Jasmonates: An Update on Biosynthesis, Signal Transduction and Action in Plant Stress Response, Growth and Development

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INTRODUCTION

In recent years, large scale analyses of gene sequences (genomics), expression (transcriptomics), protein patterns (proteomics), metabolite profiles (metabolomics) and lipid compounds (lipidomics) have been performed and remain the focus of many studies. The tremendous amount of accumulated data has led to new insights into how plants respond to biotic or abiotic stress and how a growth and developmental program takes place in the plant life cycle. An essential link within such programming is provided by small molecules, such as plant hormones. Among these, jasmonates have attracted much interest over the last two decades.

In 1962, jasmonic acid methyl ester (JAME; see Appendix for a list of abbreviations) was isolated for the first time from the essential oil of Jasminum grandiflorum (Demole et al., 1962). The first physiological effects of JAME, however, and its free acid (JA) were only observed two decades later. In 1980, Ueda’s group in Osaka, Japan, described a senescence-promoting effect of JA, and Sembdner’s group in Halle, Germany, isolated and characterized these compounds as growth inhibitors (Ueda and Kato, 1980; Dathe et al., 1981). Inhibition of root growth became the most prominent assay for screening of mutants affected in respect of JA signalling. The biosynthesis of JA was elucidated by Vick and Zimmermann (1984). The functional analysis of the mode of action was initiated by the observation in Parthier’s group in Halle that application of JA or its methyl ester to barley leaves leads to an altered protein pattern. The synthesis of abundantly accumulating proteins, so-called jasmonate-induced proteins (JIPs) and degradation of housekeeping proteins such as Rubisco were described for the first time in 1987 (Weidhase et al., 1987a, b). In 1990, another dramatic alteration of gene expression by JAME was observed in tomato plants (Farmer and Ryan, 1990). Here, a proteinase inhibitor (PIN2) was found to accumulate upon wounding (such as that caused by herbivore attack) or by treatment with airborne JAME. Subsequently, JA-induced alteration of gene expression and metabolite patterns became the focus of studies examining accumulation of vegetative storage proteins in Staswick’s group (Staswick et al., 1992) and alkaloids in Zenk’s group (Gundlach et al., 1992). In the latter case, an endogenous rise of JA was demonstrated upon elicitation of cell suspension cultures, thus indicating JA as a putative signal between the external stimulus and the response by cells of alkaloid formation. Other breakthroughs were the first cloning of a JA biosynthetic enzyme, allene oxide synthase (AOS) in Brash’s lab (Song et al., 1993) and isolation of the first JA-insensitive mutant in Turner’s lab (Fey et al., 1994). This mutant was screened by use of coronatine, a bacterial toxin with structural and functional similarity to JA (coronatine-insensitive1, coi1). Four years later, Turner’s lab were able to clone the corresponding gene. COII codes for an F-box protein, which is part of the ubiquitin-mediated proteasome pathway (Xie et al., 1998). In the same year, the corresponding F-box protein in auxin signaling, TIR1 was cloned. Consequently, much effort was spent in trying to understand hormone signalling in molecular terms and this led to the identification of TIR1 as one of the auxin receptors.

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(Dharmasiri et al., 2005; Kepinski and Leyser, 2005). The JA receptor, however, is still unknown. Other important steps in understanding the action of jasmonates were the identification of mutants affected in JA-biosynthesis (cf. Turner et al., 2002), the identification of the first transcription factors regulating JA-responsive gene expression by Memelink’s group (van der Fits and Memelink, 2001), the proof that fatty acid β-oxidation acts in JA biosynthesis (Li et al., 2005), and the cloning of JA amino acid conjugate synthase (JAR1) by Stanwick’s lab (Stanwick et al., 2002; Stanwick and Tiryaki, 2004). Subsequent to the latter, interest was shifted to JA metabolism and the action of JA metabolites.

A number of reviews emphasizing different aspects of JA physiology have appeared in recent years (e.g. Walling, 2000; Blée, 2002; Feussner and Wasternack, 2002; Wasternack and Hause, 2002; Farmer et al., 2003; Halitschke and Baldwin, 2004; Howe, 2004; Mithöfer et al., 2004; Pauw and Memelink, 2004; Pozo et al., 2004; Browse, 2005; Rosahl and Feussner, 2005; Schilmiller and Howe, 2005; Wasternack, 2006). The following review will cover some recent results in biosynthesis, metabolism, signal transduction and action of jasmonates. I apologize for references not cited due to space limitations.

THE LIPOXGENASE PATHWAY

Lipid-derived signals

Membrane lipids consist of polyunsaturated fatty acids (PUFAs) esterified to glycerol in the sn1 and sn2 positions. The third position of glycerol is linked via an inorganic ester linkage to a phosphate group. The resulting lipid molecule phosphatidic acid (PA), and the cleavage product of phosphoinositol bisphosphate, inositol triphosphate (IP3), are known as signals in Ca2+ signalling and stress responses, respectively (Bargmann and Munnik, 2006). However, it is not only the main group of this class of lipids that may serve as secondary messengers, but their fatty acid residues, for example PUFAs, are also the source of further signals, such as oxylipins, which include jasmonates. Oxylipins originate from α-linolenic acid (18 : 3) (α-LeA) released from chloroplast membranes. Lipid hydrolizing enzymes belong to at least five different families (Dörmann, 2005): (1) phospholipase A1, which cleaves in the sn1 position; (2) phospholipase A2, which cleaves in the sn2 position; (3) patatin-like acyl hydrolases with phospholipase and glycolipase activity; (4) DAD-like lipases, which degrade phospholipids and galactolipids; and (5) SAG (senescence-associated gene) 101-like acyl hydrolases.

So far a link to JA biosynthesis has only been shown for the wound-induced phospholipase A2 (Navráz-Vázquez et al., 1999) and a DAD-like phospholipase A1. The Arabidopsis mutant dad1 exhibits delayed anther dehiscence, shorter filament length and JA deficiency in flowers, indicating role of DAD1 in JA biosynthesis and of JA in filament elongation (Ishiguro et al., 2001; see below). The corresponding DAD-like lipases of leaves are unknown.

