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REVIEW PAPER

Salicylic acid accumulation: emerging molecular players and novel perspectives on plant development and nutrition

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Abstract

Salicylic acid (SA) is a central phytohormone that orchestrates genetic and physiological responses involving defense mechanisms against pathogens. This review presents cutting-edge research on emerging molecular players identified within the past 5 years contributing to SA accumulation. Furthermore, we delve into two relatively underexplored domains: the dynamic production of SA throughout the plant life cycle, with a specific focus on senescence, and the intricate interplay between SA, nutrition, and its multifaceted implications on plant development and defense response. This synthesis aims to provide a contemporary and comprehensive understanding of the diverse roles of SA in plant biology.

Keywords: Defense response, development, glutathione, nitrogen, salicylic acid, senescence, stress response, sulfur.

Introduction

Salicylic acid (SA) stands as a pivotal phytohormone in plant pathology, primarily recognized for its crucial role in defense against pathogens. When a plant detects a potential threat, it triggers an increase in SA accumulation, activating genetic programs and physiological responses in order to display a defense response to control proliferation of the pathogen, restricting disease progression (Peng *et al.*, 2021). Pharmacological or genetic disruption of SA accumulation results in a deficient defense response against a wide variety of pathogens and other stressful conditions. On the other hand, plants that hyperaccumulate SA display a resistance phenotype but this is often accompanied by a reduction in plant fitness, affecting developmental programs (van Butselaar and Van den Ackerveken, 2020) and generating detrimental phenotypes such as dwarfism or premature senescence (Chan, 2022).

The hormone has been studied from different points of view, and interesting recent reviews have been released exploring its biosynthesis mechanisms (Peng *et al.*, 2021; Lim, 2023; Ullah *et al.*, 2023), its involvement in the response against pathogens (Zhang and Li, 2019; Ding and Ding, 2020; Bauters *et al.*, 2021), its participation in abiotic stress (Castroverde and Dina, 2021; Sangwan *et al.*, 2022; Rossi *et al.*, 2023; Yang *et al.*, 2023), its involvement in plant interaction with non-pathogenic organisms (Benjamin *et al.*, 2022), its intricate interplay with other

phytohormones (Hou and Tsuda, 2022; Kaya *et al.*, 2023), and oxidative stress (Herrera-Vásquez *et al.*, 2015; Saleem *et al.*, 2021; Kohli *et al.*, 2022).

In this review, we embark on an in-depth exploration of facets that have yet to receive extensive scrutiny: the production of SA throughout the plant life cycle in non-stressed conditions with a special emphasis on senescence. Furthermore, we aim to unravel the complex interplay between two main nutritional elements nitrogen and sulfur, SA production, and the multifaceted actions of this hormone. Additionally, we turn our attention to the latest advancements in understanding the molecular determinants driving SA accumulation, incorporating it into the classically described pathways, and the breakthroughs achieved within the past 5 years. By delving into these uncharted territories, we aspire to provide a comprehensive and contemporary perspective on the roles and regulation of SA in plant development and physiology.

Emerging regulators: unveiling new molecular contributors to salicylic acid accumulation

Under normal conditions, SA concentrations remain low but detectable. However, these levels increase when plants detect some environmental conditions, such as microorganisms acting as pathogens (Peng *et al.*, 2021), abiotic stress such as UV light (Yalpani *et al.*, 1994), elevated CO_2 (Mhamdi and Noctor, 2016), nutritional deficit (Criollo-Arteaga *et al.*, 2021; Xing *et al.*, 2023), and even clues that trigger developmental programs such as senescence (Morris *et al.*, 2000; Zhang *et al.*, 2017). SA accumulation under biotic stress is one of the main fields of study, though details of this complex regulation network could cast light on the mechanisms involved in other cellular processes. The primary source of SA in response to pathogens is the iso-chorismate (IC) pathway (Wildermuth *et al.*, 2001), although, depending on the plant species, the phenylalanine ammonia-lyase (PAL) pathway may also contribute significantly (Ullah *et al.*, 2023).

Several key proteins have been identified as central players in the IC pathway (Fig. 1). CAM-BINDING PROTEIN 60-LIKE G (CBP60g) and SAR DEFICIENT 1 (SARD1) (Zhang *et al.*, 2010a) serve as master transcriptional regulators controlling the expression of *ISOCHORISMATE SYNTHASE 1* (*ICS1*) (Zhang *et al.*, 2010a), which encodes the enzyme responsible for catalyzing the conversion of chorismate into IC (Garcion *et al.*, 2008). Additionally, CBP60g and SARD1 positively regulate the expression of *ENHANCED DISEASE SUSCEPTIBILITY 5* (*EDS5*) (Sun *et al.*, 2015), a gene coding for a transporter that facilitates the movement of IC from the chloroplast to the cytoplasm (Peng *et al.*, 2021). Once in the cytoplasm, IC undergoes a two-step conversion to SA. First, *avrPphB* SUSCEPTIBLE 3 (PBS3), which is also positively regulated by SARD1 and CBP60g (Sun *et al.*, 2015), catalyzes the conversion of IC to IC-9-glutamate (IC-9G), which can then spontaneously convert into SA or be further transformed into SA by action of the ENHANCED PSEUDOMONAS SUSCEPTIBILTY 1 (EPS1) enzyme (Rekhter *et al.*, 2019; Torrens-Spence *et al.*, 2019).

In recent years, additional participants have been identified as regulators within the SA biosynthesis pathway. These regulators exert their influence by either directly impacting the master regulators or by affecting other different components of the pathway. Consequently, they play a crucial role in finely tuning the accumulation of SA, adding a layer of complexity to the regulatory network.

In this section, we will review recent literature that describes these components, with a primary focus on the regulation of the key players involved in SA accumulation (Fig. 1).

Controlling the controllers: CBP60g and SARD1 regulation

In Arabidopsis, the CBP60 protein family is composed of eight genes coding for transcription factors that act as positive and negative regulators of plant immunity (Truman *et al.*, 2013). CBP60g and SARD1 are two closely related members of this family (Truman *et al.*, 2013). They are induced by pathogens and pathogen-associated molecular patterns (PAMPs), and are known as positive regulators of SA biosynthesis (Zhang *et al.*, 2010a) by regulating the expression of several genes that participate in SA production (Sun *et al.*, 2015). The *CBP60g* gene has been identified as a direct target of the transcription factor Trihelix GT2-like 1 (GTL1), which was initially described as a regulator of the cell cycle in trichomes (Breuer *et al.*, 2009). Additionally, GTL1 binds to the *EDS5* promoter, exerting control over their expression under basal conditions (Fig. 1; Völz *et al.*, 2018). Furthermore, GTL1 contributes to up-regulating *ICS1* expression in response to the elicitor Flagelin-22 (flg22). As a result, *gtl1* mutant plants exhibit increased susceptibility compared with wild-type plants when challenged with the pathogen *Pseudomonas syringae* pv. *maculicola* (*Psm*) due to impaired SA accumulation (Völz *et al.*, 2018). In contrast, CALMODULIN-BINDING TRANSCRIPTION ACTIVATOR 3 (CAMTA3) exerts direct transcriptional repression on *CBP60g* (Fig. 1; Sun *et al.*, 2020). Along with its family members, CAMTA1 and CAMTA2, CAMTA3 was identified years ago as a mediator between Ca^{2+} signaling and the negative regulation of SA accumulation (Du *et al.*, 2009; Kim *et al.*, 2013). CAMTA3 also regulates SARD1 expression. Nevertheless, ChIP assays suggest that, unlike the direct control on CBP60g, CAMTA3 indirectly suppresses *SARD1* expression (Sun *et al.*, 2020). Moreover, CAMTA3 is implicated in the modulation of pipecolic acid (Kim *et al.*, 2020), a crucial molecule for basal immunity and systemic acquired resistance that acts in concert with SA (Hartmann and Zeier, 2019).

The *SARD1* gene is a key player in the finely tuned regulation of SA accumulation, with several proteins contributing

