Acinetobacter baumannii

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Acinetobacter baumannii is regarded as a life-threatening pathogen associated with community-acquired and nosocomial infections, mainly pneumonia.

Keywords: Acinetobacter baumannii ; community-acquired infections ; nosocomial infections

1. Introduction

The studies on *Acinetobacter* spp. began in 1911 when it was isolated from a soil sample and named *Micrococcus calcoaceticus* (Henriksen [1]). Only in 1971 was the genus *Acinetobacter* officially recognized by taxonomists based on shared biochemical features [1][2][3]. The name of this genus comes from the Greek word a-kinetos-bacter which means non-motile rod, although they do exhibit a coccobacillary morphology and twitching motility. To date, molecular approaches have allowed identification of over 65 validly published species within the *Acinetobacter* genus (https://lpsn.dsmz.de/genus/Acinetobacter; up to 18 March 2021). These bacteria are Gram-negative, strictly aerobic, non-fermentative, oxidase-negative, catalase-positive and non-pigmented or pale yellow to gray pigmented [4][5][6]. Closely related species displaying similar phenotypic and biochemical properties are included in the *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex (ACB complex), including *Acinetobacter calcoaceticus*, *Acinetobacter baumannii*, *Acinetobacter pittii*, *Acinetobacter nosocomialis, Acinetobacter seifertii* and *Acinetobacter dijkshoorniae* for which molecular methods of identification are required [7][8][9]. Apart from *A. calcoaceticus*, the other five species are associated with human diseases, with *A. baumannii* as the commonest clinical species around the world [10]. Indeed, this opportunistic pathogen causes community and nosocomial infections, predominantly ventilator-associated pneumonia and bloodstream, urinary tract and skin and soft tissue infections, especially among critically ill patients in intensive care units (ICUs) [11]. Regrettably, the number of multidrug-resistant (MDR) *A. baumannii* isolates has increased significantly [12][13][14]. Apart from innate resistance to several antibiotics, *A. baumannii* genomic plasticity is suited for acquiring or upregulating resistance genes, thereby curtailing effective therapeutic options and increasing mortality rates [14][15]. In addition to antibiotic-resistance genes, *A. baumannii* has several potential virulence traits that allow this bacterium to persist in the environment, adhere to biotic surfaces, invade host cells and escape from the human host immune system [11][16][17][18][19]. While several reviews have described the mechanisms of antibiotic resistance and ability to form biofilms on abiotic surfaces, fewer studies have focused on host–*A. baumannii* interactions.

2. A. baumannii Pan-Genomics, Genomics and Genome Plasticity

As the number of A. baumannii infections increased, it was immediately clear that isolates displayed a remarkable difference in antibiotic profile. Therefore, several investigations were focused on genotypic and phenotypic characterizations of A. baumannii isolates due to the global high rate of infections and the paucity of therapeutic options for MDR strains. Two multilocus sequence typing (MLST) schemes were introduced to study the relationships among A. baumannii isolates [20][21] (https://pubmlst.org/organisms/Acinetobacter-baumannii) (accessed on 18 March 2021). These analyses highlighted the distribution and spread of different bacterial lineages. MLST showed a specific geographical distribution for each of the different lineages as a consequence of A. baumannii isolates that underwent local expansions. Currently, among the nine international clones (ICs) identified, IC-I and -II predominate in terms of outbreaks across continents [22][23][24][25]. However, despite its advantages, MLST has provided limited information to infer the genetic relationship among the increasing number of A. baumannii isolates [15][26]. With new sequencing technologies, the study of the whole genomes has improved significantly. This approach provided the opportunity to understand the extent of the genomic heterogeneity among A. baumannii isolates, in terms of insertions, deletions, inversions and single nucleotide polymorphisms [22][23][24]. The considerable genetic differences reflect A. baumannii's high genome plasticity that allows acquisition of exogenous genetic information, mostly via horizontal gene transfer and allelic recombination at specific hotspots, along with the loss of unnecessary genes [24][27][28][29]. These data corroborate the knowledge that A. baumannii isolates display a high degree of gene diversity to better adapt to new niches; the bacterial environmental or pathogenic