Oxylipins generated in the lipoxgenase pathway

α-LeA released by lipase activity on chloroplast membranes is the substrate for numerous oxygenated compounds collectively called oxylipins including jasmonates, which comprise JA, JAME, JA amino acid conjugates and further JA metabolites (see below). The generation of oxylipins is initiated by lipoxigenases (LOXs), which form hydroperoxides from α-LeA (18 : 3) or linoleic acid (18 : 2) (Feussner and Wasternack, 2002). With α-LeA as the substrate, (13S)-hydroperoxyoctadecatrienoic acid (13-HPOT) or (9S)-hydroperoxyoctadecatrienoic acid (9-HPOT) are formed (Fig. 1). The corresponding products with linoleic acid as the substrate are (13S)-hydroperoxyoctadecadienoic acid (13-HPOD) and (9S)-hydroperoxyoctadecadienoic acid (9-HPOD). Although non-enzymatic oxygenation can take place by formation of phytoprostanes (Mueller, 2004), the LOX-catalysed reaction is indicated by the exclusive formation of the S-isomer. The increasing amount of LOX sequence data has allowed the construction of phylogenetic trees, which show gene families of different size for many plant species (Feussner and Wasternack, 2002). Analysis of the substrate-binding pockets by site-directed mutagenesis has revealed their role in the positional specificity of 9-LOXs and 13-LOXs (Liau vonchanka and Feussner, 2006). A change in the histidine residues in the binding pocket of a cucumber lipid-body 13-LOX led to a 9-LOX activity (Hornung et al., 1999). In addition to these structural requirements for positional specificity, clear differences were found for the expression of genes coding for 9-LOXs and 13-LOXs. Consequently, a concept for discrete 9-LOX and 13-LOX pathways was proposed (Howe and Schilmiller, 2002) and may explain the occurrence of numerous oxylipins (Fig. 1). The LOX products 13-HPOD and 13-HPOD represent branch points within the LOX pathway. At least seven different groups of compounds are formed by individual enzyme families (Feussner and Wasternack, 2002).

(1) Octadecanoids and jasmonates originating from 13-allene oxide synthase (13-AOSs) activity.
(2) Epoxyhydroxy-PUFAs formed by peroxygenases.
(3) Aldehydes, ω-oxo fatty acids and alcohols formed by hydroperoxy lyases (13-HPLs).
(4) Divinyl ether-containing PUFAs synthesized by divinyl ether synthases.
(5) Epoxyhydroxy PUFAs formed by epoxy alcohol synthases.
(6) Keto-PUFAs formed by LOXs.
(7) Hydroxy PUFAs formed by reductases.

Increasing examples are known where there are corresponding reactions with the 9-LOX products 9-HPOD and 9-HPOD. Subsequently acting enzymes should be specific for 9-LOX and 13-LOX products. Indeed, 9-HPLs and 13-HPLs as well as 9-AOSs and 13-AOSs have been characterized, thus supporting the concept of discrete 9-LOX and 13-LOX pathways (Stumpe and Feussner, 2006). In potato, there are two 13-AOSs and one 9-AOS (AOS3), which is...
highly specific for 9-hydroperoxides and leads in vitro to α- and γ-ketol formation (Stumpe et al., 2006). In below-ground organs, AOS3 is expressed in sprouting eyes, stolons, tubers and roots leading to α-ketol formation in vivo.

**JA BIOSYNTHESIS**

*The AOS branch in the LOX pathway: JA biosynthesis*

Conversion of 13-HPOT, the first step in JA biosynthesis, is carried out by 13-AOS, leading to an unstable allene oxide (Vick and Zimmermann, 1987). AOSs belong to the family of CYP74A enzymes, which are independent from molecular oxygen and NADPH, exhibit low affinity to CO and use the hydroperoxide group as a source for reducing equivalents and oxygen (Song et al., 1993; Feussner and Wasternack, 2002; Howe and Schilmiller, 2002). Based on structural information on AOS, an effective and selective inhibitor, JM-8686, has been designed (Oh et al., 2006). First cloned from flax seeds, more than 20 AOS sequences have been included in a phylogenetic tree analysis in which 9-AOSs and 13-AOSs were grouped separately (Stumpe and Feussner, 2006). With the exceptions of the AOS of...
guayule (Pan et al., 1995) and barley (Maucher et al., 2000), all of the 13-AOSs carry a plastid transit peptide. Plastid localization has been shown by immunolocalization and import studies, even for the barley AOSs that lack the transit peptides (Maucher et al., 2000; Froehlich et al., 2001). This compartmentation corresponds to the plastid location of 13-LOX, whereas 9-LOX activity was found in the cytosol (Feussner and Wasternack, 2002) (Fig. 2). The picture is, however, more complicated. The recently cloned potato 9-AOS is associated with amyloplasts and leucoplasts (Stumpe et al., 2006), and the recombinant AOS of A. thaliana exhibits dual 9-/13-specificity regulated by monomer-micelle association (Hughes et al., 2006). This raises the possibility that in vivo an AOS can be a versatile enzyme in respect to ‘substrate-specific’ membrane association and oligomeric state (Hughes et al., 2006).

The subsequent enzyme of the AOS branch, the allene oxide cyclase (AOC) is also plastid-located (Ziegler et al., 2000; Stintzi and Wasternack, 2000). Using the highly unstable allene oxide, the AOC establishes the enantiomeric structure at the cyclopentenone ring that occurs in JA. Non-enzymatic side-reactions in the absence of AOC are the formation of racemic OPDA and the cleavage to a- and γ-ketol (Fig. 1). Due to the instability of the allene oxide and the common localization of AOS and AOC, both enzymes were thought to be in close contact. But so far there is no proof on an AOS–AOC protein interaction (Zerbe et al., 2007). The AOC product cis(+)-12-oxophytodienoic acid (OPDA) is the final product of the plastid-localized part of JA biosynthesis. The subsequent step, reduction of the cyclopentenone ring, is catalysed by a peroxisomal OPDA reductase (OPR; Strassner et al., 2002). In Arabidopsis and tomato there are more than three enzymes, but only OPR3 exhibits specificity for cis(+)-OPDA (Schuller et al., 2000; Strassner et al., 2002). OPRs reduce conjugated enone structures including that occurring in OPDA. For OPR1 there are hints that the enzyme might be responsible for the formation of 9-ketodiienes, such as 9-KODE (Tani et al., 2006). The role of OPR3 in JA biosynthesis was shown by genetic evidence provided by the JA-deficient mutants opr3 and dde1, both affected in OPR3 (Sanders et al., 2000; Stintzi and Browse, 2000). All OPR3s cloned so far carry a peroxisomal target sequence, and a peroxisomal location of the OPR protein was shown by immunocytochemical techniques and by analysis of expression of OPR3 fused to a reporter gene (Strassner et al., 2002). Conversion of OPDA by the peroxisomal OPR3 raises the question as to how OPDA is released from the chloroplast and imported into peroxisomes. To date, an OPDA transporter of chloroplast membranes is unknown. For the import of OPDA or its CoA ester into peroxisomes, there is some evidence for transport by the ABC transporter COMATOSE (CTS), covering the PXA1 activity. The CTS mutant is partially JA-deficient, but is not male-sterile, a characteristic phenotype of complete JA-deficiency. Consequently, a parallel pathway of OPDA import by ion trapping has been suggested (Theodoulou et al., 2005).

