CHAPTER 9

FLAVONOIDS AS SIGNAL MOLECULES

Targets of Flavonoid Action

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1. INTRODUCTION

Plant-derived foods that are rich in flavonoids are regularly touted in the popular press for their benefits in ameliorating age-related diseases. A majority of these reports focus on the antioxidant characteristics of flavonoid-rich diets and their enhancement of cardiovascular health. However, a growing number of reports in the pharmacology literature characterize flavonoid interactions with cellular components implicated in neurological pathologies and cancer. As the effective flavonoid concentrations employed in pharmacological studies utilizing cell cultures are often orders of magnitude higher than the serum concentrations seen in humans, some discrimination is required when interpreting these reports. Further, as flavonoids often mimic endogenous mammalian receptor ligands (Ciolino et al., 1999; Hunter et al., 1999; Virgili et al., 2004) or interfere with the uptake of substrates not found in plants, the applicability of such studies to plant models requires caution. However, studies of flavonoid function in animal cells often provide important insights into their functions as signal molecules in plants.

Nearly every class of flavonoid has been shown to have biological activity, with a majority related to antioxidant properties. In plants, flavonoids appear to contribute to a general reduction of reactive oxygen species and therefore impact cellular processes sensitive to REDOX effects. However, flavonoids also have been implicated in more direct interactions with transport and signal transduction pathways. One well-documented example is the role of flavonoids in fertility: while a few flavonoid-deficient plants are able to germinate, grow, and set fertile seed,

most plants require flavonoids for fertility and normal pollen development. Another is flavonoid modulation of auxin transport as well as localized auxin accumulations observed during nodulation. Perhaps the best-studied example of flavonoid signaling is that of flavonoid mediation of interactions between the plants and other organisms in the environment at both competitive (allelopathy/defense) and cooperative (mycorrhizal association) levels.

In the balance of this chapter, we review potential and known molecular targets of flavonoid signaling and plant processes where flavonoids have been implicated in regulatory functions. We then describe flavonoid-dependent internal signaling processes and extraorganismal biotic interactions mediated by flavonoid signaling.

2. MOLECULAR TARGETS OF FLAVONOID ACTION

At the molecular level, potential targets of flavonoid regulation in plants range from transcription factors and kinases to ATP-binding cassette (ABC) transporters and aminopeptidases. Some of these targets are suggested primarily by similarities between plant and mammalian signaling mechanisms. Other endogenous or exogenous targets, such as receptors, ABC transporters, and hydrolases, have been directly demonstrated *in planta* or *in vivo*. Most of these interactions have been shown to be developmentally regulated. These potential and known targets are categorized below.

2.1. Transcription

Nuclear localization of flavonoids has been reported in many plant species, suggesting that flavonoids may function in transcriptional regulation of endogenous gene expression. Reports of sulfonated flavonols in nucleus in *Flaveria chloraefolia*, (Grandmaison and Ibrahim, 1996) and unidentified phenolic compounds in *Brassica napus* also were localized in the nucleus but not nucleolus (Kuras et al., 1999; Stefanowska et al., 2003). Nuclear localization of flavonols also has been shown in *Arabidopsis thaliana* (Peer et al., 2001; Buer and Muday, 2004; Saslowsky et al., 2005) and flavanols in *Tsuga canadensis*, *Taxus baccata*, *Metasequoia glyptostroboides*, *Coffea arabica*, *Prunus avium,* and *Camellia sinesis* (Feucht et al., 2004a, 2004b). Catechin binding of histone proteins has been demonstrated in plants (Polster et al., 2003; Feucht et al., 2004b), suggesting that catechins might modulate nonspecific gene transcription. Naringenin chalcone and apigenin also may influence flavonoid biosynthesis by regulating transcription of flavonoid biosynthetic enzymes (Pelletier et al., 1999) (see Chapter 4 for more details). Recent evidence that the flavonoid biosynthetic enzymes chalcone synthase (CHS) and chalcone isomerase (CHI) are localized in the nucleus, in addition to the cytoplasm, in *A. thaliana* suggests that flavonoid regulation of transcription is developmentally regulated at the subcellular level (Saslowsky et al., 2005). This observation also is consistent differential localization of phenolics in subcellular compartments observed throughout seed development and germination (Kuras et al., 1999; Stefansowska et al., 2003).

There also is evidence for flavonoid regulation of gene transcription in other organisms, like rhizobacteria. Flavonoids in root exudates from host plants are required for transcription of NodD, a bifunctional transcriptional repressor/activator of the *nod* genes in *Rhizobium leguminosarum*, in order for nodulation to occur. NodD represses its own transcription by competing with RNA polymerase (RNAP) for RNAP binding site (Hu et al., 2000). Naringenin, but not luteolin, relieves NodD binding to RNAP; thereby *nodD* can be transcribed and NodD can activate the other *nod* genes (Hu et al., 2000). The roles of flavonoids in nodulation is further developed in Section 3.2.4.

Pharmacological studies of flavonoid effects on mammalian transcription suggest other potential sites of regulation in plants. Quercetin inhibition of histone H1 and H2AX phosphorylation and genistein inhibition of H2AX phosphorylation has been documented (Notoya et al., 2004; Ye et al., 2004). Glucopyranosides of kaempferol and quercetin also specifically bind DNA polymerase α *in vitro* (Mizushina et al., 2003); however, *in vivo* binding and subsequent transcriptional induction or repression has not been shown. Flavonoids also may affect transcription by inhibiting topoisomerase (topo) activity: quercetin, myricetin, fisetin, and morin inhibited both topo I and II activity, while kaempferol, phloretin, and apigenin specifically inhibited topo II (Constantinou et al., 1995; Boege et al., 1996), and quercetin, kaempferol, and naringenin stabilized the topo II-DNA complex (Constantinou et al., 1995).

Most of the regulation of transcription by flavonoids appears to involve inhibition of phosphorylation signaling cascades or specific kinases. Quercetin specifically inhibited tumor necrosis factor α (TNFα) transcription through inhibition of phosphorylation of c-Jun N-terminal kinase/stress activated protein kinase (JNK/SAPK), thereby suppressing activator protein-1 (AP-1) from binding to TNFα promoter (Wadsworth et al., 2001; Chen et al., 2004). Apigenin inhibited inhibitor κB kinase (IκB) activity, thereby inhibiting nuclear factor κB (NF-κB)-dependent COX-2 transcription (Liang et al., 1999; O'Leary et al., 2004). The flavonols kaempferol and quercetin inhibited transcription factor AP-1 activation of nitric oxide synthase expression while the isoflavone genistein did so via NF-κB inhibition (Kim et al., 2005). Quercetin inhibited an AKT/protein kinase B (PKB) and extracellular signal-related kinase (ERK) phosphorylation and also activated transcription factor cAMP-responsive element-binding protein (Spencer et al., 2003). Quercetin activated transcription of heme oxygenase-1 via mitogen-activated protein kinase (MAPK) signaling cascade, but inhibited ERK (Lin et al., 2004). Apigenin inhibited expression of vascular endothelial growth factor and hypoxia-inducible factor-1α via PIPK/AKT and HDM2/p53 (which regulates MAPK) pathways (Fang et al., 2005). Apigenin also has been shown to inhibit Ras signaling (Klampfer et al., 2004).

