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Code blue: *Acinetobacter baumannii*, a nosocomial pathogen with a role in the oral cavity

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SUMMARY

Actinetobacter baumannii is an important nosocomial pathogen that can cause a wide range of serious conditions including pneumonia, meningitis, necrotizing fasciitis and sepsis. It is also a major cause of wound infections in military personnel injured during the conflicts in Afghanistan and Iraq, leading to its popular nickname of 'Iraqibacter'. Contributing to its success in clinical settings is resistance to environmental stresses such as desiccation and disinfectants. Moreover, in recent years there has been a dramatic increase in the number of *A. baumannii* strains with resistance to multiple antibiotic classes. *Acinetobacter baumannii* is an inhabitant of oral biofilms, which can act as a reservoir for pneumonia and chronic obstructive pulmonary disease. Subgingival colonization by *A. baumannii* increases the risk of refractory periodontitis. Pathogenesis of the organism involves adherence, biofilm formation and iron acquisition. In addition, *A. baumannii* can induce apoptotic cell death in epithelial cells and kill hyphal forms of *Candida albicans*. Virulence factors that have been identified include pili, the outer membrane protein OmpA, phospholipases and extracellular polysaccharide. *Acinetobacter baumannii* can sense blue light through a blue-light sensing using flavin (BLUF) domain protein, BlsA. The resulting conformational change in BlsA leads to changes in gene expression, including virulence genes.

Keywords

Acinetobacter; infection models; oral microbiology; periodontal disease; respiratory tract microbiology

INTRODUCTION

There are few organisms that can compare with *Acinetobacter baumannii* in terms of variety of associated diseases. Serious infections that are caused by *A. baumannii* include

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pneumonia, meningitis, necrotizing fasciitis, sepsis, urinary tract infections, skin and/or soft tissue infections, endocarditis and keratitis (Peleg *et al.*, 2008a). This gram-negative organism emerged as an important hospital-acquired opportunistic pathogen in the 1970s (Peleg *et al.*, 2008a), and more recently has been thrust into the public eye as a 'superbug', with the increasing incidence of multidrug-resistant strains. Moreover, *A. baumannii* has gained notoriety through frequent infections in wounded military personnel (Davis *et al.*, 2005; Dijkshoorn *et al.*, 2007; Perez *et al.*, 2007), which has earned it the popular nickname, 'Iraqibacter' (Howard *et al.*, 2012). Indeed, a study by the National Naval Medical Center (USA) of war wounds of US troops located in Iraq and Afghanistan from 2007 to 2008 determined that *A. baumannii* accounted for 63% of all bacterial isolates in tissue biopsies (Sheppard *et al.*, 2010). *Acinetobacter baumannii* had the highest incidence rate, at 22% 1 week post-injury, while *Enterococcus faecium* had the second highest incidence rate at only 3.3% (Sheppard *et al.*, 2010). *Acinetobacter baumannii* has an unfortunate predilection for the severely injured, compromised and elderly, and many of the infections in these cases are associated with the use of contaminated medical equipment such as catheters, ventilators, external ventricular drains and even gloves (Peleg *et al.*, 2008a; Park *et al.*, 2013). Mortality rates with bacteraemia-related diseases are around 35%; however, when accounting for just imipenem-resistant strains the mortality rate rises to an astonishing 70% (Park *et al.*, 2013; Lee *et al.*, 2014). *Acinetobacter baumannii* is a resilient organism that can resist desiccation and other stressors including disinfectants (Jawad *et al.*, 1996, 1998; Wendt *et al.*, 1997; Peleg *et al.*, 2008a; Rajamohan *et al.*, 2010). Combined with its ability to form biofilms on biotic and abiotic surfaces, the organism has an aptitude to persist in medical environments, making it especially dangerous for immune-compromised hospital patients (Gaddy *et al.*, 2009). Bacterial transmission is primarily from contact with contaminated surfaces, but can also occur by person-to-person spread in hospitals. Traditionally, the habitat of *A. baumannii* was thought to be exclusively clinical settings (Perez *et al.*, 2007; Towner, 2009); however, a comprehensive review by Eveillard *et al.* (2013) concluded that the idea that *A. baumannii* is isolated exclusively from hospitals is flawed and that extra-hospital reservoirs probably exist. Such reservoirs could include pets, slaughter animals, lice, or human carriage; as the presence of *A. baumannii* in these locations has been shown by improved identification methods (Turton *et al.*, 2006; Gundi *et al.*, 2009; Eveillard *et al.*, 2013).

