

## Subversion of MAPK signaling by pathogenic bacteria

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### Abstract

Bacterial components are recognized by host pattern recognition receptors that trigger signaling cascades, leading to inflammation and eradication of the bacteria. The main pro-inflammatory signaling pathway is the MAP kinase (MAPK)/NF- $\kappa$ B interwoven cascades, which result in transcription of pro-inflammatory genes. Many bacteria have evolved to interfere with the immune response through a mechanism that involves delivery of virulent proteins to the host cells. These proteins post-translationally modify key components in the host signaling cascades. This review will describe bacterial strategies to directly manipulate host MAPK signaling, summarizing recent discoveries in the field.

### Introduction

The innate immune response provides the first line of defense against a microbial attack. Upon infection, bacterial components, termed pathogen-associated molecular patterns (PAMPs) and the necrotic cell content are recognized by the host pattern recognition receptors. PAMP recognition elicits activation of the MAP3K TAK1, which activate the MAPK/IKK/NF- $\kappa$ B signaling pathways.<sup>1,2</sup> These pathways lead to transcription of multiple genes that control the immune response, including the pro-inflammatory cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-8, resulting in recruitment to the site of infection of phagocytic cells and other components of the immune response.<sup>3</sup>

To survive and sustain a stable infection, the pathogen must cope with the host immune response. This is often achieved by delivering into the host cells virulence factors that subvert the host inflammatory response and associated signaling pathways. Delivery of these factors is attained by secretion of exotoxins to the extracellular milieu, or via direct injection of proteins, termed *effectors*, to the host cell by attached bacteria. To inject these effectors bacteria employ surface organelles that function as nano-injectors including type three and type

four secretion systems (T3SS and T4SS). In most cases the attached bacteria inject dozens of these effectors. Common targets for these effectors are cellular immune response cascades, including MAPK/NF- $\kappa$ B pathway.<sup>4,5</sup> Importantly, in many cases pathogens employ several effectors that act sequentially or simultaneously on different components of the same signaling network to obtain the desired outcome. Furthermore, the entire effector cohort acts in concert on a number of signaling pathways to allow efficient bacterial colonization of the host.

This short review is limited to an updated description of bacterial strategies to manipulate host MAPK signaling through translocated effectors or exotoxins that directly catalyze posttranslational modification of proteins of the MAPK network including MAP3Ks, MAP2Ks and MAPKs (Table 1, Figures 1 and 2).<sup>6,30</sup> Virulence factors interfering with input and output of the MAPK pathways (*i.e.*, host components acting upstream to MAP3K or downstream to MAPK) will be mentioned, but will not be discussed extensively.

### Enteropathogenic *Escherichia coli* and related pathogens target p38 and JNK signaling cascades

Enteropathogenic and enterohemorrhagic *Escherichia coli* (EPEC and EHEC, respectively) are closely related pathogens that colonize the human small bowel or colon. They are etiological agents of severe watery diarrhea and dysentery. EPEC remain a significant cause of infant mortality, with 79,000 annual deaths.<sup>31</sup> EHEC induce severe symptoms, causing diarrhea complicated by hemorrhagic colitis and occasionally hemolytic uremic syndrome, which can be fatal.<sup>32</sup> To facilitate infection, these pathogens translocate effector proteins into host cell via T3SS, some of which manipulate MAPK/NF- $\kappa$ B pathway. Two of these effectors, NleD and NleE, directly act on MAPK signaling components.

NleD is a zinc metalloprotease that specifically cleaves the host JNK and p38 MAPKs, but not ERK. NleD cleaves these MAPKs within the activation loop that connects the MAPK N- and C-terminal. The loop contains conserved threonine and tyrosine separated by glycine or proline (TXY motif) and MAPK activation is mediated by phosphorylation of the threonine and tyrosine residues of this motif. Importantly, NleD cleaves JNK and p38 between the Gly/Pro and Tyr of the TXY motif rendering them permanently inactive. BLAST search identified a plethora of proteins that share homology with NleD. These proteins are found in pathogenic

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bacteria that cause disease in mammals (EPEC, EHEC, *Citrobacter rodentium* and *Salmonella enterica* ssp. *Arizonae*), in plants (*Pseudomonas syringae*), or in symbiotic bacteria (*Hamiltonella defensa*). This implies that EPEC NleD is a representative of a family of NleD-like proteins.<sup>6</sup> These proteins are probably zinc metalloproteases and possibly target MAPKs.

