Virulence 4:6, 435–436; August 15, 2013; © 2013 Landes Bioscience

Community-acquired pneumonia infections by *Acinetobacter baumannii*

How does alcohol impact the antimicrobial functions of macrophages?

Eliseo A Eugenin

Public Health Research Institute and Rutgers University Medical School; The State University of New Jersey; Newark, NJ USA

Keywords: *Acinetobacter baumannii*, alcohol, cytokines, macrophages, phagocytosis

In this issue of *Virulence*, Asplund et al.,[1] provides a proof of principle study indicating that physiological concentrations of alcohol impair macrophage antimicrobial functions against *Acinetobacter baumannii* (*Ab*). Thus, this communication delivers seminal evidence that alcohol and macrophages plays a key role the pathogenesis of *Ab*.

Ab is a wide spectrum of intrinsic and acquired multidrug-resistant gram-negative coccobacillus.[2] *Ab* has the ability to form biofilms on non-viable surfaces, surviving through high temperatures as well as extended periods of desiccation, making it a very resilient pathogen. Therefore, due to its high persistence, pathogenesis, and multidrug resistance, this pathogen has been associated with skin and soft tissue diseases, including necrotizing fasciitis, as well as lethal infections such as pneumonia, which can evolve to septic shock.[3] In addition, in immunosuppressed individuals, *Ab* is considered a primary causative agent of community-acquired pneumonia (CAP-*Ab*)[4-6] especially in association with alcohol abuse resulting in significant high mortality rate >50%.[5,7,8] Data around the world indicates that *Ab* is a leading cause of severe and lethal CAP within various regions of the Asia Pacific such as Taiwan,[9] Hong-Kong,[7] Singapore,[10] and Australia.[4] In the case of biofilm formation, hospital acquired pneumonia caused by *Ab* (HAP-*Ab*) is typically acquired by patients in intensive care units via artificial ventilation in which mechanical tubing is commonly contaminated resulting in 35% mortality rate.[7]

In the context of drug resistance acquired by *Ab,* the more common resistances are to carbapenems, β-lactams, rifampicin, and emerging strains against once successful colistin have been isolated.[7] *Ab* typically acquires resistance via antimicrobial inactivating enzymes such as lactamases, mutations within the bacterial genome that alters antimicrobial targets, and horizontal transfer with interactions with other microorganisms.[7] Given the increasing difficulty in treating *Ab* infections, and the high mortality rates associated to this evolving pathogen, there is an urgent need to understand its biology and mechanisms of pathogenesis.

Despite its clinical importance, relatively little is known about the innate host defense mechanisms against respiratory *Ab* infection. Similar to the neutrophil, the macrophage is another important phagocyte that is generally involved in host defense against pathogen invasion. These professional phagocytic cells are one of the first innate immune cells in the respiratory tract to be activated after infection, and function to detect and eliminate invading pathogens while activating the adaptive immunity. Only recently, Qiu et al. showed that alveolar macrophages (AMs) are essential in the clearance and cellular immune response to *Ab* by microtubule- and microfilament-dependent phagocytosis.[11] AMs upon stimulation produce elevated levels of pro-inflammatory cytokines upon stimulation, promoting the recruitment of neutrophils. Similarly, AMs produce high levels of nitric oxide (NO), an effector molecule that is important to combat *Ab* infection. However, it was unknown whether these mechanisms were present or altered in *Ab* infection in the presence or absence of alcohol abuse.

In the manuscript discussed here, for the first time, it has been proven that although macrophages are believed to play a relatively minor role in the overall host defense against *Ab* infection, they play an essential role in the initial stage of host defense against respiratory *Ab* infection, partially through an NO-dependent mechanism.[1] In addition, an important effect of alcohol has been revealed in this study that explain, the majority of CAP-*Ab* infections and the impaired immune system observed in the individuals exposed to both *Ab* and alcohol consumption. Alcohol consumption is also correlated with impaired immune responses including AM dysfunction in phagocytosis, killing of bacteria, and cytokine secretion.[4] However, there was no study available associating the direct effects of alcohol exposure on macrophage effector functions.