Initial experiments with labelled OPDA revealed β-oxidative side-chain shortening as essential steps in JA biosynthesis (Miersch and Wasternack, 2000). More recently, for Arabidopsis and tomato genetic evidence has been described showing that enzymes of fatty acid β-oxidation, such as acyl-CoA oxidase of tomato (ACX1), a multifunctional protein (MFP) and a L-3-ketoacyl CoA thiolase all have a function in JA biosynthesis (Fig. 1) (Cruz Castillo et al., 2005; Li et al., 2005; Wasternack et al., 2006). Participation of ACX1 in JA biosynthesis was clearly shown by isolation of an acxl mutant of tomato exhibiting JA deficiency but accumulating OPDA upon wounding (Li et al., 2005). In Arabidopsis only the double mutant acxl/5 shows less JA formation upon wounding, indicating redundancy among the five ACX genes (Schilmiller et al., 2007). Further proof for role of fatty acid β-oxidation enzymes in JA biosynthesis has come from analysis of the aim1 mutant, affecting one of the MFPs, and the pex6 mutant, affecting peroxisome biogenesis (C. Delker et al., unpubl. res.; Leibniz Institute of Plant Biochemistry, Halle/Saale, Germany). β-oxidative steps take place only with the corresponding CoA ester. The formation of the OPDA–CoA ester in the chloroplast has been suggested, but not proven experimentally. There are, however, several indications for synthesis of OPDA–CoA ester in peroxisomes by 4-coumarate:CoA ligase-like (4-Cl-like) enzymes encoded by a small gene family in A. thaliana (Schneider et al., 2005). Interestingly, this type of enzyme is also able to activate downstream intermediates in JA biosynthesis such as OPC-8 (Schneider et al., 2005; Koo et al., 2006) or OPC-6 (E. Kombrink, pers. comm.; Max Planck Institute for Plant Breeding Research, Cologne, Germany). These data suggest different import reactions (free OPDA versus OPDA–CoA) and activation of OPDA (or its products) where it carries a different carboxylic acid side-chain to the corresponding CoA ester. It is, however, still unclear whether OPR3 can convert the OPDA–CoA ester. The existence of gene families for 4-CL-like enzymes and for genes encoding enzymes in β-oxidation, such as acyl CoA oxidase, suggest distinct and/or overlapping roles in β-oxidation of fatty acids and in the final steps of biosynthesis of JA. Similar β-oxidation steps were found for the final steps in auxin biosynthesis. Consequently, mutant analysis requires double or triple mutants in order to dissect the role in JA-dependent, auxin-dependent or β-oxidation (development)-dependent processes. These aspects have been recently reviewed (Baker et al., 2006).

Regulation of JA biosynthesis

All genes encoding enzymes of JA biosynthesis are JA-inducible (Wasternack, 2006), and promoters analysed so far increase their activity upon JA treatment (Kubisteltilg et al., 1999; I. Stenzel and C. Wasternack, unpubl. res.). This has led to the suggestion that JA biosynthesis is regulated by a positive feedback. Further experimental evidence for this has come from the following observations. (1) Mutants with constitutively elevated JA levels, such as cev, exhibit a phenotype characteristic for JA treatment (Ellis et al., 2002) and show elevated AOC expression (I. Stenzel and C. Wasternack, unpubl. res.). (2) JA-deficient mutants, such as opr3 or coi1, show...
decreased AOC expression (Stenzel et al., 2003b; I. Stenzel and C. Wasternack, unpubl. res.). Interestingly, as shown for tomato leaves by feeding experiments with deuterated OPDA, JA biosynthesis is not induced by endogenous jasmonates, which suggests extracellular perception of JA (Miersch and Wasternack, 2000). This has been substantiated by an autoradiographic study where applied labelled-JA was detected exclusively in the apoplast of tomato leaves (Bücking et al., 2004).

Gene expression data are only part of the information necessary to understand regulation of JA biosynthesis. For example, the fully developed leaves of A. thaliana carry LOX, AOS and AOC proteins abundantly (Stenzel et al., 2003b); however, JA-formation takes place only upon external stimuli, such as wounding. Furthermore, the wound-induced rise in JA is transient and appears before expression of LOX, AOS and AOC (Howe et al., 2000; Stenzel et al., 2003a,b), and plants over-expressing AOS or AOC constitutively do not show elevated JA levels before wounding or other stimuli (Laudert et al., 2000; Stenzel et al., 2003a). These data clearly show that JA biosynthesis is regulated by substrate availability. Finally, the tissue-specific location of JA biosynthetic enzymes contribute to the outcome in JA biosynthesis. In contrast to A. thaliana (Stenzel et al., 2003b), in tomato AOC is confined to vascular bundles (Hause et al., 2000) and even the sieve elements carry AOC protein (Hause et al., 2003); consequently, cell- and tissue-specific formation of JA has been considered to have a role in wound signalling (Schilmiller and Howe, 2005; Wasternack et al., 2006).

Arabidopsides: esterified oxylipins and protein-oxylipin adducts

Most of the substrates of many enzymes within the LOX pathway occur in free and esterified form. As well as the 18:2 and 18:3 PUFAs, their 9- and 13-hydroperoxides and 9- and 13-hydroxides have been found esterified in A. thaliana leaves and tomato flower organs (Stenzel et al., 2003b; Miersch et al., 2004).