2.2. Translation

As yet, there is no evidence for direct flavonoid modulation of translation in plants. However, flavonoids have been shown to affect mammalian translation by altering

phosphorylation status. Genistein and quercetin were found to inhibit protein synthesis in mouse tumor cells via phosphorylative activation of eIF2-α kinases (Ito et al., 1999), and genistein decreased late viral mRNA translation via a tyrosine kinase-dependent mechanism (Xi et al., 2005).

2.3. Enzyme activity and signal transduction

There is increasing evidence that specific proteins or groups of proteins exhibit more specific interactions with flavonoids *in vivo*. Many of these interactions have been shown to depend on the B-ring substitution pattern of the interacting flavonoids (Marko et al., 2004). Flavonols are the most common of these molecules, and their high degree of activity is suggested by the tight developmental and spatial regulation of flavonol synthesis (Murphy et al., 2000; Peer et al., 2001). Several targets and potential targets have been identified in *Arabidopsis*: AtAPM1, a microsomal tyrosine aminopeptidase; the tyrosine phosphatase AtPTEN1 (phosphatase and tensin homolog); PINOID (PID), a serine/threonine kinase; ROOTS CURL IN NAPHTHYLPHTHALMIC ACID1 (RCN1); the subunit A of protein phosphatase 2A (PP2A); a mitogen-activated protein kinase (MAPK); a phosphatidyl inositol-3,4,5-triphosphate kinase, (PIPK); and auxin oxidase (IAA oxidase), a peroxidase-like enzyme. In *Arabidopsis*, flavonol accumulations have been noted in regions where AtAPM1, AtPTEN1, PID, and RCN1 are expressed (Deruere et al., 1999; Benjamins et al., 2001; Gupta et al., 2002; A. Murphy, unpublished).

AtAPM1, a dual function protein containing both enzymatic and protein trafficking domains, is a homolog of the mammalian aminopeptidase M (APM)/insulin-responsive aminopeptidase (IRAP) and aminopeptidase N (APN) proteins (Murphy et al., 2002; Muday and Murphy, 2002). AtAPM1 was isolated in a flavonoid-sensitive complex with a tyrosine aminopeptidase activity by affinity chromatography utilizing an immobilized form of the auxin efflux inhibitor naphthylphthalmic acid (NPA). AtAPM1 preferentially binds the aglycone flavonols kaempferol and quercetin, which inhibit its aminopeptidase activity (Murphy et al., 2000, 2002). The extent to which flavonoid inhibition of AtAPM1 enzymatic activity contributes to flavonoid inhibition of auxin transport activity *in vivo* (Murphy et al., 2000; Brown et al., 2001; Peer et al., 2004) is unknown (see Section 2.5 for AtAPM1 and trafficking).

PID is a protein kinase necessary for proper organ formation and has been isolated from *Arabidopsis* and pea (Christensen et al., 2000; Bai et al., 2005). PID is sensitive to NPA and therefore has a role in polar auxin transport (Benjamins et al., 2001). It also interacts with Ca^{2+} binding proteins, TOUCH3, a calmodulin-related protein, and PID-BINDING PROTEIN, an uncharacterized protein with Ca^{2+} binding motifs, suggesting a connection between auxin and Ca^{2+} signaling (Benjamins et al., 2003). This is consistent with a role for flavonoids in Ca^{2+} signaling (Lee et al., 2002; Montero et al., 2004). Analysis of the localization of PIN auxin efflux facilitator proteins and auxin transport in flavonoid-deficient mutant backgrounds suggests that PID-mediated kinase activity may be modulated by endogenous flavonols (Peer et al., 2004).

RCN1 was isolated in a screen for mutants with altered responses to NPA (Garbers et al., 1996). RCN1 is essential for PP2A activity and *rcn1* mutants have auxin-related phenotypes and increased sensitivity to okadaic acid, a phosphatase inhibitor (Garbers et al., 1996; Deruere et al., 1999; Zhou et al., 2004). Like PID, RCN1 may regulate polar auxin transport via MAPK activity (DeLong et al., 2002), and flavonoids have been shown to affect MAPK cascades in other systems (see Section 2.1).

AtPTEN1 is a pollen-specific protein that is required for normal pollen development (Gupta et al., 2002). AtPTEN1 is a homolog of the mammalian PTEN protein that regulates cell division and polarization (Perandones et al., 2004; Waite et al., 2005). *AtPTEN1* encodes a dual phosphatase acting on both phosphopeptides and phosphoinositol *in vitro*. As such, MAPK pathway components and phosphatidyl inositol-3,4,5-triphosphate (PIP3), which thereby inhibits AKT/PKB, may be endogenous AtPTEN substrates. AtPTEN1 also may regulate the MAPK pathway. Experimental evidence indicates that these signaling cascades are at least partially conserved between animals and plants with 24 putative MAPK pathways in *Arabidopsis* (Wrzaczek and Hirt, 2001; Anthony et al., 2004; Turck et al., 2004). As yet, there is no experimental evidence of flavonoid interactions with AtPTEN1. Flavonoids, however, are also required for pollen development and have been shown to affect AKT/PBK and MAPK activity in mammals, and kaempferol-treated petunia pollen has increased transcription of genes encoding regulatory or signaling proteins (Guyon et al., 2000). In a recent study in mammals, quercetin, genistein, and resveratrol increased PTEN lipid phosphatase activity but not protein phosphatase activity (Waite et al., 2005), suggesting that flavonoids may be more likely to affect AtPTEN lipophosphatase activity *in planta*.

Studies in animal cell lines have shown that flavonoids alter multiple kinase and phosphatase activities (reviewed in Williams et al., 2004). Apigenin inhibits protein kinase C (PKC) and MAPK (Kuo and Yang, 1995; Huang et al., 1996). Quercetin is routinely used as an inhibitor of mammalian PIPK, phospholipase A2, phosphodiesterases, and PKC by binding to the catalytic domain (Levy et al., 1984; Graziani and Chayoth, 1977, 1979; Graziani et al., 1982, 1983; Tammela et al., 2004). Quercetin also inhibits Ca^{2+}-dependent and phospholipid-dependent protein kinase activities (Gschwendt et al., 1983). Kaempferol inhibits mammalian monoamine oxidase/peroxidases, of which the IAA oxidase is a family member (Sloley et al., 2000). Kaempferol, quercetin, and genistein inhibit the CDC25A tyrosine phosphatase, a cell cycle-specific protein that is dephosphorylated in M phase (Aligiannis et al., 2001).

