mADP-RTs: versatile virulence factors from bacterial pathogens of plants and mammals

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A COMMON FOLD MEDIATES MERCILESS KILLING ON SUBTLE MANIPULATION
Several important pathogenic bacteria use secreted proteins, frequently termed “effectors,” to modify the physiology of their host cells to promote infection. One family of effectors encodes a mono-ADP-ribosyltransferase (mADP-RT) enzymatic activity. The manipulating activities of mADP-RTs often culminate in killing the infected host cell and therefore many pathogen secreted mADP-RTs are referred to as toxins (Holbourn et al., 2006). ADP-ribosylating toxins typically comprise several distinct domains that mediate attachment to host cell receptors, translocation into the host cell and mADP-ribosylation (Figure 1; Deng and Barberis, 2008). Some mADP-RTs from Gram-negative bacteria rely on host cell delivery by the bacterial type three secretion system (T3SS) and consist only of the catalytic domain preceded by a type three secretion signal and host cell targeting domains (Deng and Barberis, 2008). The catalytic domain mediates cleavage of an ADP-ribose moiety from NAD+ and its subsequent transfer onto an amino acid of the target protein (often Cys, Arg, Asn, or Diphthamide – a modified form of His). In most cases mADP-ribosylation of target proteins leads to their inactivation. The enzymatic activity of several mADP-RTs is regulated by an active site loop located adjacent to the catalytic cleft. This loop can undergo significant re-orientation to allow access to the active site upon substrate binding (Bell and Eisenberg, 1996; Sun et al., 2004; O’Neal et al., 2005).

Most mADP-RTs retain three structurally conserved features (Holbourn et al., 2006): (1) The arnoma-HR motif is composed of an aromatic amino acid followed by His or Arg. This motif either contributes to NAD+ binding or supports the structural integrity of the NAD+ binding site; (2) The ARTT loop contains the conserved catalytic Glu residue required for NAD+ cleavage and transferase activity. The catalytic Glu is often part of a Q/E-X-E motif in which the presence of Glu or Gln two residues upstream appears to determine substrate specificity for either Arg or Asn mADP-ribosylation; and (3) The STS motif that maintains the catalytic Glu and other conserved residues of the NAD+ binding site. However, the STS motif is less conserved in DT and related structures. Dependent on the conservation of additional motifs that form the active site, mADP-RTs can be annotated as DT- or CT-like in their folds. Intriguingly, both groups are not limited to bacterial toxins. The DT group also includes the mammalian poly-ADP-ribosyltransferases (PARPs) that regulate diverse cellular processes.
mechanisms including apoptosis, DNA repair, and intracellular transport (Schreiber et al., 2006). The CT group is also found in a class of eukaryotic extracellular enzymes, the Ecto-ARTs (Di Girolamo et al., 2005). Plants possess PARPs, but examples of mADP-RTs in plants have yet to be found (Wang et al., 2011a; Lamb et al., 2012). Recent structural studies on virulence effectors of plant pathogenic bacteria have revealed examples of both DT- and CT-like folds in several bacterial effector proteins, and most of these effectors have mADP-RT activity. In contrast to the fatal consequences associated with delivery of mADP-ribosylating toxins to host cells, but consistent with the (hemi-) biotrophic nature of plant pathogenic bacteria, these effectors appear to induce more subtle modifications to plant innate immunity pathways or the physiology of the infected cell. Molecular targets of selected mADP-RTs are shown in Table 1.

Table 1 | Delivery mechanisms and molecular targets of mADP-RT effectors discussed in this review.