An additional EPEC effector disrupting MAPK signaling is NleE, which inhibits activation of MAP3K TAK1 (transforming growth factor  $\beta$  activated kinase-1). TAK1 forms a complex with TAB2/3, a ubiquitin-binding protein that specifically binds to K63-linked ubiquitin chains and likely also to linear-ubiquitin chains.<sup>7</sup> Binding of TAB2/3 to the ubiquitin chains results in TAK1 activation. NleE is a methyltransferase that specifically methylates a conserved cysteine residue in the Npl4-like Zinc Finger (NZF) domains of TAB2/3. This modification abolishes the TAB2/3 ability to bind to the ubiquitin chain, preventing TAK1 activation.<sup>7</sup> Since TAK1 transmits a signal to both the MAPK and NF- $\kappa$ B pathways, both are repressed. This repression prevents production of pro-inflammatory chemokines, such as IL-6, IL-8 and TNF.<sup>33-35</sup> NleE and NleD are translocated at the same time to the host cell.<sup>36</sup>

It is thus intriguing why EPEC evolved two different effectors that redundantly block JNK and p38 signaling.

### *Shigella flexneri* reprogram the host epigenome through MAPK inactivation

*Shigella flexneri* (*S. flexneri*) is facultative intracellular pathogen that causes shigellosis or bacillary dysentery, and accounts for about one-third of the total annual deaths due to enteric infections.<sup>37</sup> *S. flexneri* employs a T3SS to invade the intestinal epithelium cells, causing inflammation and tissue damage. OspF is one of the T3SS injected effectors and it targets MAPKs. To recognize MAPKs, OspF mimics the canonical D motif, found in many MAPK substrates, that is required for MAPK docking. OspF is phospho-threonine-lyase that catalyses a  $\beta$  elimination reaction to irreversibly remove the phosphate moiety from a phospho-threonine residue in the TXY motif of MAPKs.<sup>8,9</sup> This activity irreversibly and permanently inactivates the modified MAPK. Although OspF might dephosphorylate all three families of MAPKs *in vitro*,<sup>8</sup> it seems that only ERK and p38 are its native substrates *in vivo*.<sup>10</sup> Inactivation of ERK and p38 $\beta$  by OspF promotes chromatin condensation and inhibition

of transcriptional activation by masking NF- $\kappa$ B binding sites, leading to compromised recruitment of polymorphonuclear leukocytes to infected tissues.<sup>10</sup> It was further reported that inactivation of ERK by OspF reduces the activity of the downstream kinase MSK1, thus reducing up-regulation of proliferative genes and fine-tuning of immune gene expression.<sup>38</sup> *S. flexneri* also possesses an NleE homologue, OspZ, although the gene is not functional in all isolates. Like NleE, OspZ blocks NF- $\kappa$ B activation,<sup>35</sup> probably by TAB2/3 methylation.

### The *Yersinia* effector YopJ inhibits MAPK activation by MAP2K acetylation

*Yersinia* strains (*Yersinia* st.) cause disease ranging from self-limited gastroenteritis (*Yersinia enterocolitica* and *Yersinia pseudotuberculosis*) to a devastating life threatening plague (*Yersinia pestis*). It is a gram negative, rod-shaped, facultative anaerobic bacterium. *Yersinia*'s virulence is dependent on a T3SS and injected effectors, including YopJ (YopP in *Y. enterocolitica*). Initially, YopJ was proposed to act as a deubiquitinating protease,<sup>39,40</sup> but more recent studies indicate that YopJ is an acetyl-transferase that transfers an acetyl group from acetyl-coenzyme A to

