) [a lesion in UV-DAMAGED DNA BINDING PROTEIN1 (DDB1) (89)] and bp2 [a mutation in tomato DE-ETIOLATED1 (DETI)] (107). These genes are involved in the suppression of light responses in the absence of light, and for DET1, suppression occurs by a molecular mechanism involving chromatin remodeling (24). Coordinated upregulation of core metabolic processes is responsible for the high-pigment phenotype in the DET1 lines.
Figure 4

Ripening network in fleshy fruits and comparison with events in the dehiscence of dry fruits. (a) Major known regulators of ripening in tomato. The blue circles are transcription factors; the yellow labels are genes where orthologs are also found in dry dehiscent fruits. Downstream effectors are shown in white boxes. Precisely how the gene products of NOR, CNR, and RIN interact is unknown, so dashed green lines are shown between those. (b) Brassica pod and dehiscence zone, illustrating a dry-fruit network using information obtained in Arabidopsis. Image of tomato fruit with ripening inhibited by silver thiosulfate on the left side kindly provided by Don Grierson and Kevin Davies.

Epigenetics. The lesion responsible for the Car mutation is due to an epigenetic change leading to hypermethylation of the CNR promoter and inhibition of gene expression and ripening in the mutant (95). Additionally, in normal fruit development, at least in the tomato cultivar Liberto, the promoter of CNR appears to be demethylated in a specific region just prior to the onset of ripening.

A further level of regulation controlling fruit ripening occurs through the presence of small RNAs (sRNAs). These include microRNAs.
(miRNAs) and other sRNAs of unknown function. The CNR 3′ untranslated-region sequence contains a miRNA binding site that is complementary to miR156/157 (23). Deep sequencing of the sRNAome of developing tomato fruits, covering the period between closed flowers and ripened fruits through the profiling of sRNAs at 10 time points, has revealed that thousands of non-miRNA sRNAs are differentially expressed during fruit development and ripening (106). Some of these sRNAs are derived from transposons, but many map to regions in protein-coding genes, including well-defined areas of the noncoding regulatory regions (151). Specific classes of sRNAs seem more abundant at certain stages of development, e.g., 24-mers during ripening. The function of these changes in sRNA patterns is not known, but they may play an important role in the ripening process.

FRUITS AND THE HUMAN DIET

The human genome evolved in the context of the diet prevailing before the introduction of agriculture and animal husbandry approximately 10,000 years ago, when humans were hunter-gatherers; diets were rich in fruits, vegetables, and protein and low in fats and starches (33). For primates such as chimpanzees and orangutans, more than 75% of their diet by weight is fresh fruit, and the assumption is that our primate ancestors had similar diets. Fruit is also common in the diet of modern hunter-gatherers.

The 10,000 years (~360 generations) since the first cultivation of cereals has not been enough time for humans to adapt to starchier, cereal-based diets with much higher amounts of fat and lower amounts of fresh fruit and vegetables, and it has been suggested that many chronic diseases result from our evolutionary discordance with modern diets (21). Levels of phytounutrients—compounds in plant-based foods that play potentially beneficial roles in the prevention and treatment of disease—in the diet have dropped significantly owing to a reduced variety of plants consumed (currently, just 17 plant species constitute 90% of the global human diet) and to selective breeding (161). For these reasons, most modern dietary recommendations include increased consumption of fresh or whole fruits and vegetables. The role of plants in human health is the subject of another review (98), but what is beneficial about fruit consumption?

Fruits such as eggplant, mango, and okra are good sources of soluble fiber, which has been shown experimentally to lower the glycemic index of foods and to have beneficial effects on type 2 diabetes, cardiovascular disease, and obesity (66, 73, 79, 103). Fruits are also rich in fructose (which constitutes 20–40% of the available carbohydrates in wild fruit) and intrinsic sugars; these are not subject to restrictions in dietary recommendations because their concentrations are not high enough to have adverse health outcomes (94). Fruits generally also contain high levels of phytonutrients, and include carotenoids, polyphenols (flavonoids, stilbenes), plant sterols, vitamins, and polyunsaturated fatty acids.

Some fruits are rich in carotenoids, which are thought to attract animals as dispersers through their bright colors (for example, lycopene in tomato; capsanthin, β-carotene, lutein, and violaxanthin in red pepper; lycopene and β-carotene in red grapefruit; and β-carotene, α-carotene, and lutein in mangoes). Lycopene is a methyl-branched carotenoid that has no provitamin A activity. It is a potent lipophilic antioxidant, with greater antioxidant activity than other carotenoids, and has been shown to be protective against cardiovascular disease and prostate cancer (43). Intervention and epidemiological studies have linked β-carotene consumption to enhanced protection against cardiovascular disease, including cerebral infarction, and resistance to low-density lipoprotein oxidation, ischemic stroke, and carotid atherosclerosis (7, 43, 121).

Fruits are rich sources of polyphenols that have gained significant recognition recently as being important phytounutrients, reducing the risk of chronic diseases such as cardiovascular disease, metabolic syndrome, cancer, and...
obesity. Anthocyanins represent a subset of flavonoids with particularly high antioxidant capacity and strong health-promoting effects. As part of the human diet, they offer protection against cancer, inhibiting both the initiation and progression stages of tumor development (154), reducing inflammatory inducers of tumor initiation, suppressing angiogenesis, and minimizing cancer-induced DNA damage in animal disease models. Anthocyanins also protect against cardiovascular disease and age-related degenerative diseases associated with metabolic syndrome (63, 119), have anti-inflammatory activity (134), promote visual acuity (101), and hinder obesity and diabetes (154). Inverse correlations between consumption of flavonol-rich diets and the occurrence of cardiovascular disease, certain cancers, and age-related degenerative diseases (62, 75, 105, 130, 138) have been shown in human epidemiological studies as well as by data from cell-based assays and feeding trials with animals.

