# Microbe-associated molecular patterns (MAMPs) probe plant immunity

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Microbial life manifests itself in complex communities such as the ones attached to plant surfaces. They consist of beneficial mutualists and epiphytes as well as of potential pathogens. Plants express surface receptors that recognize them according to their microbe-associated molecular patterns (MAMPs). MAMP-stimulated plant responses have been studied for a long time. Recently a number of reports have provided a deeper understanding on how perception of MAMPs contributes to basal resistance at both layers of pre-invasive and post-invasive immunity. Comparative profiling of gene expression revealed a large overlap of plant responses towards different MAMPs or plant–microbe interactions, indicating common signaling components.

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## Introduction

In nature, plants are immune to most potential pathogens (non-host disease resistance), and have the ability to reduce the disease severity of actual pathogens (basal disease resistance). Both forms of resistance involve, as an initial step, the recognition of the (potential) pathogens by way of chemical cues, originally termed elicitors or 'general elicitors' and more recently pathogen-associated molecular patterns (PAMPs). Since these molecular patterns exist in benevolent, neutral and malevolent organisms alike, they should actually be designated as MAMPs (microbial-associated molecular patterns) [1]. MAMPs are recognized by pattern recognition receptors (PRRs) at the cell surface. Activation of these PRRs leads to active defense responses, (MAMP/PAMP-triggered immunity), both in basal and non-host resistance [2•]. A successful pathogen can overcome MAMP/PAMP-triggered immunity by evading detection, called 'camouflage', and by interfering with host responses. To promote virulence, pathogens produce effector molecules that reduce or suppress the effects of MAMP-triggered host responses [2•]. Some effectors are specifically detected by cognate resistance (*R*)-gene products leading to effector-triggered immunity, which is generally accompanied by the hypersensitive response (HR), a local cell death program that ultimately restricts pathogen invasion.

## Microbe-associated molecular patterns

The MAMPs recognized by the plants correspond to molecules essential for microbial life but do not necessarily play a role in pathogenicity. Well-known examples are fungal chitin and ergosterol, main structural components of higher fungi cell walls and membranes; bacterial lipopolysaccaride (LPS), a glycolipid component of Gram-negative bacterial outer membranes; and flagellin, the major structural component of the bacterial motility organ [3•]. Perception of these MAMPs is widespread among plant families. The elicitor active MAMP epitope of flagellin has been identified as a 22 amino acid stretch (flg22) corresponding to the most highly conserved region in the N-terminal portion of this protein. Flg22 stimulates typical responses associated with immunity in various plants [4]. The MAMP of LPS has not yet been unequivocally delineated. It has been shown that the highly conserved Lipid A part is sufficient to induce plant defense responses in *Arabidopsis* [5]. LPS seems to play not only a role in plant defense, but may also be an important factor for symbiotic signaling. A recent report shows that LPS of *Sinorhizobium meliloti* can reduce the induction of defense-associated genes when concomitantly applied with the fungal elicitor invertase in cell cultures of the host plant *Medicago truncatula* [6].

Distinct plant families (or species) have developed recognition systems for additional microbial molecules. Representative examples are the bacterial elongation factor Tu (EF-Tu), bacterial cold shock proteins (CSP) [7,8]. While both EF-Tu and CSPs are abundant in bacteria, perception of EF-Tu is restricted to *Brassicacae*, and perception of CSP is restricted to *Solanaceae* [7,8]. The MAMP of bacterial EF-Tu was identified as the N-terminus of the protein, and an *N*-acetylated peptide comprising the first 18 amino acids (elf18) is sufficient as an inducer of plant defense responses [7]. For CSP, the MAMP epitope was defined as a 15 amino acid peptide comprising the highly conserved RNA-binding RNP-1 motif [8].

Interestingly, different plants seem to have evolved recognition specificities for distinct MAMPs derived from

the same matrix. β-glucan wall components are characteristic of phytopathogenic fungi and oomycetes and serve as MAMPs [9]. Several studies indicate different β-glucan fragments as potent inducers of plant defenses [11,12]. The perception of an oomycete-derived branched heptaglucoside is restricted to *Fabaceae* [13]. Another fragment, tetraglucosyl glucitol from *Pyricularia oryzae*, is active in rice cells, but not in soybean [11]. The cell wall transglutaminase (TGase) GP42 from *Phytophthora sojae* elicits defense responses in potato and parsley. Several species of the oomycete genus *Phytophthora*, but not of the closely related genus *Pythium*, possess a GP42 TGase-related gene family [14]. The MAMP epitope of GP42 was identified as a surface exposed 13 amino acid spanning domain (Pep-13), which is also essential for TGase-activity [10].

