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Phytohormones in fruit development and maturation

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SUMMARY

Phytohormones are integral to the regulation of fruit development and maturation. This review expands upon current understanding of the relationship between hormone signaling and fruit development, emphasizing fleshy fruit and highlighting recent work in the model crop tomato (*Solanum lycopersicum*) and additional species. Fruit development comprises fruit set initiation, growth, and maturation and ripening. *Fruit set* transpires after fertilization and is associated with auxin and gibberellic acid (GA) signaling. Interaction between auxin and GAs, as well as other phytohormones, is mediated by auxin-responsive Aux/IAA and ARF proteins. *Fruit growth* consists of cell division and expansion, the former shown to be influenced by auxin signaling. While regulation of cell expansion is less thoroughly understood, evidence indicates synergistic regulation via both auxin and GAs, with input from additional hormones. *Fruit maturation*, a transitional phase that precipitates ripening, occurs when auxin and GA levels subside with a concurrent rise in abscisic acid (ABA) and ethylene. During *fruit ripening*, ethylene plays a clear role in climacteric fruits, whereas non-climacteric ripening is generally associated with ABA. Recent evidence indicates varying requirements for both hormones within both ripening physiologies, suggesting rebalancing and specification of roles for common regulators rather than reliance upon one. Numerous recent discoveries pertaining to the molecular basis of hormonal activity and crosstalk are discussed, while we also note that many questions remain such as the molecular basis of additional hormonal activities, the role of epigenome changes, and how prior discoveries translate to the plethora of angiosperm species.

Keywords: plant hormones, fruit set, fruit expansion, ripening.

INTRODUCTION TO FRUIT DEVELOPMENT AND PHYSIOLOGY

Fruit development is an elegant evolutionary strategy unique to angiosperms, serving the dual purpose of protecting developing seeds and facilitating their dispersal. Following double fertilization, fruits arise from growth and enlargement of the ovary and, occasionally, from accessory tissues in cases such as apple (*Malus domestica*) or strawberry (*Fragaria* × *ananassa*) (Obroucheva, 2014). A rich diversity of fruit morphologies, generally categorized as dry or fleshy, exists across species and within families, and recent evidence suggests that dry morphotypes like the siliques of *Arabidopsis thaliana* are ancestral to the softer, flavorful tissue exhibited by fruits typically cultivated in orchards (McAtee *et al.*, 2013; Kumar *et al.*, 2014; Pesaresi *et al.*, 2014). There are also examples of phylogenies where dry fruit types have emerged from fleshy-fruited ancestors (Pabón-Mora and Litt, 2011). A key distinction between dry versus fleshy fruit types is that, rather than ripening, dry fruits senesce and develop a lignified pericarp encapsulating their seeds that either remains fused shut (indehiscent phenotype) or mechanically shatters about an abscission zone (dehiscent phenotype) (Gómez *et al.*, 2014; Pesaresi *et al.*, 2014).

Whereas dry fruits rely on abiotic means to sow their seeds, fleshy fruits like tomato (*Solanum lycopersicum*) invest in myriad cellular modifications that collectively render them aromatic and palatable, enhancing their ability to attract frugivores. These changes include the accumulation of starch during early development, cell wall remodeling to facilitate softening, changes in color as chloroplasts are degraded or de-differentiated into chromoplasts, and the fine-tuning of starch hydrolysis and the tricarboxylic acid (TCA) cycle to increase sweetness and modulate tissue acidity. The presence or extent of such changes contributes to an impressive variety of forms and flavors among fleshy fruits that one can readily observe upon beholding a tomato (a berry), peach (*Prunus persica*) (a drupe), or strawberry (an aggregate fruit) (Gómez *et al*., 2014; Roch *et al*., 2019). Fleshy fruits are further classified as climacteric or non-climacteric, the former distinguished by a spike in respiration and acute sensitivity to increased ethylene (Biale., 1964; Pesaresi *et al*., 2014). Non-climacteric fruits are less reliant upon elevated ethylene for ripening, although numerous observations suggest that they may either be more sensitive to ethylene or simply display less extreme hormone production and responses (Paul *et al*., 2012).

Interestingly, in spite of their striking phenotypic differences, a significant degree of commonality has been observed in the regulation of cellular events mediating ripening and senescence between fleshy fruits and dry fruits, respectively. A transcriptomic analysis comparing Arabidopsis siliques and tomato berries revealed that both species experience similar biological processes and parallel programs of cytological change following fruit maturation, even though minimal overlap exists between either species in terms of the number of genes being expressed (Gómez *et al*., 2014). Dry and fleshy fruiting species both require phases of cell division and expansion after fruit set, which allows for fruit size determination prior to maturation and senescence/ripening. In an interesting case of functional characterization of homologous transcription factors, it was revealed that orthologous SHATTERPROOF MADS-box genes are necessary for replum development and shattering in Arabidopsis, as well as for fruit fleshiness and ripening in tomato (Vrebalov *et al*., 2009). Both of these processes are necessary for seed dispersal in dry and fleshy fruits, respectively.

The phases of cell growth and death experienced by fleshy and dry species alike are extensively regulated by transient concentrations of phytohormones. The importance of growth-promoting agents like auxins and gibberellic acids (GAs) has been demonstrated repeatedly, as exogenous applications of both phytohormones can induce the initiation of fruit set and development in the absence of fertilization (parthenocarpy) (McAtee *et al*., 2013; Kumar *et al*., 2014). Likewise, the presence of ethylene, which is centrally responsible for regulating ripening in tomato and other climacteric fruits, also induces responses in Arabidopsis siliques (Pesaresi *et al*., 2014). Given the critical role of fleshy fruit in the human diet and the need for a deeper understanding of fruit biology in the face of evolving pest populations and a changing climate, the content of this review aims to present and highlight recent insights and open questions relevant to phytohormone-mediated fruit set, growth, and ripening.

POLLINATION, FERTILIZATION, AND FRUIT SET

Following anthesis, pollination and fertilization are critical for determining fruit set before growth and ripening commence. Fruit set initiation is regulated across many species of dry and fleshy fruits by the combined accumulation of auxin and GA, with auxin being of primary importance (Gustafson, 1936; Wittwer *et al*., 1957; Srivastava and Handa, 2005). The influence of both phytohormones has been widely demonstrated in studies comparing both pollinated and parthenocarpic fruits, including cucumbers and watermelons (Li *et al*., 2014; Hu *et al*., 2019). For example, in watermelon, auxin and auxin-responsive genes show a rapid and early spike in expression during fruit set across both normally pollinated and parthenocarpic fruit, and an accumulation of GA increases notably around 1–3 days after pollination (DAP) (Hu *et al*., 2019).