specific residues of target proteins. YopJ inhibits the MAPK pathway by acetylating serine, threonine and lysine residues in the activation loop of various MAP2Ks, including MKK2, MKK4, MKK6, MKK7 and the upstream MAP3K-TAK1.<sup>11-13</sup> Upon acetylation, these host proteins can no longer undergo phosphorylation, thus compromising the respective MAPK signaling pathway. NF- $\kappa$ B signaling is also attenuated by YopJ that acetylates IKK $\alpha/\beta$  and prevents its activation. By modulating these signaling pathways, YopJ induces apoptosis and inhibits pro-inflammatory signal transduction, preventing the production of protective cytokines such as TNF $\alpha$  and IL-8.<sup>41</sup>

### *Salmonella enterica* directly activate and repress MAPKs

*Salmonella enterica* (*S. enterica*) serovar Typhimurium is the etiological agent of gastroenteritis and systemic infections. This pathogen colonizes many niches in the host and alternates between extracellular and intracellular lifestyles. *S. enterica* employs two distinct T3SS, SPI1 and SPI2, to inject into the host a complex array of effectors. Using two T3SS provides *S. enterica* with better control over the temporal and spatial resolution of the repertoire of injected effectors. For example,

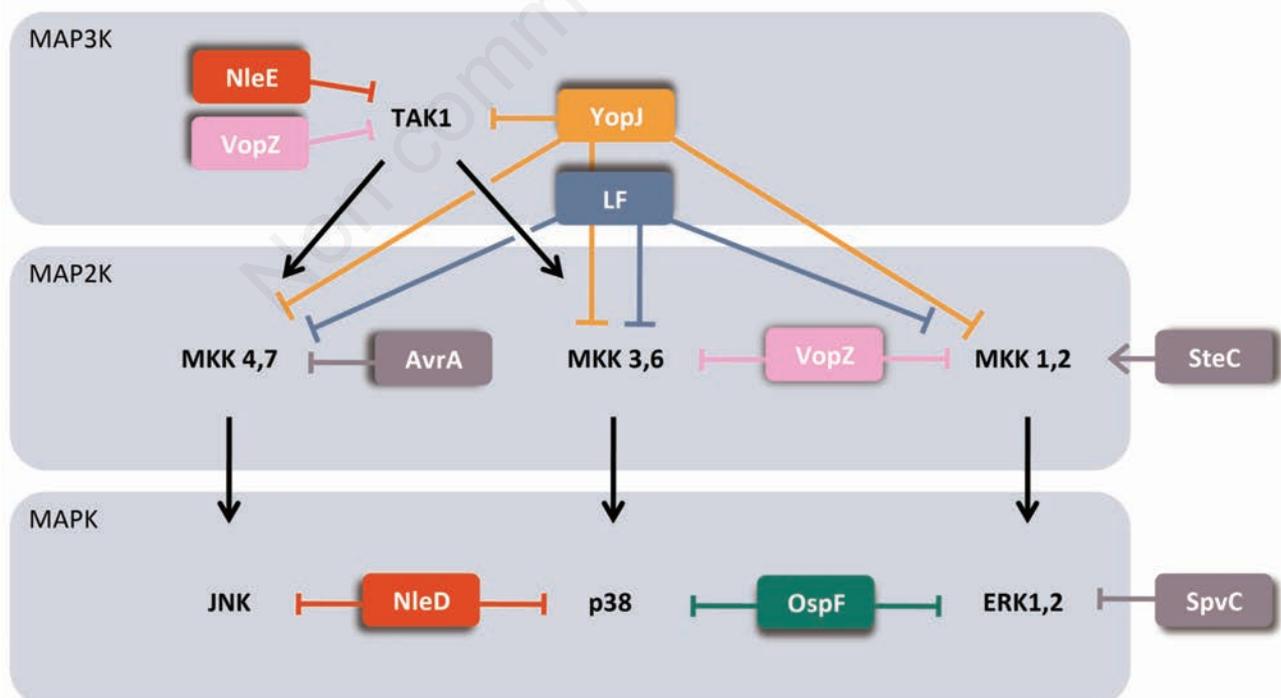


Figure 1. Manipulation of mammalian MAPK signaling by bacterial proteins. MAPK proteins are colored in black, and divided to three tiers; MAPK, MAP2K and MAP3K. Bacterial proteins that interfere with MAPK cascade are marked in squares, and each color represents different bacterial species; enteropathogenic *E. coli* (red), *Yersinia* (orange), *V. parahaemolyticus* (pink), *S. enterica* (purple), *S. flexneri* (green), *B. anthracis* (blue).

the SPI1 T3SS is used mainly by extracellular bacteria and the SPI2 by intracellular *S. enterica*. Some *S. enterica* effectors have pro-inflammatory activity, while others reduce the host immune response by inhibiting inflammation signaling.<sup>42-44</sup>

Some *S. enterica* carry NleD and NleE homologues (*S. enterica* ssp. *Arizonae*), but these effectors are missing in most *S. enterica* isolates. More common MAPK-manipulating effectors of *S. enterica* are SpvC, AvrA, and SteC. SpvC is very similar to OspF of *S. flexneri* and is also a phospho-threoninylase of MAPKs. Upon over expression, or *in vitro*, SpvC can target ERK1/2, p38 and JNK,<sup>8,14</sup> but *in vivo*, under physiological conditions, only ERK1/2 are dephosphorylated.<sup>15</sup> Genetic analyses show that SpvC is required for systemic infection in mice.