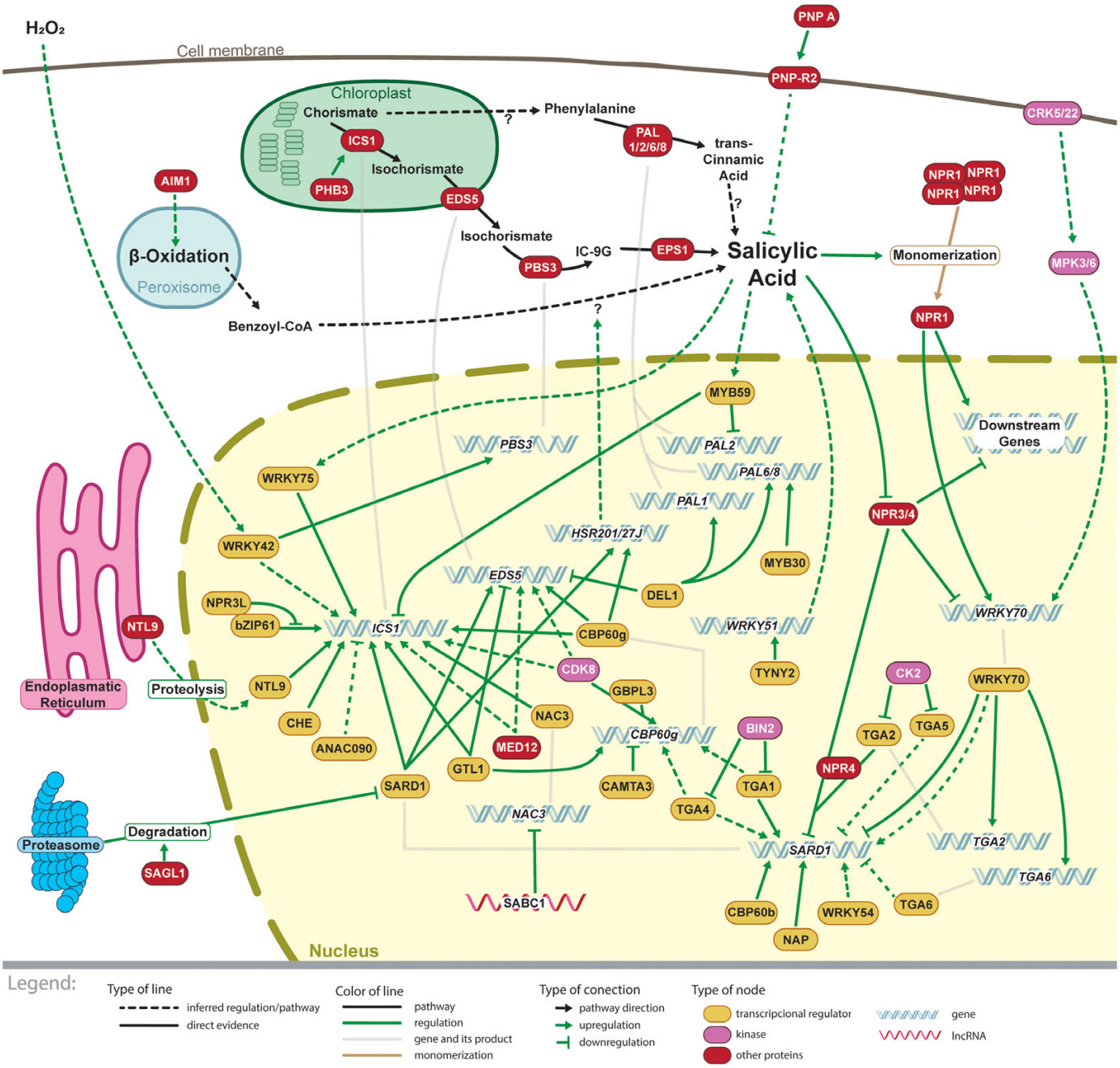

Fig. 1. Regulatory network of salicylic acid (SA) biosynthesis. The figure depicts the well-known iso-chorismate (IC) pathway of SA synthesis, alongside the less extensively studied beta-oxidation and phenylalanine lyase (PAL) pathway. It illustrates the recently described genetic regulation controlling these pathways. The evidence supporting these interactions ranges from direct evidence including genetic studies, biochemical assays, and transcriptomic analyses. It should be noted that while the figure incorporates evidence from various species, specific regulatory interactions may vary among different plant species. The most highly connected nodes, the *ICS1*, *EDS5*, and *SARD1* genes, underscore their crucial roles in SA synthesis and regulation. ICS1 and EDS5 are the rate-limiting enzymes of SA biosynthesis in the IC pathway, which is the main pathway in *Arabidopsis thaliana*, while *SARD1* is a key regulator of the network. The abbreviations of each molecular factor are described in the main text. Continuous lines indicate a regulation tested by direct evidence, while segmented lines indicate inferred information. Blank lines indicate the biochemical flux for SA production, the green lines indicate a regulatory relationship, and gray lines connect the genes and their products.

to its control. Among these, WRKY DNA-BINDING PROTEIN 70 (WRKY70) binds to the promoter of *SARD1* and basally represses its expression (Fig. 1; M. Zhou *et al.*, 2018). This suppression is not observed in plants challenged with pathogens such as *Psm* (M. Zhou *et al.*, 2018); nevertheless, WRKY70 together with WRKY54 act as positive regulators

of *SARD1* and also *CBP60g* in an *ICS1*-dependent manner when the defense response is activated (S. Chen *et al.*, 2021).

The basic leucine zipper (bZIP) transcription factor TGACG SEQUENCE-SPECIFIC BINDING PROTEIN 1 (TGA1) also plays a pivotal role by directly binding to the *SARD1* promoter, thereby positively regulating its expression (Fig. 1; Sun *et al.*, 2018). In *Arabidopsis thaliana*, TGA1, along with TGA4, belongs to clade I of the TGA protein family (Gatz, 2012), known for its involvement in the defense response, as it can interact with the SA receptor and transcriptional co-activator NONEXPRESSER OF PR GENES 1 (NPR1), an essential mediator of the downstream genetic response to SA (Després *et al.*, 2003; Lindermayr *et al.*, 2010). Notably, the *tga1/tga4* double mutant plants accumulate significantly less SA than single *tga1* or *tga4* mutants and wild-type plants in response to *Psm*, indicating that these proteins are positive regulators of SA accumulation (Sun *et al.*, 2018). Additionally, TGA1 and TGA4 are required for the PAMP-triggered immunity-mediated induction of *CBP60g*, *SARD1*, and their target *ICS1* (Sun *et al.*, 2018). In *Solanum tuberosum* (potato) plants, the transcription factor StbZIP61 contributes to the defense response against *Phytophthora infestans* (Zhou *et al.*, 2018). StbZIP61 binds to the *StICS1* promoter, enhancing its expression. This positive regulation is inhibited by the NPR1-LIKE PROTEIN 3 (StNPR3L) in an SA-dependent manner, which physically interacts with StbZIP61 (Fig. 1). The authors suggest that *StbZIP61* might regulate SA synthesis in potato plants similarly to how *SARD1* and *CBP60g* do in Arabidopsis (Zhou *et al.*, 2018).

AtTGA2 is another bZIP transcription factor that binds to the *SARD1* promoter under basal conditions (Fig. 1; Ding *et al.*, 2018). TGA2 belongs to the clade II TGA protein family in Arabidopsis, which also includes TGA5 and TGA6 (Gatz, 2012). These proteins act as repressors of SA accumulation in the defense response triggered by the avirulent *Pseudomonas syringae* pv. tomato (*Pst*) AvrRPM1 (Fonseca *et al.*, 2022). Triple *tga256* mutant plants exhibit increased expression of SA biosynthetic genes, including *SARD1*, *ICS1*, *EDS5*, and *PBS3*, and consequently an elevated SA accumulation in response to UV-C radiation and *Pst* AvrRPM1 infection (Fonseca *et al.*, 2022). These phenotypes in *tga256* plants are reversed by the expression of TGA2 (Fonseca *et al.*, 2022). In rice, OsTGA5 is the closest homolog of AtTGA2. Loss-of-function mutations in *OsTGA5* lead to increased SA accumulation and up-regulation of defense-related genes compared with wild-type plants in response to the pathogen *Magnaporthe oryzae* (Niu *et al.*, 2022). These findings suggest that the repressive effect of TGA2 on SA accumulation is a conserved function. It has been proposed that TGA2-mediated negative regulation of SA accumulation occurs through the transcriptional repression of *SARD1* by TGA2 in conjunction with the transcriptional co-regulator NPR1-LIKE PROTEIN 4 (NPR4) in Arabidopsis (Ding *et al.*, 2018). In rice, the SA accumulation in leaves mainly depends on the PAL pathway (Xu *et al.*, 2023), so the specific molecular mechanism of the negative regulation of AtTGA2/OsTGA5 on SA accumulation remains unclear.

CBP60b, a member of the same protein family as CBP60g and SARD1, also plays a regulatory role in *SARD1* expression (W. Huang *et al.*, 2021; Li *et al.*, 2021). This regulation was described by using mutant plants lacking the *CBP60g* gene and the autoimmune mutant *suppressor of npr1 constitutive-2* (*snc2-1*), which possesses a gain-of-function mutation in the *SNC2* gene coding for a pattern recognition receptor belonging to the receptor-like protein (RLP) family (Zhang *et al.*, 2010b). The double mutant *snc2-1/cbp60g* displays elevated SA concentrations (W. Huang *et al.*, 2021). Notably, the *cbp60b* mutation in the *snc2-1/cbp60g* genetic background suppresses this characteristic increase of the hormone (W. Huang *et al.*, 2021). Additionally, ChIP and transcriptional reporter assays show the *SARD1* promoter as a target of CBP60b (Fig. 1; W. Huang *et al.*, 2021). Likewise, NAC-LIKE ACTIVATED BY AP3/PI (AtNAP) positively regulates *SARD1* expression and binds to its promoter (Fig. 1; Wang *et al.*, 2022). Its binding site is essential for *SARD1* induction. Consequently, *atnap* mutant plants accumulate less SA compared with wild-type plants, while gain-of-function mutations lead to an increase in the hormone concentration (Guo and Gan, 2006; Wang *et al.*, 2022). These SA differences observed in knockout and overexpressor plants are displayed in senescent but not in young leaves. Notably, *atnap* mutant plants exhibit bacterial growth comparable with wild-type plants when challenged with *Pst*, indicating that the *AtNAP* gene does not significantly contribute to the defense response against pathogens (Wang *et al.*, 2022). Remarkably, AtNAP not only positively regulates SA accumulation but is also induced in response to the hormone, participating in a positive feedback regulatory loop of SA accumulation, particularly in late developmental stages (Guo and Gan, 2006; Wang *et al.*, 2022).

The regulation of SARD1 is not limited to transcriptional control. SMALL AND GLOSSY LEAVES1 (SAGL1) is a Kelch repeats-containing F-box (KFB) protein that mediates the proteolytic turnover of enzymes through the ubiquitin–26S proteasome system (K. Yu *et al.*, 2022). SAGL1 physically interacts with SARD1, inducing its proteasome-mediated degradation (Fig. 1; K. Yu *et al.*, 2022). Consequently, *sagl1* mutant plants accumulate more SA under basal and defense-induced conditions (K. Yu *et al.*, 2022). In rice, the CASEIN KINASE 2 (CK2) protein phosphorylates OsTGA5, mitigating its inhibitory effect on defense-responsive genes (Niu *et al.*, 2022). Likewise, in Arabidopsis, TGA2 is phosphorylated by CK2 (Fig. 1), affecting its DNA binding capacity (Kang and Klessig, 2005). Furthermore, the BRASSINOSTEROID-INSENSITIVE 2 (BIN2) protein, known for its role as a suppressor of the brassinosteroid response (He *et al.*, 2002), interacts with and phosphorylates TGA4 (Fig. 1), modulating the SA downstream response (Y.-W. Kim *et al.*, 2022). Given the positive contribution of TGA4, along with TGA1, in SA accumulation through the regulation of *SARD1* (Sun *et al.*,

2018), it is plausible that BIN2 indirectly influences SA accumulation through post-translational modification of TGA4 participating in the growth–defense trade-off (Y.-W. Kim *et al.*, 2022). Similarly, the phosphorylation of OsTGA5/AtTGA2 by OsCK2/AtCK2 could disrupt the repressive function of these transcription factors on SA accumulation, although further research is needed to validate this hypothesis.