Auxin biosynthesis within the seed is largely influenced by an abundance of YUCCA (YUC) flavin monooxygenases and enzymes within the TAR family, while bioactive GA production is dependent upon activities of GA 20 oxidases and GA 3 oxidases (GA20ox/GA3ox) expressed in ovary tissue (Sun, 2008; Zhao, 2014; Pattison *et al*., 2015). A key aspect of auxin's role in regulating fruit set is its ability to influence GA levels, as the release of auxin from within the ovule can induce GA accumulation in the ovary (McAtee *et al*., 2013; Kumar *et al*., 2014). Both YUC and GA20/3ox expression have been observed in strawberry achenes, for example, and Pattison *et al*. (2015) noted an overlap between transcript abundance for GA biosynthetic genes and sites with high auxin activity in young tomato fruit tissue. Application of 2,4-dichlorophenoxyacteic acid (2,4-D), a chemical mimic of auxin, can also stimulate the expression of GA20ox and GA3ox in pear (*Pyrus communis*) to increase GA biosynthesis and induce parthenocarpic fruiting (Cong *et al*., 2019).

The ability to accumulate and perceive auxin and GA directly impacts plant fertility and pollination, and the molecular mechanisms underlying sensitivity towards both phytohormones continues to be an area of active research. In tomato, microsporogenesis, the development of pollen grains, is influenced by controlled expression of SlGRAS24 (Huang *et al*., 2017). Transcription factors within the GRAS family regulate a range of developmental processes, and their functions have been investigated in multiple plant species (Cenci and Rouard, 2017; Huang *et al*., 2017; Shinozaki *et al*., 2018; Zhang *et al*., 2018a). Overexpression of SlGRAS24 results in the downregulation of key genes involved in auxin/GA-responses (i.e., *SlDELLA* and *GA20/3ox*) and impairs pollen sac development. *SlGRAS24* is a direct target of micro-RNA 171 (*miR171*), and transcript abundance for both genes has been observed in floral tissue.

These expression and overexpression results collectively suggest that SlGRAS24 is a transcriptional repressor of fruit set initiation until it is degraded prior to pollen maturity (Huang *et al*., 2017). Yan *et al*. (2019) also noted that the presence of a *KNOTTED-like* homeobox gene, *Tkn4*, is vital for modulating auxin/GA sensitivity in tomato seeds, as it is correlated with accelerated rates of pollen grain germination and fruit set, suggesting that *Tkn4* overexpression may induce higher rates of pollen grain germination and tube growth through modulation of phytohormone sensitivity and perception. These studies point to the multiple molecular means of regulating auxin/GA synthesis and sensitivities. Experimental confirmation of these regulatory systems and their prevalence through diverse taxa will be important areas to address in further defining the molecular regulation of auxin and GA in early fruit development.

Phytohormonal crosstalk during early fruit development

While auxin and GA do possess unique roles during fruit set, as well as during later cell division and expansion, it is clear that they co-regulate pollination and fertilization through crosstalk (Figure 1). Auxin–GA communication is facilitated via the action of Auxin/Indole-3-Acetic Acid (Aux/IAA) and auxin response factor (ARF) proteins, while products of the *auxin-responsive Gretchen Hagen3* (*GH3*) gene family function to maintain phytohormone homeostasis by conjugating free auxin molecules (Li *et al*., 2016a, 2016b; Luo *et al*., 2018). Aux/IAA elements such as IAA9 and the *ARF* gene family are integral to the regulation of fruit set (Wang *et al*., 2005), as well as a range of other vegetative and reproductive processes. Individual ARFs act as transcription factors with both distinct and overlapping properties, and they have been widely investigated in both Arabidopsis and tomato. Under conditions of high auxin, Aux/IAA proteins are ubiquitinated and kept at low levels as ARFs form homodimers via their C-termini and bind to AuxRE regions within the promoter sequences of target genes, thus either activating or repressing auxin-driven responses. Conversely, conditions of low auxin promote the binding of ARFs to Aux/IAA proteins, which recruit TOPLESS (TPL) co-repressors and suppress ARF activity (Li *et al*., 2016a, 2016b; Luo *et al*., 2018). Additionally, ARFs interact with other transcription factors and gene products, including the GA-signaling repressor DELLA. In tomato, SlARF7 has the capacity to dimerize with both SlIAA9 and SlDELLA through two different protein-binding regions, and both interactions prevent the transcription of growth-inducing genes prior to fertilization. Specifically, a SlARF7–SlIAA9 interaction prevents GA biosynthesis and auxin metabolism via inhibiting *GA20ox1*/*GA3ox1* and *GH3.2* expression, and both SlARF7–SlIAA9 and SlARF7–SlDELLA complexes prevent the transcriptional activation of genes that promote fruit set. Upon fertilization, however, auxin and GA are released by the ovule and respectively promote the ubiquitination and degradation of SlIAA9 and DELLA, thus freeing SlARF7 to upregulate auxin- and GA-related responses (Li *et al*., 2016a, 2016b; Hu *et al*., 2018). The capacity for ARFs to interact with a host of gene products is crucial for facilitating auxin–GA crosstalk. Furthermore, variation among the different Aux/IAAs and ARFs within a plant are key for enabling auxin and GA to co-regulate multiple processes underpinning fruit set. Both SlIAA9 and SlIAA27 share a high degree of sequence homology and mediate auxin sensitivity in tomato, for instance, but SlIAA27 is distinctly necessary for pollen and ovule fertility while SlIAA9 mediates the expression of genes promoting post-fertilization growth (Bassa *et al*., 2012; Hu *et al*., 2018).

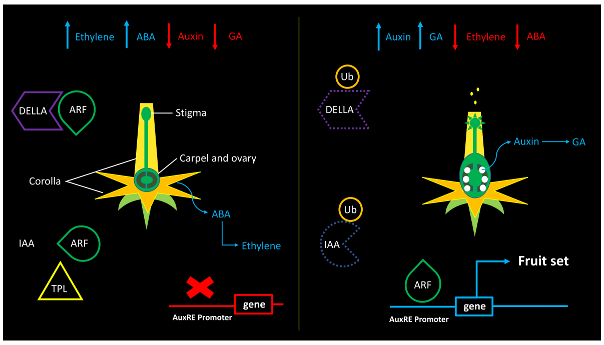

Figure 1. Summary of fleshy fruit set and the role of pollination in tomato. (a) Prior to pollination in tomato, fruit set is inhibited under conditions of low auxin and GA as ARFs binds to IAAs, which recruit TPL co-repressors to prevent ARFs from binding to the promoters of their target genes. ARF activity is also repressed through interactions with other proteins, such as DELLAs, while ethylene and ABA synthesis antagonizes auxin and GA levels to keep the ovary in a dormant state. (b) Upon pollination and fertilization, ethylene and ABA levels decrease in many tissues within the flower, allowing auxin and GA biosynthesis to increase. Higher levels of auxin and GAs promote ubiquitination and degradation of IAAs and DELLAs, which allow ARFs to bind to target gene promoters and stimulate fruit set initiation.