<sup>45</sup> Inhibition of MAPK by SpvC reduces expression of pro-inflammatory cytokines (e.g., IL-8, TNF $\alpha$ ) and diminishes inflammation and neutrophil infiltration at infection sites during early stages of infection.<sup>14,15</sup> In addition to ERK inhibition, *S. enterica* employ the AvrA effector to block JNK signaling. AvrA is a SPI1 T3SS effector protein that is a close homologue of YopJ.<sup>46</sup> Like YopJ, AvrA is an acetyl-transferase and under physiological conditions it acetylates specific serine residues of MKK4 and MKK7.<sup>16,17</sup> The modified MAKK4/7 can no longer be phosphorylated and activated, thus specifically compromising JNK pathway, host inflammatory response and apoptosis.<sup>47</sup> The *S. enterica* SteC effector is a serine/threonine kinase delivered through the SPI2 T3SS into the host cells by intercellular bacteria.<sup>18,19</sup> SteC catalyzes MEK1 and MEK2 phosphorylation, triggering their activation by auto-phosphorylation, resulting in activation of ERK1/2 signaling. Through this activity, SteC promotes the formation of the F-actin meshwork around *S. enterica*-containing vacuoles.<sup>18,19</sup> In conclusion, *S. enterica* exhibit intricate manipulation of MAPK signaling, particularly that of ERK1/2.

### ***Vibrio parahaemolyticus* abolishes the three main MAPK signaling cascades**

*Vibrio parahaemolyticus* (*V. parahaemolyticus*) is a Gram-negative halophilic bacterium inhabiting marine or estuarine environments. It is an important causative agent of gastroenteritis, usually related to the consumption of undercooked seafood.<sup>48</sup> The *V. parahaemolyticus* T3SS effector VopA is an acetyl transferase, member of the YopJ acetyl-transferases protein family. Like YopJ, it modifies MKKs, including MKK1 and MKK6 on serine, threonine, and lysine residues. The VopA activity

abolishes the three main MAPK signaling cascades, ERK, p38 and JNK, but does not affect NF- $\kappa$ B.<sup>20</sup> Interestingly, this virulence protein acetylates not only the activation loop of MKKs, but also a residue in the catalytic loop that is required for ATP binding, thereby blocking MAPKs in a dual way: i) inhibiting activation through phosphorylation; and ii) inhibiting the kinase function.<sup>21</sup> An additional effector of *V. parahaemolyticus* that down regulates MAPK and NF- $\kappa$ B cascades is VopZ, which leads to inhibition of MAPK through repression of TAK1 MAP3K. It is unclear whether VopZ acts directly on TAK1, and its enzymatic activity has yet to be uncovered.<sup>22</sup>