| mADP-RT effector | Pathogen | Host cell delivery | Target protein(s) and amino acid | Role in pathogenesis | Reference |
|------------------|-----------|--------------------|----------------------------------|----------------------|----------|
| HopU1            | P. syringae | T3SS               | At GRP7, Arg49                   | Suppression of PAMP-triggered immunity | Fu et al. (2007), Jeong et al. (2011) |
| HopF1            | P. syringae | T3SS               | Unknown                          | Unknown              | Singer et al. (2004) |
| HopF2            | P. syringae | T3SS               | At MXX5, RIN4                   | Suppression of defense signaling | Wang et al. (2010), Wilton et al. (2010) |
| 6b               | Agrobacterium sp. | T3SS               | AT SE, AGO1                     | Alteration of plant hormone levels | Wang et al. (2011a) |
| C3bot2           | Clostridium botulinum | T3SS               | GTPase (ABC), Ans41             | Disintegration of actin cytoskeleton | Chardin et al. (1989) |
| Cholera toxin    | Vibrio cholerae | Receptor-mediated endocytosis | G$_{I_{a}}$, Arg201             | Activation of heterotrimeric G protein G$_{I_{a}}$ | Cassel and Pfeiffer (1978) |
| Diphtheria toxin | Corynebacterium diphtheriae | Receptor-mediated endocytosis | Eukaryotic EF-2, conserved diphthamide residue | Inhibition of protein synthesis | Collier (1967), Honjo et al. (1968) |
| ExotoxinA        | P. aeruginosa | Receptor-mediated endocytosis | Eukaryotic EF-2, conserved diphthamide residue | Inhibition of protein synthesis | Iglesias et al. (1977) |
Recently, the crystal structure of HopU1 has been determined (Jeong et al., 2011). This showed that the HopU1 catalytic subunit shares structural homology to mADP-RTs of the CT-class. For example, 86 $\alpha$-carbon atoms of HopU1 can be superimposed onto the structure of the Clostridium botulinum mADP-RT C3bot2 with a root mean square deviation of 2.12Å. The two opposing $\beta$-sheets, that support the ARTT loop with the catalytic Glu and the STS motif (STT in HopU1), align well with the corresponding $\beta$-sheets of C3bot2 (Figure 2A). In both structures the first Ser of the STS motif forms hydrogen bonds with the catalytic Glu.

**FIGURE 2** | Plant and animal pathogen mADP-RTs share the same protein fold. (A) HopU1 structure (green) superimposed on the catalytic subunit of C3bot2 (light blue). Highlighted in the HopU1 structure are the conserved Arg of the arom-H/S motif (orange), the STS motif (blue) and the catalytic Glu (dark red). The corresponding amino acids of C3bot2 are shown as sticks. The two loops that mediate binding to GRP7 are shown in magenta. PDB: 3U0J (HopU1), 1R45 (C3bot2). (B) HopF1 structure (green) superimposed on the catalytic subunit of DT (light blue) in complex with the NAD$^+$ analog adenylyl $3',5'$-uridine $3'$-monophosphate (beige). Highlighted in the HopF1 structure are the conserved Arg of the arom-H/S motif (orange) and the catalytic Asp (dark red). The corresponding amino acids of DT are shown as sticks. PDB: 1S21 (HopF1), 1DDT (DT). (C) Homology model of HopF2 (green) based on the HopF1 structure (light blue). Amino acids colored in blue contribute to the active site and are conserved in both effectors. Also include the catalytic Asp174/175 (dark red) and Arg72/71 (orange) as well as Arg135/134 and Ala187/188 (purple) that form hydrogen bonds with Arg and Asp, respectively. (D) Agrobacterium vitis 6b structure (green) superimposed on the catalytic subunit of Exotoxin A (light blue) in complex with the inhibitor PJ34 (beige). Highlighted is the conserved arrangement of $\beta$-strands with 6b residues Tyr66 and Thr93 (orange) as well as the proposed catalytic Tyr153 (red). The catalytic Glu553 and His440 of Exotoxin A are shown as sticks. The amino acid of 6b that is located closest to the position of the catalytic Glu of Exotoxin A is Tyr155 (green). PDB: 3AG2 (6b), 1XKO (Exotoxin A).
Whereas the catalytic subunits of mADP-RTs are structurally conserved, the regions mediating substrate binding can adopt more divergent conformations. The structure of HopU1 revealed two protruding loops that are not conserved in other mADP-RTs (Jeong et al., 2011). Ala substitutions in both of these loops were shown to affect GRP7 binding in vitro and abolish mADP-ribosylation of GRP7, suggesting they are essential for substrate recognition. Two Arg residues located in the GRP7 RNA binding domain have been previously identified as potential HopU1 target amino acids (Vo et al., 2007). Using a proteomics approach Jeong et al. (2011) further demonstrate that at least one residue, Arg49, is mADP-ribosylated by HopU1 in vitro. This is consistent with the close proximity of the putative HopU1 active site and Arg47/Arg49 in a structural model of the HopU1/GRP7 RNA binding domain complex. Interestingly, GRP7 Arg49 makes direct contact to RNA (Schöning et al., 2007). Therefore, HopU1 specifically targets an amino acid of GRP7 that is essential for RNA binding.