lifestyle drives genetic differences, considering environmental strains those mainly isolated in hospitals (i.e., inert surfaces) and pathogenic strains those associated with the human host. To gain insights into A. baumannii adaptation to specific niches, most studies have focused on its pangenome. Up to March 2021, a total of 5076 A. baumannii genome sequences are available in the NCBI database (www.ncbi.nlm.nih.gov/) (accessed on 18 March 2021). Pangenome encompasses both core and accessory genomes; the core defines the genes commonly shared by all strains included in the analysis, whereas the accessory includes genes retrieved in one (unique gene families) or some strains. A recent work estimated that A. baumannii core genome consists of around 2200 genes, whereas the pangenome is notably larger harboring over 19,000 different genes [30]. By analyzing the shared set of genes among 2467 genomes, Mangas et al. distinguished two main A. baumannii groups; the first group, accounting for 34% of investigated A. baumannii strains, rarely carries plasmids and is characterized by clustered regularly interspaced short palindromic repeat (CRISPR), CRISPR-associated (cas) or restriction-modification system (rms) genes, and prokaryotic toxin-antitoxin systems (TASs) [30]. TASs are important virulence factors in stressful environmental conditions since they are involved in cellular metabolism, growth activities such as cell cycle process and apoptosis [31][32][33]. Conversely, the second group, accounting for the majority of investigated A. baumannii strains (66%) shared a higher number of genes, annotated as plasmid genes with exonuclease activity whereas a limited content of genes involved in biofilm formation was found [30]. It was recently suggested that the presence of CRISPR/Cas systems reduces the acquisition rate of antibiotic resistance genes, being negatively associated with A. baumannii MDR isolates [34]. Hence, it can be hypothesized that environmental strains are characterized by the presence of CRISPR/Cas systems that positively influence biofilm production to enhance persistence and inhibit the acquisition of foreign DNA, including antibiotic resistance genes. Vice versa, human-associated strains lose the CRISPR/Cas systems to evolve more easily into MDR strains and reside in antibiotic rich niches. Moreover, if iron acquisition systems are considered, isolates collected from infected samples show a set of genes required for the biosynthesis of acinetobactin, whereas the same set of genes is missing from environmental samples which, in turn, have genes involved in the uptake of iron through xeno-siderophores [35].

Overall, the more that data are acquired from genome sequencing of *A. baumannii* strains, the higher the heterogeneity found among them as a consequence of their high genome plasticity. However, this approach highlighted the genomic divergence of environmental and human-associated strains; although genome sequencing data are biased by the larger number of clinical isolates, it seems that unique strain-specific gene pool arises from genetic changes driven by niche variations [9][21][23][24][27]. Further genome comparison analyses between nonclinical and clinical isolates will help our understanding about the evolutionary process of *A. baumannii* as well as antibiotic-resistance spread and nosocomial persistence.

3. A. baumannii and the Treasure of its Virulome

Despite being an opportunistic pathogen, the *A. baumannii* mortality rate of patients with hospital- and community-acquired infections is 23–68% and up to 64%, respectively [11]. Being a major cause of infections, *A. baumannii* belongs to the ESKAPE group together with *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Enterobacter* species [36]. The high mortality rate is tightly associated with the worldwide rise in the number of carbapenem-colistin-resistant *A. baumannii* strains [11]. Due to the paucity of therapeutic options in the treatment of *A. baumannii* infections, in 2017 the World Health Organization (WHO) placed this microorganism in the critical priority list of bacteria that urgently require the development of effective drugs as well as alternative strategies (www.who.int) (accessed on 18 March 2021). Since recent papers provide detailed coverage of the genes and mechanisms used by *A. baumannii* to gain resistance to antibiotics, including carbapenems and colistin, this topic will not be discussed in detail and the reader is referred to [37][38][39]. To improve our knowledge of *A. baumannii* pathogenesis and develop new strategies to combat infections, several studies investigated its virulence factors [11][18][40][41][42]. Remarkably, *A. baumannii* has a huge pathogenic potential that enables it to firmly resist in the environment, form biofilms, move, interact with host cells, capture micronutrients, and secrete proteins [3][13][16][18][41][42][43][44]. An overview of the virulence factors described in this review is presented in Table 1.