Recently, esterified OPDA has received particular attention. First, esterified OPDA was found in galactolipids (MGDG) in the sn-1 position in untreated A. thaliana leaves (Stelmach et al., 2001). Subsequently, so-called arabidopsides A and B, derived from MGDG, and arabidopside C and D, derived from DGDG, were found containing OPDA and dinor-OPDA, respectively (Hisamatsu et al., 2003, 2005). Finally, 13-OPDA-, 18- and 16-carbon ketol-containing MGDG, DGDG and PC species were found (Buseman et al., 2006). The diversity of esterified OPDA and the large amount found in lipid membranes (Stelmach et al., 2001) raise the question as to its biological functions. OPDA exhibits individual signalling in plant defence reactions (Stintzi et al., 2001), and there is a specific subset of genes that is specifically expressed in response to OPDA (Taki et al., 2005). Hence release of esterified OPDA would greatly influence defence reactions. Indeed, wounding leads to a dramatic increase of free OPDA (Stelmach et al., 2001; Buseman et al., 2006). A specific function in the hypersensitive response of A. thaliana was found for a new esterified
OPDA, arabidopside E. Here, OPDA is bound to the sn1 and the sn2 position, and one dinor-OPDA to the galactose of MDGD (Andersson et al., 2006). This compound accumulates up to 7–8% of the total lipid content in a race-specific defence reaction against bacterial pathogens and inhibits bacterial growth in vitro (Andersson et al., 2006). This suggests an important role of the 13-LOX pathway in the hypersensitive response-(HR) associated cell death. Furthermore, there was an increase in non-enzymatically formed hydroxy fatty acids and F1-phytoprostanes (reviewed by Mueller, 2004) being esterified in membranes upon infection with a virulent and with an avirulent strain of Pseudomonas syringae that was up to 30-fold greater in level than that of the corresponding free compounds (Grun et al., 2007).

Whilst induction of plant senescence has been known for a long time as a characteristic property of JA (Ueda and Kato, 1980; Parthier, 1990; Wasternack, 2004), recently a much stronger senescence-promotion effect was shown for arabidopside A (Hisamatsu et al., 2006). It will be interesting to see whether arabidopside occurs in species other than Arabidopsis thaliana and which other JA-related processes are affected by these compounds.

Many oxylipins generated by the LOX pathway display cell toxicity and antimicrobial activity (Rusterucci et al., 1999; Prost et al., 2005). Therefore, the observation that oxylipins can be trapped by binding to lipid transfer proteins (LTPs) is an exciting result in helping to understand cell injury and the role of LTPs (Bakan et al., 2006). LTPs are ubiquitously occurring plant lipid-binding proteins known for a long time to be associated with developmental and stress responses. But their function is still unknown. Direct inhibitory activity of LTPs on microbes was initially hypothesized, but the role in stress signalling is now the preferred suggestion. This is strongly supported by the identification of an abundantly occurring LTP1 in germinating barley seeds, which is covalently modified by the α-ketol 9-hydroxy-10-oxo-12(Z)-octadecanoic acid. This reactive oxylipin is formed by 9-LOX and AOS activity and is specifically trapped by covalent linkage to LTP1 (Bakan et al., 2006). It will be interesting to know whether other LTPs form adducts with other oxylipins or hydrophobic molecules. Another putative candidate is a JA-binding LTP occurring in JA-loaded cells (Buhot et al., 2004)

First crystal structures of enzymes in JA biosynthesis

AOS. So far, there is no crystal structure determined for a higher plant AOS. Interestingly, in corals a fusion protein with LOX and AOS domains has been found (Koljak et al., 1997). These organisms form eicosanoid compounds similar to mammals. The AOS domain has weak activity and a sequence homology to a catalase. Recent crystal-structure analysis has revealed that in the coral AOS the switch from activity of a catalase to that of an AOS is facilitated (Oldham et al., 2005). It is possible that the LOX–AOS fusion protein has been evolved by successive mutations in discrete but interacting LOX and AOS proteins.

Recently the first crystal structure has been described for the AOC2 of A. thaliana (Hofmann et al., 2006). This is of special interest for understanding JA biosynthesis, since it is in the AOC reaction that the correct enantiomeric form of naturally occurring jasmonates is established. Knowledge of the crystal structure has led to insights into the oxylipin cyclization reaction. The stereoselectivity occurring in AOC catalysis was found to be a steric restriction for the essential substrate isomerization. Surprisingly, AOC2 of Arabidopsis was detected as a trimeric protein in crystals and in planta, and forms a hydrophobic binding cavity with two distinct polar patches (Hofmann et al., 2006). The folding pattern and sequence homology suggest that AOC2 is a member of the lipocalin family. This type of protein represents a widely distributed protein family characterized by a six- or eight-stranded β-barrel and a highly conserved motif with functions in the transport of small, hydrophobic molecules (Grzyb et al., 2006). Consequently, implications for functions in cell growth, membrane biogenesis, induction of apoptosis, environmental stress responses and regulation of immune stress responses have been suggested (Charron et al., 2005). The identification of AOC2 as a member of plant lipocalins is exciting and sheds new light on the diverse functions of lipid-based signalling and jasmonates.

OPR1 and OPR3. OPRs belong to a family of flavoproteins identified first with Warburg’s old yellow enzyme (OYE). OYEs reduce the C=C double bond of α,β-unsaturated carbonyl compounds, but only for OPR3 has a physiological function been identified. This enzyme reduces all four 1-stereoisomers of OPDA with preference for the only intermediate in JA biosynthesis, (9S,13S)-OPDA, whereas OPR1 reduces (9R,13R)-OPDA (Schaller et al., 1998, 2000). This specificity for enantiomers has now been explained by the crystal structures of OPR1 (Breithaupt et al., 2001) and OPR3 (Breithaupt et al., 2006). The overall structures of OPR1 and OPR3 are very similarly characterized by a (βα) barrel fold. The substrate-binding cavity, however, reveals a narrow entrance for OPR1 and a more ‘released’ cavity for OPR3 (Breithaupt et al., 2006). Surprisingly, OPR3 was found as an extraordinary self-inhibited dimer in the crystal structure. A weak association in vitro but a strong dimerization in vivo by a putative phosphorylation at Tyr-364 has been suggested as a regulatory mechanism for OPR3 (Breithaupt et al., 2006). This scenario accords with an activation of pre-existing JA biosynthetic enzymes leading to the early rise in JA before expression of JA biosynthetic genes (Stenzel et al., 2003a, b).