Controlling iso-chorismate biosynthesis: ICS1 regulation

The *ICS1* gene represents another crucial checkpoint in SA accumulation. In Arabidopsis, the absence of ICS function significantly suppresses SA accumulation by ~90% in response to pathogens (Wildermuth *et al.*, 2001). Alongside the previously mentioned control mechanisms over the *ICS1* gene involving SARD1 and CBP60g, NAC DOMAIN CONTAINING PROTEIN 3 (NAC3) transcription factor also contributes to SA accumulation by directly and positively affecting *ICS1* regulation (Fig. 1; Liu *et al.*, 2022). *NAC3* is an H_2O_2-responsive gene known to participate in Arabidopsis senescence processes (Balazadeh *et al.*, 2011). Plants lacking this protein exhibit reduced SA accumulation and consequently display increased susceptibility to the avirulent *Pst* AvrRPT2 (Liu *et al.*, 2022). Furthermore, *SALICYLIC ACID BIOGENESIS CONTROLLER 1* (*SABC1*), a long non-coding RNA (lncRNA), represses the basal expression of the NAC3 transcription factor by modulating the H3K27 methylation status on the *NAC3* promoter (Fig. 1; Liu *et al.*, 2022). When plants activate the defense against pathogens, *SABC1* is down-regulated, increasing NAC3 expression (Liu *et al.*, 2022). Consequently, the indirect regulation of *ICS1* by *SABC1*, mediated through epigenetic repression of *NAC3*, plays a significant role in controlling SA accumulation and its downstream defense responses (Liu *et al.*, 2022).

AtWRKY42 is another recently described transcription factor that positively controls the expression of *ICS1* (Fig. 1; Niu *et al.*, 2020). ChIP assays showed that it binds to the *ICS1* and the *PBS3* promoter (Niu *et al.*, 2020). *wrky42* mutant plants accumulate significantly less SA compared with wild-type plants (Niu *et al.*, 2020). Conversely, the transgenic up-regulation of *WRKY42* elevates the transcript abundance of *SARD1*, *CBP60g*, *ICS1*, *PBS3*, and *EDS5* genes, resulting in increased SA accumulation (Niu *et al.*, 2020). WRKY75 is a different WRKY protein that also positively regulates ICS1 expression (Fig. 1; Guo *et al.*, 2017). Its binding to the *ICS1* promoter was demonstrated using EMSAs, reporter transactivation assays, and also by ChIP-qPCR (Guo *et al.*, 2017). In contrast to the positive regulation of these WRKY proteins, the transcription factor MYB DOMAIN PROTEIN 59 (MYB59) plays a suppressive role in SA accumulation (He *et al.*, 2023). MYB59 also binds to the *ICS1* and *PAL2* promoters (Fig. 1), but reporter assays suggest a repressive transcriptional activity on its target genes (He *et al.*, 2023). A similar effect was described for the transcription factor NAC DOMAIN CONTAINING PROTEIN 90 (ANAC090), which also binds to the *ICS1* promoter (Fig. 1; Kim *et al.*, 2018). Both *myb59* and *anac090* mutant plants exhibit higher SA levels under basal conditions compared with wild-type plants (Kim *et al.*, 2018). Moreover, MYB59 transcript is up-regulated by SA in leaves, which suggests a feedback control mechanism orchestrating the hormone accumulation (He *et al.*, 2023). Notably, the MYB59 SA-dependent induction is not observed in other tissues, such as roots (Wiśniewska *et al.*, 2021), suggesting differential tissue-specific regulatory mechanisms, as has been described for development-associated hormones such as auxins and cytokinins (Wong *et al.*, 2023). These findings complement our understanding of SA regulation by adding to the previously described controllers such as NTM1-LIKE 9 (NLT9), CCA1 HIKING EXPEDITION (CHE) (Zheng *et al.*, 2015), and NPR3/4 (Ding *et al.*, 2018), whose functions in modulating SA accumulation have been reviewed in earlier studies.

ICS1 is also post-translationally regulated. PROHIBITIN 3 (PHB3) controls SA accumulation by regulating the stability of the ICS1 protein (Fig. 1; Seguel *et al.*, 2018). In addition to its presence in mitochondria (Van Aken *et al.*, 2007), PHB3 localizes in the chloroplast and interacts with ICS1. *phb3* mutant plants display reduced SA accumulation in response to UV-C radiation and infection with an avirulent strain of *Pst* (Seguel *et al.*, 2018). These differences were not accompanied by changes in the *ICS1* transcript, suggesting a mechanism of SA accumulation regulation mediated by ICS1 protein stabilization (Seguel *et al.*, 2018).

Regulation of the PAL pathway

In plant species such as rice and tobacco, the PAL pathway plays a significant role in basal and pathogen-induced SA accumulation (Pallas *et al.*, 1996; Tonnessen *et al.*, 2015), where several proteins have been identified as regulators of this specific SA biosynthetic pathway.

In rice, knockout mutant plants for the OsMYB30 transcription factor show a decrease in SA accumulation, ultimately enhancing disease symptoms in response to the insect brown planthopper (*Nilaparvata lugens*). OsMYB30 exerts positive control over the expression of *OsPAL6* and *OsPAL8* through direct binding to their promoters (Fig. 1). This positive regulation supports SA accumulation mediated by the PAL pathway in a MYB30-dependent manner (He *et al.*, 2020).

In tobacco, the hypersensitivity-related (HSR) genes *HSR201* and *HSR203J* encode a benzoyl-CoA:benzyl alcohol benzoyl transferase (BEBT) and an enzyme with esterase activity, respectively (Baudouin *et al.*, 1997; D'Auria *et al.*, 2002). *NbSARD1* and *NbCBP60g* transcriptionally control these genes, and their silencing compromises SA accumulation in response to the fungal elicitor INF1 (Baudouin *et al.*, 1997; D'Auria *et al.*, 2002). Although the exact biochemical reactions by which these proteins contribute to SA

accumulation remain unknown, comparative analysis with other species suggests that HSR201 may act downstream of peroxisomal β-oxidation, converting benzoyl-CoA into an intermediate of SA biosynthesis that enters into the PAL biosynthetic pathway (Takagi *et al.*, 2022). Accordingly, in rice, ABNORMAL INFLORESCENCE MERISTEM (AIM1)-dependent β-oxidation is critical for the basal accumulation of SA (Xu *et al.*, 2023), since *aim1* mutant plants accumulate only 10% of SA in basal conditions compared with wild-type plants (Xu *et al.*, 2017).

The E2F transcriptional repressor DP-E2F-LIKE 1 (DEL1) also negatively regulates SA accumulation. DEL1 binds to the *EDS5* promoter (Fig. 1), repressing its expression under basal conditions, thereby restricting SA accumulation in leaves (Chandran *et al.*, 2014). Additionally, SA accumulation in roots increases in *del1* mutant plants in response to the pathogen *Meloidogyne incognita* (Nakagami *et al.*, 2020). Accordingly, lignin levels and transcripts associated with lignin biosynthesis are elevated (Nakagami *et al.*, 2020). Among the up-regulated genes, *PAL1* and *PAL2* have been identified as players in PAL-mediated SA biosynthesis (Huang *et al.*, 2010; Nakagami *et al.*, 2020). Thus, *DEL1* modulates basal SA accumulation through *EDS5* repression in leaves and may also contribute to modulating pathogen-triggered SA accumulation by affecting the PAL pathway in roots (Huang *et al.*, 2010). The transcription factor VqWRKY31 from *Vitis quinquangularis* also positively regulates SA accumulation (Yin *et al.*, 2022). Its overexpression up-regulates the expression of SA-responsive genes and promotes the accumulation of resistance-related secondary metabolites such as stilbene and flavonoid derivatives from the PAL pathway, contributing to the resistance to the biotrophic fungus *Erysiphe necator* (Yin *et al.*, 2022).

Other regulators of SA biosynthesis

The transcriptional Mediator complex also contributes significantly to SA accumulation. This multiprotein complex bridges transcription factors and RNA polymerase II (Mathur *et al.*, 2011). Among its components, cyclin-dependent kinase 8 (CDK8) from the kinase module of the complex has garnered attention (Huang *et al.*, 2019). Mutations in the *CDK8* gene lead to compromised basal expression of *ICS1* and *EDS5*, resulting in reduced basal SA levels compared with wild-type plants (Fig. 1; Huang *et al.*, 2019). Interestingly, defense responses against *Hyaloperonospora arabidopsidis* and *Psm* are also compromised in these mutants (Huang *et al.*, 2019). Surprisingly, the SA accumulation in *cdk8* mutants remains unaltered when challenged with *Psm* compared with wild-type plants, suggesting that CDK8 positively regulates SA accumulation only under uninfected conditions (Huang *et al.*, 2019). Additionally, mutations in the *MEDIATOR 12* (*MED12*) gene, encoding another subunit of the Mediator complex, yield phenotypes akin to *cdk8* mutants, upholding the complex's positive role in regulating SA accumulation and basal defense (Huang *et al.*, 2019). This is not the only *MED* gene implicated in SA-mediated defense. MED14, MED15, and MED16 were previously described as having a role as positive regulators of SA accumulation and downstream signaling (Canet *et al.*, 2012; Wathugala *et al.*, 2012; Zhang *et al.*, 2012, 2013b). Further expanding our understanding of the Mediator complex in SA regulation, recent studies have shown that GUANYLATE BINDING PROTEIN-LIKE 3 (GBPL3), a key component involved in Arabidopsis immunity, interacts with MED15, MED16, CDK8, and other MED subunits (S. Huang *et al.*, 2021). The recruitment and binding of GBPL3 to these subunits and the *CBP60g* promoter highlight its role in modulating SA accumulation (Fig. 1; J.H. Kim *et al.*, 2022).