Some microbial molecules do not conform to our classical understanding of MAMPs or effectors. These molecules are important for pathogenicity, and upon host perception they induce an HR. The fungal ethylene inducing xylanase (EIX) is probably an important factor for the success of *Trichoderma viride* as an invasive pathogen [15,16]. EIX is not recognized by its enzyme activity (β-1,4 endoxylanase). Instead, a MAMP composed of five amino acids of a surface-exposed β-strand of EIX is essential for its defense response triggering activity [16]. AvrXa21 produced by a number of *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) strains triggers an HR in rice cultivars expressing Xa21. Interestingly, AvrXa21 appears to be also present in *Xanthomonas campestris campestris*, and this conservation across species is typical for MAMPs. AvrXa21 could be a secreted peptide that is produced in a cell-density dependent manner suggesting a function in quorum sensing [17•]. It is noteworthy that flagellins derived from *Pseudomonas avenae*, *P. syringae* pv. *glycinea*, and *P. syringae* pv. *tomato* were shown to trigger hypersensitive cell death in non-host rice and tobacco plants [18,19,20•]. Such microbial molecules could be inducers of an *R*-gene-mediated HR, or constitute a specialized form of MAMP/PAMP-triggered immunity.

## Pattern recognition at the surface

Receptors consisting of an extracellular ligand-binding domain—often comprised leucine-rich repeats (LRR), a single transmembrane domain and an intracellular serine/theronine kinase-signaling domain are referred to as receptor-like kinases (RLK). Receptor-like proteins (RLPs) are similarly structured, but lack the cytoplasmic kinase domain. In *Arabidpsis*, 610 RLKs and 56 RLPs have been identified [21,22]. To date, only few of them have been functionally characterized, for example BRASSINOSTEROID 1 (BRI1) and CLAVATA 1 (CLV1), both playing roles in plant development [21]. It is not known to what extent RLKs and RLPs are involved in plant immunity. A large number of genes encoding RLKs and RLPs are transcriptionally induced upon MAMP treatment, which suggests a potential role in defense [23•,24••]. The best-characterized RLK mediating MAMP perception is the flagellin receptor FLAGELLIN SENSING 2 (FLS2) in *Arabidopsis* [25]. FLS2 and flg22 were found to co-precipitate, which suggests physical interaction [27••]. In addition, FLS2 expression was sufficient to transfer the *Arabidopsis* flagellin perception system into tomato. This demonstrated that FLS2 is the *bona fide* receptor for flg22. FLS2 normally localized to the plasma membrane and was found to be internalized upon flg22 stimulation [26•]. Intracellular accumulation of FLS2 is reminiscent of an endocytic process, which likely involves receptor phosphorylation and the function of a PEST-like motif, and possibly is important for flg22 signaling. The EF-Tu receptor (EFR) has been identified from the *Arabidopsis* RLK subfamily XII that also includes FLS2 [24••]. Mutant lines devoid of EFR are insensitive to elf18 while maintaining responsiveness to flg22. Expression of EFR in *Nicotiana benthamiana*, that normally lacks a perception system for EF-Tu, conferred elf18 responsiveness. This suggests physical interaction of elf18 and EFR. Interestingly, EFR contains a typical endocytic motif indicating possible intracellular trafficking. Another LRR-RLK involved in perception of pathogens is rice Xa21, which recognizes the effector-type molecule AvrXa21 [17•,28]. Xa21 appears to be proteolytically cleaved, a process controlled by Xa21 phosphorylation [28]. Moreover, an E3 ubiquitin ligase has been identified as a substrate of Xa21 [29].

The second class of surface receptors, the RLPs, have been described mainly as mediators of effector recognition [22]. However, RLPs are also involved in MAMP detection. Recently, CEBiP, the high affinity-binding site for fungal chitin, has been identified in rice [30••]. CEBiP carries two LysM motifs in its extracellular domain. A *CEBiP*-specific knockdown resulted in strong suppression of the chitin-induced generation of reactive oxygen species (ROS), while LPS-triggered ROS production was unaffected. It remains elusive whether there are CEBiP homologues of similar function present in other plants. An LRR-RLP from tomato constitutes the receptor recognizing fungal xylanase (EIX) [31•]. Genetic mapping identified LeEix1 and LeEix2 as two highly homologous proteins. Silencing of the *LeEix* gene family abolishes EIX responsiveness in *N. tabacum* cv. *samsun*. Expression of either LeEix1 or LeEix2 in normally EIX non-responsive *N. tabacum* cv. BY2 cell lines showed that both LeEix1 and LeEix2 mediate binding of EIX. However, only LeEix2 appears to trigger an HR upon EIX elicitation. This might indicate the existence of heteromeric receptor complexes. Moreover, LeEix proteins contain an endocytic motif that upon mutation renders LeEix2 nonfunctional.