Another important group of plant-based bioactive polyphenols is the hydroxycinnamic acid esters, of which chlorogenic acid is the major soluble phenolic in solanaceous species such as potato, tomato, and eggplant as well as in coffee. Chlorogenic acid is one of the most abundant polyphenols in the human diet and is the major antioxidant in the average developed-world diet. It has significant antioxidant activity, and consumption can limit glucose absorption and possibly weight gain (146).

Epicatechins are the major polyphenolic compounds in green tea, and the most significant active component is thought to be epigallocatechin gallate. Cell, animal, and human studies have shown that green tea extract/epicatechins prevent cancer development, particularly prostate cancer (22, 31). Similar effects may be gained by consumption of fleshy fruits such as cranberry, blueberry, and grape or by consumption of berry-juice products; these have relatively high levels of catechins and epicatechins, which also protect against cardiovascular disease (27).

Dietary intervention studies support the view that consumption of fruit (especially when replacing calorie-dense food) helps maintain a healthy weight and reduce the risk of a wide range of cancers (150, 163) and cardiovascular disease (59, 60, 82). Consequently, dietary improvement by increasing fruit consumption or by improving fruit to contain higher levels of fiber or phytonutrients should have a positive impact on the incidence and progression of chronic disease. Such improvement of fruit crops could be carried out through genetic modification (11) or marker-assisted selection using existing variation.

**CROP IMPROVEMENT**

High-throughput sequencing technologies have provided a powerful new set of tools to reveal genetic and epigenetic variation on a genome-wide scale and therefore new insights into the evolution of genomes and trait variation. Fruit crop genomes that have been sequenced include grapevine (*Vitis vinifera*) (70), apple (*Malus × domestica*) (157), diploid strawberry (*Fragaria vesca*) (135), tomato (*Solanum lycopersicum*) (151), and banana (*Musa acuminata*) (28). These resources will underpin advances in the breeding of fruit crops by (a) greatly facilitating marker-assisted selection and allowing efficient cloning of genes underpinning quantitative trait loci, (b) providing the reference genomes for rapid allele mining in crop wild relatives (87), (c) providing a guide for direct sequencing of monogenic mutants, and (d) maximizing opportunities to optimize reverse-genetics tools such as targeting-induced local lesions in genomes (TILLING) for gene functional studies (142). Genome-wide information also allows rapid analyses of gene structure, binding-site motifs, and gene regulatory regions.

In the future, high-throughput sequencing technologies will allow routine screening of crop epigenomes and therefore permit detection of epigenetic variation that impacts phenotypes. Additionally, translational biology from models to crop species has clear utility in enhancing important crop traits; e.g., fine-tuning the expression of the value margin
identity gene \textit{IND} in \textit{Brassica} gives a potentially useful partial dehiscence phenotype (52). Harnessing variation in crop wild relatives in combination with direct genetic modification provides a powerful route for a massive step change in crop improvement.

**SUMMARY POINTS**

1. True fruits are found only in the angiosperms, or flowering plants. They are often defined as structures derived from a mature ovary containing seeds, but many structures we call fruit are composed of a variety of tissues. Fruit structures can be dehiscent or indehiscent, can have a dry or fleshy exterior, and include grains, nuts, capsules, and berries.

2. Recent work on the model plant \textit{Arabidopsis} and on tomato nonripening mutants has uncovered the complex high-level regulatory network controlling fruit maturation and ripening. Striking parallels have been revealed between the molecular circuits in dry fruits and those in fleshy fruits. In both types, similar MADS-box transcription factors play a central role, and in some cases they seem to be directly orthologous.

3. Tomato is a good model for understanding aspects of the molecular framework controlling ripening in other fleshy fruits. Classes of transcription factors controlling tomato ripening have been shown to govern this process in other fleshy-fruit-bearing species.

4. The human genome evolved in the context of the diet prevailing before the introduction of agriculture and animal husbandry approximately 10,000 years ago, when humans were hunter-gatherers; diets were rich in fruits, vegetables, and protein and low in fats and starches. Fruits provide vitamins, minerals, and phytochemicals that are essential for human health.

5. The genomes of a variety of fleshy-fruited species have been sequenced and provide guides for revealing previously hidden genetic and epigenetic variation that will open a new frontier for crop improvement.

**FUTURE ISSUES**

1. Can predictive models of the ripening regulatory network be generated for tomato and other fleshy- and dry-fruited species? And can major ripening processes—e.g., texture and color development—be separated to allow better control over the process?

2. Is it possible to modify regulatory networks to easily transition from a dry- to fleshy-fruit phenotype or vice versa?

3. One of the best-characterized natural epigenetic mutations was discovered in tomato. To what extent is epigenetic variation responsible for controlling important quality traits in crops and crop wild relatives?

**DISCLOSURE STATEMENT**

C.M. is a director of Norfolk Plant Sciences, an SME for the development of phytonutrient-enriched fruits and vegetables.
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