Hypermucoviscosity: An Extremely Sticky Phenotype of *Klebsiella pneumoniae* Associated with Emerging Destructive Tissue Abscess Syndrome

**Toshihisa Kawai**
Department of Immunology, The Forsyth Institute, Boston, Massachusetts

*(See the article by Yu et al. on pages 1351–8)*

*Klebsiella pneumoniae* is an opportunistic pathogen found in the environment and on mammalian mucosal surfaces. *K. pneumoniae* has been characterized as a community-acquired pulmonary pathogen since it was discovered >100 years ago. The classic clinical symptoms are represented by rapid onset, high fever, and hemoptysis (currant jelly–like sputum), in conjunction with the radiographic findings of bulging interlobar fissures and cavitations [1]. The incidence of community-acquired *K. pneumoniae* has apparently decreased [2, 3], whereas the mortality rate for pneumonia due to *Klebsiella* species remains fairly high as a result of the underlying disease that tends to be present in affected patients [2]. In Western countries, most *K. pneumoniae* infections occur in the lungs and urinary tract. At the same time, however, *K. pneumoniae* has been found to be the leading cause of liver abscess in Taiwan [4]. *K. pneumoniae*–mediated liver abscess occurred almost exclusively in patients from Taiwan, followed by Singapore and Korea, in reports from 1990 to 1999 [2, 5]. A few cases of liver abscess due to *K. pneumoniae* have also recently been reported from Hong Kong, Thailand, and Japan [2]. During the 1990s and early 2000s, >900 patients with liver abscess due to *K. pneumoniae* were reported from East and Southeast Asian countries, whereas only ~50 reports of such cases were reported from countries outside of East and Southeast Asia in this same period [2, 6, 7]. It has also been shown that patients with diabetes mellitus in Taiwan are more susceptible to *K. pneumoniae* infection than are those without diabetes mellitus [4]. Emerging in Taiwan are *K. pneumoniae* infections in addition to liver abscess that involve destructive clinical syndromes, such as metastatic meningitis and endophthalmitis, osteomyelitis, and brain abscess [4, 8]. Despite the production of possible virulence factors, such as polysaccharide capsule, different adhesins, lipopolysaccharide, and iron-scavenging proteins [9], the pathogenicity of *K. pneumoniae* has not been completely elucidated.

In this issue of *Clinical Infectious Disease*, Yu et al. [10], based in Taiwan, investigated the possible correlation between the incidence of bacteremia due to *K. pneumoniae* and the frequency of putative pathogenic genes, such as *kfu*, *rmpA*, and *magA*, and the hypermucoviscosity phenotype in clinical isolates of *K. pneumoniae* from a total of 151 clinical cases at the 2 largest medical centers in southern Taiwan from July 2003 to December 2004. The results demonstrated that nosocomial strains are significantly less prone to form abscesses than are community-acquired *K. pneumoniae* and that the strains positive for *rmpA*, but not for *magA* or *kfu*, are significantly associated with the virulent hypermucoviscosity phenotype and purulent tissue infections in the liver and other organs.

Fang et al. [11] reported that *magA* (mucoviscosity-associated gene A) is associated with the hypermucoviscosity phenotype of *K. pneumoniae* strains that cause liver abscess in Taiwan. Klebsiellae are gram-negative bacteria with a prominent polysaccharide capsule that produce large, sticky colonies when plated on an agar plate with nutrient media. The strains with the hypermucoviscosity phenotype demonstrate extremely high viscosity, determined by a string test of the colony cultured in the laboratory [11]. According to the study by Fang et al. [11], the prevalence of hypermucoviscosity-positive strains was higher for cases of *K. pneumoniae* infection causing liver abscess than from other sites of *K. pneumoniae* infection (98% vs. 17%). To identify genetic loci associated...
with the hypermucoviscosity phenotype, a mutant library of *K. pneumoniae* was constructed using transposon mutagenesis. The mutation in *magA* and other genetic loci, including the *cps* cluster [12], the *wb* cluster [13], and *rmpA* [14], resulted in a deficiency in the hypermucoviscosity phenotype. However, only *magA* had a significantly higher incidence in invasive strains than in noninvasive clinical isolates of *K. pneumoniae* (98% vs. 29%). The *magA* mutants lost the hypermucoviscosity phenotype and became extremely serum sensitive, phagocytosis susceptible, and avirulent to mice [11].