A. BAUMANNII IN THE ORAL CAVITY

An increasing range of medically relevant pathogens are recognized in the oral cavity. Respiratory and systemic pathogens that have been isolated from chronic periodontitis and aggressive periodontitis patients include *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, along with *A. baumannii* (Didilescu *et al.*, 2005; da Silva-Boghossian *et al.*, 2011). Furthermore, *A. baumannii* was identified with a significantly higher prevalence in patients with chronic or aggressive periodontitis compared with healthy individuals or patients with gingivitis (Slots *et al.*, 1991; Ali *et al.*, 1996; Colombo *et al.*, 2002; Souto *et al.*, 2006; da Silva-Boghossian *et al.*, 2011; Silva-Boghossian *et al.*, 2013), particularly in patients with human immunodeficiency virus (Goncalves *et al.*, 2007). While the role of *A. baumannii* in periodontal disease has yet to be investigated, the presence of the organism in conjunction with the traditional periodontal pathogens

Porphyromonas gingivalis, *Tannerella forsythia*, *Treponema denticola* and *Aggregatibacter actinomycetemcomitans* along with *P. aeruginosa* increases the likelihood of aggressive periodontitis (da Silva-Boghossian *et al.*, 2011). Additionally, the odds of a subject being refractory to periodontal treatment increase when *A. baumannii* is present (Colombo *et al.*, 1998). As *A. baumannii* is well-equipped to survive in polymicrobial communities (see below) further study of interspecies interactions involving the organism may begin to elucidate any contribution to periodontal disease.

The presence of respiratory pathogens establishes the oral microbiota as an extra-hospital reservoir, and aerosolization of these bacteria into the lower respiratory tract can cause pneumonia and chronic obstructive pulmonary disease (Scannapieco *et al.*, 2003). Consistent with this, hospitalized chronic lung disease patients have a higher incidence of respiratory pathogens, including *A. baumannii*, present in supra-gingival plaque (Didilescu *et al.*, 2005). In addition, due to the anatomical closeness, aerosolized bacteria can enter the bloodstream and cause septicemia (Scannapieco & Ho, 2001). A corollary to an oral reservoir for pulmonary disease is that efforts have been made to reduce respiratory diseases by addressing oral health. For example, *A. baumannii* is a major pathogen in ventilator-associated pneumonia, which is a large problem in hospitals, especially in intensive care units (Ayraud-Thevenot *et al.*, 2012; Lee *et al.*, 2012; Martinez-Lamas *et al.*, 2014). Özçako *et al.* (2012) showed that by simply swabbing the teeth of ventilated patients with 0.2% chlorhexidine gluconate the risk of ventilator-associated pneumonia was reduced.

POLYMICROBIAL INTERACTIONS

In the host and environment *A. baumannii* encounters and interacts with other organisms. It colonizes the multispecies oral biofilms on tooth surfaces, and although individual synergistic or antagonistic inter-species interactions have yet to be examined in detail, *Streptococcus sanguinis* produces an extracellular compound that is bactericidal to *A. baumannii* (Watanabe *et al.*, 2009). Antagonism between *A. baumannii* and the early-colonizing *S. sanguinis* may be one reason *A. baumannii* is often associated with the gram-negative anaerobic later colonizers. Mixed infections with *A. baumannii* have also been documented with other gram-negative pathogens in intensive care unit patients (Didilescu *et al.*, 2005; Souto *et al.*, 2006; Mammina *et al.*, 2013). Moreover, carbapenem-resistant *A. baumannii* is commonly found in mixed infections with other carbapenem-resistant pathogens such as *Klebsiella pneumoniae*, Enterobacteriaceae and *P. aeruginosa* (Marchaim *et al.*, 2012; Mammina *et al.*, 2013). Carbapenem-resistant *A. baumannii* may also shelter carbapenem-susceptible bacteria in a polymicrobial infection, exacerbating disease progression during carbapenem treatment (Liao *et al.*, 2014). Secondary bacterial infection with *A. baumannii* has also been seen in pandemic outbreaks of respiratory illness associated with the influenza A (H1N1) virus (Palacios *et al.*, 2009; Champunot *et al.*, 2010; Schoindre *et al.*, 2011).

It was recently established that *A. baumannii* possess a type VI secretion system (T6SS), a bacterial protein export machine that resembles the tail assembly of contractile bacteriophages (Carruthers *et al.*, 2013). T6SS are often used to inject toxic effector molecules into other bacteria (Carruthers *et al.*, 2013), and the T6SS of *A. baumannii* allows

the organism to outcompete *E. coli* in mixed cultures (Carruthers *et al.*, 2013). In addition, *A. baumannii* has the ability to inhibit *Candida albicans* filamentous growth and biofilm formation (Peleg *et al.*, 2008b). However, if *C. albicans* biofilm is first allowed to mature it can inhibit the growth of *A. baumannii* through the quorum-sensing molecule, farnesol (Peleg *et al.*, 2008b). Attachment of *A. baumannii* to *Candida* is mediated by the outer membrane protein A (OmpA), and secretion of OmpA can kill *Candida* by the induction of apoptosis (Gaddy *et al.*, 2009). These processes demonstrate unique cross-kingdom extracellular signaling, probably to control microbial composition in niches containing both organisms, and modulate the virulence of the mixed species community. Such antagonistic interactions also suggest the potential for novel therapeutic agents to combat diseases that are challenging to treat due to antibiotic resistance.