ACX1. In the recently isolated tomato mutant acc1, a single point mutation of the conserved residue Thr138 is substituted by isoleucine (Li et al., 2005). The crystal structure of tomato ACX1 showed an unusual packing arrangement compared to other ACX enzymes (Powers et al., 2006); in tomato ACX1, three monomers form an asymmetric unit.
METABOLITES OF JA

Diversity among naturally occurring jasmonates and structure–activity relationships

Since the first isolation of JAME as a constituent of the oil of Jasminum grandiflorum (Demole et al., 1962), numerous jasmonate compounds have been detected in diverse plant phyla (Meyer et al., 1984). Jasmonates occur in algae, mosses, fungi, gymnosperms and angiosperms. The capacity to form or to convert various jasmonates is remarkably high in fungi; for example, more than 20 jasmonates were detected in culture filtrate of Fusarium oxysporum (Miersch et al., 1999a), whilst Aspergillus niger grown on liquid medium could form more than 25 jasmonate compounds upon application of JA, 9,10-dihydro-JA and their methyl esters (Miersch et al., 1999c). Some fungi, such as Botryodiplodia theobromae, are able to accumulate up to 500 µg mL⁻¹ of culture medium of (+)-7-iso-JA, the initial product in JA biosynthesis (Miersch et al., 1989). Whereas in fungi the biological function of various jasmonates is unknown, application of jasmonates and their structural analogs to higher plants led to the first insights into their structural requirements for biological activity. Based on different assays, such as alkaloid formation (Blechert et al., 1995), tendril coiling (Blechert et al., 1999), tuber formation (Koda, 1992), or gene expression (Miersch et al., 1999b), the following structural requirements have been found (Fig. 3).

1. (−)-JA and its derivatives are more active than (+)-derivatives.
2. An intact pentenyl side-chain is most active, whereas hydroxylation at C-11 or C-12 and reduction between C-11 and C-12 reduce biological activity.
3. Chain elongation of the carboxylic acid side-chain retains activity only with an even number of C-atoms.
4. Activity is retained or increased by methylation or conjugation to amino acids.
5. A cyclopentanone ring carrying a keto group at C-6 is essential.

More recently, highly active JA compounds such as coronalon (Schüler et al., 2004) and other 6-substituted 4-oxo- indanoyl-isoleucine conjugates have been synthesized (Mithöfer et al., 2004). The construction of these compounds was deduced by modelling based on the structure of the bacterial toxin coronatine. The extremely high biological activity of coronatine has been used as a tool and has led to isolation of the first JA-insensitive mutant of A. thaliana, coi1 (Feys et al., 1994). Recent data have revealed distinct responses for JA and coronatine (Uppalapati et al., 2005).

Metabolic fate of JA

Homoestasis between various metabolites is a common mechanism in plants to sustain the level of active hormones such as auxins, cytokinines, gibberellins and jasmonates. In the case of JA, seven different metabolic routes have been suggested by identification of the corresponding products, but only a few enzymes have been cloned so far (Fig. 4).

1. Formation of amino acid conjugates by a JA conjugate synthase (JAR1) (Staswick and Tiryaki, 2004) upon adenylation at the carboxylic acid side-chain of JA by the AMP-transferase activity of JAR1.
2. Methylation of JA by a JA-specific methyl transferase (Seo et al., 2001).
3. Hydroxylation at C-11 or C-12 of the pentenyl side-chain and subsequent O-glucosylation (Sembdner and Parthier, 1993; Swiatek et al., 2004) or sulfation (Gidda et al., 2003).
4. Decarboxylation of JA to cis-jasmone (Koch et al., 1997).
5. Formation of cucurbic acids by reduction of the keto group of the cyclopentanone ring (Sembdner and Parthier, 1993).
6. Formation of jasmonoyl-1-β-glucose, jasmonoyl-1-β-gentiobiose and hydroxyjasmonoyl-1-β-glucose (Swiatek et al., 2004).
7. Conjugation of the ethylene precursor ACC to JA (Staswick and Tiryaki, 2004).

JA amino acid conjugates are permanent constituents of plant tissues (Sembdner and Parthier, 1993) and their levels increase upon osmotic stress (Kramell et al., 1995).
In barley leaves applied JA amino acid conjugates are active per se without cleavage (Kramell et al., 1997). Many of them induce a subset of genes compared with JA or JAME (Kramell et al., 2000). Among the various conjugates, JA-Ile mainly accumulates in leaves (Kramell et al., 1997), flowers (Hause et al., 2000) and mycorrhizal roots (Hause et al., 2002, 2007). This preference is reflected by the enzymatic properties of the JA amino acid conjugate synthase (JAR1), and the jar1 mutant can be complemented by JA-Ile (Staswick and Tiryaki, 2004). JAR1 belongs to a large gene family encoding enzymes that adenylate a carboxylic acid-containing substrate followed by exchange with a second substrate. In the case of JAR1, AMP is exchanged with an amino acid (Staswick et al., 2005; Staswick and Tyriaki, 2004). Similar reactions are catalysed by auxin conjugate synthase (Staswick et al., 2005) and 4-CL-like CoA ligases activating OPDA or OPC-8 to the corresponding CoA esters (Schneider et al., 2005; Koo et al., 2006). The tobacco homologue of JAR1 has recently been cloned as JAR4 from N. attenuata (Kang et al., 2006). Interestingly, JAR4-silenced plants were shown to be more susceptible to Manduca sexta attack, indicating the role of JA-Ile in plant defence. Another JA metabolite highly active in plant–insect interactions was cis-jasmon. Jasmonate-induced swelling of mitochondria and release of cytochrome c was observed, this being characteristic for an apoptotic pathway (Kim et al., 2004; Rotem et al., 2005). The selectivity of jasmonates on cancer cells was surprisingly high. Another target of jasmonates was detected in human myeloid leukemia cells. Here, jasmonates exert a growth-inhibitory and differentiation-induced effect by activating a NO-activated protein kinase (MAPK) pathway in a cAMP-independent manner (Ishi et al., 2004). Among the various jasmonates tested, a methyl-4,5-didehydrojasmonate was 30-times more active than JAME. Jasmonates have not been detected so far in mammalian cells, but they are ubiquitous in plants. Some plant extracts have for a long time been used as therapeutic agents in cancer therapy. It will be interesting to see whether such plants contain high levels of jasmonates.