Cysteine-rich receptor-like kinases (CRKs) are integral components of the plant signaling network, facilitating communication between cells and their external environment. Typically located in the plasma membrane, CRKs possess extracellular domains capable of recognizing PAMPs and other stimuli, initiating signaling cascades that govern the cell's response (Zeiner *et al.*, 2023). Several CRK proteins have been described as defense regulators (Zeiner *et al.*, 2023), and some of them in particular as players in SA accumulation (Acharya *et al.*, 2007; Zhang *et al.*, 2013a). Recently, CRK5 and CRK22 were identified as new regulators of SA accumulation and signaling in response to *Verticillium dahliae* toxins in Arabidopsis (Zhao *et al.*, 2022). *CRK5*- and *CRK22*-deficient plants exhibit diminished SA levels and fail to induce SA-responsive genes (Zhao *et al.*, 2022). This effect can be attributed to their potential involvement upstream of the MITOGEN-ACTIVATED PROTEIN KINASE 3 and 6 (MPK3/6) proteins, which are positively regulated by the CRKs (Zhao *et al.*, 2022). Furthermore, MPK3/6 interact with the transcription factor WRKY70, resulting in the positive regulation of the expression of TGA2 and TGA6 (Fig. 1; Zhao *et al.*, 2022) and possibly SARD1 and CBP60g (S. Chen *et al.*, 2021).

The involvement of certain genes in SA accumulation has yielded conflicting results. A notable example is the *ZINC TRANSPORTER OF ARABIDOPSIS THALIANA 1* (*ZAT18*) gene (Gao *et al.*, 2022; W. Li *et al.*, 2022). This C2H2 transcription factor harbors a functional EAR motif known as a transcriptional repressor module (Kagale and Rozwadowski, 2011). According to Gao *et al.* (2022), *ZAT18* is induced by *Pst* to suppress the SA-mediated defense response in a MYC2-dependent manner. *ZAT18* induction directly represses *EDS1* expression, subsequently reducing SA accumulation. Conversely, W. Li *et al.* (2022) demonstrate that the *zat18* mutation leads to the down-regulation of SA signaling transcripts, increasing susceptibility in response to *Psm* ES4326 (W. Li *et al.*, 2022). The differing conclusions between these research groups may stem from variations in the *Pseudomonas* strains used in the respective studies and differences in infection methods; for instance, W. Li *et al.* (2022) conducted infections by spraying the *Psm* ES4326 strain, whereas Gao *et al.* (2022) performed direct leaf infiltration with *Pst*. The apparently contradictory result

suggests a differential mechanism contingent on the attacking pathogen.

While several genes play significant roles in SA accumulation, the intricate molecular mechanisms underlying some of their functions justify further investigation. For instance, APETALA2/ETHYLENE RESPONSIVE FACTOR in cotton (*Gossypium hirsutum*), GhTINY2, has emerged as a positive regulator of SA accumulation, whose up-regulation bolsters resistance against the pathogenic fungus *V. dahliae* (Xiao *et al.*, 2021). To dissect the molecular basis of this phenotype, researchers demonstrate that in a heterologous system, GhTINY2 exerts positive control over the expression of the Arabidopsis gene *WRKY51*, a positive transcriptional regulator of SA accumulation (Gao *et al.*, 2011). This suggests a potential role for *GhTINY2* in regulating the expression of the Arabidopsis homolog *GhWRKY51* in cotton, thus influencing SA accumulation (Fig. 1; Xiao *et al.*, 2021).

ACT DOMAIN REPEATS 11 (ACR11) is a chloroplast protein that lacks any known catalytic domain (Singh *et al.*, 2018). Interestingly, mutations in this gene lead to a mimic-lesion phenotype characterized by an increase in reactive oxygen species (ROS) levels, elevated SA concentrations, and the activation of SA downstream genes. Consequently, *acr11* mutant plants exhibit enhanced resistance to *Pst* (Singh *et al.*, 2018). These results support the link between the imbalance of ROS in chloroplast signaling and SA accumulation (Bali *et al.*, 2023).

Another intriguing example is the PLANT NATRIURETIC PEPTIDE A (PNP A), which was identified as a negative regulator of the SA response (Lee *et al.*, 2020). PNP A is secreted into the apoplastic space, where it interacts with its putative receptor PNP-R2 (Fig. 1), thereby suppressing SA signaling in the *lesion simulating disease 1* (*lsd1*) mutant background, known for increased SA accumulation in response to stress (Lv *et al.*, 2019). Notably, the *pnp-a* mutation in the *lsd1* mutant background amplifies SA accumulation under light stress compared with the single *lsd1* mutant. Conversely, overexpression of PNP-A suppresses SA accumulation (Lee *et al.*, 2020). Moreover, *PNP-A* is transcriptionally up-regulated in response to various stress conditions, encompassing both biotic and abiotic stress sources (Lee *et al.*, 2020). This intriguing finding suggests that this gene might exert regulatory control over plant physiological responses that involve SA accumulation facing a spectrum of environmental factors (Lee *et al.*, 2020). Nevertheless, the downstream mechanisms following PNP-A perception remain a subject of ongoing investigation.

In summary, elucidating the intricate network of molecular participants in SA biosynthesis provides a foundational understanding of how plants modulate accumulation of this phytohormone to orchestrate diverse aspects of plant physiology, particularly in stress response. Beyond its established role in defense against pathogens, SA has emerged as a multifaceted regulator with far-reaching implications in plant biology. Subsequent sections of this review will explore intersections between SA accumulation and plant development, exploring their effects on processes such as floral transition and senescence (Fig. 2). Additionally, we will describe the dynamic interplay between plant nutrition and SA accumulation, shedding light on how nutrient availability influences SA biosynthesis and, reciprocally, how SA modulates nutrient utilization. Through these discussions, we aim to provide a comprehensive perspective on the pivotal role of SA in shaping the intricate tapestry of plant growth, development, and adaptation.

A life without stress: SA production in plant development

Several studies have explored the effects of SA on plant development in different species. Typically, these studies employ models featuring stress-induced SA accumulation, mutant plants with altered SA production, or exogenous SA treatments (Xie *et al.*, 2007; Alonso-Ramírez *et al.*, 2009; Rivas-San Vicente and Plasencia, 2011; Xu *et al.*, 2017; Pasternak *et al.*, 2019). Under these experimental conditions, SA has been positively and negatively related to cell division and expansion processes, also acting in a cross-regulation with other hormones canonically associated with development (Rivas-San Vicente and Plasencia, 2011; Bagautdinova *et al.*, 2022; A. Li *et al.*, 2022). This is the case of the recently described SA inhibition of gibberellic acid (GA) signaling through the NPR1-mediated GA INSENSITIVE DWARF 1 (GID1) degradation, which modulates plant growth (Yu *et al.*, 2022).

SA concentration in non-stimulated plants varies according to the plant species, even though external stimuli can induce changes in the SA accumulation in all of them, suggesting different functions and SA sensitivity in plant development. For example, compared with Arabidopsis which possesses 1 μg SA g^{-1} fresh tissue in basal conditions (Wildermuth *et al.*, 2001; Mateo *et al.*, 2006), plants such as rice and potato possess up to one order of magnitude more, reaching 15 μg SA g^{-1} fresh tissue (Coquoz *et al.*, 1998; Pál *et al.*, 2020). These differences make establishing a general rule of SA effects on non-stressed plants difficult, considering contrasting developmental effects depending on SA concentration (Pasternak *et al.*, 2019).

Throughout Arabidopsis development, there is an increase in SA accumulation in leaves, particularly during the floral transition, reaching approximately twice the amount compared with the early developmental stages (2 μg SA g^{-1} fresh weight) (Abreu and Munné-Bosch, 2009). This increase depends on the IC pathway, which is also responsible for the SA accumulation in seeds where wild-type plants reach 0.3 μg g^{-1} seed (Abreu and Munné-Bosch, 2009). The deficit in SA accumulation positively influences the plant biomass and the number of siliques, seeds, and shoots (Abreu and Munné-Bosch, 2009), and delays flowering induction in Arabidopsis (Martínez *et al.*, 2004). Accordingly, applying the pharmacological inhibitor of the PAL pathway, aminooxyacetic acid

