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Yersinia perturbs host cell signaling

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Abstract

YopJ, a virulence factor of *Yersinia pseudotuberculosis*, can bind to several key intracellular signaling proteins, members of the MAPKK family, preventing their activation and protecting the pathogen from host defense mechanisms.

Significance and context

The bacterial pathogen *Yersinia pestis* is responsible for bubonic plague. Pathogenic *Yersinia* species contain a 70 kilobase plasmid, which encodes virulence factors (called Yops, *Yersinia* outer proteins) that are injected into the host cell and disrupt cellular signaling pathways. In this way, Yops enable the bacterium to avoid the normal host immune response to infection. The YopJ virulence factor protein has multiple effects on kinase signaling pathways, pro-inflammatory cytokine gene regulation and host cell survival. Furthermore, YopJ-related proteins are found in a range of plant and animal pathogens, suggesting common functions in regulating bacterial-host-cell interactions. Relatively little is known about the mode of action of YopJ. Here, the authors show that YopJ can bind directly to mitogen-activated kinase kinases (MAPKKs) and prevent their phosphorylation and activation. YopJ can also inhibit the NFκB signaling pathway.

Key results

The authors use yeast two-hybrid protein-protein interaction assays and 'pull-down' of fusion proteins with GST (glutathione-*S*-transferase) to show that YopJ specifically interacts with the MAPKK family members MKK1, MKK2, MKK4/SEK1 and MKK5, but not with the related kinases ERK, JNK, p38 or BRaf. They go on to show that in the human epithelial 293 cell line, YopJ can inhibit MAPKK signaling stimulated by epidermal growth factor (EGF), activated Ras GTPase or oncogenic v-Raf kinase. YopJ inhibited phosphorylation of MAPKKs and their activation. Furthermore, MAPKK activation was inhibited when murine macrophages were infected with wild-type bacteria, but not when *yopJ*-mutant strains were used. Finally, the authors show that YopJ can also inhibit alternative pro-inflammatory pathways downstream of MEKK1; YopJ interacts with the IKKα protein, a signaling kinase of the NFκB pathway, but not with the related IKKβ protein.

Conclusions

The authors emphasize that a single bacterial protein, YopJ, can prevent the activation of multiple downstream MAPKK and NFκB pathways. They propose that these effects combine inhibition of cytokine gene regulation with the deregulation of anti-apoptotic factors (such as NFκB-regulated genes). The result is decreased inflammatory cytokine production and host cell apoptosis.

Reporter's comments

The study illustrates how pathogenic genomes have evolved to generate versatile, multi-talented proteins that can interact with several host signaling pathways to ensure bacterial survival. As the authors mention, it will be interesting to determine whether YopJ-related proteins from other species, such as the plant pathogen AvrRxv protein, act in identical ways. It will also be important to dissect which portions of the YopJ protein bind to MAPKK and IKKα (for example, are they distinct or overlapping sequences?). The creation of YopJ variants that interact with particular pathways will allow determination of which ones are really responsible for regulating cytokines and/or apoptosis. Understanding the way that YopJ manipulates the immune response may give us clues to strategies for combating inflammatory diseases.

Table of links

Science

References

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