### ***Pseudomonas syringae* tightly regulate the plant MAPK**

*Pseudomonas syringae* (*P. syringae*) is a gram-negative plant pathogen that causes a wide variety of diseases, including blights, leaf spots, and galls in different plant species.<sup>49</sup> To facilitate stable infection, *P. syringae* subvert MAPK signaling via T3SS effectors HopA11 and HopF2 (Figure 2). HopA11 belongs to the OspF-like protein family of phospho-threonine-lyases. In Arabidopsis, HopA11 targets MPK3, MPK4 and MPK6 and inactivates them to suppress plant defense responses.<sup>24,25</sup> An additional interesting *P. syringae* effector is HopF2, an ADP-ribosyltransferase that suppresses two branches of the MAPK cascade. Firstly, it catalyzes ADP-ribosylation of MKK5, thereby suppressing downstream MPK3 and MPK6 activation.<sup>23</sup> In addition, it indirectly suppresses MPK4 by inhibiting a component upstream of

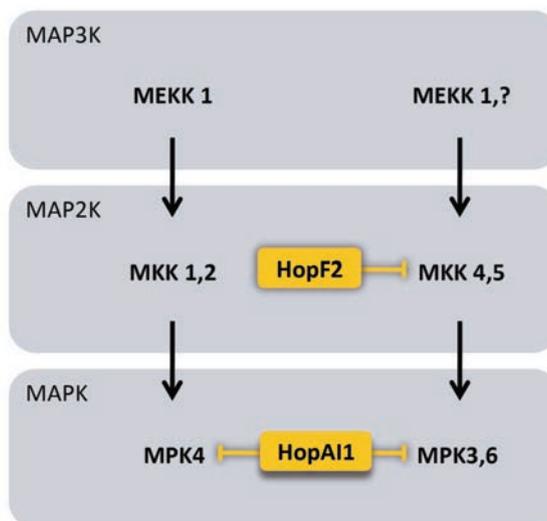
MKK1, BAK1.<sup>50</sup> Interestingly, BAK1 is also a target for additional *P. syringae* virulence factors, such as AvrPto and AvrPtoB.<sup>51</sup>

### ***Bacillus anthracis* secretes a toxin to block MAPK signaling**

*Bacillus anthracis* (*B. anthracis*) the causative agent of anthrax, are Gram-positive, rod-shaped, spore-forming bacteria. A major virulence factor of this pathogen is the secreted anthrax toxin. The lethal factor subunit of this toxin is a zinc metalloprotease that cleaves the N-terminus from several MKKs, including MKK1-4 and MKK6-7, resulting in a kinase that can no longer interact with its substrate.<sup>26-28</sup> The cleavage of these kinases leads to the inactivation of the ERK1/2, p38, and JNK signaling pathways. The inactivation of the MAPK pathway in macrophages and dendritic cells leads to inhibition of pro-inflammatory cytokine secretion, down regulation of costimulatory molecules such as CD80 and CD86, and ineffective T cell priming. The result is an impaired innate and adaptive immune response.<sup>52</sup>

### ***Mycobacterium tuberculosis* changes the JNK phosphorylation balance**

Nearly one-third of the world's population is a carrier of *Mycobacterium tuberculosis* (*M. tuberculosis*), the major causative agent of



**Figure 2. Manipulation of plant MAPK signaling by bacterial proteins. MAPK proteins are colored in black, and divided to three tiers: MAPK, MAP2K and MAP3K. Bacterial proteins that interfere with MAPK cascade are marked in squares.**