**HopF1: IN SEARCH OF A TARGET**

Structural homology to mADP-RTs has also been observed for other T3SS effectors from *P. syringae*. The crystal structure of HopF1 (formerly AvrPphF) from the bean-infecting *P. syringae* pathovar phaseolicola reveals structural similarity to DT (Figure 2B). However, to date, no mADP-RT activity has been shown for HopF1 in vitro, or in a plant cell extract (Singer et al., 2004). One explanation for this lack of activity could be changes in the amino acid composition at key positions compared to DT. This includes the catalytic Gla (Glu148, DT-numbering), which is an Asp in HopF1 (Asp174) and His21, part of the amin-H/S motif in DT (Bennett and Eisenberg, 1994), which is replaced by an Arg in HopF1 (Arg122). Interestingly, the side chains of each of these residues occupy almost identical positions in the active sites (Figure 2B). However, in the case of the DT/Glu148/HopF1(Asp174) substitution, the residues originate from different secondary structure elements (β7 in DT and β6 in HopF1). Despite the lack of mADP-RT activity under the conditions tested, Arg72 and Asp174 are still required for the virulence and avirulence activities of HopF1. Whilst wild type HopF1 enhances growth of *P. syringae* on the susceptible bean cultivar Tendergreen eightfold, Ala substitutions of either Arg72 or Asp174 completely abolish this virulence activity (Singer et al., 2004). In bean cultivar Red Mexican the R1 disease resistance gene confers recognition of HopF1 (Tsiamis et al., 2000). This recognition event requires both Arg72 and Asp174 as *P. syringae* expressing the corresponding Ala substitutions evades recognition on Red Mexican (Singer et al., 2004). Therefore, even though HopF1 does not exhibit mADP-RT activity under the conditions tested, the conserved cleft forming the putative active site is essential for both HopF1 virulence activity and recognition on resistant host plants. The side chains of both Arg72 and Asp174 form hydrogen bonds to other residues located within the cleft and these intramolecular interactions would be impaired by Ala substitutions, suggesting that the structural integrity of the cavity is required for HopF1 virulence function and recognition by R1. It is conceivable that the interface supported by Arg72 and Asp174 forms a binding site for virulence target(s) of HopF1. As the same binding site is required for HopF1 recognition on resistant bean cultivars this recognition event might be mediated by a “decoy” protein mimicking a virulence target (van der Hoorn and Kamoun, 2008). In this scenario modification of the decoy protein would trigger defense gene activation by the R1 resistance protein.

**HopF2: TARGETING KINASE CASCADES**

In contrast to HopF1, the sequence related *P. syringae* strain DC3000 effector HopF2 is known to be an active mADP-RT (Wang et al., 2010). HopF2 contributes to virulence of *P. syringae* as it enhances growth of the bacteria in *Arabidopsis* and tomato (Robert-Seilaniantz et al., 2006; Wilton et al., 2010). When delivered via the TSS of a non-pathogenic *Pseudomonas* strain, HopF2 suppresses MAMP-triggered MAP-kinase activation and direct interaction of HopF2 with several MAP-kinase kinases (MKKs) has been shown in vitro and in planta (Wang et al., 2010). Using biotin-labeled NAD⁺ as co-factor, HopF2 is able to transfer biotin-ADP-ribose onto MKKs and this impairs phosphorylation of MPK6 (Wang et al., 2010). Interestingly, HopF2 appears to modify the constitutively active MKK5(DO) mutant more efficiently than the wild type form, suggesting that the effector may preferentially target activated MKKs. ADP-ribosylation of MKK3 is dependent on a conserved Arg in the C-terminus of MKK3 and an Ala substitution of this residue largely impairs MKK3-mediated activation of the defense marker gene FRK1. Hence, one virulence activity of HopF2 is to interfere with MKK signaling to suppress MAMP-triggered immunity (Wang et al., 2010).