A soluble extracellular protein lacking a transmembrane domain has been identified as the binding site for β-glucans [32,33]. The glucan-binding protein (GBP) binds

the heptaglucoside elicitor from oomycetes and has intrinsic endo-β-glucanase activity. It is proposed to act firstly as a glucan hydrolase on heptaglucosides, releasing β-glucans, which are subsequently perceived by a different domain of GBP. Homologues of this glucanase seem to be present in diverse plant species, however, high-affinity-binding and elicitor response to the heptaglucoside is restricted to a few species of the *Fabaceae* [32]. The receptor component that is involved in signal transduction remains to be identified. GBP is predominantly localized to the cytoplasmatic side of the cell wall but also to intracellular vesicles.

## MAMP triggered defense responses

Pre-invasive resistance is important to arrest fungal penetration [34]. Pathogenic bacteria also have to enter plant tissues, which requires flagellar motility [35]. Studying flg22 recognition, Zipfel and co-workers [23•] demonstrated that MAMP perception contributes to plant disease resistance. Mutant *fls2* plants showed increased susceptibility towards *P. syringae* pv. *tomato* DC3000 (*Pst*) upon bacterial inoculation onto the leaf surface. This was not observed when bacteria were injected into the leaf tissue. Furthermore, Melotto and co-workers [36••] have recently shown that pathogenic bacteria swim towards open stomata. To prevent bacterial ingress, stomata close in response to *Pst* and to *Escherichia coli*. However, only phytopathogenic bacteria were able to re-open stomata. Stomatal closure could be triggered by application of individual MAMPs such as LPS or flg22, which appeared to be receptor-mediated involving FLS2. MAMP-triggered stomatal closure was dependent on abscisic acid and nitric oxide (NO), indicating a link between biotic and abiotic stress pathways. Pathogen as well as LPS triggered stomatal closure was dependent on salicylic acid (SA).

Typical early MAMP responses are ion fluxes across the plasma membrane, the generation of ROS, NO, ethylene, and later also deposition of callose and synthesis of antimicrobial compounds [3•,4]. MAMPs trigger calcium-dependent protein kinases (CDPK), activation of mitogen-activated protein kinase (MAPK) cascades, and lead to changes in the transcription of numerous genes [23•,24••,37,38]. Remarkably, the majority of flg22 upregulated genes represent members of RLKs and *R*-genes, indicating that MAMP perception increases the recognition capacity for microbial molecules [23•,24••]. Thus, flg22 as well as elf18 are capable of inducing plant resistance towards leaf injected virulent *Pst*. This illustrates that flg22 also affects post-invasive immunity. Surprisingly, flg22-induced resistance appeared not to employ components of SA, jasmonic acid, and ethylene-signaling pathways typically associated with disease resistance [23•]. This seems to be in contrast to the involvement of SA in MAMP-triggered stomatal closure, which might reflect differences between guard cells and mesophyll cells mediating pre- and post-invasive immunity, respectively.

Elf18 perception by EFR is important for post-invasive immunity in *A. thaliana*. Recently, Zipfel and co-workers [24••] demonstrated that mutant plants lacking EFR exhibited an increase in transgene expression upon *Agrobacterium*-mediated transient transformation. In addition, they reported that flg22 and elf18 stimulate plant responses in a similar manner, regulate nearly identical sets of genes, and either MAMP treatment enhanced the recognition capacity of the other. This indicates that flg22 and elf18 share common signaling pathways although they are recognized by distinct receptors. Global transcript profiling using *Pst* and mutant variants including strains lacking flagellin revealed an almost complete overlap of transcriptional changes induced by flagellin and other bacterial MAMPs [39]. Comparisons of further transcript profiles revealed co-regulation by a non-virulent *Pst* mutant, the non-host *Pseudomonas syringae* pv. *phaseolicola* (*Pph*), flg22 and LPS [40]. Moreover, changes in gene expression upon stimulation with LPS are highly correlated to those treated with fungal chitin [41]. This provides evidence that unrelated MAMPs induce a largely overlapping set of genes possibly through convergent signaling pathways. Moreover, both flg22 and chitin induced phosphorylation of AtPhos43 [42]. However, a global protein phosphorylation study comparing flg22 and EIX elicited cells only uncovered a limited overlap, thus indicating some specificity of MAMP responses [43].