Ethylene and abscisic acid (ABA) also demonstrate the capacity to influence pollination and fertilization through crosstalk with auxin and GA, as well as with one another. A transient burst in ethylene occurs in tomato ovaries upon pollination, as *ACS* and *ACO* genes are upregulated to facilitate senescence of some floral tissues, but this spike declines within 12 h after pollination as ethylene emissions decrease and fruit set progresses (Llop-Tous *et al*., 2000; Pattison *et al*., 2015). During pollination in tomato flowers, communication between ethylene and auxin regulates pollen grain germination and tube growth, as ethylene precursor metabolites and the expression of ethylene biosynthesis and response genes (*ACC synthase* and *ETR* ethylene receptors, respectively) increase in pollen grains prior to anthesis (Kovaleva *et al*., 2017; An *et al*., 2020). Indeed, the function of ethylene receptors as negative regulators of ethylene responses is consistent with reduced ethylene responses in the presence of elevated receptor proteins. Auxin accumulates in both the stigma and the pollen tube tip after pollination, while ethylene emissions (also rising within the stigma) accelerate the degeneration of the transmission tissues that lead to the ovary- redistributing nutrients to surrounding tissues within the pistil and providing a low-resistance path for the pollen tube. Additionally, ethylene plays a role in ensuring that only a single pollen tube deposits two sperm cells in the ovary, as activation of *EIN1* and *EIN2* genes within the ethylene signaling pathway induces the death of the second synergid cell and ceases any attractive signals for a second pollen tube (An *et al.*, 2020). Ethylene emissions also antagonize GA biosynthesis, as ethylene suppresses SlGA20ox and stabilizes DELLA proteins. Conversely, blocking ethylene perception allows for GA accumulation to spike and proceed to induce parthenocarpy (Kumar *et al.*, 2014; Shinozaki *et al.*, 2015). In unpollinated watermelon flowers, it was observed that strong ethylene and ABA biosynthesis correlated with a higher expression of DELLA proteins and IAA9, thus suppressing GA and auxin levels to keep the ovary in a protected, dormant state prior to fertilization (Hu *et al.*, 2019). Following fertilization in many fleshy fruits, including tomato, however, auxin has been shown to negatively regulate ethylene (Shinozaki *et al.*, 2015). Indeed, although elements of the ethylene signaling pathway, such as ETHYLENE RESPONSE FACTORS (ERFs), briefly increase upon fertilization, ethylene- and ABA-associated genes are repressed in concert with fruit set (Figure 1) (Kumar *et al.*, 2014). Interestingly, ethylene and ABA signals interact with each other before and during pollination. A rise in ABA biosynthesis via expression of *NCED1* precedes a concurrent increase in ACS expression such that both phytohormones are upregulated in fig flowers prior to pollination (Chai *et al.*, 2017). ABA and ethylene also co-regulate water transport in pollen tubes during the growth phase of the microgametophyte in petunia (*Petunia hybrida*) (Kovaleva *et al.*, 2017).

Regulation via cytokinins, brassinosteroids, and jasmonic acid

Additional phytohormones such as cytokinins (CKs), brassinosteroids (BRs), and jasmonic acid (JA) have demonstrated the capacity to influence fertilization and fruit initiation in some angiosperms. Both CKs and BRs generally increase after fertilization, and there is evidence in Japanese persimmon that exogenous application of BRs can significantly increase fruit set (McAtee *et al.*, 2013; Kumar *et al.*, 2014; Baghel *et al.*, 2019). CKs also proved to be functional in concert with auxin and GA during fruit set initiation in both pollinated and parthenocarpic cucumber (*Cucumis sativus*) (Li *et al.*, 2014). Furthermore, within the transcriptome of set fruits, Li *et al.* (2014) noted a significant overlap between genes responsive to auxin and those responsive to BRs, suggesting that the latter might also be influential in coordinating fruit set in cucumber. In tomato, evidence suggests that perception of JA is necessary for *SlMYB21* transcription, which is involved in micro- and megagametophyte development prior to fertilization. Indeed, mutant plants unable to respond to JA, or with attenuated *SlMYB21* expression, experienced abnormal pollen development and pistils that were not conducive to pollen tube growth (Niwa *et al.*, 2018). In short, molecular data from an array of species suggest that, while auxin and GA are central to the regulation of fruit set in coordination with ethylene and ABA, additional hormones likely contribute to the fidelity of the fruit set response and may play greater or lesser roles across different species. Elucidating the precise roles of CKs, BRs, and JA, as well as the molecular basis of their interactions with each other and established fruit set hormones, will lead to a clearer picture of fruit set control.

FRUIT GROWTH (CELL DIVISION AND EXPANSION)

Fruit growth in tomato and many other species commences after fruit set and ceases prior to fruit maturation, although certain species such as grape (*Vitis vinifera*) initiate maturation before growth has fully ceased. Growth of the fruit organ can be divided into discrete phases of cell division and cell expansion. Following pollination, tomato, grape, and strawberry initiate early cell division: a phase that can endure from a few days to more than a week. Following cell division, later fruit growth is primarily due to cell expansion. Arabidopsis siliques similarly display an early phase of cell division, although this is followed by a period of combined cell division and expansion. Apple is characterized by an initial combination of cell division and expansion, with cell division subsiding to allow for a subsequent phase of predominant cell expansion. In tomato, a model fleshy fruit in which growth is well studied, regulation of cell division and expansion is similar to that of fruit initiation in that auxin and GA are the primary regulatory phytohormones. While continued research is needed to better understand areas of differential regulation between the cell proliferation versus enlargement phases, cell division generally relies on auxin synthesized from within the seed while expansion is mediated by a combination of auxin and GA from both the seed and placental tissues (Crane, 1964; Ozga *et al.*, 1992; Pattison and Catalá, 2012).