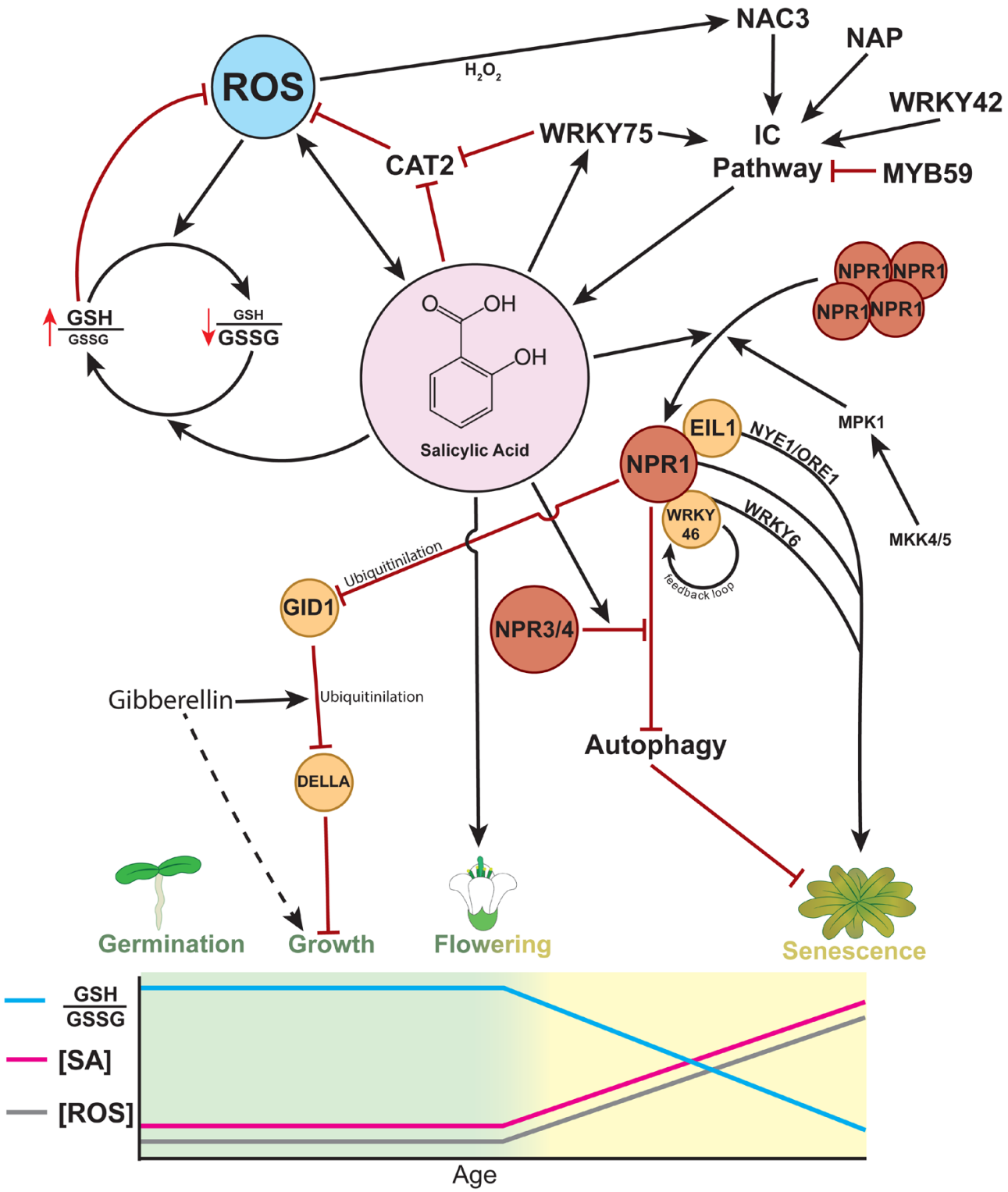

Fig. 2. Regulatory network of salicylic acid (SA) production in senescence. This scheme illustrates the relationship between SA, oxidative status, growth, and senescence, along with key molecular players. The main points depicted include the gradual increase of SA from flowering time onwards, regulated by the feedback loop of WRKY75 and the IC pathway. Additionally, it highlights changes in oxidative status indicated by reactive oxygen species (ROS) accumulation and the GSH/GSSG index. Moreover, it illustrates the suppression of gibberellin signaling leading to growth inhibition and the irreversible progression towards senescence mediated by the feedback loop of WRKY46 and associated genetic reprogramming. These effects collectively represent the outcomes of SA signaling. Lines connecting nodes indicate regulation, while black arrows indicate activation and red lines indicate repression.

(AOA), reduces floral induction by low nutrient availability in *Pharbitis nil* (Wada *et al.*, 2010). At the same time, the use of AOA in combination with SA restores the normal phenotype (Wada *et al.*, 2010). These results suggest SA participation in floral induction. This hypothesis is also supported by evidence showing that exogenous application of SA induces flowering in Arabidopsis (Martínez *et al.*, 2004) and other plant species such as duckweed (Fu *et al.*, 2020), apple (Shah *et al.*, 2022), and saffron (Rastegari *et al.*, 2022). On the other hand, SA accumulation, which is induced in long-day conditions in *Chenopodium ficifolium* plants, does not correlate with flowering time, that is induced under short-day conditions where SA is not detected in the same species (Gutierrez-Larruscain *et al.*, 2022). This effect could be explained by the interaction of SA with other phytohormones, such as abscisic acid (ABA), which is also induced in long-day conditions (Gutierrez-Larruscain *et al.*, 2022) and blocks SA-triggered flowering (Fu *et al.*, 2020).

Interestingly, in wild-type Arabidopsis plants, flowering time coincides with a phenomenon known as age-related resistance (ARR) (Rusterucci *et al.*, 2005). ARR refers to increased plant resistance against pathogens at an advanced ontological age (reviewed in Hu and Yang, 2019). Even though the increase in SA accumulation and the onset of ARR correlates with the flowering transition, mutation on genes that influence flowering time, such as *CONSTANCE 9* (*CO9*) or *FLOWEING LOCUS T* (*FT*), does not affect ARR (Lyons *et al.*, 2015; Gutierrez-Larruscain *et al.*, 2022), indicating that floral transition is not directly linked to the onset of ARR. However, the *SHORT VEGETATIVE PHASE* (*SVP*) gene controls ARR in leaves by repressing the expression of *SUPPRESSOR OF OVEREXPRESSION OF CO 1* (*SOC1*; Wilson *et al.*, 2017) whose particular expression in the shoot apical meristem initiates flowering by activating *LEAFY* (*LFY*), a master regulator of the process (Lee *et al.*, 2008; Liu *et al.*, 2008; Siriwardana and Lamb, 2012). Thus, while the *SVP* gene molecularly links the phenomena of flowering and ARR, its tissue-specific regulation functionally separates them. ARR requires SA accumulation (Kus *et al.*, 2002), but it acts in an NPR1-independent fashion since *npr1-1* mutant plants display age-dependent resistance similar to wild-type plants (Kus *et al.*, 2002; Cameron and Zaton, 2004). The evidence indicates that the apoplastic SA acts as a molecule with antibiotic activity itself, affecting the proliferation of microorganisms (Cameron and Zaton, 2004).

SA has also been implicated in pre- and post-harvest traits in fruit (Chen *et al.*, 2023). These relationships have been primarily explored through exogenous applications of SA (Chen *et al.*, 2023). A recent study, however, revealed a correlation between endogenous SA accumulation in fruit and post-harvest maturation traits, including ethylene evolution and extended shelf life (Changwal *et al.*, 2021). These data suggest the hormone's involvement in this process. Nevertheless, further research is required to definitively attribute these post-harvest traits to SA.

A natural developmental stage in which SA accumulation has been extensively studied and represents a pivotal event is senescence (Morris *et al.*, 2000; Zhang *et al.*, 2017). Senescence in plants involves the execution of a genetically programmed process that possesses essential functions such as nutrient recycling and energy conservation (Woo *et al.*, 2019). Various internal and external factors can influence this process, including hormonal regulation and environmental conditions (Woo *et al.*, 2019). SA accumulation contributes to the expression of senescence-associated genes (SAGs) and phenotypes such as chlorophyll catabolism (Morris *et al.*, 2000). Current knowledge indicates that the SA accumulated by the IC pathway plays a substantial role in the senescence phenotype, as evidenced by delayed chlorotic symptoms in the *ics1* mutant compared with Arabidopsis wild-type plants (Morris *et al.*, 2000; Guo *et al.*, 2017). Accordingly, transcriptional regulators such as MYB59, NAP, NAC3, and WRKY42 are positively regulated in senescent tissue, and they modulate the IC pathway as described above (Figs 1, 2) (Niu *et al.*, 2020; Liu *et al.*, 2022; Wang *et al.*, 2022). Among them, the NAP transcription factor possesses the particular characteristic that seems to participate in SA accumulation in senescence but not in the defense response against pathogens (Wang *et al.*, 2022).

The inhibition of SA accumulation, achieved through using *ics1* mutant plants or applying aminobenzotriazole to block SA biosynthesis, leads to a delayed senescence phenotype (Zhang *et al.*, 2023). A similar phenotype is observed in plants lacking the SA receptor and transcriptional co-activator NPR1, highlighting the significance of SA downstream signaling (Zhang *et al.*, 2023). Furthermore, the SA-dependent senescence process relies on a signaling cascade mediated by the MKK4/5 and MPK1/2 proteins (J. Zhang *et al.*, 2020), of which MPK1 phosphorylates NPR1, mediating its monomerization (J. Zhang *et al.*, 2020) which is required for the activation of the NPR1 downstream effects (Mhamdi, 2019). Additionally, NPR1 interacts with the transcription factor WRKY46, positively regulating the expression of the *WRKY46* and *WRKY6* genes, thereby positively influencing leaf senescence (Fig. 2; Zhang *et al.*, 2021). Surprisingly, unlike Arabidopsis, where the increase in SA accumulation is required for senescence, aspen trees initiate the metabolic process of senescence through enhanced SA catabolism, which implies a reduction in SA levels (Lihavainen *et al.*, 2023). Considering these findings and others, the authors have concluded that induced and sustained SA levels can delay the onset of senescence in aspen trees under field conditions (Lihavainen *et al.*, 2023). This contrasts with Arabidopsis and other annual species studied under controlled conditions (Lihavainen *et al.*, 2023).

SA acts in a coordinated and synergistic manner with ethylene during the senescence process (C. Wang *et al.*, 2021; Yu *et al.*, 2021). This orchestrated interplay involves the interaction between NPR1 and the key transcriptional regulator of the ethylene response, ETHYLENE-INSENSITIVE3-LIKE 1 (EIL1). In the presence of SA, this interaction enhances the

expression of the genes *NON-YELLOWING 1* (*NYE1*) and *ORESARA 1* (*ORE1*), which positively regulates developmental senescence (Fig. 2; Qiu *et al.*, 2015; C. Wang *et al.*, 2021; Yu *et al.*, 2021).

