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REVIEW

N-Acylhomoserine lactone-dependent cell-to-cell communication and social behavior in the genus *Serratia*

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Abstract

Members of the genus *Serratia* are increasingly responsible for nosocomial infections, the treatment of which may be complicated by the appearance of multi-antibiotic-resistant strains. Some but not all *Serratia* strains and species produce *N*-acylhomoserine lactones (AHLs), and possess *luxR* and *luxI* homologous genes. Phylogenetic comparisons have provided evidence for the lateral transfer of these quorum-sensing systems, and in at least one strain of *S. marcescens*, transfer via a complex transposon has been experimentally demonstrated. AHL-dependent quorum sensing in *Serratia* controls population surface migration, biofilm development, the biosynthesis of a carbapenem antibiotic and production of the red pigment, prodigiosin. *Serratia* also possesses LuxS and produces autoinducer-2 (AI-2) which appears to function as a second quorum-sensing system controlling many of the same phenotypes as the LuxR/AHL systems.

Keywords: Serratia; Quorum sensing; *N*-Acyl-homoserine lactone; LuxS; Pathogenicity; Multicellular behavior

Contents

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Introduction

Serratia are Gram-negative bacteria which can be isolated from water, soil, plants and air (Grimont and Grimont, 1978). They are opportunistic pathogens of hospital patients where treatment may be complicated by the resistance of many strains to multiple antibiotics (Hejazi and Falkiner, 1997). While *Serratia* spp. secrete a number of virulence factors (Hejazi and Falkiner, 1997) capable of damaging human cells and tissues, some strains also synthesize useful secondary metabolites (e.g. antibiotics, red pigments and surfactants) which have potential applications in the pharmaceutical industry and in environmental bioremediation.

The expression of several *Serratia* virulence factors as well as the synthesis of secondary metabolites is controlled in a cell population density-dependent manner and may also be regulated coordinately with population migration (swarming and sliding) (Eberl et al., 1999; Horng et al., 2002). Diverse environmental and cellular cues are involved (Harshey, 2003) and a number of different regulatory systems have evolved to permit rapid bacterial adaptation to fluctuating environmental conditions (Miller and Bassler, 2001; Stock et al., 2000). These include ''quorum-sensing'', a mechanism which enables bacteria to sense their cell population density and use this information to coordinately regulate gene expression (Williams et al., 2000). Quorum sensing allows bacterial populations to efficiently adapt to changes in the surrounding environment (Fuqua et al., 2001; Henke and Bassler, 2004; Withers et al., 2001). Like many other bacterial species, *Serratia* strains produce diffusible, low-molecular-mass signal molecules which accumulate in their surroundings as the population increases. When the concentration of the molecule exceeds a threshold value, signalling pathways are activated (or de-repressed) and the bacteria respond by altering gene expression so modulating physiological processes in a concerted manner throughout the population. Two classes of quorum-sensing systems have been described in *Serratia*, the *N*-acylhomoserine lactone (AHL)-dependent LuxIR type (Fuqua et al., 1994; Withers et al., 2001) and the autoinducer-2 (AI-2)/LuxS type (Bassler et al., 1997; Winzer et al., 2003). Here both systems will be discussed but the focus will primarily be on AHL-dependent quorum sensing since this has been much more extensively investigated in *Serratia*.

The genus *Serratia*

In 1823, Bartolomeo Bizio, a pharmacist from Padua, Italy, discovered and named *Serratia marcescens* when identifying this bacterium as the cause of a miraculous bloody discoloration in a cornmeal mush called polenta. Bizio named *Serratia* in honour of an Italian physicist named *Serratia*, who invented the steamboat, and Bizio chose *marcescens* from the Latin word for decaying because the bloody pigment was found to deteriorate quickly. *S. marcescens* has been used as a biological marker for studying the transmission of microorganisms since 1906, as it was considered harmless. This changed in the 1960s when the pathogenic potential of *S. marcescens* was recognized (Whea et al., 1951). *S. marcescens* causes nosocomial infections including respiratory tract, urinary tract and wound infections, as well as meningitis, septicaemia, and pneumonia (Acar, 1986; Hejazi and Falkiner, 1997). A recent Centres for Disease Control (CDC), USA health advisory network (HAN) reported *S. marcescens* blood stream infections associated with contaminated magnesium sulfate solutions (Health Alert Network, CDC Health Advisory 2005). *S. marcescens* has also developed multiple resistance toward β-lactams, aminoglycosides and fluoroquinolones (Stock et al., 2003; Traub, 2000). As the incidence of *Serratia* infections increases, drug-resistance problems may become increasingly important (Livermore, 1998a, b). *S. marcescens* is now considered not only as an insect pathogen (Kurz and Ewbank, 2000) but also as an emerging harmful human pathogen.

The genus *Serratia* belongs to the *Enterobacteriaceae*. Apart from *S. marcescens*, this genus includes *Serratia liquefaciens*, *Serratia plymuthica*, *Serratia rubidaea*, *Serratia fonticola*, *Serratia marnorubra*, *Serratia proteamaculans*, and *Serratia odorifera* (Skerman et al., 1980). *Serratia* strains produce DNase, lipase, and gelatinase, which distinguish them from other genera belonging to the *Enterobacteriaceae* (Anahory et al., 1998; Kawai et al., 1998; Li et al., 1995; Nestle and Roberts, 1969). *S. marcescens* also produces a number of other virulence factors, including a haemolysin, proteases, chitinase, chloroperoxidase, multiple isozymes of alkaline phosphatase, and has the ability to swim and swarm (Anahory et al., 1998; Braun and Schmitz, 1980; Hase and Finkelstein, 1993; Hertle, 2000; Hines et al., 1988; Yanagida et al., 1986). Using *Caenorhabditis elegans* as a model system for in vivo identification of bacterial virulence factors, the haemolysin ShlA together with LPS and iron uptake systems were shown to be the major virulence factors of *S. marcescens* (Kurz et al., 2003). ShlA represents a unique type of haemolysin. Structure, activation and secretion analyses show that ShlA has little in common with the pore forming RTX-type toxins of *Escherichia coli*, the *Staphylococcus aureus* alpha-toxin or the thiol-activated toxin of group A β-hemolytic streptococci (streptolysin O). The mechanism of pore formation of ShlA on eukaryote membranes is also different (Hertle, 2000).

Although *S. marcescens* produces multiple virulence factors, it is not a major enterobacterial pathogen like *Salmonella* or *Shigella*. Environmental temperature shift plays an important role in the regulation of