Jasmonates as signals in biotic and abiotic stresses

Solanaceae. One of the best-studied signal-transduction pathways of jasmonates is that of wound-response, which was initially studied mainly in tomato. Briefly, a sequential action of the 18-aa peptide systemin, cleaved from proystemin upon local wounding, activates JA biosynthetic enzymes such as AOC and leads to local rise in JA (Fig. 5). An amplification in JA formation has been suggested due to JA-dependent PROSYSTEMIN expression, a systemin-dependent AOC expression, and their common location in vascular bundles (Stenzel et al., 2003a; Narváez-Vásquez and Ryan, 2004). It is possible that JA acts as a systemic signal, leading also to systemic expression of genes encoding proteinase inhibitors (PINs) and other foliar compounds with negative effects on herbivore performance. Consequently the plant becomes immunized against a subsequent herbivore attack. Grafting experiments with JA-deficient and JA-signalling mutants in G. Howe’s laboratory have shown that JA...
signalling – but not JA biosynthesis – is necessary in the systemic leaf. The numerous data on the wound response pathway have been reviewed repeatedly, including discussions on cross-talk to other signals, further elements of the wound-response pathway such as MAP kinases, and additional herbivore-induced compounds such as volatiles and their consequences for diverse plant–insect interactions, together with overlap to plant pathogen–interactions (Farmer et al., 2003; Howe, 2004; Schilmiller and Howe, 2005; Wasternack, 2006). Here, I want to mention only few important new developments.

For a long time, an active systemin was found only in tomato (*Solanum lycopersicon*), but not in tobacco. Even in the closely related *Solanum nigrum* the systemin-homolog of *Solanum lycopersicon* is not active in defence responses (Schmidt and Baldwin, 2006). In tobacco, hydroxyproline-rich homologs of tomato systemin have been found that do not induce PIN expression in tomato (Pearce et al., 2001; Pearce and Ryan, 2003). Recently, peptides active in wound-signalling have been identified outside the Solanaceae species. In *A. thaliana* a 23-aa peptide (AtPEP1) processed from a 92-aa precursor is part of the innate immune response (Huffaker et al., 2006). *PROPEP1* expression is induced by wounding, JA and ethylene leading to H$_2$O$_2$ formation and PDF1-2 expression. *Arabidopsis thaliana* plants over-expressing *PROPEP1* show altered root development and enhanced resistance to the root pathogen *Pythium irregulare*. *PROPEP1* belongs to a small gene family, and AtPEP1 exhibits striking similarities in structure and function to tomato systemin (Huffaker et al., 2006). The receptor of AtPEP1 has been isolated and characterized as a functional LRR receptor, which is active even if transformed in tobacco (Yamaguchi et al., 2006). The link between defence against pathogens and wound signalling provided by AtPEP1 suggests that receptor-mediated defence-signalling peptides generated upon wounding may amplify defence against pathogens in *A. thaliana* (De Vos et al., 2006). Resistance against pathogens can also be increased by modified emission of green-leaf volatiles initially released upon herbivory (Shiojiri et al., 2006).

The JA-mediated wound response following herbivore attack leads to indirect (volatile emissions) and direct (formation of defence proteins and small compounds) defence (cf. reviews by Halitschke and Baldwin, 2004; Howe, 2004; Pieterse et al., 2006), and even mechanical wounding is sufficient to give a volatile pattern similar to that caused by herbivore attack (Mithöfer et al., 2005). Among the defence proteins formed in tomato there are PINs that are thought to inhibit proteolytic degradation in the midgut of herbivores. Herbivore-induced proteins in tomato also include leucine aminopeptidases, threonine deaminase (TD) and arginase (Walling, 2000; Chen et al., 2004). Their direct role in the digestive tract of herbivores has recently been shown (Chen et al., 2005). All these wound-induced plant proteins were detected in the midgut, and TD showed extremely high activity (Chen et al., 2005). TD catalyzes the initial step in isoleucine biosynthesis of plants and bacteria and is negatively regulated by Ile via a C-terminal regulatory domain. Interestingly, the TD occurring in the midgut of a herbivore following infestation on tomato leaves lacked its regulatory domain. Consequently,
threonine degradation could take place in the presence of high Ile concentrations. Correspondingly, larvae infested on transgenic lines over-expressing arginase exhibited high arginase activity in their midgut and produced much less weight (Chen et al., 2005). Obviously, catabolism of higher amino acids in the midgut of herbivores following their infestation on leaves acts synergistically to the deterrent role of PINs. The appearance within the midgut of a distinct set of proteins with altered properties, as in case of TD, and their anti-nutritional effects by perturbing amino acid homoeostasis may be evolved in plants such as Solanaceae species attacked by herbivores. Dual strategies seem to occur. The TD can exert an anti-nutritive defence in the midgut of herbivores, and within the plant contributes to the formation of Ile as an essential substrate for synthesis of JA-Ile, a highly active wound-response signal. In TD-silenced tobacco plants, JA-Ile-dependent defences are impaired (Kang et al., 2006). It is possible that chemically based and developmentally based defence strategies co-evolved: the central element of JA-regulated gene expression, COI1, an F-box protein functioning in the SCF proteasome pathway, is essential for proper trichome development of tomato (Li et al., 2004), and PIN2 of Solanum americanum is constitutively expressed in glandular trichomes and positively regulates trichome density (Liu et al., 2006).