2.4. Membranes and lipids

In *Arabidopsis*, aglycone flavonols are localized at the plasma membrane (Murphy et al., 2000; Peer et al., 2001). In addition to regulating membrane proteins, flavonoids also may influence the nature of the lipid bilayer itself. Flavonoids may modify the membrane directly by changing membrane fluidity or the phosphorylation state of lipids or proteins or indirectly via signaling cascade to

change the membrane composition. The orientation of hydrophobic flavonoids in the lipid bilayer can modify membrane fluidity/rigidity (Scheidt et al., 2004). Rapidly growing cells in embryonic or tumor tissues, which have less fluid membranes with lower cholesterol/phosphatidylcholine ratios and a higher degree of phosphatidylcholine unsaturation, exhibit increased susceptibility to rigidifying flavonols like quercetin (Tsuchiya et al., 2002). The antiaggregatory and disaggregatory effects of flavonoids on human blood platelets also appear to be a function of altered membrane fluidity (Furusawa et al., 2003). In contrast to quercetin, tannins have been shown to increase membrane fluidity (Labieniec and Gabryelak, 2003).

Flavonoids also may modify the plasma membrane by altering the lipid composition. During nodulation, flavonoids induce expression of *NOD* genes but also appear to alter the membrane composition of *Rizobium leguminosarum*. After nodulation induction, accumulation of the phospholipid diglycosyl diacylglycerol occurred in wild type but not in mutant bacteria lacking the *nod* genes (Orgambide et al., 1994). The root morphology of the host plants but not of nonhost plants was altered by diglycosyl diacylglycerol, which also induced a mitogenic response on the host (Orgambide et al., 1994). Flavonoids also can function in concert with ascorbic acid as antioxidants to protect the membrane from oxidative damage (Bandy and Bechara, 2001; Verstraeten et al., 2003). In addition to free radical scavenging, flavonoids induced lipid ordering at the lipid–water interface, which also reduced lipid oxidation (Erlejman et al., 2004).

2.5. Trafficking, anion channels, receptors, and cell communication

Intracellular molecular trafficking between subcellular compartments plays an important role in flavonoid biosynthesis (see Chapter 5). For example, the anion channel blocker NPPB inhibits blue light-dependent anthocyanin accumulation in *Arabidopsis* seedlings despite unaltered flavonoid biosynthetic gene transcription (Noh and Spalding, 1998), suggesting that anthocyanin accumulation requires transport of flavonoids into the vacuole. Altered pH or altered vacuolar morphology also appears to affect subcellular flavonoid accumulations, as *Arabidopsis AHA10* mutants, which harbor a defect in a plasma membrane H^+ ATPase, exhibit both altered vacuole formation and flavonoid content (Baxter et al., 2005). Similar changes in subcellular flavonol distribution also are seen in *Arabidopsis* roots when strong buffers are used to increase or decrease apoplastic pH (W. Peer and A. Murphy, unpublished). However, intercompartmental movement of flavonoids appears also to affect the abundance and distribution of some nonbiosynthetic proteins, as the transcription and subcellular localization of the flavonol-binding glutathione-*S*-transferase GSTF2 are altered in flavonoid-deficient *Arabidopsis tt4* mutants (Smith et al., 2003). Flavonoids within the membrane also may interact with membrane proteins: one study indicates that luteolin and its glucoside interacted with transmembrane domains in addition to the cytosolic loops of human MRP1 (Trompier et al., 2003).

Flavonols can interact with vesicular processes in tissues exhibiting brefeldin A (BFA)-sensitive trafficking (Peer et al., 2004); BFA is a lactone antibiotic from *Penicillium brefeldianum* that is used to inhibit protein secretion. The auxin efflux facilitator protein PIN1 has been shown to traffic to the plasma membrane through BFA-sensitive compartments via a mechanism that is also sensitive to the auxin efflux inhibitors triiodobenzoic acid (TIBA) and NPA (Geldner et al., 2001). When flavonoid-deficient *tt4 Arabidopsis* mutants were treated with flavonols, PIN1 was irreversibly retained in BFA-sensitive compartments (Peer et al., 2004). The effect was reversible in wild type, suggesting indirect flavonol modulation of trafficking in cells where they accumulate but direct interference with trafficking in cells not conditioned to their presence (Peer et al., 2004) (Figure 9.1). Flavonoids may alter the activities of proteins required for trafficking by binding them directly or altering their phosphorylation states.

Flavonoids also directly and indirectly affect vesicular cycling and protein trafficking in mammals (Almela et al., 1994; Ale-Agha et al., 2002; Lim et al., 2004). Quercetin, myricetin, and catechin-gallate were found to directly inhibit glucose uptake mediated by GLUT4; in addition, flavonoid uptake also appears to be mediated by GLUT transporters in mammalian cells (Strobel et al., 2005). GLUT4 cycling is regulated by APM/IRAP, and these data suggest that APM/IRAP is the likely mechanism regulating glucose uptake. AtAPM1 from plants has a trafficking domain and binds flavonols, suggesting that flavonol–AtAPM1 interactions also may modulate membrane trafficking in plants (Murphy et al., 2002, 2005; Muday and Murphy, 2002; Muday et al., 2003).

Flavonoid-sensitive activity of multiple drug-resistance/P-glycoprotein (MDR/PGP) ABC transporters has been demonstrated in plants and animals (Scambia et al., 1994; De Vincenzo et al., 2000; Limtrakul et al., 2005; Geisler et al., 2005; J. Blakeslee and A. Murphy, unpublished). The PGPs from plants were isolated from flavonoid-sensitive, high-affinity fractions from NPA chromatography (Murphy et al., 2002). Flavonoids alter the function of mammalian PGPs by binding to ATP binding sites or by changing the conformation of the protein (Ferte et al., 1999; Castro et al., 1999). Quercetin can bind to the first of two ATP-binding domains, resulting in inhibition of activity. In contrast, kaempferol can bind a site adjacent to the second ATP-binding domain and activate the transporter/channel. In animals cells, flavonols and isoflavones inhibit PGP activity, but only flavonols reduce PGP transcription (Limtrakul et al., 2005). Flavonol inhibition of PGP activity recently has been demonstrated in *Arabidopsis* (Geisler et al., 2005), where PGPs also appear to be required for flavonol stability on the membrane (J. Blakeslee and A. Murphy, unpublished).

The mammalian mitochondrial Ca^{2+} uniporter also can be activated by kaempferol, quercetin, and genistein (Montero et al., 2004) and quercetin can bind the Ca^{2+} release channel in sarcoplasmic reticulum, resulting in a localized Ca^{2+} flux into the cytoplasm (Lee et al., 2002). In contrast, naringenin and naringenin glycosides blocked hERG K^{+} channels (Zitron et al., 2005) perhaps indirectly through kinase activity.