*Arabidopsis NHO1*, a glycerol kinase, is required for resistance against the fungus *Botrytis cinerea* and non-host bacteria [44]. *NHO1* expression is stimulated by flagellin, which appeared to be required for resistance against *Pseudomonas syringae* pv. *tabaci* (*Ptab*). Leaf injected *Ptab* mutants lacking flagellin were able to multiply in *Arabidopsis* whereas wild-type strains did not [45••]. However, injected *Pst* host bacteria and its flagellin-lacking mutant were both capable of colonizing *Arabidopsis*. Likewise, many genetically defined components known to play a role in non-host or basal resistance appear to be flg22 induced, including *PEN1*, *PEN2*, and *PEN3* involved in pre-invasive defense, and *EDS1*, and *PAD4* mediating post-invasive defense [23•,34]. Interestingly, PEN1, its closest homologue SYP122, and PEN3 were differentially phosphorylated in response to MAMP treatment [43,46].

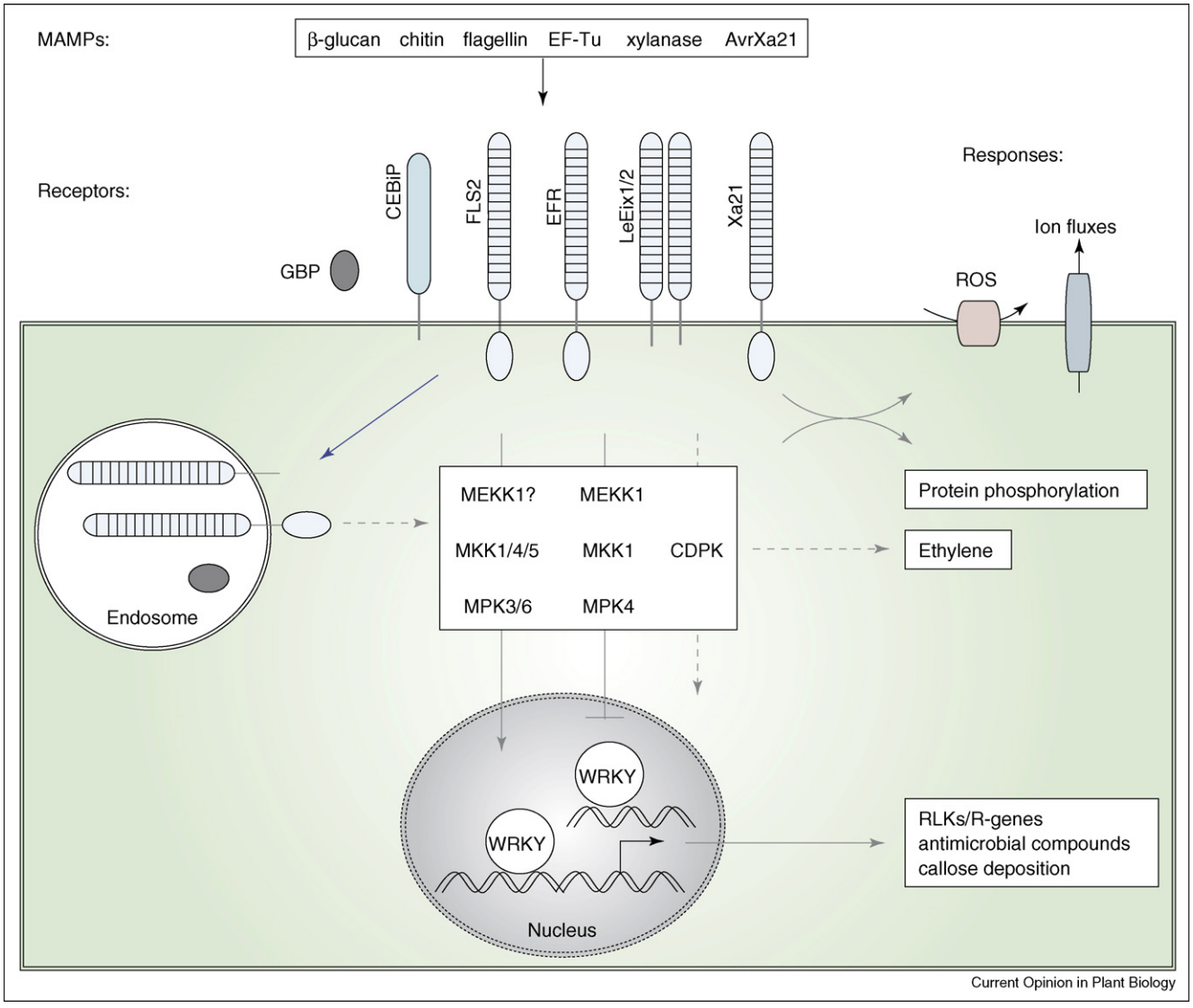
## MAMP signaling and regulation

Using a cell system and transient expression of candidate MAP, MAPK, MAPKK kinases and mutant variants thereof, a complete MAP kinase cascade mediating flg22 signaling was identified in *Arabidopsis* [38]. This cascade consists of MEKK1, MKK4/5 and MPK3/6 and could also be stimulated by other MAMPs [47]. MPK6 has been shown to mediate basal and specific resistance by gene silencing [48]. Two recent reports, however, conclude that MEKK1 does not regulate flg22-triggered MPK3/6, but rather MPK4 activation [49,50]. Furthermore, flg22-induced activation of MPK3/4/6 is dependent

on MKK1, whereas MPK3/6 are also activated by MKK4 [51]. These studies indicate at least two MAPK cascades involved in MAMP signaling. The MPK3/6 pathway appears to positively regulate MAMP responses, while MPK4 exerts a negative regulatory function.

A number of WRKY transcription factors are upregulated upon flg22 stimulation, e.g. WRKY22, 25, 29, 33, and 53 with high induction values [23•]. WRKY22 and 29 were previously placed downstream of MPK3/6, and WRKY25, 33 were identified as substrates of MPK4 [38,52]. This indicates that WRKY factors both positively and negatively regulate MAMP-triggered transcriptional changes. Recently, WRKY11/17 and WRKY18/40/60 have been demonstrated to function as negative regulators of basal resistance in bacterial and fungal interactions [53,54,55••]. Homologues of these WRKY factors were found to physically interact with the *R*-gene product MLA in barley [55••]. This suggests that MAMP-induced transcriptional changes in basal resistance are under negative control but