The importance of auxin and GA during fruit growth has been established across multiple plant species: a rise in auxin levels following fruit set results in higher rates of cell division in young cucumber fruit (Li *et al.*, 2014), and auxin has been found to be the primary hormone affecting fruit size in apple (Devoghalaere *et al.*, 2012). Furthermore, a number of genes encoding components of auxin signaling were differentially expressed 8 DAP between two lines of maize (*Zea mays*) with different kernel sizes. Large kernels contained significantly higher levels of auxin and were more enriched in genes involved in kernel development, suggesting that maize plants producing larger kernels might have experienced longer phases of cell proliferation (Ma *et al.*, 2019). Increases in auxin similarly stimulate cell division in GA-deficient tomato (*gib-3* mutant lines) during early growth while applications of GA to auxin-insensitive plants (*dgt* mutant lines) have a minimal effect on cell division, which supports the notion that auxin is mainly necessary for the early cell proliferation phase (Liu *et al.*, 2016). With respect to GA, *GA3ox* is expressed during silique development in Arabidopsis in the replum, funiculus, and receptacle (Hussain *et al.*, 2020), and three distinct GA receptor genes (*CaGID1b.1*, *CaGID1b.2*, *CaGID1c*) are expressed in sweet pepper during fruit development for the purpose of binding to CaGAI (a DELLA protein) in the presence of GA (Ya-Cong *et al.*, 2016).

Cell division

Auxin signaling and auxin–GA interaction are key elements influencing fruit growth, and these pathways rely on Aux/IAA, ARF, and GH3 activities. GH3.1 expression is elevated during cell division in apples to maintain free auxin levels, and MdARF106 is among a number of *Malus* ARFs predominant in fruit development (Devoghalaere *et al.*, 2012). While different ARFs participate in distinct phases of growth, Liu *et al.* (2016) observed that a group of four auxin-/GA-responsive ARFs (SlARF6, 8, 10, and 16) act redundantly to restrict cell division in tomato pericarp during early growth after fruit set. Upon auxin accumulation, however, transcripts from all four *ARF* genes are targeted by *miR160* and *miR167* for repression, thus promoting early pericarp cell division. Conversely, GA application to auxin-insensitive tomatoes promotes expression of ARFs 6, 8, 10, and 16, which, given the role of GA in promoting expansion, could suggest that a combination of GA accumulation and elevated ARF expression favors cell expansion over division during later development (Liu *et al.*, 2016). ARFs 10 and 16 also display responsiveness to *miR160* and *miR167* in peach, although treatment with synthetic auxin downregulated micro-RNA transcription and resulted in elevated *ARF* expression (Shi *et al.*, 2017). In tomato, SlARF9 also negatively regulates cell division, as transgenic plants with elevated *SlARF9* mRNA levels experience lower rates of cell division and bear smaller fruits relative to wild-type plants and *SlARF9* repression lines (De Jong *et al.*, 2015). Furthermore, repression or silencing of *SlARF7* induces the accumulation of both auxin and GA, which promotes premature cell expansion and inhibits cell division (Kumar *et al.*, 2014). The presence of redundant ARFs with roles in restricting cell division and facilitating the transition to cell expansion is consistent with the developmental program of tomato, where division and expansion are tightly segregated. Apparent differences between fruit growth in tomato and peach, in conjunction with variation in how different fruits regulate cell division and expansion, underscores the potential of a system comprised of GA, ARFs, and associated miRNAs as a research target to better understand the unique fruit expansion profiles of diverse and important species.

Beyond ARFs, which act as key upstream regulators during auxin signaling, another area of focus is the characterization of downstream auxin-responsive genes affecting cell division. Among these are genes encoding ATP-binding cassette transporters (ABCBs), members of the GRAS family, and proteins that function in the histone de-acetylase (HDAC) machinery (Huang *et al.*, 2017; Ofori *et al.*, 2018; Zhang *et al.*, 2020b). It is possible that ABCBs function during early fruit growth in tomato to transport and distribute auxin during cell proliferation, as cell division in tomato occurs within 1–2 weeks of pollination, depending on the genotype, and it was observed that expression of *SlABCB4* peaks around 14 DAP. Co-immunoprecipitation assays have also revealed that ABCBs can directly interact with PIN proteins (auxin transporters) in Arabidopsis, so it is plausible that a similar interaction takes place in tomato via SlABCB4 (Ofori *et al.*, 2018). Proteins within the GRAS family appear to have an opposite effect on auxin and GA responses, however, as overexpression of SlGRAS24 not only impairs pollen grain germination and tube growth, but it also suppresses cell division and expansion in tomato fruits (Huang *et al.*, 2017).

Finally, recent evidence suggests the involvement of epigenome modifications in hormonal regulation of fruit growth. The *SF2* locus encodes a homolog of AtHDC1 in cucumber that functions as an important component of the HDAC complex, and its expression is highest in meristematic tissues that experience elevated rates of cell division. SF2 specifically targets and represses genes that suppress responses to auxin, GA, and CK signaling, and cell division rates were significantly decreased in *sf2* mutants (Zhang *et al.*, 2020b). These recent observations regarding the intersection of hormonal pathways and epigenome modifications in the regulation of fruit cell division and growth present an exciting opportunity to peel back an additional layer of regulatory control in this process.

