

# Bacterial Virulence Strategies That Utilize Rho GTPases

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**Abstract** The ability to modify central host cellular functions is a major advantage to many bacterial pathogens that use such strategies as part of their virulence mechanisms. Small GTPases, including Rho GTPases, make particularly attractive targets for pathogens because of their central roles in modulating cellular functions such as cytoskeletal control. Such modifications of these GTPases can include direct chemical modification of the GTPase or interfacing with some of the regulatory elements associated with GTPase control. Pathogens use these alterations in GTPase functions for a variety of functions, including killing the host cell, mediating bacterial uptake into the host cell (invasion), reprogramming actin to form a lesion in host cells underlying adherent bacteria, to mediate intracellular survival by affecting intracellular trafficking, or to provide polymerized actin mechanisms to propel microbes around inside host cells and into adjacent cells. Collectively, these examples represent many key microbial virulence mechanisms that have led to a much deeper understanding of both microbial pathogens and GTPase functions.

## 1 Introduction

There are approximately 100 pathogenic microbes that cause significant disease in humans, accounting for one-third of all deaths on the planet, in addition to many other pathogens that infect other mammals, animals, and plants. These pathogenic microbes possess many sophisticated virulence strategies that are designed to overcome generally effective host defense mechanisms that defend against the continual exposure to microbes [7]. Generally, these virulence mechanisms target one or more normal host cellular processes, and it is the collective action of these mechanisms that ultimately ends in disease.

The choice of host processes to target are numerous: signaling mechanisms, cell division, host immune response, phagocytosis, epithelial barrier integrity, chemotaxis, phagosome-lysosome fusion, etc.. Most virulence factors target a specific host molecule to mediate these effects. This entails direct contact of the bacterial virulence factor with the appropriate host molecule, which may be on the host cell surface or, in many cases, inside the host cell. Thus bacterial pathogens have developed various strategies to deliver their virulence factors, from binding to the cellular surface, being taken up by normal endocytic routes, and then escaping the membrane bound inclusion (many toxins use this route) to being injected directly into the host cell with specialized type III and type IV secretion systems [11, 14] and then targeting to the appropriate intracellular location. Recent knowledge in cell biology has advanced very rapidly, and much of this progress is due to the use of virulence factors as tools to study normal cellular processes. Indeed, the function of such key cytoskeletal regulators such as Rho, N-WASP, and Arp2/3 were discovered by using bacterial factors that modulate them.

An ideal virulence factor target should be one that controls one or more important cellular processes, and whose manipulation will provide the invading pathogen with a subsequent advantage for surviving and multiplying within the infected host. Thus the more “ideal” the host target, the more examples there are of virulence factors that aim to alter and/or disrupt such a target. One of the most extensively targeted cellular processes is the ability to alter cytoskeletal rearrangements, especially the subset of actin-based processes (as opposed to microtubules or intermediate filaments). The actin-based cytoskeleton has many important roles in eukaryotic cells, including cell motility, phagocytosis, and cell division, and is an essential process to eukaryotic cells. Not surprisingly, many bacterial pathogens go after the “master controls” of the cytoskeleton, the small GTP-binding proteins belonging to the Rho family of GTPases, and have devised many clever ways to activate, inactivate, modulate, and generally manipulate these important cellular regulators, ultimately using these mechanisms as part of their overall virulence strategy.

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### **Small GTPases**

Although ATP serves as the main energy source within cells, many proteins (called G proteins) can bind and cleave GTP to regulate cellular processes and mechanisms. Generally, G proteins are divided into two groups, with a major family being the small G proteins or small GTPases (20–40 kDa).