The process of autophagy is notably intertwined with senescence. Plants with genetically compromised autophagy, such as *autophagy 2* (*atg2*) and *atg5* mutants, display an early senescent phenotype dependent on SA (Yoshimoto *et al.*, 2009). Interestingly, under senescence induced by carbon starvation conditions, SA inhibits autophagy through NPR1 (Fig. 2; Zhang *et al.*, 2023). Surprisingly, SA also promotes autophagy via NPR3/NPR4 (Wang *et al.*, 2016). Thus, the equilibrium between these co-regulators is fundamental for the coordination between autophagy and senescence, as well as the immune response (Ding *et al.*, 2018). It is important to consider that chlorotic phenotypes associated with senescence could be related to cell death propagation, which is well described in the defense response as a consequence of the increase in SA (Yoshimoto *et al.*, 2009).

The signals that trigger SA accumulation in developmental- and/or carbon deprivation-induced senescence remain elusive. However, ROS emerge as an important candidate due to their close association with SA production and the cellular redox balance (Herrera-Vásquez *et al.*, 2015; Saleem *et al.*, 2021). In senescent tissue, a significant ROS increase is supported by a reduction in ROS-detoxifying enzyme activities, such as catalase (CAT), that correlates with a decrease in the expression of CAT-coding genes, such as *CATALASE 2* (*CAT2*) (Zimmermann *et al.*, 2006), that contribute to 90% of CAT activity in Arabidopsis leaves (Queval *et al.*, 2007; Mhamdi *et al.*, 2010). Furthermore, SA inhibits CAT2 and the total CAT activity in plant tissues (Yuan *et al.*, 2017), providing additional evidence of its role in modulating ROS levels during senescence.

Mutation of *CAT2* induces ROS accumulation and cell death, resulting in a senescent-like chlorosis phenotype dependent on the photoperiod (Queval *et al.*, 2007; Mhamdi *et al.*, 2010). Accordingly, *cat2* mutant plants accumulate more SA compared with wild-type plants (Yuan *et al.*, 2017) and display a light regime-dependent chlorosis that is genetically reversed by the *ics1* mutation (Chaouch *et al.*, 2010), emphasizing the pivotal role of SA in this tissue degeneration and death. Moreover, the early senescent phenotype seen in *nac domain containing protein 75* (*nac075*) mutant plants can be rescued by *CAT2* overexpression (Kan *et al.*, 2021). Similarly, the premature senescence observed in Arabidopsis plants overexpressing the transcription factor WRKY75 is suppressed by CAT2 overexpression, which mitigates the heightened ROS accumulation resulting from WRKY75 overexpression (Guo *et al.*, 2017). Notably, the *ics1* mutation also suppresses the early senescent phenotype of WRKY75 overexpressor plants (Guo *et al.*, 2017).

Glutathione (GSH), one of the primary redox buffers that control the ROS increase in stressed and non-stressed conditions (Dorion *et al.*, 2021), undergoes modifications in senescent tissue (Ding *et al.*, 2016). In standard growth conditions, older leaves exhibit a reduction in the total GSH content as well as a decreased ratio of the reduced to oxidized GSH form (GSH/GSSG ratio), indicating a shift towards a more oxidative cellular status (Fig. 2; Ding *et al.*, 2016). Additionally, mutation in the *GLUTATHIONE REDUCTASE-2* (*GR2*) gene, involved in converting oxidized glutathione (GSSG) to GSH, leads to premature leaf senescence (Ding *et al.*, 2016). Despite an increased total GSH content (GSH+GSSG), these plants exhibit an enhanced and early decrease in the GSH/GSSG ratio, supporting the early senescence onset (Ding *et al.*, 2016). These results indicate that the alteration of GSH homeostasis influences the onset of senescence. In line with this, *cat2* mutant plants display an increased oxidized form of GSH compared with wild-type plants (Queval *et al.*, 2007; Mhamdi *et al.*, 2010). Notably, the increased GSH/GSSG ratio in the *cat2* mutant is similar to the ratio in the *cat2/ics1* double mutant (Chaouch *et al.*, 2010), suggesting that the SA increase in senescent tissue is more a consequence than a cause of the redox imbalance.

SA has also been associated with root development (Xu *et al.*, 2017; Pasternak *et al.*, 2019; Wang *et al.*, 2021). The root architecture is modified by SA in a concentration-dependent fashion in Arabidopsis (Pasternak *et al.*, 2019). Additionally, SA modulates the activation of cell division in the root meristem of rice (Xu *et al.*, 2017) and also the quiescent center in Arabidopsis (Wang *et al.*, 2021). All these observations have been made in experiments with exogenous SA treatment. Interestingly, some evidence shows a possible modulation of SA accumulation in response to soil nutritional status. This suggests a potential bidirectional relationship between plant nutrition and SA accumulation, wherein nutritional conditions could modulate SA levels, influencing root architecture.

Additionally, nutrient imbalances profoundly impact the intricate interplay between plant growth and stress defense responses, which has been called the 'growth–defense tradeoff' (Chan, 2022). The effects depend on each element's concentration in the plant, which is directly linked to their availability in the soil. The plant's nutritional status significantly influences and sometimes even defines its ability to develop and withstand adverse environmental conditions. In the following section, our search focused on uncovering updated evidence directly linking nutrient availability to the accumulation of SA. Our findings predominantly show that the synthesis and accumulation of SA are directly impacted by the nutritional status of sulfur (S) and nitrogen (N).

Have sulfur and nitrogen something to say in the SA pathway?

Sulfur stands as a crucial element that plants must assimilate. The uptake form of this element is sulfate (SO_4^{2-}), which is

incorporated into and mobilized through the plant by specialized transporters (Takahashi, 2019). Once sulfate enters the plant cell, it undergoes a series of reduction steps, leading to the production of sulfite (SO_3^{2-}) and, finally, sulfide (S^{2-}). The reaction between S^{2-} and *O*-acetyl-serine (OAS) results in the formation of Cys, which is the final S assimilation product (Watanabe *et al.*, 2010; Künstler *et al.*, 2020). The reduction of SO_4^{2-} to S^{2-} occurs in plastids (mainly in the chloroplast), but the synthesis of Cys takes place in chloroplasts, mitochondria, and the cytosol (Abadie and Tcherkez, 2019; Li *et al.*, 2020). The production of Cys plays a central and pivotal role in orchestrating the production of S-containing biomolecules. Thus, S insufficiency negatively impacts the synthesis of Cys and, as a consequence, the synthesis of GSH, methionine antimicrobial agents, and signaling peptides fulfilling essential functions in plant development, growth, and defense responses against pathogens (Krueger *et al.*, 2010; Hu *et al.*, 2018). The direct influence of soil sulfur on SA synthesis has been relatively underexplored. However, evidence suggests that the availability of this nutrient impacts the accumulation of SA and subsequently influences the plant's defense response (Criollo-Arteaga *et al.*, 2021). Supporting this idea, Arabidopsis wild-type plants grown in S deprivation showed constitutive expression of the *PATHOGENESYS RELATED 1* (*PR1*) gene in an SA-dependent manner (Criollo-Arteaga *et al.*, 2021). Accordingly, these plants display a resistance phenotype after the challenge with *Pst* DC3000, compared with plants in standard S concentration (Criollo-Arteaga *et al.*, 2021). The opposite effect is observed in plants supplemented with S in excess (Criollo-Arteaga *et al.*, 2021). These results show that the lack of S activates the defense response in an SA- and NPR1-dependent manner. In this study, Cys and GSH/GSSG levels were not addressed (Criollo-Arteaga *et al.*, 2021); however, S deprivation on *Brassica napus* roots showed a down-regulation of genes involved in GSH metabolism, which was reflected in a decrease in the general GSH content, suggesting an uncontained ROS accumulation under S deprivation (Courbet *et al.*, 2021). These results are consistent with the findings presented by Henriquez-Valencia *et al.* (2018), who analyzed transcriptomic data from several published experiments involving S treatments. They found that the most consistent biological functions differentially regulated by S treatment include the Gene Ontology classification of 'response to biotic stimulus' and also 'glutathione metabolism' along with 'sulfate assimilation and metabolism' as expected (Henríquez-Valencia *et al.*, 2018). Thus, these results suggest that SA accumulation by deprivation of S might result from the imbalance of Cys and GSH, resulting in an impairment of ROS containment due to the lack of one of the main antioxidant cellular buffers (Zechmann, 2020).

An optimal balance of Cys is paramount for plant immunity, as illustrated by Álvarez *et al.* (2012a). Mutant plants lacking functional cytosolic L-Cys DESULFHYDRASE (DES1), an enzyme involved in the catabolism of cytosolic Cys into sulfide, ammonia, pyruvate, and H_2S, show hyperaccumulation of cytosolic Cys (Álvarez *et al.*, 2012a, b). This accumulation is accompanied by elevated total GSH content and SA accumulation, as well as the up-regulation of *PR1*, *WRKY54*, and *RPM1* genes. Consequently, this mutant displays an increased resistance to pathogen challenges (Álvarez *et al.*, 2012a). The *des1* mutant also displays an early senescent phenotype accompanied by the up-regulation of the senescence-associated transcription factor gene *SENESCENCE-ASSOCIATED GENE 21 (SAG21)* and the NAC transcription factor gene *NAP* (Fig. 1), responses which support the increase of SA concentration (Álvarez *et al.*, 2012a). In contrast, the *phytoalexin deficient 2* (*pad2-1*) Arabidopsis mutant accumulates five times more Cys than the wild-type plants and displays an enhanced susceptibility to *Psm* E4326 (Parisy *et al.*, 2007). Although *des1* and *pad2-2* mutant backgrounds have higher Cys levels than wild-type plants, only *des1* exhibits higher total GST (Parisy *et al.*, 2007). *PAD2* encodes a γ-GLUTAMYL-CYSTEINE SYNTHASE 1 (GSH1) enzyme, part of the GSH synthesis pathway (Parisy *et al.*, 2007). Indeed, GSH levels correlate with plant resistance to several pathogens. For instance, the artificial increase of GSH content by overexpressing *GSH1* (Ghanta *et al.*, 2011) or by directly infiltrating GSH in tobacco plants (Künstler *et al.*, 2019) increases the SA accumulation and shows a resistance phenotype to *P. syringae* pv. *tabaci* and tobacco mosaic virus (TMV), respectively.