Cell expansion

During the onset of tomato fruit cell expansion, rising auxin and GA levels from the seed promote *GA3ox* and *GA20ox* expression within fruit tissues to increase cellular concentrations of bioactive GA (McAtee *et al.*, 2013; Kumar *et al.*, 2014). The ability of auxin to stimulate GA biosynthesis has been demonstrated in pear, where exogenous application of 2,4-D (a synthetic auxin mimic) can stimulate expression of *GA20ox* and *GA3ox*, increase the accumulation of bioactive GA in fruit tissue, and upregulate both cell division and expansion (Cong *et al.*, 2019). Following its increase and release, GA promotes cell expansion synergistically with auxin in a range of fleshy fruits such as plum (*Prunus* subg. *Prunus*) and wild strawberry (*Fragaria vesca*). During the course of fruit development, plums regulate the expression of three DELLA-like repressors (PslGAI, PslRGL, and PslRGA) to control the timing of GA signaling. The expression of both PslRGA and PslRGL are highest at peak fruit cell division, suggesting that GA levels are kept relatively low during this time. During the phase of fruit growth when cell expansion is highest, however, expression of all three DELLAs is low, consistent with involvement of GA (El-Sharkawy *et al*., 2017). In wild strawberry, a similar DELLA-like repressor (FaRGA) in receptacle cells decreases from the green to the white stage, coinciding with a transition from cell division to expansion and elevated GA biosynthesis (Csukasi *et al*., 2011). Liao *et al*. (2018) also observed that auxin uniquely controls cell division, as well as fruit length and width of wild strawberry. Upon auxin-mediated upregulation of GA, however, both auxin and GA co-regulate fruit size by promoting both cell elongation and expansion. Interestingly, auxin and GA also appear to mediate the duration of fruit development versus ripening through crosstalk with ABA, the primary ripening hormone in strawberry. Both auxin and GA impact the expression of NCED (ABA biosynthesis) and CYP (ABA degradation), and elevated auxin and GA during development upregulate FveCYP707A4a to promote ABA degradation. During the onset of ripening, however, reduced levels of auxin and GA allow ABA accumulation to increase and auto-catalyze its own biosynthesis through upregulation of FveNCED (Liao *et al*., 2018). While full characterization of responsive genes downstream of auxin–GA signaling remains ongoing, target genes of auxin and GA include cell wall-modifying enzymes such as expansins and pectate lyases (McAtee *et al*., 2013; Kumar *et al*., 2014). The variation observed among different species in terms of how cell division and expansion contribute to fruit growth thus highlights the need to characterize the molecular basis of auxin and GA responses within model plants of unique expansion profiles to more fully appreciate hormonal regulation of fruit growth.

Fruit growth and cytokinins, brassinosteroids, and jasmonic acid

In addition to auxin and GA, input from CKs and BRs can also influence cell division and expansion, although the magnitude of effect varies among different angiosperm species. Endogenous levels of CKs can increase proportionally with fruit growth in certain species, and exogenous applications of BRs (in tandem with GA) increase rates of cell division and expansion in grape berries (Kumar *et al*., 2014; Baghel *et al*., 2019). CKs supersede auxin as the primary phytohormone affecting fruit growth in kiwifruit (*Actinidia deliciosa*), as is suggested by Nardozza *et al*. (2020), who subjected kiwifruit to conditions of carbon starvation. Low carbon levels directly impacted fruit size, resulting in smaller fruits with attenuated expression of CK biosynthetic enzymes like isopentenyltransferases (IPTs) and CYP735As. The transcription levels of expansins were also lower in fruits with reduced CK accumulation, consistent with CKs contributing to cell enlargement in kiwis through regulation of cell wall-modifying enzymes (Nardozza *et al*., 2020). It has been suggested that CKs engage in crosstalk with auxin or GA during fruit development, as might be the case in bottle gourd where differentially expressed genes between long and short fruit cultivars include both auxin-responsive genes and genes related to CK biosynthesis and metabolism. Specifically, CK dehydrogenase (CKX), which catabolizes CK, was observed to be specifically downregulated in short fruits, suggesting that CK can function alongside (or in place of) auxin and GA in establishing fleshy fruit size (Zhang *et al*., 2020a, 2020b). It has also been shown that CKs directly regulate dry fruit size in plants such as Arabidopsis. During fruit development, CKs bind to histidine kinases (HKs), which donate phosphate groups to downstream response elements via the action of AHPs. Consequently, a mutation reducing AHP activity results in CK insensitivity and smaller siliques, while attenuated CKX expression leads to increased CK and larger siliques (Hussain *et al*., 2020). In Arabidopsis, as well as in strawberry, BRs function alongside other phytohormones in controlling fruit size. Mutations in multiple enzymes within the BR biosynthetic pathway in Arabidopsis lead to shorter siliques (Hussain *et al*., 2020) while downregulation of BR receptors in strawberries reduces cell division (Baghel *et al*., 2019).

JA and ethylene additionally contribute to fruit growth. JA accumulation is initially high in strawberry flowers and mirrors the concentration profiles of auxin and GA such that it decreases at the end of development as ABA levels begin to increase. As it was observed that exogenous application of JA reduced levels of ABA via downregulation of FaNCED1, it is possible that JA acts antagonistically towards ABA in non-climacteric strawberry (Garrido-Bigotes *et al*., 2018). During late fruit development and maturation in bottle gourd, several ERFs were upregulated in plant cultivars that produced long fruit (Zhang *et al*., 2020a, 2020b). Reduced ethylene levels during fruit development in Arabidopsis also results in smaller siliques with fewer seeds (Hussain *et al*., 2020). As is the case within fruit set, multiple observations indicate roles for CKs, BRs, and JA in fruit growth, and likely in ways that vary among species and growing conditions. Further study of CKs, BRs, and JA present opportunities for additional inquiry toward a more complete understanding of hormonal regulation of fruit growth.

RIPENING

The transition from growth to maturation is characterized by (often discrete) shifts in phytohormone profiles in order to fully cease fruit expansion and promote fruit senescence and ripening in dry fruits and fleshy fruits, respectively (Forlani *et al*., 2019). As elevated levels of auxin, GA, and CK delay ripening, biosynthesis of each phytohormone generally decreases in concert with the transition to fruit maturation (McAtee *et al*., 2013; Kumar *et al*., 2014). This has been demonstrated in grapes, where berries exposed to exogenous applications of CK and GA at veraison grow larger fruits and accumulate lower amounts of hexose sugars during ripening. In treated berries, downregulation of ABA and ethylene biosynthesis was directly correlated with reduced color changes and prolonged greenness in the fruit pericarp, whereas ABA and ethylene signaling were unsuppressed in control fruits that exhibited unperturbed ripening (Suehiro *et al*., 2019).

Ripening in climacteric versus non-climacteric fruits

While ABA and ethylene are the primary phytohormones involved in ripening of many fleshy fruits, their regulatory roles differ significantly between well-studied climacteric and non-climacteric fruits. In non-climacteric fruits like sweet cherry (*Prunus avium*), strawberry, and grape, 9-*cis*-epoxycarotenoid dioxygenase (NCED) (Xiong and Zhu, 2003) catalyzes ABA biosynthesis, which influences subsequent, though often limited, ethylene production. ABA is generally acknowledged as the main regulatory phytohormone during ripening of such fruits (Leng *et al*., 2014; Iqbal *et al*., 2017). This has been especially well studied in strawberry, where ABA levels are low during early ripening as biosynthetic enzymes are suppressed and the activity of ABA-degrading enzymes (CYP and UGT) is relatively high. As ripening proceeds, ABA levels progressively increase as FvNCED1 and FvABA2 are upregulated, and its accumulation peaks at the 'fully red' stage (Kim *et al*., 2019). Through the course of ripening in such crops, ABA is directly associated with decreased fruit acidity, changes in pericarp color (mainly via anthocyanin production), increased vacuolar hexose concentrations, and cell wall modifications contributing to fruit softening (Forlani *et al*., 2019).