**Figure 1**




Overview of currently known MAMPs and cognate receptors mediating plant immunity. MAMPs are recognized by soluble-binding proteins (GBP), transmembrane LysM-containing RLPs (CEBiP), LRR-type RLPs (LeEix) and LRR-RLKs (FLS2, EFR, Xa21). They can undergo subcellular redistribution and accumulate in endosomes. MAMP-mediated receptor signaling triggers activation of at least two MAP kinase cascades positively and negatively regulating transcriptional changes possibly by targeting WRKY transcription factors. Transcriptional changes include upregulation of *RLK*s and *R*-genes, production of antimicrobial compounds and callose deposition. Furthermore, MAMP perception stimulates ion fluxes across the plasma membrane, generation of ROS, NO and ethylene, and elicits differential protein phosphorylation. Largely overlapping sets of genes induced by diverse MAMPs suggest common steps of signaling pathways. The blue arrow indicates relocalization, grey arrows signaling pathways, and dashed arrows possible pathways.

can be de-repressed upon resistance gene activation. Such a negative regulatory interaction between MAMP responses and isolate specific resistance has also been reported for RIN4, required for RMP1-mediated specific resistance [56•].

## Conclusions

Plants possess an array of highly sensitive and specific surface receptors to monitor microbial communities according to their molecular patterns and thereby control pathogen infection. In recent years a number of exciting studies have revived attention to MAMP perception and have provided a further understanding of plant immunity. Current reports show that MAMP perception is important in pre-invasive and post-invasive immunity, and is actively contributing to basal and non-host resistance. Figure 1 summarizes all receptors of MAMPs known to date and illustrates subsequent signaling pathways and host responses. Typically, MAMP-triggered host responses are elicited quickly and transiently. Distinct MAMPs seem to elicit largely overlapping immune responses, and MAMP signaling employs at least two MAP kinase cascades. MAMP/PAMP-triggered immunity appears to be under negative control that could be released by effector-triggered immunity, suggesting connectivity of both pathways. In the future, the cognate receptors for a large number of MAMPs need to be identified. Moreover, the questions of how diverse MAMP signals are integrated and how MAMP signaling interferes with other plant stress responses remain to be resolved.

## Note added in proof

Recently, three papers were published that report a novel function for the LRR-RLK BRI1-ASSOCIATED KINASE 1 (BAK1) in plant immunity. BAK1 was described to limit pathogen-triggered cell death [57], and BAK1 was found to form a complex with FLS2 upon flg22 stimulation, thereby regulating flg22 responses [58,59].

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