ANTIBIOTIC RESISTANCE

The prevalence of extensively drug-resistant and pan-drug-resistant strains is causing concern for the end of the 'antibiotic era' (Hsueh *et al.*, 2002; Kuo *et al.*, 2012). *Acinetobacter baumannii* is a member of the ESKAPE group of organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species) which are (generally) nosocomially acquired pathogens that have a high rate of antibiotic resistance (Rice, 2008). The frequency of carbape-nem-resistant isolates is on the rise with the increased use of broad-spectrum antibiotics in hospitals (Towner, 2009). For example, imipenem, a carbapenem that is considered a last-resort drug, is now ineffective against ~15% of isolates (Towner, 2009). A study on US combat casualties from 2005 to 2007 observed that *Acinetobacter baumannii–calcoaceticus* complex was the most commonly recovered multi-drug-resistant pathogen of interest, and the only one to have increasing microbial resistance each year (Murray *et al.*, 2009). Current antibiotic treatment regimens consist of combination therapy, which has so far been effective in eliminating multidrug-resistant strains (Perez *et al.*, 2007); however, the failure of this approach seems only a matter of time.

An almost bewildering number of antibiotic resistance mechanisms has been acquired by *A. baumannii* (Table 1). High-density pyrosequencing of *A. baumannii* strain ATCC 17978 showed 75 potential drug-resistance genes composed of 32 efflux pumps and 11 permeases (Smith *et al.*, 2007). Other mechanisms that *A. baumannii* strains have adopted include, but are not limited to; class A–D β-lactamases, modifications of outer-membrane proteins and penicillin-binding proteins, aminoglycoside-modifying enzymes, and modifications or loss of lipopolysaccharides (Fernandez-Cuenca *et al.*, 2003; Perez *et al.*, 2007; Moffatt *et al.*, 2013). Many of the associated genes and other putative virulence genes are located within pathogenicity islands (Smith *et al.*, 2007). Fournier *et al.* (2006) identified an 86-kb hotspot in *A. baumannii* strain AYE that has two different genomic island insertions containing 45 of its 52 drug-resistance genes. This hotspot, named AbaR1, is surrounded by broad-host-range mobile genetic elements such as insertion sequences, transposons and class 1 integrons (Fournier *et al.*, 2006). These genes are predicted to have originated from other gram-negative organisms such as *E. coli*, *Salmonella* spp. and *Pseudomonas* spp. (Fournier *et al.*, 2006). Clearly *A. baumannii* has an unparalleled ability to change, rearrange and

acquire genetic elements, making it highly adaptable to its surroundings and causing variation among strains (Averhoff & Friedrich, 2003).

Acinetobacter baumannii is naturally transformable through type IV pili (TFP) mediated uptake of foreign DNA and incorporation into the genome via homologous recombination (Metzgar *et al.*, 2004; Harding *et al.*, 2013). This accounts for the large strain variability and rapid development of antibiotic resistance. *Acinetobacter* species do not produce flagella, which led to the genus name which means non-motile rod in Greek. However, this is a misnomer, as *A. baumannii* is capable of twitching motility via the extension and retraction of the TFP (Harding *et al.*, 2013). The TFP also play a role in adherence to surfaces (Harding *et al.*, 2013), and strikingly *A. baumannii* is capable of moving along wet surfaces and picking up DNA, a process dependent on functional TFP (Wilharm *et al.*, 2013). As an adjunct to conventional horizontal gene transfer, *A. bauamannii* is also able to secrete outer membrane vesicles containing antibiotic resistance genes, which can be acquired by susceptible strains thereby providing them with protection (Rumbo *et al.*, 2011).