**Arabidopsis.** Analyses of transcript accumulation upon wounding or pathogenic attack have greatly improved our understanding of plant responses to biotic and abiotic stress (Pieterse et al., 2006). Mutants in JA biosynthesis and JA signalling have become an important tool in dissecting signalling pathways and in determining signalling properties of JA and related compounds (Turner et al., 2002; Lorenzo and Solano, 2005; Delker et al., 2006; Wasternack, 2006). Initial expression analyses with the JA-deficient but OPDA-accumulating opr3 mutant revealed OPDA-specific gene expression (Stintzi et al., 2001). Following the first large-scale transcription analysis, genes could be grouped into COI1-dependent and COI1-independent types (Reymond et al., 2000, 2004). Recent transcription analyses have shown distinct and overlapping groups of genes being expressed dependently and independently with respect to COI1, OPDA and JA (Devoto et al., 2005; Taki et al., 2005). Similar differences and overlaps in action have been found at the level of transcription factors acting in JA-/OPDA-dependent processes (Fig. 6). Among transcription factors acting downstream of JA in stress responses are the ethylene response factor 1 (ERF1), the bHLHZip-type transcription factor ATMYC2 (Lorenzo et al., 2004), WRKY70 and the newly found family of ORAs (identified by J. Memelink’s group). ORAs are the Arabidopsis homologs of ORCAs initially identified in Catharanthus roseus cell suspension cultures (Memelink et al., 2001). Among them, ORA47 is a COI1-dependent positive regulator of JA biosynthesis, whereas ORA59, ERF1, ORA37, MYC2 and WRKY70 act positively or negatively on different groups of defence genes (Fig. 6). The antagonistic action of MYC2 and ERF1 may cause the independence between wound signalling and pathogen-defence signalling (Lorenzo et al., 2004; Lorenzo and Solano, 2005).

**Jasmonates in development**

Some aspects on role of jasmonates in developmental processes are summarized in Table 1.

**Root growth inhibition.** This was one of the first physiological effects detected for JA (Dathe et al., 1981; Staswick et al., 1992). JA or its methyl ester supplemented to the

### Table 1. Jasmonates in development

<table>
<thead>
<tr>
<th>Developmental process</th>
<th>Putative signal</th>
<th>Alteration/species</th>
<th>Reference for initial observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root growth</td>
<td>JA, JA-Ile</td>
<td>Inhibition</td>
<td>Dathe et al. (1981); Staswick et al. (1992)</td>
</tr>
<tr>
<td>Seed germination</td>
<td>JA</td>
<td>Inhibition</td>
<td>Corbaneau et al. (1988)</td>
</tr>
<tr>
<td>Tuber formation</td>
<td>12-OH-JA</td>
<td>Induction/potato</td>
<td>Yoshihara et al. (1989)</td>
</tr>
<tr>
<td>Tendril coiling</td>
<td>OPDA</td>
<td>Stimulation/Bryonia</td>
<td>Falkenstein et al. (1991)</td>
</tr>
<tr>
<td>Nyctinasty</td>
<td>12-OH-JA Glu</td>
<td>Stimulation/Ambizia</td>
<td>Nakamura et al. (2006)</td>
</tr>
<tr>
<td>Trichome formation</td>
<td>JA</td>
<td>Induction/tomato</td>
<td>Li et al. (2004)</td>
</tr>
<tr>
<td>Senescence</td>
<td>JA</td>
<td>Stimulation</td>
<td>Ueda and Kato (1980)</td>
</tr>
<tr>
<td>Flower development</td>
<td>JA</td>
<td>Induction/Arabidopsis</td>
<td>McCaonn and Browse (1996)</td>
</tr>
<tr>
<td>Anther development +</td>
<td>JA</td>
<td>Induction</td>
<td>Li et al. (2004)</td>
</tr>
<tr>
<td>Female organ</td>
<td>JA</td>
<td>Induction/tomato</td>
<td>Stintzi and Browse (2000)</td>
</tr>
<tr>
<td>development + dehiscence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filament elongation</td>
<td>JA</td>
<td>Induction/Arabidopsis</td>
<td></td>
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</tbody>
</table>
growth medium are active in a picomolar range. Consequently, JA-insensitive mutants such as coil, jin1, or jar1 are similar in root length upon JAME treatment compared with the untreated wild type (Fig. 7). In contrast, mutants such as cev1, cet1, joo2 or cex1 that are characterized by constitutive over-expression of JA-responsive genes due to constitutively elevated JA levels have reduced root length and a stunted growth phenotype similar to JA-treated plants (Ellis et al., 2002). Most mutants that are affected in components of JA- and COI-dependent signal transduction (including transcription factors such as MYC2, the SCF proteasome and its upstream-acting proteins such as AXR1, JAI4/SGT1b or MPK4) exhibit a reduction in root-growth inhibition (Fig. 6; cf. Browse, 2005; Wasternack, 2006).

Tuber formation. This has been known for a long time to be induced by 12-OH-JA (tuberonic acid; Yoshihara et al., 1989), the glucoside of which has been suggested to be the transport form. Initially, 12-OH-JA was found mainly in Solanaceaen species. More recently, it has been detected in A. thaliana and identified as the substrate of a sulfotransferase (AtST2a), one of the 18 sulfotransferases occurring in the Arabidopsis genome (Gidda et al., 2003). A recent screening revealed abundant occurrence of 12-OH-JA in different tissues and plant species, for example seeds of Glycine max (O. Miersch and C. Wasternack, unpubl. res.).

Tendril coiling and touch. Touch-mediated processes in plants are initiated by specific organs, such as tactiles. In the case of tendril coiling in Bryonia, a highly sensitive JA-dependent mechanism has been found (Falkenstein et al., 1991; Weiler, 1997). Inspection of the response kinetics revealed that OPDA was more active than JA, and this was substantiated by the endogenous rise of OPDA upon touch (Stelmach et al., 1998; Blechert et al., 1999). More recently, an excellent approach combining cell biology, chemistry and biochemistry has given indications as to how nycytinasty takes place in Albizia plants. The leaf movement of Albizia was shown to be dependent on a specific enantiomer of 12-OH-JA-O-glucoside, which binds with cell-type-specificity to the motor cells of leaves of Albizia julibrissica (Nakamura et al., 2006).

Flower development. This is essentially linked to intact JA biosynthesis and JA signalling. Clear evidence for a JA-dependent phenotype in flower development has come from Arabidopsis mutants affected in JA biosynthesis, such as dad1, fad3-2fad7-2fad8, dde2-2, dde1, opr3 and aim1 as well as mutants in JA-signalling, such as coil. All these mutants are male-sterile due to delayed anther development and incomplete anther dehiscence, or are impaired in filament elongation (cf. Turner et al., 2002; Delker et al., 2006). Surprisingly, in Arabidopsis an impaired F-box protein COI1 leads to male sterility, whereas its tomato homolog is essential for proper female fertility (Xie et al., 1998; Li et al., 2004).