GSH is also able to react with nitric oxide (NO) to produce *S*-nitrosogluthathione (GSNO), a crucial molecule that facilitates *S*-nitrosylation (SNO) on reactive Cys residues on target proteins (Lindermayr, 2018; T. Zhang *et al.*, 2020). Regarding the SA signaling, SNO regulates NPR1, promoting its oligomeric state and retaining it in the cytosol, as well as TGA1, enhancing its DNA binding capacity (Lindermayr *et al.*, 2010). Recently, T. Zhang *et al.*, (2020) demonstrated that the activation of the SA pathway dependent on intracellular H_2O_2 relies on GSH to maintain the *S*-nitrosoglutathione reductase 1 (GSNOR1) gene up-regulated, thereby ensuring an optimal level of SNO-modified proteins.

Hydrogen sulfide (H_2S) is a gas produced by the plant when S is assimilated and, as a consequence of the excess of S fertilization, it has become a contaminant gas present in the environment (Álvarez *et al.*, 2012a; Ausma and De Kok, 2019). Initially, it was thought that its production was the plant's way to eliminate the excess S in their tissue. Yet, many reports in the literature support this molecule as a player in the stress defense response. This fact was primarily proposed when environmental regulations reduced H_2S emissions in Europe, and the crops started to suffer diseases caused by fungi (Sehar *et al.*, 2021; Khan *et al.*, 2022). There is evidence connecting H_2S and SA production; Shi *et al.* (2015) modified the endogenous production of H_2S in Arabidopsis by modulating the expression of *L-CYSTEINE DESULFHYDRASE* (*LCD*) and *D-CYSTEINE DESULFHYDRASE 1* (DCD), encoding enzymes which participate in the H_2S synthesis pathway

in Arabidopsis (Khan *et al.*, 2022). Plants overexpressing the *LCD* or the *DCD* gene showed an increase in the endogenous concentration of H_2S and an increased resistance to *Pst* (Shi *et al.*, 2015). Expression analysis showed an up-regulation in the SA-responsive genes *PR1*, *PR3*, *PR2*, and also *EDS1* and *PHYTOALEXIN DEFICIENT 4* (*PAD4*) genes, which participate in upstream SA signaling, suggesting an increase in SA accumulation (Shi *et al.*, 2015). Consistently, treatment with exogenous H_2S showed improved resistance to *Pst* DC3000, and the *lcd* and *dcd* knockout lines showed the opposite phenotype (Shi *et al.*, 2015).

Similarly, plants also respond to other oxidized forms of S, such as sulfur dioxide (SO_2), which is also an air pollutant derived mainly from volcanoes and the combustion of S-containing fossil fuels (Fioletov *et al.*, 2016). SO_2-pre-treated Arabidopsis plants are more resistant to *Botrytis cinerea*, and *PAL*, *PROTOPORPHYRINOGEN OXIDASE* (*PPO*), *PR2*, and *PR3* genes are induced, as well as their enzymatic activity, compared with unprimed plants (Fioletov *et al.*, 2016). Although the up-regulation of these genes suggests a potential involvement of SA, the authors propose that the augmented defense response is also attributed to the repression of the auxin signaling pathway induced by SO_2 exposure (Xue and Yi, 2018). Conversely, it has been shown that *Zea mays* (maize) plants pre-treated with SO_2 improve the heat shock response in an SA-dependent manner (Xue and Yi, 2018). When SO_2-pre-treated plants were exposed to heat stress, the amount of ROS [H_2O_2 and malondialdehyde (MDA)] was reduced, consistent with the increased activity of antioxidant enzymes such as SUPEROXIDE DISMUTASE (SOD) and CAT, and higher levels of SA, compared with plants without SO_2 pre-treatment (Li *et al.*, 2023). The SA accumulation correlates with the up-regulation of *ZmICS1* and *ZmPAL* genes. Plants treated with paclobutrazol (PAC), an SA synthesis inhibitor, fail to show SO_2-induced heat tolerance (Li *et al.*, 2023). These results agree with the well-established role for SA in improving the thermotolerance response and the role of SA in controlling the ROS burst (Rai *et al.*, 2020; Sangwan *et al.*, 2022). Thus, the described results suggest that Cys, H_2S, and SO_2 could prime the plant stress response through the SA signaling pathway.

The influence of nitrogen availability in the defense response to pathogens and its connection with SA accumulation is not straightforward. Whether the plant defense response improves with high or low N depends on the host, the pathogen, and even the form of N used to fertilize the plant (Ballini *et al.*, 2013; Vega *et al.*, 2015; Mur *et al.*, 2017). The primary source of nitrogen in dry land is nitrate (NO_3^-), while in flooded or acidic soils, it is ammonium (NH_4^+) (Xuan *et al.*, 2017). The assimilation forms of N influence the defense response (Ding *et al.*, 2021). This issue has been explored recently in tomato plants where their defense response to *Pst* DC3000 and *Ralstonia solanacearum* was analyzed using both main forms of soil N, NH_4^+ and NO_3^-, in high and low concentrations. Tomato plants were shown to be more resistant to *Pst* DC3000 when nitrogen was limited, regardless of the form of N supplied (NO_3^- or NO_3^-/NH_4^+), although plants supplied with NO_3^- alone showed more resistance than plants fed with the mix NO_3^-/NH_4^+, when keeping the same low concentration (Ding *et al.*, 2021). Moreover, defense in low N concentrations correlates with increased SA accumulation and up-regulation of the *PAL1*, *PR2*, and *PR4* genes (Ding *et al.*, 2021).

Nitrogen uptake from soil and its incorporation into the plant cell is mediated by transporters regulated at both transcriptional and post-translational levels (Vidal *et al.*, 2020). NO_3^- and NH_4^+ uptake is mediated by the nitrate peptide family/transporters (NPF/NRTs) and ammonium transporters, respectively, located in the roots (O'Brien *et al.*, 2016). Notably, NO_3^- treatment induces NRT2.2, a high-affinity N transporter, as well as NTR1.1, a dual-affinity nitrate transporter and putative NO_3^- sensor (Vidal *et al.*, 2020). Furthermore, NO_3^- also triggers the expression of *TGA1/4* genes, which are partially responsible for the positive regulation of the transcription of both transporters. The *tga1/4* double mutant plants show a differential nitrate-dependent lateral root phenotype compared with wild-type plants (Alvarez *et al.*, 2014). Interestingly, TGA1/4 transcription factors positively regulate the expression of *SARD1* and, consequently, SA accumulation (Fig. 1) (Sun *et al.*, 2018).

Once NO_3^- is transported into the root cells, it is mobilized to the shoot and converted to NH_4^+ by the enzymes NITRATE REDUCTASE (NR) and NITRITE REDUCTASE (NiR) (Chamizo-Ampudia *et al.*, 2017). Both sources of NH_4^+ (the naturally absorbed and the reduced form NO_3^-) are further assimilated into the organic repertoire by the glutamine synthase/glutamate synthase cycle (Xing *et al.*, 2023). This cycle provides glutamine and glutamate amino acids and the initial substrates synthesizing all the N-containing biomolecules in the plant (Lam *et al.*, 1996). Glu, a pivotal molecule primarily associated with proteins and a source of N, is directly linked to SA synthesis and response pathways (Toyota *et al.*, 2018; Tsuruda and Yoshida, 2023). Glu and IC are substrates of PBS3 in the SA synthesis pathway to produce the intermediary IC-9G (Fig. 1). Glu is also one of the three amino acids making up GSH. Tsuruda and Yoshida (2023) demonstrated that the exogenous application of L-Glu induces the accumulation of SA and up-regulates the expression of *ICS1* and *PR1* genes in wild-type Arabidopsis plants. This effect is not observed in *glutamate receptor-like 3* (*glr3.1*), *npr1.1*, and *ics1* mutant plants (Tsuruda and Yoshida, 2023). Previous studies have shown that the ion channel glutamate receptor-like family protein is involved in Ca^{2+} signaling, suggesting that an increase in cytosolic Ca^{2+} could be involved in the Glu-induced SA accumulation (Toyota *et al.*, 2018).

While transcriptional regulation of genes is the main mechanism for modulating transcript abundance, the alternative splicing and polyadenylation of mRNAs could be additional levels of expression modulation (Wu *et al.*, 2023). For instance, the classical 3'-untranslated region (UTR) polyadenylation

could also occur within introns, coding regions, in more than one place within the 3'-UTR and even in 5'-UTRs, a phenomenon known as non-canonical polyadenylation or alternative polyadenylation (APA) (Wu *et al.*, 2023). APA has been reported as an important feature of plant stress response, especially associated with abiotic stress, producing truncated proteins and changes in mRNA stability (Wu *et al.*, 2023). In their 2020 study, Conesa *et al.* assessed the influence of N availability on APA by using a mutant allele of the *FACTOR INTERACTING WITH POLY(A) POLYMERASE 1* (*FIP1*) protein involved in APA (Téllez-Robledo *et al.*, 2019; Conesa *et al.*, 2020). Their findings in Arabidopsis plants subjected to nitrogen deficiency stress revealed significant alterations in the APA patterns of genes primarily associated with nitrogen assimilation and stress response pathways, especially in the SA signaling pathway (Conesa *et al.*, 2020). The authors report that in plants grown under low nitrogen conditions (50 μM), SA accumulates considerably in shoots and roots, compared with plants grown under control conditions (2.5 mM nitrogen) (Conesa *et al.*, 2020).