PATHOGENIC MECHANISMS

Despite the significant threat to human health posed by *A. baumannii*, comparatively little is known about its virulence mechanisms. The four main pathogenic mechanisms and factors described to date are biofilm formation, outer membrane protein A (OmpA or Omp38), the K1 capsule and a siderophore-mediated iron-acquisition system (Dorsey *et al.*, 2003, 2004; Tomaras *et al.*, 2003; Choi *et al.*, 2005) (Fig. 1). Establishment of a biofilm is crucial to colonization by *A. baumannii*, and biofilm formation depends on pilus production mediated by the CsuA/BABCDE chaperone-usher assembly system (Tomaras *et al.*, 2003; Gaddy *et al.*, 2009). CsuA/B is thought to constitute the pilin subunit, and CsuE is the tip adhesin (de Breij *et al.*, 2009). Transposon mutagenesis studies have also identified an RNase T2 family protein as a positive regulator of biofilm formation and motility (Jacobs *et al.*, 2014). The biofilm-associated-protein, Bap which is homologous to the *Staphylococcus aureus* Bap protein, is required for maintenance and maturation of the biofilm (Loehfelm *et al.*, 2008; Goh *et al.*, 2013). Bap also plays an important role in the colonization of the host as it is involved in initial adherence to eukaryotic cells (Loehfelm *et al.*, 2008; Brossard & Campagnari, 2012). Production of OmpA is necessary for the development of robust biofilms on abiotic surfaces and while the mechanistic basis is unclear, OmpA functions in conjunction with the pili (Gaddy *et al.*, 2009). OmpA is essential for adherence to epithelial cells. Interestingly, when OmpA enters eukaryotic cells, via an unknown mechanism of entry, it localizes to the mitochondria, leading to the release of cytochrome *c* and apoptosis-inducing factor, and ultimately apoptotic cell death (Choi *et al.*, 2005). *Acinetobacter baumannii* is resistant to serum killing, and OmpA contributes to serum resistance through binding and acquiring Factor H, an inhibitor of the alternative complement pathway (Kim *et al.*, 2009). Biofilm formation, pilus and OmpA expression, along with serum sensitivity are regulated by the BfmS/R two-component system, which may sense and integrate signals derived from multiple environmental stimuli (McConnell *et al.*, 2013).

Carbohydrates have a number of important functions for *A. baumannii*. Surface polysaccharide comprised poly-β-(1-6)-*N*-acetylglucosamine, the product of proteins

encoded by the *pgaABCD* locus, contributes to biofilm development (Choi *et al.*, 2009). The core sugars of both the lipopolysaccharide and capsular polysaccharide contribute to serum resistance and are necessary for full virulence in animal models (Luke *et al.*, 2010; Russo *et al.*, 2010). A recent study showed that type I capsular polysaccharide and *O*-glycoproteins are dependent on the activity of the PglC glycosyltransferase, and pentameric glycan subunits are used both individually for *O*-glycosylation, or polymerized for capsular polysaccharide. The synthesis of these structures appears to be common at the early stages; however the pathways bifurcate in the periplasm (Lees-Miller *et al.*, 2013).

Acinetobacter baumannii produces phospholipases, lipolytic enzymes that can disrupt eukaryotic cell membranes. A phospholipase D is important for resistance to serum killing and epithelial cell invasion. In addition, in a murine model of pneumonia a phospholipase D mutant showed diminished dissemination from the lungs (Jacobs *et al.*, 2010). *Acinetobacter baumannii* has two potential phospholipase C genes and disruption of one phospholipase C gene results in a decrease in *A. baumannii*-induced epithelial cell apoptosis (Camarena *et al.*, 2010).

To enable survival in the iron-limiting conditions of the host, *A. baumannii* produces a unique catechol siderophore, which is structurally related to that of *Vibrio anguillarum*, termed acinetobactin (Yamamoto *et al.*, 1994). Acinetobactin synthesis and export requires an 18-gene cluster organized into seven operons, some of which have been demonstrated to be upregulated under conditions of iron-limitation (Fiester & Actis, 2013). When iron conditions are plentiful the bacteria favor a planktonic lifestyle; while in the presence of iron-chelators, the bacteria increase attachment and biofilm formation, and decrease motility (Tomaras *et al.*, 2003; McQueary *et al.*, 2012). In the nosocomial environment *A. baumannii* will be exposed to iron-limiting conditions, thus promoting bio-film formation. Acinetobactin is important for virulence, as mutants deficient in acinetobactin production are compromised in their ability to persist and cause damage in epithelial cells, mice and caterpillars (Gaddy *et al.*, 2012).

Acinetobacter baumannii is capable of quorum-sensing through the production of an *N*-acyl-homoserine lactone (AHL) by the synthase AbaI, which is homologous the *LuxI* family of molecules (Niu *et al.*, 2008). An *abaI* mutant has a reduced biofilm-forming and motility phenotype, indicating a role for quorum-sensing in these processes (Niu *et al.*, 2008; Clemmer *et al.*, 2011). In a study of 32 *Acinetobacter* strains, 63% produced more than one AHL, suggesting that additional roles of quorum-sensing in *A. baumannii* remain to be discovered (Gonzalez *et al.*, 2009). As mentioned, *A. baumannii* is frequently co-isolated with *P. aeruginosa* and the presence of these species together in the oral cavity increases the likelihood of aggressive periodontitis. AHL-dependent cross-talk between *A. baumannii* or *P. aeruginosa* can occur as the AHL of either species can induce the heterologous promoter in a mixed infection (Bhargava *et al.*, 2012). In addition, the toxin, pyocyanin, produced by *P. aeruginosa*, does not affect the growth of *A. baumannii*, so removing a significant impediment to synergism between the organisms (Bhargava *et al.*, 2012). Indeed, pyocyanin stimulates quorum-sensing-mediated tolerance to oxidative stress and increases the ‘persister’ cell population in *A. baumannii* (Bhargava *et al.*, 2014). Mixed-species biofilms also have increased resistance to antibiotics compared with single-species biofilms

(Burmolle *et al.*, 2006). Such interspecies interactions may aid in the co-existence of *A. baumannii* with organisms in mixed infections and increase disease severity (Bhargava *et al.*, 2012).