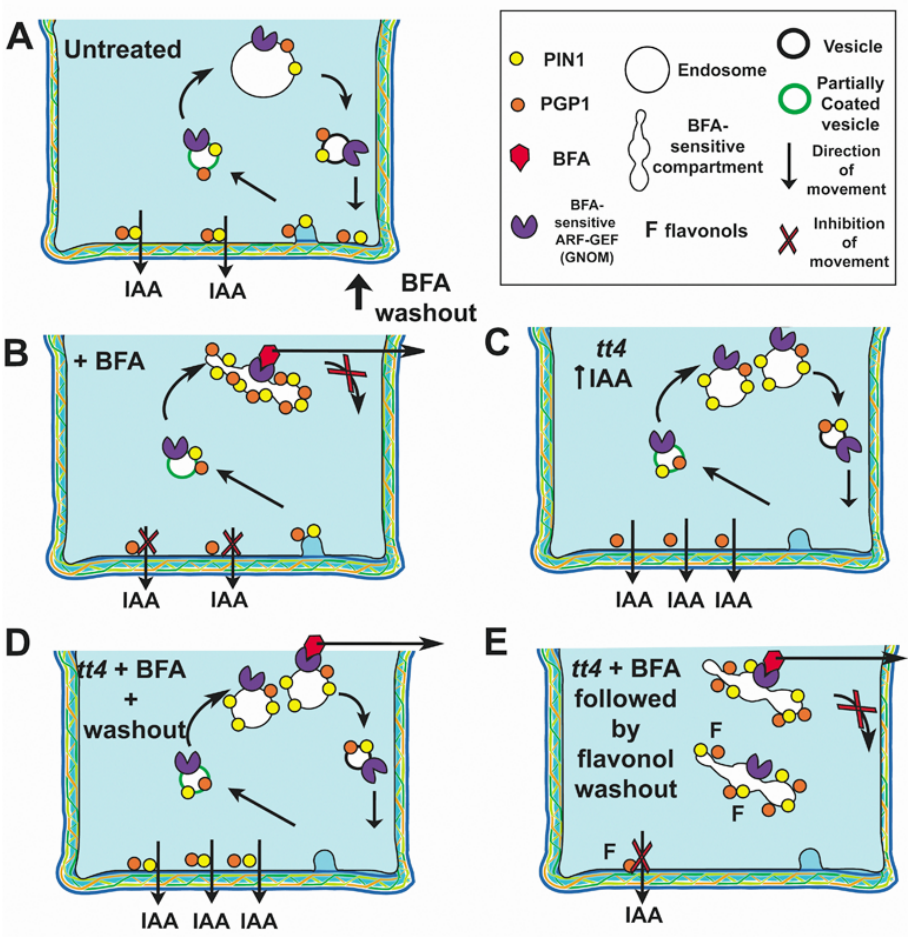

Figure 9.1 *Flavonols and the BFA-induced compartmentalization. (A) Endocytotic cycling of the PIN1 auxin efflux facilitator to and from the plasma membrane (PM) has been shown in root tips of wild-type Arabidopsis seedlings (Geldner et al., 2001). (B) When plants are treated with the fungal toxin brefeldin A (BFA), protein secretion from the Golgi complex is inhibited and the early Gogli cisternae collapse into the endoplasmic reticulum. When wild-type Arabidopsis seedlings are treated with BFA, PIN1 exocytosis is blocked, endocytosis continues, and PIN1 is sequestered in BFA-sensitive intracellular bodies (Geldner et al., 2001). When BFA is washed out of the cells with buffer or flavonols, PIN1 exocytosis resumes as in A, and PIN1 is again observed on the PM. (C) The Arabidopsis tt4 mutant has a lesion in chalcone synthase, and therefore does not synthesize flavonoids. Auxin efflux is enhanced in tt4, but PIN1 is observed in intracellular bodies and not on the PM (Peer et al., 2004). (D) When tt4 seedlings are pretreated with BFA, PIN1 is observed in the PM in addition to intracellular bodies after BFA washout (Peer et al., 2004). (E) Unlike wild-type seedlings, when tt4 seedlings are treated with BFA and then BFA is washed out with flavonols, PIN1 is*

If flavonoids bind a plasma membrane receptor, which is then internalized and trafficked to the nucleus, then the flavonoid can affect transcription. There is evidence that flavonoids are natural dietary ligands in animals. Quercetin and kaempferol have been shown to enhance and inhibit, respectively, CYP1A1 transcription mediated by the aryl hydrocarbon (AhR) receptor (Ciolino et al., 1999; Ramadass et al., 2003). Although flavonoid nuclear localization has not been investigated, quercetin-bound AhR apparently interacts with the CYP1A1 promoter to activate transcription. Flavonoids also may mimic endogenous compounds and receptor ligands for estrogen receptors α and β (Hunter et al., 1999; Virgili et al., 2004; Lee et al., 2004) and the estrogen-inducible type 11 estrogen-binding site (Garai and Aldercruetz, 2004). Flavonoids like quercetin and apigenin can activate and modulate benzodiazepene/GABA receptors, and some flavonoids act through classic GABA pathways, while other flavonoids act through a different pathway (Wasowski et al., 2002; Goutman et al., 2003; Kavvadias et al., 2004). A benzodiazepine receptor has been identified in plants (Lindemann et al., 2004), suggesting that flavonoids could be an endogenous ligand in plants.

Flavonoids also appear to enhance cell–cell communication in mammalian systems. Apigenin enhanced gap–junction communication and counteracted tumor inhibition of intercellular communication (Chaumontet et al., 1994, 1997). Kaempferol inhibited phosphorylation of signal transducer and activator of transcription 3 (STAT3) and extracellular-related kinase (ERK), thereby inducing differentiation and gap–junction communication (Nakamura et al., 2005). Cell–cell communication in plants has not been investigated, although flavonoids localized to the plasma membrane have been observed in plasmodesmata (Figure 9.2).

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retained in intracellular bodies that are larger than those found in BFA-treated wild-type (Peer et al., 2004), suggesting that flavonols either directly bind or alter the activity of proteins necessary for cycling. Apparently, as flavonols are present in wild-type seedlings, the activities and/or phosphorylation states of proteins required for cycling are already in the functional state. When flavonols are absent, as in tt4, and then introduced after BFA treatment, the wild-type pattern of PIN1 exocytosis is not restored, reminiscent of wild-type seedlings treated with auxin efflux inhibitors (Geldner et al., 2001). Treatment with flavonols or naringenin alone restored wild type auxin transport and flavonoid patterns (Murphy et al., 2000; Brown et al., 2001). Figure is derived from Murphy et al. (2005). See Color Section for figure in colors.