When over-expressed in *Arabidopsis*, HopF2 also interferes with activation of the resistance protein RPS2 by its cognate *P. syringae* effector AvrRpt2 (Wilton et al., 2010). AvrRpt2 is a Cys protease that cleaves *Arabidopsis* RIN4 and the disappearance of RIN4 triggers RPS2 activation (Axtell and Staskawicz, 2003; Mackey et al., 2003). HopF2 interferes with AvrRpt2-mediated cleavage of RIN4 and in vitro assays show that HopF2 binds to and mADP-ribosylates RIN4 (Wang et al., 2010; Wilton et al., 2010). Therefore, a possible mechanism of HopF2 interference with RIN4 cleavage is mADP-ribosylation of an amino acid in the RIN4 peptide that is cleaved by AvrRpt2 (Day et al., 2005; Kim et al., 2005).

HopF2 elicits a hypersensitive response in the non-host plant *Nicotiana tabacum* (Robert-Seilaniantz et al., 2006). In striking accordance to the requirement of Arg72 and Asp174 residues for HopF1 virulence function and recognition, the conserved two amino acids of HopF2 (Arg71 and Asp175) are essential for both the virulence and avirulence activities of HopF2 (Wang et al., 2010). HopF2 has 48% amino acid identity and 92% amino acid similarity to HopF1. The level of sequence conservation between the two effectors allows building of a reliable homology model of HopF2 based on the HopF1 structure (Figure 2C).

According to this homology model, amino acids forming the putative active site, including the Arg/Asp pair critical for effector virulence and recognition, are conserved in both effectors. The enzymatic activity of HopF2 suggests that replacement of the catalytic Glu residue, which is highly conserved in ADP-ribosylating toxins, by Asp174 in HopF1 does not explain why...
HopF1 is enzymatically inactive. Based on the structural conservation of the active site in both effectors and the requirement of corresponding amino acids for virulence and avirulence functions, it would be surprising if only HopF2 but not HopF1 functions as a mADP-RT. Hence, it would be informative to re-test whether HopF1 has mADP-RT function under conditions used for HopF2.

Based on the finding that Al substitutions of HopF2 Arg71 or Asp175 abolishes MKK5 binding, Wang and co-workers (Wang et al., 2011b) suggest that Arg71/Asp175 are more likely to be involved in substrate binding than in catalysis. However, both functions are likely to depend on the structural integrity of the active site and loss of hydrogen bonding mediated by Arg71 and Asp175 might affect its overall conformation. In a similar manner, substitutions of the conserved Glu 233/235 in the HopU ARRT loop impair not only mADP-ribosylating activity, but also decrease binding to GRF7 (Joneig et al., 2011).

**AGROBACTERIUM 6b: A DIVERGENT mADP-RT**

Plant pathogen effectors adopting the mADP-RT core fold are not limited to *P. syringae*. The *Agrobacterium* 6b protein, encoded on the Ti plasmids of *A. tumefaciens* and *A. vitis*, shows structural homology to mADP-ribosylating toxins such as Exotoxin A from *P. aeruginosa* (Wang et al., 2011b). Although the 6b protein is dispensable for crown gall formation in a natural infection, ectopic expression of 6b in several host species is sufficient to induce tumors, probably by altering auxin and cytokinin physiology of the host cell (Hooykaas et al., 1988; Tiuland et al., 1989). Further, ectopic expression of 6b in *Arabidopsis* leads to formation of serrated leaves, a phenotype also observed in mutants deficient in microRNA (miRNA) metabolism (Wang et al., 2011b).