INTERACTIONS WITH THE IMMUNE SYSTEM

Immune responses to *A. baumannii* have yet to be extensively studied. *Acinetobacter baumannii* can incite a proinflammatory response in airway epithelial cells through recognition of microbe-associated molecular patterns such as lipopolysaccharide, and subsequent activation of mitogen-activated protein kinase and NF-κB signaling pathways (March *et al.*, 2010). Innate immune mediators that are induced by *A. baumannii* include the neutrophil chemokine IL-8 and antimicrobial molecules such as β-defensins (March *et al.*, 2010). Neutrophil recruitment to the lung is important in controlling multiplication and dissemination of *A. baumannii* (van Faassen *et al.*, 2007), and both neutrophils and macrophages have been shown to internalize and kill the bacteria via reactive oxygen and nitrogen species (Qiu *et al.*, 2009, 2012). Conflicting reports on the involvement of Toll-like receptors and their ability to recognize *A. baumannii* suggest that innate immunity against *A. baumannii* is strain variable and other innate immune factors are involved (Knapp *et al.*, 2006; Erridge *et al.*, 2007; Lin *et al.*, 2012). One of those factors may be the NOD1/2 recognition and signaling pathway. NOD1/2 are intracellular pattern recognition receptors that signal downstream to Rip2 in the induction of NF-κB activation and apoptosis (Nembrini *et al.*, 2009). Upon depletion of NOD1, NOD2 or Rip2 in lung epithelial cells, *A. baumannii* replication dramatically increased; however, this was not observed in macrophages, indicating cell-specific responses to the organism (Bist *et al.*, 2013). OmpA is another immunomodulatory microbe-associated molecular pattern of *A. baumannii* that can upregulate nitric oxide synthase and Toll-like receptor 2 responses in laryngeal epithelial cells (Kim *et al.*, 2008). At sublethal concentrations OmpA activates dendritic cells leading to differentiation of $CD4^+$ T cells toward a T helper type 1 polarizing phenotype (Lee *et al.*, 2007). Hence OmpA is an important determinant of the nature and extent of immune responses to *A. baumannii*.

No vaccine against *Acinetobacter* is currently available. Approaches in antigen-specific vaccine development include targeting OmpA, Bap, K1 capsule polysaccharide, and a membrane transporter Ata (Garcia-Quintanilla *et al.*, 2013). Other strategies have involved inactivated whole cells, outer membrane complexes, and outer membrane vesicles (Garcia-Quintanilla *et al.*, 2013). A mouse model has been developed, and has demonstrated the success of intranasal immunization with an inactivated whole cell vaccine against respiratory infection (Kuolee *et al.*, 2014). *Acinetobacter baumannii* is generally viewed as an extracellular pathogen but more evidence is being discovered that an intracellular lifestyle can be supported, further complicating delivery of immune efforts required for a successful vaccine (Choi *et al.*, 2008; Smani *et al.*, 2012).

BLUE-LIGHT SENSING

Sensing of the surrounding environment is important to the survival of any organism. The environment provides crucial information that, in return, the organism will respond to,

