BACTERIAL PATHOGENESIS

An epigenetic effector

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URLs

Shigella flexneri
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&prjcmd=Retrieve&dopt=Overview&list_uids=12334

Many bacterial pathogens use secreted effectors to interfere with host signalling pathways, but the specific mechanisms used to alter the expression of particular host genes have been largely unknown. Now, a paper in *Nature Immunology* has revealed that *Shigella flexneri* inhibits the transcription of nuclear factor (NF)- κ B-regulated genes by preventing histone H3 phosphorylation.

Arbibe *et al.* were interested in the interaction of *S. flexneri* with the host cell mitogen-activated protein kinase (MAPK) signalling pathways. The phosphorylation status of various components of these pathways was examined in the presence and absence of the type III secretion system (T3SS). The results showed that *S. flexneri* could inactivate the MAPK Erk in the nucleus and that the T3SS was required for this effect. The protein responsible was subsequently identified as the type III-secreted effector OspF and it was found that

OspF also dephosphorylated the MAPK p38. Moreover, dephosphorylation occurs at two distinct residues, that is, OspF has dual-specific phosphatase activity.

Transcriptome analysis of HeLa cells infected with an *ospF* mutant revealed that OspF can repress a subset of the NF- κ B-regulated genes involved in the host immune response, such as the gene encoding interleukin-8. How is this selective repression achieved? In eukaryotes, the genomic DNA is wrapped around histone proteins. The N-terminal tails of the histones remain accessible and covalent modifications of these tails can alter transcriptional regulation. Phosphorylation of a serine residue in H3 has previously been shown to increase the accessibility of the promoters of NF- κ B-responsive genes to NF- κ B. Arbibe *et al.* found that the phosphorylation of H3 is strongly repressed in the presence of OspF and that this effect is specific for an

NF- κ B-regulated gene subset. Finally, the function of OspF was investigated in a ligated ileal loop infection model in rabbits and it seems that *in vivo*, OspF restricts *S. flexneri* invasion of intestinal tissues and inhibits the recruitment of polymorphonuclear leukocytes to infected areas.

Collectively, these results show that the *S. flexneri* OspF type III effector is capable of epigenetic modification. This dual-specific phosphatase dephosphorylates MAPKs in the nucleus, thereby inhibiting the phosphorylation of H3. This leads to the downregulation of transcription of a specific subset of NF- κ B-regulated genes, thereby impairing the ability of the host to respond to *S. flexneri* infection.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Arbibe, L. *et al.*
 An injected bacterial effector targets chromatin access for transcription factor NF- κ B to alter transcription of host genes involved in immune responses. *Nature Immunol.* **8**, 47–56 (2007)