In climacteric fruits such as tomato and banana (*Musa* spp.), ripening occurs in association with a rapid spike in ethylene biosynthesis, catalyzed via the actions of the genes *ACC synthase* (*ACS*) and *ACC oxidase* (*ACO*). Both genes encode the terminal enzymes of the ethylene biosynthetic pathway and are upregulated in addition to SAM synthetase (SAMS), which yields the ethylene pathway precursor SAM (Kumar *et al*., 2014; Palma *et al*., 2019). During the onset of ripening, climacteric fruits experience an auto-inhibitory phase (i.e., 'system 1' ethylene) characterized by basal levels of ethylene accumulation and reduced ethylene sensitivity of the ripening response (Kumar *et al*., 2014). Subsequentially, a rapid increase in ethylene emissions transpires during the initiation of an -catalytic phase (i.e., 'system 2' ripening), where the fruit experiences high sensitivity to ethylene and a positive feedback loop that fuels increased ethylene biosynthesis. The shift from system 1 to system 2 ethylene is a developmental transition providing a reservoir of insights to ripening regulatory molecular events (Klee and Giovannoni, 2011; Giovannoni *et al*., 2017), one of which involves the downregulation of auxin transport via RIN and Sl-SAUR69 to allow for high ethylene sensitivity characteristics of system 2 (Shin *et al*., 2019). Unsurprisingly, as ethylene emissions increase sharply during the transition from system 1 to system 2, the expression profiles of ethylene biosynthetic, signaling, and responsive genes also change in concert with numerous downstream genes (Carrari and Fernie, 2006; Zouine *et al*., 2017; Shinozaki *et al*., 2018). For example, in nectarine (*Prunus persica* var. *nucipersica*), *PpACS5* expression is downregulated at the end of fruit maturation and supplanted by heightened activity of *PpACS1* and *PpACS4* during system 2 (Zeng *et al*., 2015), while a shift from *ACS1* to *ACS2* and *ACS4* has been observed in tomato and other fruits (El-Sharkawy *et al*., 2008; Forlani *et al*., 2019). Interestingly, as ABA biosynthesis begins prior to ethylene release in both climacteric and non-climacteric fruits and exogenous applications of ABA can stimulate ethylene emissions, it is possible that such changes in ACS expression are mediated in part by ABA in species presenting both ripening physiologies (McAtee *et al*., 2013; Kumar *et al*., 2014; Leng *et al*., 2014).

Considerable crosstalk occurs between ethylene and auxin signaling systems, as well as between ABA and auxin during ripening. In both tomato and peach, auxin and ethylene increase in proportion to one another, and auxin has been shown to induce ethylene biosynthesis via upregulation of both *ACS* and *ACO* genes (McAtee *et al*., 2013; Kumar *et al*., 2014; Iqbal *et al*., 2017). In papaya, *CpIAA27* is upregulated during ripening, and a number of *CpIAA* family genes are differentially expressed upon application of either ACC or ethylene inhibitors (Liu *et al*., 2017). ABA and auxin, however, appear to have an antagonistic, neutralizing effect: a combination of ABA and auxin applied to mature green bananas did not induce changes in genes associated with chlorophyll degradation, carotenoid metabolism, or cell wall modifications (Lu *et al*., 2018). These results collectively suggest that ethylene and ABA co-regulate auxin levels during ripening.

Regulation via ethylene response factors (ERFs)

Numerous transcription factors have been shown to influence ripening, including many that have direct effects on ripening and ethylene synthesis upon being altered through a mutation or transgenic intervention (e.g., repression, overexpression, or gene editing). Reviews on this aspect of ripening control are numerous and informative from the overall standpoint of ripening, as well as from the perspective of new gene editing technologies that offer deeper insight and raise new questions regarding how the transcriptional control of specific regulators influences ripening (see Giovannoni *et al.*, 2017; Li *et al.*, 2019; Wang *et al.*, 2019; Wang *et al.*, 2020 and references therein). We focus here on regulators specific to the ethylene signal transduction pathway.

Given the importance of ethylene during ripening, transcription factors from the *APETALA2/ethylene response factor* (*AP2/ERF*) superfamily have proven instrumental for the regulation of ethylene-responsive genes. *ERF*s are responsive to both ethylene and to ABA, and they function by binding to the GCC-box regions of target genes in order to modulate downstream ethylene responses (Gao *et al.*, 2020). Similar to the diversity observed among *ARF*s, an impressive number of *ERF*s is expressed within and across fruits: over 70 different *ERF*s are encoded within the tomato genome, for instance, and *ERF*s can coordinate such processes as pigment accumulation, fruit softening, and fruit flavor/aroma in both climacteric and non-climacteric fruits (Phukan *et al.*, 2017; Forlani *et al.*, 2019; Gao *et al.*, 2020). In peach, multiple genes encoding AP2/ERFs were differentially expressed between 'melting flesh' and 'stony hard' cultivars. In melting flesh peaches, expression of multiple *AP2/ERF* genes coincides with a spike in ethylene emissions during late ripening, while one *ERF* gene was notably upregulated during the same stage in the stony hard cultivar (Wang *et al.*, 2017b). Furthermore, these results reveal that ERFs have the capacity for both positive and negative regulation. In fact, certain ERFs function to downregulate ethylene emissions via negative feedback. In apple, expression of MdERF2 is suppressed in conditions of high ethylene, and downregulation of this ERF allows for heightened ethylene emissions and accelerated ripening. A similar observation for an AP2/ERF was made in tomato (Chung *et al.*, 2010). When MdERF2 is upregulated, ethylene biosynthesis is inhibited due to MdERF2's ability to target the promoter of *MdACS1* and prevent its transcription. Additionally, MdERF2 has the capacity to directly bind to MdERF3, a positive transcription factor for *MdACS1* (Li *et al.*, 2016b). Similarly, in banana, *MaERF11* has the capacity to repress ripening through binding either to the promoter of a target gene or by directly interacting with a positive regulator. During early ripening, MaERF11 binds to MaHDA1 via an 'EAR' motif and suppresses ethylene emissions and fruit softening through preventing the acetylation of MaACO1 and MaEXP2, 7, and 8. MaERF11 is also able to bind to the promoters of these genes. As ethylene levels rise, however, accumulation of MaERF11 is inhibited and thus allows for the expression of genes that promote autocatalytic ethylene emissions and additional ripening processes, including cell wall loosening (Han *et al.*, 2016).