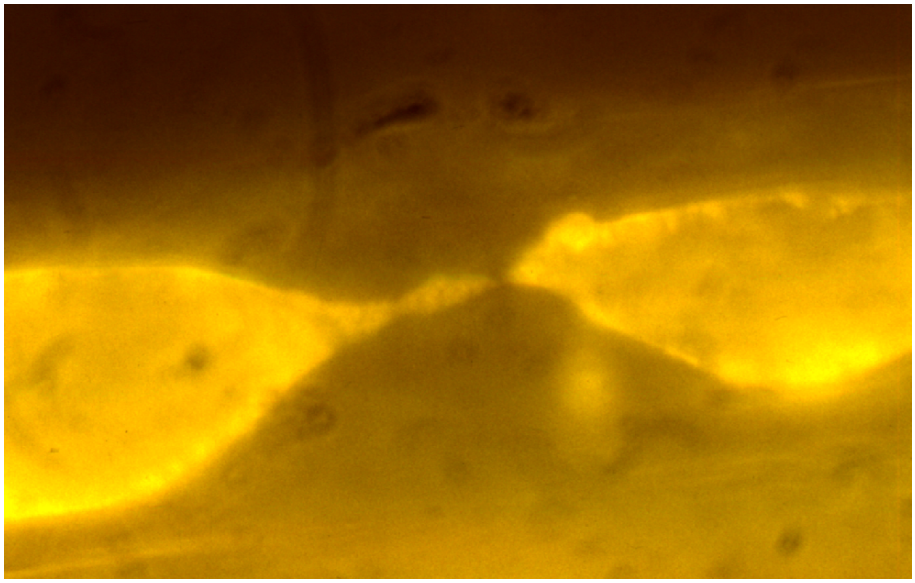

Figure 9.2 *Flavonols in the plasmodesma between two partially plasmolyzed cells in Arabidopsis roots. Roots of 5.5d wild–type seedlings were stained with DPBA and observed with an epifluorescence microscope (for methods see Peer et al., 2001). See Color Section for figure in colors.*

2.6. Cell cycle regulation, cell differentiation, and homeostasis

Flavonoids and flavonoid glycosides also may be involved in mitosis and cellular homeostasis in plants. UDP-glucuronosyltransferase1 (UGT1) is required for cell cycle regulation in pea and alfalfa, and antisense expression of *PsUGT1* under its native promoter was found to be lethal, although overexpression of antisense *PsUGT1* under the constitutive *CaMV35S* promoter was not (Woo et al., 1999). Partial inhibition of UGT1 in alfalfa resulted in an extended cell cycle and reduced growth rate, while *PsUGT1* overexpression in *Arabidopsis* resulted in a reduced life cycle (Woo et al., 2003). The likely substrate for PsUGT1 is a flavonoidlike compound, which is reversibly converted between active and inactive aglycone and glucuronic acid forms (Woo et al., 1999, 2005), and *PsUGT1* expression colocalizes in regions of flavonoid accumulation (Woo et al., 2003; Murphy et al., 2000; Peer et al., 2001).

The activity of dihydroflavonol-4-reductase (DFR) also may contribute to metabolic homeostasis. DFR requires NADPH as a coenzyme and DFR overexpression results in increased NAD activity and transcription. This in turn alters NAD oxidation state, subsequent changes in activity, and NAD homeostasis (Hayashi et al., 2005). Although this is not a direct flavonoid target, the feedback

regulation of flavonoid synthesis and the activity of this flavonoid biosynthetic enzyme has global cellular effects.

Analysis of the expression of transcription factors regulating flavonoid biosynthetic genes during early embryogenesis suggests that flavonoids also function in development (Hennig et al., 2004). Flavonoids appear to be required for proper pollen and seed development (Preston et al., 2004; Debeaujon et al., 2003) but may be negative regulators at other developmental stages: soybeans that accumulate the flavonol glyscoside kaempferol-3-*O*-2-glycosyl-gentiobioside exhibited a significant reduction in the number of stomata compared to wild type (Liu-Gitz et al., 2000).

In mammalian cell systems, flavonoids have been shown to differentially affect the cell cycle. Tangeretin induced G1 arrest through inhibiting cyclin-dependent kinase (CDK) activity and/or elevating CDK inhibitors; however, quercetin did not arrest cells after viral infection in G1 phase (Pan et al., 2002; Beniston and Campo, 2005). Apigenin was found to induce differentiation in G2/M arrested cells, while genistein arrested cells in G2/M phase and down-regulated transcription of metalloproteinases associated with cancer metastasis (Sato et al., 1994; Kousidou et al., 2005). Quercetin suppressed differentiation and disrupted actin rings formed during cytokinesis in osteoclasts (Park et al., 2004; Woo et al., 2004).

3. FLAVONOID SIGNALING

The role of flavonoids in extraorganismal plant signaling has been described extensively, but the role of flavonoids in intra- and intercellular signaling is not as well documented. Flavonoid signaling between organisms may involve visual cues, as in pollinator attractants, as well as molecular cues. For example, flavonoid signaling via root exudates has been well studied in cases of pathogen defense, allelopathy, and nodulation where flavonoid molecules directly interact with a receptor or enzyme activity in the other organism, such as NodD in *Rhizobium spp*. Flavonoid signaling within the plant generally involves enzyme activities or cell–cell communication, but has been more difficult to characterize. However, flavonoid signaling appears to play a more direct role in auxin transport and wounding responses. Extracellular signaling of endogenous flavonoids has not been described in plants, although flavonoid-sensitive extracellular kinases have been described in mammalian systems (Spencer et al., 2003; Lin et al., 2004; Nakamura et al., 2005), suggesting that this also may be the case in discrete plant tissues.

3.1. Autocrine and paracrine effectors

Although flavonoids modulate plant signal transduction, they are not endocrine hormones, as they are not synthesized in one location and transported to another where they have activity. Flavonoids are best described as autocrine or paracrine effectors, as they are active within the cells in which they are synthesized and in adjacent cells. Developmental regulation of localized flavonoid accumulations and their localization in specific subcellular compartments supports this interpretation of

their activity (Kuras et al., 1999; Murphy et al., 2000; Peer et al., 2001; Stefanowska et al., 2003; Saslowsky et al., 2005).

Some of the autocrine effects of flavonoids should be viewed as nonspecific. For instance, reactive oxygen species (ROS) recently have been shown to play a significant role in plant development and environmental responses (Foreman et al., 2003; Freeman et al, 2004). Heavy metal exposure induces ROS (Freeman et al., 2004), and flavonols that accumulate after heavy metal stress may act both as metal chelators and antioxidants (Skorzynska-Polit et al., 2004; Brown et al., 1998; Malinowski et al., 2004). Anthocyanins also may have a role metal chelation and metal storage in vacuole (Hale et al., 2001, 2002). However, although ROS-mediated signal transduction mechanisms may be altered in a flavonoid-deficient background, flavonoids might be better regarded as part of the cellular context in which the response takes place than as a specific signaling mechanism (Figure 9.3).

