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## ***Klebsiella* sweet deadly kiss.**

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The World Health Organization identified antimicrobial resistance (AMR) as one of the greatest threats to human health. Drug-resistant infections already kill hundreds of thousands a year globally, and by 2050 that figure could be more than 10 million (amr.review.org). Of particular concern is the mounting prevalence of infections caused by multidrug resistant (MDR) Gram-negative bacteria. Although *Escherichia coli* is the most common cause of invasive Gram-negative infections, the most significant challenge comes from *Klebsiella pneumoniae*. The percentage of isolates resistant to last generation antibiotics continues to increase worldwide. In fact, the isolation of *Klebsiella* strains resistant to “*last resort*” antimicrobials has significantly narrowed, or in some settings completely removed, the therapeutic options for the treatment of *Klebsiella* infections. To further complicate this scenario, recent population genomic studies have shown that virulent and MDR resistant clones have access to a diverse mobile pool of virulence and antimicrobial resistance genes of high penetrance<sup>1,2</sup> hence making possible the emergence of an extremely drug-resistant hypervirulent *K. pneumoniae* clone capable of causing untreatable infections in healthy individuals. It is then not surprising that MDR *K. pneumoniae* has been singled out as an “*urgent threat to human health*” by several institutions including the UK government, the CDC and the WHO. However, and despite the clinical relevance, there is still scant evidence on *K. pneumoniae* pathogenesis at the molecular and cellular level. Therefore, the development of new therapeutic strategies requires a better

understanding of *K. pneumoniae* pathophysiology in the context of the complex interactions between bacterial pathogens and their hosts.

In this issue of *Virulence*, Lee et al<sup>3</sup> investigate the relationship between glycemic control and the onset of *Klebsiella*-triggered invasive infections. This study is of clinical relevance given the increasing number of *Klebsiella* disseminated infections in patients with underlying conditions such as diabetes and liver disease, mostly in East Asian countries. However, the high prevalence of obesity worldwide, which is associated with risks of developing type 2 diabetes, anticipates an overall increase of this type of *Klebsiella* invasive infections worldwide. Unfortunately, the clinical data presented in this work further confirms previous studies demonstrating a correlation between community-acquired *Klebsiella* disseminated infections and type 2 diabetes mellitus<sup>4</sup>. Further analysis of the clinical data by Lee et al<sup>3</sup> revealed a remarkable correlation between disseminated infections and patients with poor glycemic control compared with diabetic patients with good glycemic control. Interestingly, previous studies have suggested that poor glycemic control impairs neutrophils phagocytosis of *K. pneumoniae* capsule serotypes K1 and K2<sup>5</sup>. Taken into consideration the important role of neutrophils in *Klebsiella* clearance, this reduced phagocytosis may explain the increased disseminated *Klebsiella* infections in these patients. In this study, Lee et al decided to investigate the other side of the coin: whether poor glycemic control, in other words high glucose levels in blood, may affect the pathogenicity of *Klebsiella*. Not surprisingly, they chose to explore the effect of high glucose on the single most important virulence factor of *K. pneumoniae*, the capsule polysaccharide<sup>6</sup>. Capsule mutants are attenuated in the pneumonia mouse model and in the *Galleria mellonella* one<sup>6, 7</sup>. The capsule polysaccharide protects *Klebsiella* against the bactericidal action of complement and antimicrobial peptides<sup>8, 9</sup>, limits the activation of inflammatory responses<sup>10-12</sup>, and reduces phagocytosis by neutrophils and even amoebas<sup>13, 14</sup>. In this work, Lee et al<sup>3</sup> conclusively demonstrate that high glucose levels, but not high glycerol ones, up regulate the transcription of the *cps* operon with a concomitant increase in the levels of surface exposed polysaccharide. Further studies are required to

decipher the molecular basis of this upregulation. In fact, capsule regulation in *Klebsiella* is still poorly understood. As anticipated, glucose-induced high capsule levels were associated with a further increased in *Klebsiella* resistance to neutrophils phagocytosis and whole blood leukocyte killing. Since previous studies have shown that there is a correlation between the capsule levels and the resistance to antimicrobial peptides and the induction of inflammatory responses<sup>15-17</sup>, it is tempting to postulate that poor glycemic control enhances capsule-dependent *Klebsiella* anti-immune mechanisms and, therefore, the virulence of the pathogen. However sounded this hypothesis, further studies are warranted to provide a global view of *Klebsiella* transcriptome when grown in high glucose to investigate, for example, whether the expressions of other known *Klebsiella* virulence factors such as the siderophores, the lipopolysaccharide and the OmpA outer membrane protein are also affected<sup>12, 16, 18-22</sup>. Nevertheless, the time is ripe to carry out these studies in vivo using well established obesity or diabetes mellitus animal models thereby allowing a better understanding of *Klebsiella* biology in the context of the host. This fundamental knowledge is absolutely essential not only to inform the management of diabetic patients but also to develop new therapeutics based on new targets and approaches.

In conclusion, this study by Lee et al establishes that type 2 diabetes mellitus with poor glycemic control is a risk factor for *Klebsiella* disseminated infections. The reported in vitro data indicates that high glucose may enhance capsule-dependent evasion of the immune system hence contributing to develop disseminated infections. Taken together, this means that therapeutics targeting *Klebsiella* capsule, or interfering with capsule-mediated anti-immune mechanisms, may be a potential strategy to fight *Klebsiella* infections.

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