Brassinosteroids, NO, and calcium

Beyond ethylene and ABA, input from phytohormones, including BRs, is also important in facilitating the effects of ripening. BRs have the capacity to promote ripening, as exogenous application of BRs can upregulate ACS and ACO activity to increase ethylene biosynthesis. In strawberry, expression of FaBRI1 (a BR receptor) increases markedly from the white stage to the early red stage (Chai *et al.*, 2013). In tomato, transgenic plants expressing a BR biosynthetic gene from cotton (*Gossypium hirsutum*) (*GhDW4*) experience accelerated ripening and accumulate higher levels of soluble sugars and Vitamin C in their fruit tissue. *GhDW4* bears a high degree of homology to tomato *SlCYP90B3*, whose expression begins during fruit maturity and increases throughout ripening (Shu-e *et al.*, 2015) and presents an interesting candidate for functional studies to better define the role of BRs in ripening.

Fruit ripening is also affected by the presence of nitric oxide (NO) and secondary messengers such as calcium ions. In banana, application of ethylene upregulates expression of a calcium-dependent protein kinase, MaCDPK7. The induction of MaCDPK7 not only precedes induction of ACS/ACO and a subsequent increase in respiration typical of climacteric ripening, but blockage of calcium ion signaling also suppresses ripening through inhibition of MaCDPK7, MaACS, and MaACO (Wang *et al.*, 2017a, 2017b). Conversely, NO (in high amounts) acts antagonistically towards ripening. *Short root* (*shr*) tomato mutants overproducing NO experience delayed ripening, and NO has further been demonstrated to suppresses ethylene biosynthesis in strawberry, apple, and peach through nitrosylation and inactivation of SAMS (Palma *et al.*, 2019). The overabundance of NO in *shr* mutants specifically represses ABA accumulation, which, as noted previously and below, is emerging as an important regulator of climacteric ethylene (McAtee *et al.*, 2013; Kumar *et al.*, 2014; Leng *et al.*, 2014; Bodanapu *et al.*, 2016).

Ripening phenotypes influenced by phytohormones

Changes in fruit color occur as chlorophyll molecules are degraded with a concomitant increase in the biosynthesis of pigment compounds, including anthocyanins and carotenoids. The effects of ethylene and ABA on fruit color vary widely between plant species. For example, ethylene promotes carotenoid biosynthesis via upregulation of *PSY1* in tomato, whereas lower levels of ABA via the silencing of *SlNCED1* result in overpigmentation and higher levels of lycopene and beta-carotene in berries (McAtee *et al.*, 2013; Kumar *et al.*, 2014; Leng *et al.*, 2014). In tomato, downregulation of *SlNCED1* also results in higher ethylene levels, and ethylene induces the activity of the MADS-box transcription factors RIN, TAGL1, FUL1, and FUL2, which bind to the promoters of *ACS*, *ACO*, and a number of additional

*ETR*s in order to drive flux through the carotenoid pathway (Liu *et al.*, 2015; An *et al.*, 2018; Li *et al.,* 2019; McQuinn *et al.*, 2020). The role of ethylene in apple coloration varies by genotype and likely through activation of *MYB* gene expression, while additional evidence indicates that ABA upregulates neoxanthin synthase (VmNSY) and anthocyanidin synthase (VmANS) to increase anthocyanin accumulation in bilberry (*Vaccinium myrtillus*) (Whale *et al.*, 2004; Leng *et al.*, 2014; An *et al.*, 2018). CKs and JA can also influence fruit color. In tomato, downregulation of SlIPT4, which catalyzes CK biosynthesis, results in orange fruits that do not accumulate lycopene. Consequently, expression of the gene encoding ZISO, an isomerase in the carotenoid biosynthetic pathway, decreases in *SlIPT4*-RNAi lines while *SlPSY1* transcripts increase, indicating CK interaction with ethylene signaling (Zhang *et al.*, 2018a, 2018b). Methyl jasmonate has also been observed to increase during ripening in apple, pear, and mango (*Mangifera indica*) (Kumar *et al.*, 2014), and JA appears to specifically promote lycopene biosynthesis in tomato (Liu *et al.*, 2015).

Fruit softening is achieved through the actions of cell wall-modifying enzymes, the expression patterns of which occur in a species-specific manner. For example, ethylene induces methylesterase, polygalacturonase, and pectate lyase to catalyze pectin depolymerization in tomato and kiwifruit (Iqbal *et al.*, 2017; Wang *et al.*, 2019. Expansins and beta-galactosidases also accumulate in maturing tomato, whereas endo-polygalacturonase functions specifically in 'melting flesh' but not 'stony hard' peaches to allow softening (Forlani *et al.*, 2019). As is the case with fruit color, the effects of ethylene and ABA (or a combination of the two) also vary between different species. In banana, ethylene and ABA synergistically stimulate softening, whereas the presence of ABA during cell wall modification in tomato actually leads to increased fruit firmness (McAtee *et al.*, 2013; Kumar *et al.*, 2014).

The dual qualities of sweetness and tartness unique to many fruits arise from changes in the accumulation of acids and free soluble sugars. The presence of ABA is correlated with the accumulation of sugars in grape berries and the uptake of hexoses within the vacuoles of apples, and overexpression of an ABA-binding element in tomato (*SlAREB1*) favorably impacts organoleptic quality in ripe fruit (Kumar *et al.*, 2014; Leng *et al.*, 2014). Overexpression of *SlAREB1* specifically leads to higher levels of citric, malic, and glutamic acid in immature green, mature green, and red ripe berries. Vacuolar glucose and fructose levels were also higher in overexpression lines via the upregulation of a sucrose synthase and a vacuolar invertase (Bastías *et al.*, 2011; Bastías *et al.*, 2014).