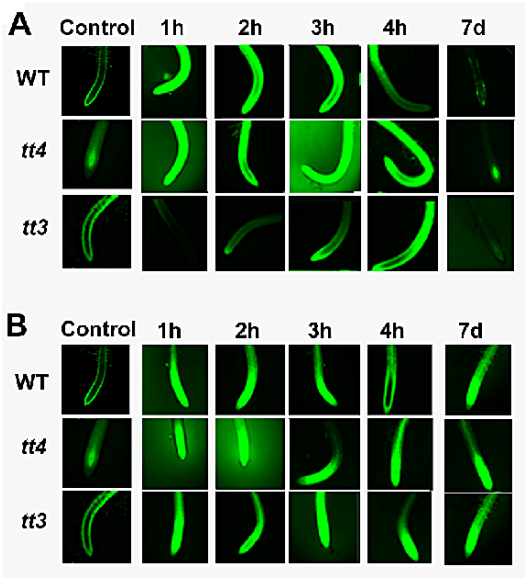

Figure 9.3 *Flavonols and oxidative stress. Wild type, tt4, and tt3 (DFR mutant that accumulates excess kaempferol and quercetin) were stained with carboxy-H2-DCFDA following treatment with (A) 1 µM IAA or (B) 10 µM $CuCl_2$ to induce the generation of reactive oxygen species (ROS) (for methods see Freeman et al., 2004). These data suggest that flavonols can provide short-term protection from lower levels of ROS such as those generated by IAA treatment, but not longer-term protection or protection from the greater degree of oxidative stress induced by copper treatment. These results also suggest that flavonol accumulations in regions of auxin accumulation accompanying tropic bending may be increased as localized auxin levels increase. See Color Section for figure in colors.*

3.1.1. Polar auxin transport

The phytohormone auxin, or indole-3-acetic acid (IAA), is primarily synthesized at the shoot and root apices (Ljung et al., 2002, 2005) and is transported across plasma membranes to other parts of the plant. From the acidic extracellular matrix of the apoplast, protonated IAAH may enter the cell by either diffusion or via a H^+ symporter. Once inside the neutral pH of the cell, IAA is found almost exclusively in an anionic form and may only exit the via cell polar-localized anion efflux carriers. This is often referred to as the chemiosmotic model of auxin transport (Lomax et al., 1985).

Phenolic modulation of polar auxin transport was proposed by Kenneth Thimann in the 1960s (Thimann, 1965), and studies of the effects of auxin efflux inhibitors such as NPA (Katekar and Geissler, 1979, 1980) were used as a model for the analysis of flavonoid function. Jacobs and Rubery (1988) demonstrated that quercetin, kaempferol, and genistein could displace NPA from zucchini microsomal vesicles and suggested that flavonoids could regulate auxin transport. Using a series of tyrosine kinase inhibitors, Paul Bernasconi (1996) found that genistein, but not daidzein, could displace and compete with NPA binding to membrane vesicles, thus introducing a model of flavonoid modulation of the phosphorylation state of regulatory proteins and/or lipids associated with auxin efflux. Bernasconi also showed that calmodulin antagonists, protein serine/threonine kinase inhibitors, and phosphatase inhibitors lacked the activity seen with flavonoids and tyrosine kinase inhibitors. Using wild-type and flavonoid-deficient mutants of *Arabidopsis*, Murphy et al. (2000) demonstrated that endogenous flavonoids and a tyrosine aminopeptidase regulated auxin transport *in vivo*. The flavonoid-sensitive tyrosine aminopeptidase activity was associated with low-affinity binding of NPA and the purified protein involved was identified as AtAPM1 (Murphy et al., 2000, 2002). AtAPM1 is a dual-function aminopeptidase and trafficking protein, and both functions may be involved in regulation of auxin transport (see Sections 2.3 and 2.5).

Another flavonoid-binding activity also was observed in fractions with a high affinity for NPA. These were the plasma membrane phosphoglycoproteins (PGPs) (Murphy et al., 2002) (see Section 2.5). The PGPs (also known in the mammalian literature as multiple drug resistance proteins, MDRs) are members of the ABC transporter family and have 21 functional members in *Arabidopsis*. *PGP* mutants exhibit growth defects consistent with altered auxin transport, and double mutants have more severe phenotypes, suggesting overlapping function (Noh et al., 2001; Geisler et al., 2003, 2005). Recently, IAA and IAA degradation products were shown to be substrates for AtPGP1 transport activity, and efflux of IAA was found to be inhibited by NPA and quercetin (Geisler et al., 2005). AtPGP1 is localized in shoot and root apices in light-grown seedlings where auxin is synthesized and loaded into the auxin transport stream (Sidler et al., 1998; Geisler et al., 2005). Flavonols colocalize with AtPGP1 in these regions, where the flavonols affect polar auxin transport (Peer et al., 2004) (Figure 9.4).

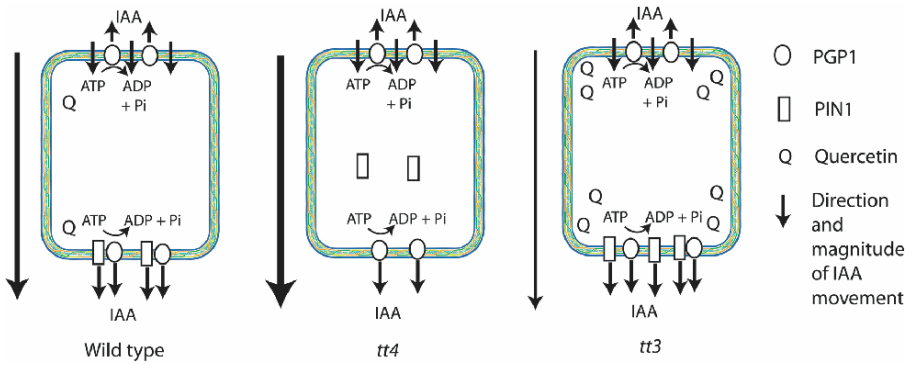

Figure 9.4 *Flavonols and auxin transport. Protonated IAA enters the cell via a H+ symporter or diffusion. Anionic IAA must exit the cell through an efflux carrier. tt4 accumulates no flavonoids and tt3 accumulates 5× more quercetin at the cotyledonary node and 10× more quercetin in the root tip than wild type (Peer et al., 2001). Auxin transport in tt4 is faster than in wild type, while transport in tt3 is slower (Peer et al., 2004). This is likely due to flavonoid regulation of auxin loading and efflux into the auxin transport stream at the apices. One mechanism through which flavonols may be acting is the plasma membrane P-glycoproteins (PGPs). The alglycone flavonol quercetin can bind to the first ATP-binding fold of PGPs, which inhibits auxin efflux (Ferte et al., 1999; Geisler et al., 2005). This is consistent with the excess quercetin accumulation in tt3 and its absence in tt4, and suggests that flavonols are involved in "fine-tuning" auxin efflux. See Color Section for figure in colors.*

The PIN family of facilitator proteins is essential for establishing the vector of auxin movement (Benkova et al., 2003; Blilou et al., 2005), but are apparently not solely responsible for auxin transport. The *pin* mutants were named after their pin-formed inflorescence phenotype (Okada et al., 1991). Transcription, subcellular localization, and tissue-specific distribution of some *PIN* family members are directly or indirectly affected by flavonoids, while other PIN proteins are unaffected by altered flavonoid levels (Peer et al., 2004). Coexpression of specific PIN-PGP combinations in heterologous systems results in enhanced auxin transport, auxin substrate specificity, and sensitivity to both NPA and flavonols (J. Blakeslee and A. Murphy, unpublished). Since specific PIN and PGP proteins differentially co-localize in the plant, PIN and PGP pairs may interact to regulate cellular auxin transport and together establish the vector and velocity of auxin efflux.