Yu et al. [10] discovered an article published in 1989 [14] demonstrating that the *rmpA* (regulator of the mucoid phenotype A) is a regulatory gene for the synthesis of extracapsular polysaccharide and positively controls the mucoid phenotype of *K. pneumoniae*. It is the overproduction of polysaccharide, not capsule production, that is responsible for the mucoid phenotype of *K. pneumoniae*. Although the *rmpA* gene is encoded by the chromosome, the mucoid phenotype is regulated by *rmpA* located in a plasmid [14]. Knockout and restoration of the *rmpA* gene showed the loss and recovery of the mucoviscous phenotype [14]. On the basis of these lines of evidence, Yu and colleagues hypothesized that the mucoid phenotype regulated by the *rmpA* gene may correspond to the hypermucoviscosity phenotypes of *K. pneumoniae* isolated from tissue abscess. They further demonstrated that the frequency of the *rmpA* gene positively correlates with the incidence of tissue abscess formation due to *K. pneumoniae* with the hypermucoviscosity phenotype [10]. Of interest, the experiments using transposon mutagenesis by Fang et al. [11] also revealed that *rmpA* is associated with the hypermucoviscosity phenotype. In contrast to the study by Fang and colleagues, in which *magA*-positive strains were most frequently isolated from liver abscess, Yu and colleagues found relatively low frequencies of *magA*, as well as *kfu*, in their isolates from liver abscess. An iron-uptake system encoded in the *kfu* gene is highly correlated with *magA* expression in *K. pneumoniae* [15].

The discrepancy between the 2 studies, both performed in Taiwan, may be related to the geographic distribution of the genes that correlate with the genotypes of *K. pneumoniae*. In fact, the clinical isolates studied by Yu et al. [10] were from the southern region of Taiwan, whereas the isolates studied by Fang et al. [11] were almost all from northern Taiwan.

The geographic distribution of *K. pneumoniae* strains that cause liver abscess seems to be restricted to East and Southeast Asian countries, with the exception of some reports of cases from South Africa and the United States [2, 6, 7]. If *rmpA* and/or *magA* are responsible for the pathogenesis of *K. pneumoniae* tissue abscess, then expression of these genes should be identified only in clinical isolates of *K. pneumoniae* in East and Southeast Asian countries. The geographic restriction of *K. pneumoniae* tissue abscess also suggests that susceptibility to infection with the *K. pneumoniae* strains that cause tissue abscess may be attributed to a certain host genetic background that is distinct to the geographic region. During the period of 1993–2003, for example, 23 cases of *K. pneumoniae* liver abscess were recorded at 2 hospitals in New York. Of note, 18 (78.3%) of the patients were of Asian ethnicity, indicating a possible genetic linkage to disease susceptibility [6]. Meanwhile, future global etiology studies may elucidate the possible engagement of *rmpA* and/or *magA* in the context of *K. pneumoniae* tissue abscess.

In an additional observation, the possession by *K. pneumoniae* of resistance plasmids that express genes conferring antibiotic resistance may account for the rapid spread of this organism in communities and may lead to nosocomial outbreaks. For instance, epidemics of gentamicin-resistant *K. pneumoniae* in hospitals were frequently reported in the late 1970s [16]. *K. pneumoniae* is naturally resistant to ampicillin and amoxicillin because of the production of SHV-1 β-lactamase encoded on the chromosome or on a transferable resistance plasmid [17]. Therefore, it is crucial to know whether it is the *rmpA* or *magA* gene that is expressed in resistance plasmids.

Irrespective of the conflicting results between the frequencies of *rmpA* and *magA*-positive strains, the consensus of the 2 studies carried out in Taiwan is that the hypermucoviscosity phenotype of *K. pneumoniae* appears to be associated with purulent infection with *K. pneumoniae*. Both *rmpA* and *magA* genes are requisite for the induction of the hypermucoviscosity phenotype by *K. pneumoniae*. Thus far, *K. pneumoniae* strains with the hypermucoviscosity phenotype have been identified only in Taiwan, except for 1 case reported from the United States [18]. However, it is still unclear whether the hypermucoviscosity phenotype is critically related to the pathogenesis of *K. pneumoniae*. The problem arises because a number of genetic loci appear to be associated with the hypermucoviscosity phenotype of *K. pneumoniae* [11], and hypermucoviscosity-negative strains have also been isolated from the abscesses of liver and other organs [10]. Therefore, not only hypermucoviscosity phenotypes but also other characteristics may be involved in purulent infection along with those presented in *K. pneumoniae*.

In summary, the hypermucoviscosity phenotype, as well as the *rmpA* and *magA* genes, can be used in the diagnosis of bacteremia due to *K. pneumoniae* strains with putative virulence. This can, perhaps, result in the early detection and prevention of tissue abscess disease that results from *K. pneumoniae* infection.

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**References**


