Internalization of
Staphylococcus aureus by
Nonprofessional Phagocytes

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1. INTRODUCTION

One general means of grouping pathogenic microorganisms is based on their location relevant to host cells during infection. Some organisms such as the rickettsia, chlamydia, and viruses are considered to be obligate intracellular pathogens since they are unable to replicate outside of host cells. Other pathogens may be grown on axenic media in the laboratory and do not require an intracellular environment. Within this second group are two subgroups, extracellular pathogens and the facultative intracellular pathogens. Many facultative intracellular organisms are known for their ability to survive, and even replicate, in an intracellular environment. These include organisms within a variety of genera such as Mycobacterium, Salmonella, Shigella, and Listeria, in addition to certain fungi and protozoa. Some of these species are typically engulfed by actively phagocytic cells such as neutrophils or macrophages. These pathogens have evolved unique mechanisms for evading the host cell killing mechanisms. Other organisms are internalized by nonprofessional phagocytes such as epithelial or endothelial cells. By necessity, these organisms have developed mechanisms by which they induce cytoskeletal rearrangements leading to uptake of the organism. Extracellular pathogens are becoming less well defined for several reasons and the distinction between facultative intracellular organisms and extracellular pathogens is becoming unclear. The main reason is that many pathogens long considered to be extracellular...
pathogens have been shown, in recent years, to have properties similar to facultative intracellular pathogens. Thus as we now see, the designation of organisms as to their cellular location is a useful but imperfect classification system.

*Staphylococcus aureus* is one such organism that is not internalized efficiently by nonprofessional phagocytes and has been traditionally considered to be an extracellular pathogen. However, as new information is obtained, it is becoming clearer that *S. aureus* and many other organisms traditionally considered to be extracellular have an intracellular niche that may be important for pathogenesis. Our understanding of the mechanisms and consequences of internalized staphylococci is currently somewhat limited. However, techniques developed for the study of other organisms are generally applicable to *S. aureus* and crucial events employed by internalization of this organism often overlap those of other well-characterized pathogens. The purpose of this review is to summarize our current knowledge concerning the mechanisms by which *S. aureus* is internalized by non-professional phagocytes and the potential effects of this interaction in pathogenesis.

2. EARLY KEY STUDIES DEMONSTRATING THE INTERNALIZATION OF *S. AUREUS* BY VARIOUS TYPES OF NONPROFESSIONAL PHAGOCYTES

The study of intracellular *S. aureus* in nonprofessional phagocytic cells is a relatively new field of investigation. Prior to 1990, only a few published reports on this topic existed in the literature. Although there have been numerous descriptions of intracellular staphylococci from clinical specimens, the organisms were typically shown to be localized in phagocytic cells or their location was not designated. The initial demonstration of internalization of *S. aureus* by nonprofessional phagocytes was made using endothelial cells. Since then, other investigators have employed a number of model systems including various sources of epithelial cells, osteoblasts, and fibroblasts. Each cell line has its own unique advantage as far as serving as a model for a particular infectious disease or clinical situation.

**Endothelial Cells**

The first clear demonstration of active internalization by endothelial cells was a report in 1985 by Ogawa *et al.* These investigators, while assessing the adherence of *S. aureus* to cells, demonstrated internalized