Indeed, the accumulation of several miRNAs is altered in plants expressing 6b and the reduced levels of one particular miRNA, miR319, could provide a direct link to activation of auxin signaling (Navarro et al., 2006). 6b interacts with two proteins involved in miRNA processing, SE and AGO1, in vitro and in plant cells (Künder and Martinussen, 2004; Yang et al., 2006; Wang et al., 2011b). Thus, manipulation of the miRNA processing machinery, to alter hormone levels in host cells, appears to be one virulence mechanism of 6b proteins.

Despite the lack of sequence similarity, the structure of 6b can be superimposed on Exotoxin A and CT with a root mean square difference of <4Å (Figure 2D; Wang et al., 2011b). Although the overall position of the central β-sheets in both proteins is conserved, dramatic changes can be observed at amino acids forming the putative active site of 6b (Wang et al., 2011b). There is a notable lack of residues in 6b that could functionally substitute for the Arg/His of the α-helix 5 motif and the catalytic Gln in CT/Exotoxin A. Remarkably, the authors still provide evidence that 6b is an active mADP-RT. (1) the morphological phenotype induced by 6b expression in *Arabidopsis* can be rescued by application of the less-hydrolysable NAD⁺ analog TAD; (2) in the presence of the putative target, SE, 6b is able to hydrolyze the NAD⁺ analog ε-NAD⁺ in vitro and this activity is dependent on these Tyr and one Thr residue that contribute to the active site; (3) the hydrolytic activity of 6b is enhanced >20-fold in presence of an *Arabidopsis* ARF protein. This observation is in striking accordance with activation of CT by human ARF6-GTP (O’Neal et al., 2005). ARF6-GTP binding to CT leads to a conformational change in the active site loop rendering the catalytic cleft accessible to NAD⁺ and the substrate. A similar active site loop occluding the NAD⁺ binding site in absence of ARF is found in the 6b structures. Thus, it appears that an ARF-GTP-dependent activation mechanism has been conserved in mADP-RTs of mammalian and plant pathogens.

How do 6b proteins catalyze NAD⁺ hydrolysis without the conserved catalytic Gln? Although the detailed reaction mechanisms of most mADP-RTs remain to be elucidated, the conserved Gln is generally assumed to play a critical role in stabilizing the bound NAD⁺ molecule in a transition state that renders the anionic carbon of the nicotinamide ribose more vulnerable to nucleophilic attack by the substrate (Holbourn et al., 2006). It has been proposed that Tyr153 might perform the same function in 6b (Wang et al., 2011b). Consistent with this, the 6b Tyr153Ala mutant is impaired in ε-NAD⁺ hydrolysis. However, it is debatable whether amino acids less electronegative than Gln or Asp would be able to stabilize the NAD⁺ transition state. It is equally plausible that Tyr153, together with Tyr66 and Tyr121, contributes to the structural integrity of the active site.

An alternative explanation for retention of enzymatic activity in absence of a catalytic Gln is suggested by research on mammalian PARPs. Human PARP10 and PARP14, which both lack the conserved Gln in the catalytic core motif, do not function as PARPs (Kleine et al., 2008). However, both enzymes show mADP-ribosylating activity. Based on their findings, Kleine et al. (2008) proposed an alternative substrate-assisted catalytic mechanism where the catalytic Gln is provided not by the enzyme but by the substrate. It is conceivable that the enzymatic activity of *Agrobacterium* 6b effectors relies on a similar mechanism.

The work reviewed here suggests that several plant pathogenic bacteria evolved host-targeted enzymes with mADP-RT activity to manipulate the physiology and immune system in infected host cells. Notably, mADP-RTs from plant pathogens appear to show greater structural diversity than secreted mADP-RTs from mammalian pathogens, or the eukaryotic Ecto-ARTs. How some of these effectors retain enzymatic activity despite considerable changes in the active site is an intriguing question. The approaches summarized here need to be extended to include mADP-RT structures in the presence of non-hydrolysable NAD⁺ analogs and complemented with more sophisticated enzymatic analysis. Elucidating how this structurally diverged group of host-targeted effectors catalyzes transfer of mADP-ribose onto target proteins, and defining their target specificity, will not only provide new insights into manipulation of plant immunity but also extend our functional understanding of mADP-RTs.

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