Further analysis of APA patterns indicated shifts in polyadenylation site choice for genes such as that encoding the SA receptor and transcriptional co-regulator *NPR3* and the transcription factors that regulate the SA biosynthesis *TGA5*, *CAMTA1*, and *CAMTA3* (Fig. 1; Conesa *et al.*, 2020). The authors hypothesized that these APA changes potentially modulate the activity of these proteins, thereby influencing the accumulation of SA (Conesa *et al.*, 2020). These findings add another regulation level in SA production, connecting SA production, N availability, development, and defense response.

The effects of N on SA accumulation have also been observed in cotton plants. In this experimental system, plants grown under N deprivation demonstrated a notable increase in SA accumulation, observed in both the primary root and lateral roots, in contrast to plants cultivated under N-sufficient conditions. Notably, an excess of N also led to SA accumulation, although this effect was less pronounced than in N-deprived plants and confined to the main root (Chen *et al.*, 2021).

In this context, it is intriguing to highlight the involvement of SA in various developmental processes. Notably, in roots, SA plays a pivotal role in mediating the interaction between plants and soil microorganisms (Lebeis *et al.*, 2015; Lemarié *et al.*, 2015; Benjamin *et al.*, 2022), but it also contributes to determining root architecture. While extensive research has investigated the effects of SA on this process, establishing a universal rule is challenging because the morphological effects depend on treatment intensity and plant species. This topic has been extensively reviewed by Bagautdinova *et al.* (2022). Given that plant nutrition primarily relies on acquiring molecules from the soil, modification of root architecture becomes a critical factor in optimizing nutrient uptake. Consequently, SA could play a role in shaping the plant's nutritional status by influencing this process. This field remains relatively unexplored, presenting an intriguing and promising study area with substantial potential for future research.

Discussion

This comprehensive review on SA biosynthesis and its regulatory mechanisms in plants elucidates several important aspects of SA accumulation, revealing the intricate interplay between developmental processes, nutrient signaling, and stress responses.

One of the key themes that emerged is the accumulation of SA fulfilling different roles depending on the specific biological outcome, which can be observed particularly in defense and development. The dynamic nature of SA biosynthesis across various stages of plant development, especially during flowering (Martínez *et al.*, 2004; Fu *et al.*, 2020; Shah *et al.*, 2022), senescence (Morris *et al.*, 2000; Guo *et al.*, 2017; Lihavainen *et al.*, 2023), and in response to nutrient status (Conesa *et al.*, 2020; Criollo-Arteaga *et al.*, 2021), underscores the hormone's critical role in modulating plant physiology. The discovery of new molecular regulators at different levels, such as transcription factors and post-translational regulators detailed in our review (Fig. 1), enhances our understanding of SA regulation, particularly how these factors contribute to its synthesis and accumulation under different physiological conditions. Interestingly, so far, core components seem to participate in all processes involving SA accumulation, such as ICS1 (Wildermuth *et al.*, 2001) or its transcriptional regulator SARD1 (Zhang *et al.*, 2010a). Although traditionally recognized for their roles in defense, these proteins also trigger senescence and respond to nutritional status (Morris *et al.*, 2000; Zhang *et al.*, 2017; Criollo-Arteaga *et al.*, 2021). This involvement across different physiological processes suggests the existence of a shared group of proteins governing SA dynamics. Intriguingly, the regulators upstream of these components may be process specific, suggesting that while a core part of the pathway is shared, other aspects are uniquely tailored to specific physiological events, thus conferring specificity to SA production.

An interesting example of this is the NAP transcription factor which modulates *SARD1* expression (Fig. 1; Wang *et al.*, 2022). NAP participates in SA production during senescence, but it does not participate in the defense response against pathogens (Wang *et al.*, 2022).

Additionally, tissue-specific regulation can influence SA function. Specific stimuli sensed by different organs may lead to distinct regulatory processes, as illustrated by the gene *MYB59*, which suppresses SA production (Fig. 1) and exhibits differential regulation in roots or leaves in response to SA (Wiśniewska *et al.*, 2021; He *et al.*, 2023). Similarly, the gene *SVP* regulates flowering when expressed in the meristem and controls ARR when expressed in leaves (Wilson *et al.*, 2017), presenting a compelling candidate for linking flowering and ARR through SA modulation. These ideas collectively suggest a sophisticated regulatory architecture where shared and unique components

interplay, fine-tuning SA roles across various physiological landscapes, thus reinforcing its essential function in plant adaptability and survival. Most of the upstream regulators of these core components are described predominantly within single processes, and their roles in other processes that involve SA accumulation remain largely unexplored. Additionally, while the IC pathway and its regulation are the most thoroughly described (because of its relevance in Arabidopsis), the PAL pathway crucial for plants such as rice and tobacco (Pallas *et al.*, 1996; Huang *et al.*, 2010; Tonnessen *et al.*, 2015) is almost underexplored in terms of its regulators. This gap in our understanding of regulation of the PAL pathway, combined with the limited exploration of the broader roles of upstream regulators, represent significant areas where further research could be immensely beneficial in understanding the regulatory landscape of SA accumulation.

The diverse outcomes that arise from the accumulation of SA could be explained by the interaction with other phytohormones. For example, SA has a combined effect with auxin on the modification of the root meristem (Pasternak *et al.*, 2019; Bagautdinova *et al.*, 2022), or it can act in conjunction with ethylene to influence the senescence process (Yu *et al.*, 2021). NAP and SAG21, marker genes of senescence, are upregulated in *des1* plants, which have a high level of Cys, early senescent phenotype, accumulation of SA, and a greater resistance to pathogens (Álvarez *et al.*, 2012a, b). This suggests that although there are common players involved in both responses, the final outcome has to be influenced by others factors such as the activation of pathways of other hormones. In this particular case, senescence involves the activation of the ethylene pathway, while Cys abundance is related to the availability of S. Cys availability also indirectly influences the immunity response since it is abundant in the Cys-rich receptor-like kinases and GSH.

An essential element involved in controlling SA accumulation is the interaction with ROS and oxidative balance (Herrera-Vásquez *et al.*, 2015). This dimension crosses all the physiological processes where SA is accumulated, including defense response, developmental processes, and nutritional imbalance. In senescence, the signal that induces SA accumulation remains elusive; however, ROS is a strong candidate due to its increase as a product of the diminished ROS-scavenging enzymatic activities, and SA would be a signal to the positive feedback loop enhancing its production (Zimmermann *et al.*, 2006; Herrera-Vásquez *et al.*, 2015; Yuan *et al.*, 2017). Additionally, the role of redox balance in floral development has been recognized, linking oxidative cues with the regulation of flowering time (Schippers *et al.*, 2016). Given the modulation of SA levels during these developmental stages, it is plausible that SA interacts with redox signaling pathways to influence these processes. On another note, changes in GSH levels triggered by sulfur starvation (Krueger *et al.*, 2010; Kopriva *et al.*, 2019; Li *et al.*, 2020) could lead to oxidative imbalances, subsequently triggering SA accumulation driven by nutritional deficits. Despite ROS being almost universally produced under various stress conditions, not all of these conditions result in the accumulation of SA, indicating that other signals different from ROS must be integrated to induce SA increase.

Nutritional status involving nitrogen or sulfur has a less explored role in modulating SA accumulation. We summarize some evidence supporting this link, for instance, the straightforward modulation by nitrogen of APA of core enzymes for SA accumulation (Conesa *et al.*, 2020). Furthermore, key regulators of nitrogen metabolism, such as the transcription factors TGA1 and TGA4 (Alvarez *et al.*, 2014), are identified as positive regulators of SA accumulation (Fig. 1; Sun *et al.*, 2018). Despite these findings, detailed molecular mechanisms connecting N nutrition and SA accumulation remain largely unexplored. Similarly, in conditions of sulfur deficiency, although solid evidence supports an increase in SA (Criollo-Arteaga *et al.*, 2021), the underlying molecular mechanisms are still elusive. These observations underscore significant gaps in our understanding of how nutrient availability influences SA accumulation and, importantly, the physiological functions associated with these hormonal changes.

Conclusion

In conclusion, SA emerges as a multifaceted player in plant physiology, influencing diverse aspects of plant development, senescence, and stress responses. From its concentration-dependent effects on root architecture to its intricate involvement in floral transitions, SA exhibits a nuanced relationship with developmental processes. Moreover, SA's pivotal role in senescence, where it orchestrates a cascade of genetic and biochemical events, highlights its significance in nutrient recycling and energy conservation. The interplay of SA with other phytohormones, such as ethylene, auxin, and abscisic acid, further underscores its complex regulatory network. Intriguingly, the regulators upstream of these components may be process specific, suggesting that while a core part of the pathway is shared, other aspects are uniquely tailored to specific physiological events, thus conferring specificity to SA production depending on the physiological process that triggers the hormone increase. This specificity underscores the need to investigate the molecular components involved in controlling the nutritional response, particularly how it might relate to the defense response and the maintenance of ROS balance as a result of an increase in SA.

Nevertheless, despite significant strides in understanding SA's contributions, intriguing questions remain surrounding its precise signaling mechanisms and interactions with other regulatory pathways. Continued research in this area promises to unveil even deeper insights into the intricate role of SA in plant biology. More knowledge comes with more possibilities for plant biotechnology, opening up new avenues for enhancing crop resilience and productivity in an ever-changing environment.

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Author contributions

PS and AH-V: conceptualization, investigation, writing—original draft, review and editing; SV: visualization, review and editing; AH-V: funding acquisition, supervision.

Conflict of interest

The authors declare no conflict of interest.

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