The reduced filament elongation in JA-deficient mutant such as dad1 and opr3 corresponds to reduced JA levels in filaments of the double mutant arf6/arf8. These mutants are impaired in two auxin response factors responsible for proper filament elongation, and they indicate auxin signalling upstream of JA (Nagpal et al., 2005). Recently, a large-scale analysis of gene expression in opr3 stamen development following JA treatment has led to an excellent overview on JA-dependent processes in stamen development (Mandaokar et al., 2006). Among 13 transcription factors identified to function in stamen maturation, two of them, MYB21 and MYB24, are JA-inducible and mediate the jasmonate response during stamen development (Mandaokar et al., 2006).

Specific roles for JA and other oxylipins are also suggested by the abundant occurrence of AOC protein in ovules of tomato flowers and by the distinct oxylipin signature in different tomato-flower organs (Hause et al., 2000) (Fig. 8). The total amount and the ratio between OPDA and JA can be increased by constitutive over-expression of AOC (Miersch et al., 2004). It will be interesting to see whether the oxylipin signature is responsible for distinct steps in flower development, flower abscission, embryo development and seed formation.

Senescence. One of the first biological activities observed for jasmonates was the senescence-promoting effect (Ueda and Kato, 1980; Parthier, 1990). Although it occurs ubiquitously following JA treatment, monocotyledonous plants are more sensitive. Senescence is the last stage in plant development. Consequently, genes expressed during leaf senescence (senescence-associated genes, SAGs) code for proteins with functions in sink/source relationships, photosynthesis, intermediary metabolism, proteolysis and plant defence (cf. Wasternack and Hause, 2002; Wasternack, 2004). The role of JA in senescence is linked to (1) downregulation of housekeeping proteins encoded by photosynthetic genes and (2) upregulation of genes active in defence reactions against biotic and abiotic stresses (Wasternack, 2004, 2006). Several microarray analyses have led to more detailed

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**Fig. 7.** Root growth inhibition by 100 μM methyl jasmonate in wild-type (Col) and the JA-insensitive mutant coil-16 (photograph: C. Delker).
information, including cross-talk between plant hormones (Lin and Wu, 2004; Buchanan-Wollaston et al., 2005; van der Graaff et al., 2006). A direct role of JA in leaf senescence of *A. thaliana* was shown by expression-analysis of JA biosynthetic genes (He et al., 2002). Another molecular explanation for the role of JA in leaf senescence was given by identification of a novel nuclear-localized CCCH-type zinc finger protein in rice (Kong et al., 2006). This protein acts as a negative regulator of the JA pathway and leads to a delay in the onset of leaf senescence. Another negative regulator of senescence is ORE9, an F-box protein (Woo et al., 2001). However, there are also JA-independent processes in leaf senescence, as shown by identification of NAC family transcription factors that have an important role in leaf senescence (Guo and Gan, 2006).

CONCLUSIONS

In the last few years interesting new data on JA biosynthesis and action have appeared. Crystal structures for several JA biosynthetic enzymes now allow molecular explanations for substrate specificity. Fatty acid β-oxidation enzymes and 4-Cl-like CoA ligases have been identified to function in JA biosynthesis. New esterified oxylipin derivatives such as the arabidopsides suggest new functions in defence reactions. Occurrence and specific functions of JA metabolites have been detected. Transcription factors acting in JA signalling have shed new light on cross-talk in signalling pathways that are active following biotic and abiotic stresses, as well as in developmental processes. Finally, it is possible that a putative role of jasmonates in cancer formation may be substantiated.

Future work will address questions on specific actions of JA metabolites, on JA and oxylipin perception, on MAP kinases active in JA signalling, on the diversity of action of JA in plant–plant and plant–microbe interactions; and, finally, cell- and organ-specific functions of jasmonates in plant development will be analysed.

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### APPENDIX

*Abbreviations used in the text*

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACX</td>
<td>Acyl-CoA oxidase</td>
</tr>
<tr>
<td>α-LeA</td>
<td>α-linolenic acid</td>
</tr>
<tr>
<td>AOC</td>
<td>Allene oxide cyclase</td>
</tr>
<tr>
<td>AOS</td>
<td>Allene oxide synthase</td>
</tr>
<tr>
<td>ERF1</td>
<td>Ethylene response factor 1</td>
</tr>
<tr>
<td>HPL</td>
<td>Hydroperoxide lyase</td>
</tr>
<tr>
<td>HPOD</td>
<td>Hydroperoxyoctadecadienoic acid</td>
</tr>
<tr>
<td>HPOT</td>
<td>Hydroperoxyoctadecatrienoic acid</td>
</tr>
<tr>
<td>IP₃</td>
<td>Inositol triphosphate</td>
</tr>
<tr>
<td>JA</td>
<td>Jasmonic acid</td>
</tr>
<tr>
<td>JAME</td>
<td>Jasmonic acid methyl ester</td>
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<tr>
<td>JAR1</td>
<td>JA conjugate synthase</td>
</tr>
<tr>
<td>JIP</td>
<td>Jasmonate-induced protein</td>
</tr>
<tr>
<td>LOX</td>
<td>Lipooxygenase</td>
</tr>
<tr>
<td>LTP</td>
<td>Lipid transfer protein</td>
</tr>
<tr>
<td>MFP</td>
<td>Multifunctional protein</td>
</tr>
<tr>
<td>OPDA</td>
<td>cis(−)-12-oxophytodienoic acid</td>
</tr>
<tr>
<td>OPR</td>
<td>OPDA reductase</td>
</tr>
<tr>
<td>OYE</td>
<td>Warburg’s old yellow enzyme</td>
</tr>
<tr>
<td>PA</td>
<td>Phosphatidic acid</td>
</tr>
<tr>
<td>PIN</td>
<td>Proteinase inhibitor</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acid</td>
</tr>
<tr>
<td>SAG</td>
<td>Senescence-associated gene</td>
</tr>
<tr>
<td>TD</td>
<td>Threonine deaminase</td>
</tr>
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</table>