Flavonoids are present in the root cap and columella of *Arabidopsis* seedlings (Murphy et al., 2000; Peer et al., 2001, 2004). Kaempferol is present in the columella and root cap, but quercetin only accumulates after an auxin pulse or NPA treatment (Peer et al., 2004). As kaempferol inhibits mammalian monoamine oxidases that are similar to characterized IAA oxidases (Sloley et al., 2000) and flavonoid-deficient *Arabidopsis* mutants exhibit increased leakage of radiolabeled IAA or oxidized IAA from the root tip (Murphy et al., 2000; Peer et al., 2004), kaempferol may function in limiting the oxidation of auxin destined for basipetal redirection at the root tip. Quercetin accumulation in response to increased IAA

levels may serve to scavenge reactive oxygen species that accumulate during IAA catabolism (Joo et al., 2001; Schopfer et al., 2002; Ljung et al., 2002).

3.1.2. Wounding and defense responses

Wounding in plants may be caused by mechanical damage, herbivory, or infection. Each of these can elicit different responses in the plant. However, two common responses among all three are the induction of auxin synthesis and *CHS* expression near the injured site (Stzein et al., 2002; Djordjevic et al., 1997; Richard et al., 2000; Cheong et al., 2002; Lo et al., 2002). Expression of other early genes of the flavonoid biosynthetic pathway is also seen after wounding, but differential expression of *CHS* genes and flavonoid accumulation between infected and uninfected plants suggest that different signaling pathways are involved (Ryder et al., 1987; Wingender et al., 1989; Lawson et al., 1996). Jasmonic acid (JA)/methyl jasmonate signaling appear to mediate some flavonoid responses to wounding, as both compounds can induce *CHS* expression (Richard et al., 2000). Both auxin-sensitive and auxin-insensitive components of JA signaling pathways have been identified, as well as species-specific responses in transcription of homologous genes involved in JA-mediated responses (Rojo et al., 1998; Seo et al., 1999; He et al., 2005). JA responses are regulated by MAPK-dependent signaling and reversible protein phosphorylation regulates JA signaling itself (Seo et al., 1999; Rojo et al., 1998), suggesting a molecular a target for flavonoid regulation.

3.1.3. Testa–embryo interactions

Flavonoids are the major color constituent in the maternally derived testa, and they have been shown to directly affect the embryo. The flavonoids in testa influence seed weight and size, dormancy, germination, and longevity among an array of *Arabidopsis* flavonoid mutants (Debeaujon et al., 2000). Although the function of flavonoids in the testa may appears to be structural by protecting the embryo from desiccation and solute leakage, damage from pathogens, and oxidative stress (Debeaujon et al., 2000), flavonoids may indirectly affect embryo development and germination. In addition to the possibility of the testa influencing the embryo, there is evidence that communication between the embryo and testa cells can alter flavonoid content, although it is unclear whether flavonoids themselves are involved in this signaling (Downie et al., 2003).

3.2. Other extraorganismal signaling

3.2.1. Plan–plant interactions

Flavonoids play a role in fertilization in many plant species. Because of alteration of generations, interactions between the sporophyte and pollen gametophyte can be regarded as extraorganismal. These interactions include pollination, self-

compatibility/incompatibility chemistry and recognition (pollen allelopathy), pollen germination, and pollen tube growth (Roshchina, 2001). Flavonoids accumulate in pollen, stigmas, and petals of most flowers. Flavonoid-deficient mutants in most species are also male-sterile, as is the case with petunia, which is also self-incompatible (Napoli et al., 1999; Robbins et al., 2000). Although germination of petunia pollen can be induced with exogenous kaempferol, the basis of self-incompatibility in the Solanaceae is S-RNase activity in which the RNases within the stigma degrade pollen rRNA and inhibit pollen tube growth (Wheeler et al., 2001). Therefore, while pollen germination in petunia may be flavonoid-dependent, self-incompatibility is not. Pollination-induced or wound-induced kaempferol accumulation in petunia stigmas also enhances seed production (Vogt et al., 1994), although this is not universal in the Solanaceae (van Eldik et al., 1997).

However, flavonoid-deficient *tt4 Arabidopsis* mutants are fertile, although *tt4* exhibits reduced set seed (Burbulis et al., 1996; Ylstra et al., 1996). Like wild type, *tt4* is self-compatible. The aglycone flavonol quercetin is observed in the pollen and papillae of the stigma in wild-type *Arabidopsis* species (Peer et al., 2001; W. Peer and A. Murphy, unpublished). Application of kaempferol to the stigma in self-incompatible *Arabidopsis* species prior to hand pollination allows self-fertilization to occur (W. Peer and A. Murphy, unpublished). Since the mechanism of self-incompatibility in the Brassicaceae requires the activity of a serine/threonine protein kinase (SRK) on the stigma surface that inhibits pollen tube growth (Wheeler et al., 2001; Kusaba et al., 2001), exogenous application of kaempferol may enhance self-pollination in self-incompatible Brassicaceae by inhibiting SRK activity (see Section 2.3). It appears that quercetin, which is present in the pollen and stigma, is not involved in self-incompatibility. As such, engineered accumulation of kaempferol in the stigma of self-incompatible Brassicaceae may be of agricultural interest.

Flavonoids also are among many of the allelopathic agents that plants produce to reduce competition. Flavones from rice leaves inhibited weed growth but not rice biomass, and luteolin from chrysanthemum also inhibited weed biomass (Kong et al., 2004; Beninger and Hall, 2005). Quercetin-3-dimethylether, naringenin, and eriodictyol found in *Dittichia* root exudates induced agravitropic growth in lettuce seeds (Levizou et al., 2004). (-)-Catechin, kaempferol, and dihydroquercetin in root exudates from the invasive species *Centaurea maculosa* can trigger a wave of reactive oxygen species (ROS) and subsequent Ca^{2+} signalling, leading to root death in sensitive plant species (Bais et al., 2003a, 2003b).

3.2.2. Plant–animal interactions

In addition to pollen germination, fertilization, and seed set, flavonoids function in the attraction of animal pollinators. In flower petals, visible flavonoids such as anthocyanins, delphinidin, and cyanidin serve as attractants for pollinators like birds, small mammals, and some insects. Natural pollinators can prefer or discriminate against petal color, and therefore play an important role in the evolution of petal color; often a petal color is preferred and flowers of that color are visited more often,

which enhances seed yield (Clegg and Durbin, 2000; Jones and Riethel, 2001). UV-fluorescent flavonols serve as nectar guides for bees and other insects and enhance the frequency of pollinator visits, indirectly contributing to increased seed yields (Thompson et al., 1972; Sasaki and Takahashi, 2002). Night-blooming and bird-pollinated flowers, however, often lack nectar guides (Stpiczynska et al., 2004).