**Table 1. Bacterial proteins that interfere with MAPK signaling.**

Microbe	Bacterial effector/toxin	Enzymatic activity	Host substrate	Subversion mechanism*	References
Enteropathogenic <i>E. coli</i>	NleD	Protease	p38, JNK	Prevents p38/JNK activation by cleaving within their activation loops	6
Enteropathogenic <i>E. coli</i>	NleE	Methyl transferase	TAB2/3	Blocks TAK1 activation by methylation of the TAB2/3 components of the TAK1 complex	7
<i>S. flexneri</i>	OspF	Phosphothreonine lyase	ERK, p38	Irreversibly inactivate ERK and p38 by cleavage of the C-OP bond in the phosphothreonine residue in the TXY motif	8-10
<i>Yersinia st.</i>	YopJ	Acetyl transferase	TAK1, MKK2,4,6,7	Prevents MKK2,4,6,7 and TAK1 phosphorylation by acetylating residues in their activation loops	11-13
<i>S. enterica</i>	SpvC	Phosphothreonine lyase	ERK	Similar to OspF with preference to ERK OspF homolog	8,14,15
<i>S. enterica</i>	AvrA	Acetyl transferase	MKK4/7	Similar to YopJ Prevents MKK4 and MKK7 phosphorylation by acetylating residues in their activation loops	16,17
<i>S. enterica</i>	SteC	Kinase	MEK1	Induce MEK1 and MEK2 activation by phosphorylating them to promote their auto-phosphorylation	18,19
<i>V. parahaemolyticus</i>	VopA	Acetyl transferase	MKK1,6	Similar to YopJ Prevents MKK1,6 phosphorylation by acetylating residues in their activation loops and catalytic loops	20,21
<i>V. parahaemolyticus</i>	VopZ	Unknown	Unknown	Inhibits activation of TAK1	22
<i>P. syringae</i>	HopF2	ADP-ribosyl transferase	Plant MKK5	Blocks MKK5 kinase activity by ADP-ribosylating it	23
<i>P. syringae</i>	HopA1	Phosphothreonine lyase	Plant MAPK (MPK3,4,6)	Similar to OspF Irreversibly removes the phosphate moiety from a phosphor-threonine residue in the TXY motif of the plant MPK3,4 and 6	24,25
<i>B. anthracis</i>	LF	Protease	MKK1-4, MKK6-7	Cleaves the N-terminus from MKK1-4 and MKK6-7, resulting in a kinase that cannot interact with its substrate	26-28
<i>M. tuberculosis</i>	Eis	Acetyl transferase	DUSP16	Activates through acetylation the JNK phosphatase DUSP16s JNK is therefore inhibited by increased dephosphorylation	29,20

\*A more extensive description of the subversion mechanism.

tuberculosis, and the leading cause of death from a bacterial infection worldwide.<sup>53</sup> This pathogen invades and thrives in the host professional phagocytic cells, such as macrophages, neutrophils, monocytes and dendritic cells, by arresting phagosome maturation and fusion with lysosomes. *M. tuberculosis* secrete the enhanced intracellular survival (Eis) protein, an efficient N-acetyltransferase that activates the JNK specific phosphatase DUSP16 through acetylation on Lys55.<sup>29</sup> DUSPs are enzymes that can dephosphorylate, and thereby inactivate, both the threonine and tyrosine residues in the activa-

tion loop of MAPKs. JNK is therefore inhibited by increased dephosphorylation,<sup>30</sup> which enhances pathogen survival inside cells by reducing autophagic cell death and inflammation.<sup>54</sup>

### Closing remarks

Microbes and hosts maintain an ongoing complex molecular cross talk. Bacteria, viruses and parasitic pathogens developed fascinating techniques to maneuver the host MAPKs sig-

naling pathway and gain control over inflammation. Many bacteria have more than one effector that manipulates the MAPK pathway, differing in the MAPK substrates or time of action. Interestingly, some effectors block the MAPK cascade while others induce it, suggesting a complex balance between them. Although many bacterial effector mechanisms are being revealed in recent years, our understanding of how all the effectors cooperate in order to achieve a stable infection is still incomplete and represents a major challenge to future research.

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