generally through a series of complex signal transduction pathways. It was recently discovered that *A. baumannii* ATCC 17978 and many other strains have the unique ability to sense blue light and alter virulence factors in response (Mussi *et al.*, 2010). Current dogma limits light to be a driving force only in photosynthetic/phototropic organisms that are dependent on light for energy; however, that idea is quickly changing as new discoveries are made about the use of light by non-photosynthetic organisms, e.g. circadian rhythms and phototaxis. The original unexpected discovery was made in *Brucella abortus*, another non-photosynthetic pathogen capable of causing severe infection in humans; in response to visible light these bacteria become more virulent (Swartz *et al.*, 2007). This response is mediated by a light, oxygen, or voltage (LOV) histidine kinase, a newly described light sensor and regulator, whose enzymatic activity is increased in the presence of light (Swartz *et al.*, 2007). In *B. abortus*, the LOV domain containing protein is directly responsible for survival and replication within macrophages (Swartz *et al.*, 2007). Conversely, the light-sensing protein discovered in *A. baumannii* ATCC 17978 does not contain a LOV domain but instead uses a blue-light sensing using flavin (BLUF) domain (Mussi *et al.*, 2010) (Fig. 2). The BLUF domain, upon excitation by blue light at a wavelength of 470 nm, causes a conformational change in the protein, known as a red-shift (signaling state). This allows for the binding of the chromophore, flavin adenine dinuclecotide, between two α-helices, in a reversible process (Nagai *et al.*, 2008; Mussi *et al.*, 2010; Brust *et al.*, 2014). The protein identified in *A. baumannii*, named Blue-light-sensing protein A (BlsA), is small and lacks an effector or output domain, making functional and binding predictions difficult (Mussi *et al.*, 2010). The transcript level of *blsA* is upregulated in the dark (Mussi *et al.*, 2010), and BlsA is involved in several virulence attributes of the organism (Mussi *et al.*, 2010). In the presence of blue light, *A. baumannii* fails to produce biofilms and pellicles, does not move on semisolid media plates (Mussi *et al.*, 2010), and exhibits an enhanced killing of *C. albicans* hyphae (Mussi *et al.*, 2010). It is interesting to note that light regulation is only observed at the environmental temperature of 24° C rather than the pathologically relevant temperature of 37° C. Light regulation is not limited to *A. baumannii* but is widespread within the genus of *Acinetobacter* (Golic *et al.*, 2013). Some species contain more than one BLUF-containing protein; many of these being environmental strains. Phylogenetic evidence suggests that the different BLUF proteins are derived from a common original predecessor (Golic *et al.*, 2013). Adding to the difficulty in interpretation of the original role of blue-light sensing, *A. baumannii* regulation in response to light is different from most of the other *Acinetobacter* species in that it produces the opposite effect on bio-film formation (Golic *et al.*, 2013). Also, many of the other species exhibit light regulation at 37° C, which could be a result of having multiple BLUF proteins (Golic *et al.*, 2013).

CONCLUSIONS

Over the last few decades the importance of *A. baumannii* has increased as a result of its rapidly evolving antibiotic resistance, its predilection for infecting battlefield wounds and its persistence in hospital environments. Indeed, there are many factors that make *A. baumannii* a dangerous organism, and many more likely to be discovered. Pathogenicity is multifactorial involving specific virulence factors in combination with metabolic capabilities and resistance to environmental stresses. Adaptation to stress involves intricate and

interconnected regulatory pathways that integrate environmental signals with growth and survival decisions that in turn impact pathogenic potential. The oral cavity can act as a reservoir for serious pulmonary infections, and sub-gingivally *A. baumannii* may increase the risk of aggressive periodontitis. A unique blue-light sensing and response system is present in *A. baumannii*, further study of which will reveal hitherto unrecognized aspects of the interface between bacteria and the environment. Given the versatility and pathogenic potential of the *A. baumannii* it is imperative that we make further progress understanding how to control its spread and render it incapable of damaging the host.

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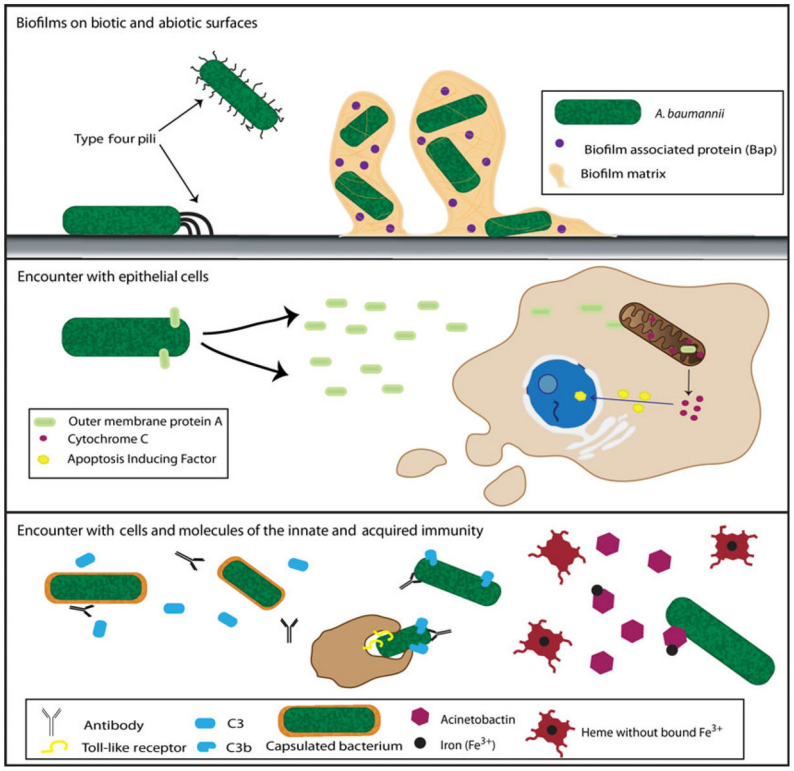

Figure 1.