It is likely that changes in sugar levels and acidity occur concurrently, as starch hydrolysis and carbon metabolism via the TCA cycle are tightly coupled. Furthermore, both processes are heavily modified during ripening, as sink strength for carbon skeletons increases. Considering this network, it is likely that ethylene, ABA, and even auxin are each of some influence during ripening-driven modification of starch breakdown and organic acid metabolism. Strong correlations indeed exist between ripening-related transcripts and changes in flux through the TCA cycle. For example, suppression of *NCED* is linked to a parallel downregulation of genes that induce changes in the TCA cycle, and rising ethylene emissions mirror increases in citrate, malate, and hexoses in peach (Batista-Silva *et al.*, 2018). Prior to ripening, auxin plays an important role during fruit development in influencing fruit acidity and sugar accumulation. Reduced expression of *SlARF4* in tomato impacts auxin signaling pre-maturation and results in young fruits with increased chlorophyll per plastid and higher levels of starch in pericarp tissue. Increased chlorophyll in plastids endows affected fruits with increased photosynthetic capacities, which allows them to accumulate more starch for later hydrolysis and attain higher levels of soluble solids. SlARF4, which is expressed in the pericarp during fruit development roughly 25 DAP and normally decreases during the onset of ripening, also represses the actions of SlAGPase (a starch biosynthetic enzyme) (Sagar *et al.*, 2013). In addition, auxin activity during ripening can downregulate enzymes involved in TCA cycle modification, lowering fruit respiration rates and, in some cases, increasing acidity through promoting succinate, malate, and citrate accumulation (Batista-Silva *et al.*, 2018).

The ability of a fruit to emit alluring scents and attract beneficial frugivores is rooted in the specialized metabolism that occurs during ripening to modify flavor and aroma. Like the control of sugar levels and acidity, knowledge in the area of aroma and flavor regulation is limited, but it is established that ABA, ethylene, JA, and salicylic acid (SA) can affect this aspect of ripening. Ethylene emissions influence alcohol dehydrogenase activity in melon (*Cucumis melo*), and attenuated ethylene biosynthesis and release have been shown to decrease emissions of volatile organic compounds in apple and melon, reducing fruit aroma (Ayub *et al.*, 1996; Kumar *et al.*, 2014; Iqbal *et al.*, 2017). ABA also affects flavonoid biosynthesis in blueberry (*Vaccinium* spp.) while, in tomato, JA influences polyamine levels and SlSAMT catalyzes the biosynthesis of SA into methyl salicylate to enhance the taste of ripe fruit (Tieman *et al.*, 2010; Kumar *et al.*, 2014). An exciting and currently expanding area of inquiry pertains to the genetic understanding of the accumulation of flavor and aroma volatiles (Tieman *et al.*, 2017; Gao *et al.*, 2019a, 2019b; Li *et al.*, 2020a, 2020b) and, while plant hormones likely play a role in their production, this is an area open to further exploration.

CONCLUSION AND FURTHER

A deeper understanding of fruit physiology is necessary in order to maintain food and nutritional security in the

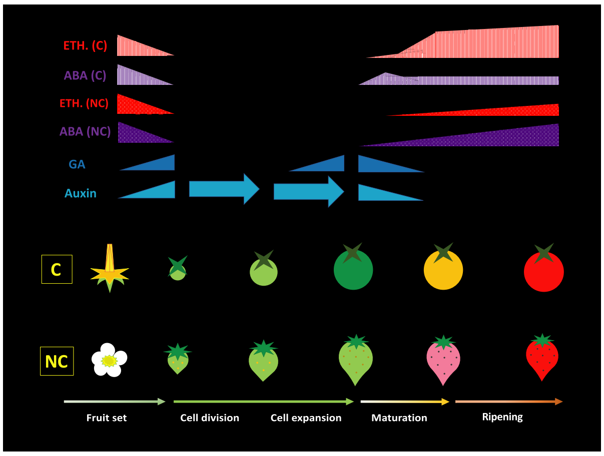

Figure 2. Fruit set and growth (cell division and expansion) are regulated similarly by auxin and GA signaling across different species of fleshy fruit. Maturation and ripening in tomato, a climacteric (C) fleshy fruit, are primarily regulated by a spike in ethylene emissions (system 2 ethylene) that occurs after low ethylene emissions and sensitivity during maturation (system 1 ethylene). In strawberry, a non-climacteric (NC) fleshy fruit, ABA is of central importance to the regulation of ripening. In both climacteric and non-climacteric species, synthesis of ABA precedes and influences that of ethylene.

context of a growing world population and limited resources. Here we have explored insights developed within the last decade regarding the roles and interactions of phytohormones in the processes of fruit development and maturation (Figure 2), and we have also made a concerted effort to include information developed in less well-studied systems.

Fruit set initiation is regulated by auxins and GAs at the levels of pollination and fertilization, and both phytohormones engage in crosstalk via Aux/IAAs and ARF transcription factors. Ethylene can also crosstalk with auxin and antagonize GA levels during fertilization, although the mechanisms underlying this communication remain to be fully understood.

Similarly, multiple recent studies further support the central role of auxin in controlling cell division and the synergistic regulation of cell expansion via both auxin and GA. During cell division, auxin–GA crosstalk via ARFs can be regulated by microRNAs (e.g., *miR160*, *miR167*), and auxin and GA appear to influence the duration of fruit development by affecting ABA accumulation in some cases. Indeed, insights that better elucidate the linkages between auxin–GA signaling, the control of ABA biosynthesis, and the variation of such mechanisms among fleshy fruit species would have important biological and practical implications. ABCBs and GRAS proteins also play important roles as downstream regulators of auxin responses in tomato, but the persistence of these mechanisms in other species remains to be fully explored. Additionally, recent observations of less well-characterized processes in fleshy fruit, including the activities of additional hormones like CKs and the interplay between epigenome modification and fruit hormonal activity, invite further exploration that will approach a more complete understanding of fruit development and ripening.

Fruit ripening, the terminal stage of fleshy fruit development, is a uniquely complex network of biological pathways whose coordination is dependent upon phytohormone signaling, and ongoing research continues to underscore the importance of both ethylene and ABA in both climacteric and non-climacteric fruits. Recent evidence emphasizes the importance of ethylene–auxin crosstalk in climacteric fruits, as well as the role of AP2/ERFs in mediating crosstalk between ethylene and other hormones. Additional signaling molecules like NO and calcium ions are also instrumental to ripening. The last decade has seen considerable advancement in our understanding of the contributions of multiple phytohormones to fruit development and maturation, as well as central insights into aspects of hormonal interactions. Considerable insight has been developed through recent years into the roles of transcription factors beyond those at the end of hormone signal transduction chains in ripening control (Klee and Giovannoni, 2011; Giovannoni, 2017), and determining the relationship and feedback between hormones and various genetic regulators continues to be an area of active inquiry (Gao *et al*., 2019b; Li *et al*., 2020a; Wang *et al*., 2020). Finally, in addition to building a more complete mechanistic understanding of the molecular events underlying hormonal regulation of fruit biology, the nature and degree of variation within these themes across diverse fruiting species remain open to exploration.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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