Flavonoids are also one of the classes of herbivory deterrents, which may be constitutive or induced. For example, constitutively produced aglycone flavonoids, primarily 5-hydroxy-4′,7-dimethoxyflavanone, in the glandular trichomes of emerging white birch leaves are mortally toxic to the larvae of the autumnal moth (Lahtinen et al., 2004). Herbivory-induced changes in flavonoid gene expression and accumulation are found in most plant species; wounded and unwounded leaves within the same aspens had increased phenylpropanoid expression (Peters and Constabel, 2002), while the herbivory-induced volatiles released from spider mite damage to lima beans leaves induce increased flavonoid biosynthetic gene expression in undamaged neighboring plants (Arimura et al., 2000).

Nematode infection induces the formation of root galls. The formation of a symbiotic nodule or a parasitic gall is similar in that auxin accumulation and flavonoid synthesis are observed at the site of infection (Hutangura et al., 1999). In contrast to symbiotic associations, a plant defense response is initiated. In oats, the accumulation of many flavonoid glycosides were induced by nematode invasion or methyl jasmonate application, and *O*-methylapigenin-*C*-deoxyhexoside-*O*-hexoside was identified as the active phytoalexin against two genera of parasitic nematodes (Soriano et al., 2004). In addition to inducible phytoalexains, the isoflavone medicarpin is constitutively high in roots of nematode-resistant alfalfa and is toxic to nematodes (Baldridge et al., 1998).

3.2.3. Plant–fungal interactions

Arbuscular mycorrhizae form mutualistic or symbiotic associations with plants. In addition to the novel flavonones 3,7-dihydroxy-4′-methoxyflavone and 5,6,7,8-tetrahydroxy-4′-methoxyflavone, quercetin, acacetin, and rhamnetin accumulated in roots of clover inoculated with mycorrhizae but not in noninoculated plants (Ponce et al., 2004), suggesting that flavonoids may mediate colonization. In addition, the root and shoot flavonoid composition was altered between colonized and non-colonized plants, which may be a direct or indirect effect of colonization (Ponce et al., 2004). Under low phosphate conditions, melons synthesized a *C*-glycosylflavone, isovotexin 2″-O-β-glusoside, which increased mycorrhizal colonization (Akiyama et al., 2002), thereby enhancing phosphate uptake. Apigenin, coumestrol, and daidzein increased mycorrhizal root colonization in soybean (Xie et al., 1995). Although the signal that initiates colonization is unknown, flavonoids modulate the development of the association.

Flavonoids also appear to provide defense against fungal infection. A flavone found in rice is allelopathic to rice fungal pathogens; quercetin, querectin 3-methyl ether, and its glycosides inhibited conidia germination in *Neurospora*, and taxifolin appeared to be an antifungal agent in pine (Bonello and Blodgett, 2003; Kong et al.,

2004; Parvez et al., 2004). In addition to increased amounts of heptamethoxyflavone, nobiletin, sinensetin, and tangeretin, the amounts of glycosylated hesperetin and naringenin decreased while the amounts of the aglycone forms increased after fungal infection in citrus (Arcas et al., 2000; del Rio et al., 2004). *C*-Glycosylflavonoids accumulated at the plasma membrane immediately at the powdery mildew infection site and inhibition of *CHS* expression reduced resistance to fungal infection (McNally et al., 2003; Fofana et al., 2005). Theses studies suggest that different classes of flavonoids and their derivatives have differential functions.

3.2.4. Plant–microbe interactions

Recently, Ann Hirsch (2004) proposed that plant–microbe interactions occur on a continuum from commensalisms to parasitism. The multiple roles of flavonoids observed in plant-microbe interactions support this view, as flavonoid signals can attract both beneficial and parasitic bacteria. Similar to antiherbivory or anti-parasitic strategies discussed above, flavonoids also are inducible and constitutive components of the defense mechanism against infection (Dixon and Paiva, 1995; Dixon et al., 2002). Several flavones also have been shown to have antimicrobial activity (Mustafa et al., 2003; Yadava et al., 2003). Subtle changes in flavonoid speciation can determine the nature of plant microbe interactions. (+)-Catechin and its derivatives appear to be antimicrobial (Kajiya et al., 2004).

Nodulation is a special case of plant–microbe signaling. Nodulation is the formation of nitrogen-fixing nodules in roots of legumes (beans, peas, alfalfa, clover, for example) and *Parasponia*, a nonlegume, by bacteria in the Rhizobiaceae, and occurs when the host plant and the rhizobium form a symbiotic relationship. Although some rhizobia are generalists, many plant–rhizobium pairs are specialized, with species-specific flavonoids in the roots exudates that are stimulatory to compatible species of rhizobia and inhibitory to noncompatible rhizobia and other soil flora and fauna.

Flavonoids have roles both as interorganismal signaling molecules and autocrine effectors in nodulation. Flavonoids present in root exudates are perceived by the bacteria, which require flavonoids for the initiation of transcription of *nod* genes (see Section 2.1). Flavonoid levels in root exudates are sufficient to induce *nod* gene expression. For example, when flavonoid quatities were measured in root exudates from germinating bean seeds, they were found to contain 450 nmole of aglycone flavonols (myricetin, quercetin, kaempferol) and 2500 nmole aglycone anthocyanins (elphinidin, petunidin, malvidin) (Hungria et al., 1991). However, *nod* gene expression to flavonoids exhibits specificity: naringenin was found to stimulate nodulation and quercetin inhibited nodulation by *Rhizobium leguminosarum* in pea (Novak et al., 2002). Luteolin induced nodulation by *Sinorhizobium meliloti* in alfalfa (Yeh et al., 2002), while daidzein and genistein induced nodulation by *Bradyrhizobium japonicum* in soybeans (Kosslak et al., 1987) and 7,4'-dihydroxyflavone induced nodulation by *Rhizobium leguminosarum* bv. *trifolii* in white cover (Orgambide et al., 1994).

Secreted NOD factors (*N*-acetylchitooligosaccharides) also alter apoplastic pH and initiate a Ca^{2+} cascade, which is thought to either initiate or repress defense responses in the plant (Felle et al., 2000). Nodulation is initiated when the bacteria invade the root and is completed when a vascular bundle is formed in the nodule. Auxin accumulates during early nodule formation and is thought to result from flavonoid inhibition of auxin transport to the root tip (Djordjevic et al., 1997; Mathesius et al., 1998a,b). Flavonoids also likely regulate localized auxin concentrations within the nodule: 7,4′-dihydroxyflavone and its derivative inhibited IAA breakdown, while formontonin, an isoflavone, enhanced it (Mathesius, 2001). The process of rhizobial nodulation is not similar to lateral root formation, as cortical cell proliferation occurs followed by vasculature formation in the nodule.

4. CONCLUDING REMARKS

Flavonoids are bioactive molecules with specific and nonspecific effects on intra- and extraorganismal plant signaling mechanisms. However intraorganismal flavonoid signaling is probably a by-product of the evolution of plant signaling and trafficking mechanisms in an environment where flavonoids are present for purposes of extraorganismal signaling and defense and a role in initial protection from oxidative stress. Recently developed molecular biological tools and high throughput metabolic profiling technologies provide new opportunities to identify specific and nonspecific sites of flavonoid regulation.

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