Virulence mechanisms of *Acinetobacter baumannii*. The organism is capable of forming biofilms on biotic and abiotic surfaces by attaching via its type IV pili. Subsequently Bap is secreted to help biofilm maturation and adherence to eukaryotic cells. Contact with host cells leads to secretion of OmpA, which induces apoptosis in the host by causing cytochrome *c* release from the mitochondria. This in turn stimulates to Apoptosis Inducing Factor localization in the nucleus. Capsulated *A. baumannii* are protected from detection by the host due to the inability of antibodies and complement to bind to the bacterial surface and diminished recognition by Toll-like receptors. To acquire the iron needed for survival, *A. baumannii* secretes Acinetobactin, a siderophore, which sequesters iron from the host.

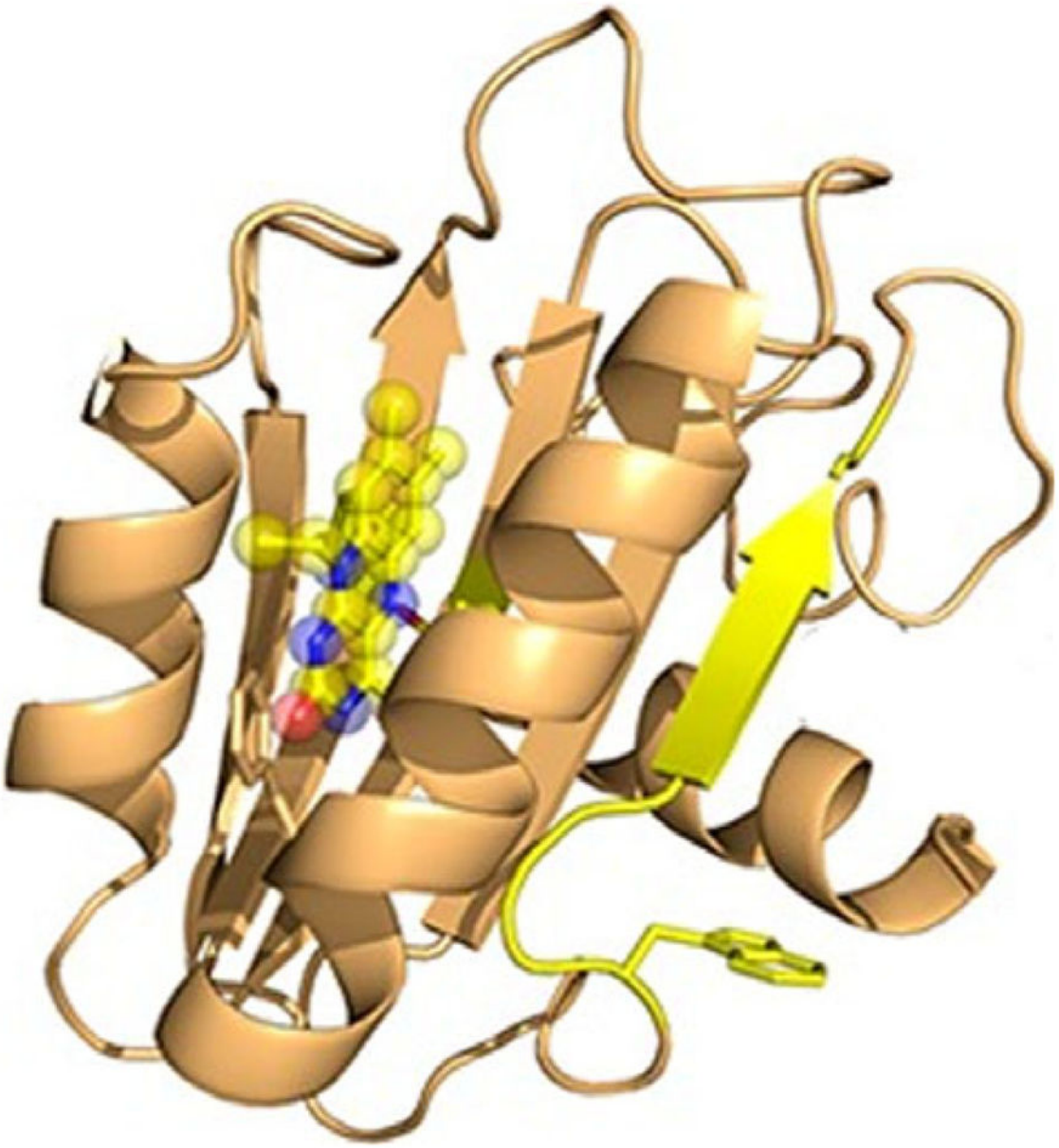

Figure 2.
Structure of BlsA. The Blue-light sensing protein of *Acine-tobacter baumannii*. The protein consists of two α helices that bind flavin adenine dinucleotide upon excitation by blue light at a wavelength of 470 nm. From Brust *et al.* (2014).