In this issue, Asplund et al. provide a proof-of-principle study suggesting that physiological alcohol concentrations impair macrophage antimicrobial functions against *Ab* using a J774.16 macrophage-like cell line. Alcohol-exposed macrophages shown

Correspondence to: Eliseo A Eugenin; Email: eliseo.eugenin@rutgers.edu
Submitted: 07/11/13; Accepted: 07/13/13
http://dx.doi.org/10.4161/viru.25747
Editorial to: Asplund MB, et al. Virulence 2013; 4:467-72; PMID:23863607; http://dx.doi.org/10.4161/viru.25641

decreased phagocytosis and killing of *Ab*. Interestingly, alcohol-mediated macrophage phagocytosis dysfunction may be associated with reduced expression of GTPase-RhoA, a key regulator of the actin polymerization signaling cascade and formation of the phagocytosis pocket, enabling the engulfment of the pathogen. Notably, this is the first study that suggests a specific protein expression cascade interruption in macrophages by alcohol leading to impairment of phagocytosis in the setting of a microbial infection. Furthermore, alcohol inhibited NO generation via inducible NO-synthase inactivation, which enhanced *Ab* survival within macrophages. Moreover, alcohol alters cytokine production, resulting in a dysregulated immune response, providing a plausible explanation for the occurrence of CAP-*Ab*-related complications, such as septic shock and impairment of adaptive immune cellular recruitment. This study opens a novel area of research and potential new therapeutic targets to reduce the devastating consequences of this opportunistic microbe that has been underestimated as a serious threat for human health.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Asplund MB, Coelho C, Cordero RJB, Martinez LR. Alcohol impairs J774.16 macrophage-like cell antimicrobial functions in *Acinetobacter baumannii* infection. Virulence 2013; In this issue
2. Maragakis LL, Perl TM. Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis 2008; 46:1254-63; PMID:18444865; http://dx.doi.org/10.1086/529198
3. Giamarellou H, Antoniadou A, Kanellakopoulou K. *Acinetobacter baumannii*: a universal threat to public health? Int J Antimicrob Agents 2008; 32:106-19; PMID:18571905; http://dx.doi.org/10.1016/j.ijantimicag.2008.02.013
4. Anstey NM, Currie BJ, Hassell M, Palmer D, Dwyer B, Seifert H. Community-acquired bacteremic *Acinetobacter* pneumonia in tropical Australia is caused by diverse strains of *Acinetobacter baumannii*, with carriage in the throat in at-risk groups. J Clin Microbiol 2002; 40:685-6; PMID:11825997; http://dx.doi.org/10.1128/JCM.40.2.685-686.2002
5. Peng C, Zong Z, Fan H. *Acinetobacter baumannii* isolates associated with community-acquired pneumonia in West China. Clin Microbiol Infect 2012; 18:E491-3; PMID:23057470
6. Falagas ME, Karveli EA, Kelesidis I, Kelesidis T. Community-acquired *Acinetobacter* infections. Eur J Clin Microbiol Infect Dis 2007; 26:857-68; PMID:17701432; http://dx.doi.org/10.1007/s10096-007-0365-6
7. Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired *Acinetobacter baumannii* pneumonia as a distinct clinical syndrome. Chest 2006; 129:102-9; PMID:16424419; http://dx.doi.org/10.1378/chest.129.1.102
8. Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to *Acinetobacter baumannii.* Chest 2001; 120:1072-7; PMID:11591541; http://dx.doi.org/10.1378/chest.120.4.1072
9. Wang JT, McDonald LC, Chang SC, Ho M. Community-acquired *Acinetobacter baumannii* bacteremia in adult patients in Taiwan. J Clin Microbiol 2002; 40:1526-9; PMID:11923388; http://dx.doi.org/10.1128/JCM.40.4.1526-1529.2002
10. Ong CW, Lye DC, Khoo KL, Chua GS, Yeoh SF, Leo YS, et al. Severe community-acquired *Acinetobacter baumannii* pneumonia: an emerging highly lethal infectious disease in the Asia-Pacific. Respirology 2009; 14:1200-5; PMID:19909464; http://dx.doi.org/10.1111/j.1440-1843.2009.01630.x
11. Qiu H, KuoLee R, Harris G, Van Rooijen N, Patel GB, Chen W. Role of macrophages in early host resistance to respiratory *Acinetobacter baumannii* infection. PLoS One 2012; 7:e40019; PMID:22768201; http://dx.doi.org/10.1371/journal.pone.0040019