Table 1

Drug resistance mechanisms of *Acinetobacter baumannii*[1]

Drug class	Mechanism of resistance	Example of effector molecules	Reference(s)
Aminoglycosides	Modifying enzymes		
	Acetyltransferase	ACC	Bakour *et al.* (2013)
	16S rRNA methylation	ArmA	Doi *et al.* (2007)
	Phosphotransferase	APHA1, StrA, StrB	McGann *et al.* (2014), Nigro *et al.* (2013)
	Adenylytransferase	AadAB	Bakour *et al.* (2013)
	Efflux pump	AdeABC, AdeM	Magnet *et al.* (2001), Su *et al.* (2005)
Carbapenems	Carbapenemases	Oxa-23, -58, -64, -65, -66, -68, -70, -71, -78, -79, -80	Perez *et al.* (2007)
	Loss of protein function	CarO	Mussi *et al.* (2005)
	Decreased expression	33–36 kDa OMP	Clark (1996)
	Efflux pump	AdeIJK	Coyne *et al.* (2011)
Cephalosporins	Efflux pump	AdeIJK	Coyne *et al.* (2011)
	β-lactamases	AmpC	Rezaee *et al.* (2013)
Lincosamides	Efflux pump	AdeFGH, AdeIJK, MsrA, MsrB	Coyne *et al.* (2011), Taitt *et al.* (2014)
Macrolides	Efflux pump	AdeABC, MsrA, MsrB	Magnet *et al.* (2001), Taitt *et al.* (2014)
Monobactams	Efflux pump	AdeIJK	Coyne *et al.* (2011)
Penicillins	Altered penicillin-binding proteins	PBP1-3,5-8	Cayo *et al.* (2011)
	β-lactamases	PER-1, TEM-1, VEB-1, CTX-M	Bae *et al.* (2011), Perez *et al.* (2007), Walther-Rasmussen & Hoiby (2004)
	Metallo-β-lactamases	IMP-1, -2, -4, -5, -6, -11 VIM-2, NDM-1	Walsh *et al.* (2005)
	Efflux pump	AdeABC, AdeIJK	Yum *et al.* (2002), Jones *et al.* (2014)
	Decreased expression	46 kDa OMP	Magnet *et al.* (2001), Coyne *et al.* (2011)
Polypeptides	Gene mutations	*pmrAB*	Lesho *et al.* (2013)
	phosphoethanolamine modification of lipid A	PmrC	Arroyo *et al.* (2011)
Quinolones/Fluoroquinolone	Efflux pump	AdeABC, AdeIJK, AdeM, AdeFGH	Magnet *et al.* (2001), Su *et al.* (2005), Coyne *et al.* (2011)
	Production of protective proteins	QnrA	Touati *et al.* (2008)
	Gene mutations	*gyrA, parC*	Hamouda & Amyes,
Rifamycin	Efflux pump	AdeIJK	Coyne *et al.* (2011)
	ADP-ribosyltransferase	ARR-2	Houang *et al.* (2003)
Sulfonamides	Drug-resistant variant	Sul1, Sul2	Nigro *et al.* (2013)
Tetracyclines	Efflux pump	AdeABC, AdeIJK	Magnet *et al.* (2001),
		TetAB	Coyne *et al.* (2011)
	Decreased expression	CarO, $OmpA_{38}$, $OmpA_{32}$, OmpW	Guardabassi *et al.* (2000)

Drug class	Mechanism of resistance	Example of effector molecules	Reference(s)
Other	Aminocoumarin		
	Efflux pump	AdeIJK	Coyne *et al.* (2011)
	Chloramphenicol		
	Efflux pump	AdeABC, AdeFGH, AdeIJK, CmlA, CraA	Magnet *et al.* (2001), Coyne *et al.* (2011)
	Acetyltransferase	Cat	Turton *et al.* (2005)
	Fusidic acid		
	Efflux acid	AdeIJK	Coyne *et al.* (2011)
	Streptogramin		
	Efflux pump	MsrA, MsrB	Taitt *et al.* (2014)
	Tigecycline		
	Efflux pump	AdeABC, AdeIJK	Coyne *et al.* (2011)
	Trimethoprim		
	Efflux pump	AdeABC, AdeFGH, AdeIJK, AdeM	Coyne *et al.* (2011)
	Drug-resistant variant	FolA, DrfA1, DrfA7, DrfA19	Taitt *et al.* (2014)

[1]Drug-resistance mechanisms vary greatly among strains and combinations of drug resistance genes are different. Many of these genes have been acquired by *A. baumannii* to confer drug-resistance, while some occur naturally.