Table 1. Overview of *A. baumannii* virulence factors reported in this review.

Gene(s)	Virulence Factor(s)	Function(s)	Reference
K locus	**capsule**	**Persistence**	**[44]**
OC locus	**Lipo-oligosaccharide (LOS)**	**Dryness resistance**	**[45]**
csuA/BABCDE	**Csu pili**	**Biofilm formation**	**[46]**

Gene(s)	Virulence Factor(s)	Function(s)	Reference
bap	Bap	Biofilm formation	[47]
M215_09430 locus	Repeats-in-Toxin (RTX)-like domain	Biofilm formation	[12]
pgaABCD locus	PNAG	Biofilm formation	[48]
recA	RecA	DNA damage repair	[49]
katG	KatG	Oxidative stress resistance	[50]
katE	KatE	Oxidative stress resistance	[50]
abuO	AbuO (component of an ABC efflux pump)	Oxidative stress response	[51]
adeABC	AdeABC (RDN efflux pump)	Osmotic stress resistance	[52]
emrAB	EmrAB (MFS efflux pump)	Osmotic stress resistance	[53]
abeD	AbeD (component of an RND-type efflux pump)	Osmotic stress resistance	[54]
amvA	AmvA (component of an MFS efflux pump)	Resistance to disinfectants	[55]
aceI	AceI (component of a PACE efflux pump)	Resistance to disinfectants	[56]
abaI	AbaI (component of the QS system)	Virulence, motility, conjugation, biofilm formation and host-pathogen interactions	[57]
abaR	AbaR (component of the QS system)	Virulence, motility, conjugation, biofilm formation and host-pathogen interactions	[57]
bfmS	BfmS	QS-regulated two-component system involved in biofilm formation	[58]
bfmR	BfmR	QS-regulated two-component system involved in biofilm formation	[58]
pilA	PilA (major pilin of type IV pili)	Twitching motility and evasion of the host immune system	[59]
ompA	OmpA	Antibiotic- and serum-resistance, biofilm formation, host-interaction, cytotoxicity, interference with autophagy and apoptosis	[60][61][62][63][64][65][66][67]
carO	CarO	Resistance to carbapenems	[68][69][70]
omp33	Omp33 (also known as Omp33-36 kDa or Omp34)	Induction of apoptosis and modulation of autophagy	[71][72]
occAB1	OccAB1 (also known as OprD-like or porinD)	Uptake of antibiotics and iron, host-interaction	[70][73][74][75][76]
ompW	OmpW	Iron uptake and cytoxicity	[77]
Acinetobactin gene cluster	Acinetobactin	Iron chelator	[78]
Fimsbactins gene cluster	Fimsbactins A-F	Iron chelators	[78]
Baumannoferrin gene cluster	Baumannoferrin A-B	Iron chelators	[78]
fur	Fur	Iron metabolism transcriptional regulator	[79]
plc1 and *plc2*	PLC	Lipolytic activity for iron acquisition	[80]

Gene(s)	Virulence Factor(s)	Function(s)	Reference
pld1-3	**PLD**	**Lipolytic activity for iron acquisition**	[81]
oxyR	**OxyR**	**ROS response regulator**	[82]
soxR	**SoxR**	**Superoxide response regulator**	[83]
znuA, znuCB, znuD1* and *znuD2	**ZnuA, ZnuB, ZnuC, ZnuD1 and ZnuD2**	**Uptake of zinc**	[84]
zur	**Zur**	**Zinc metabolism transcriptional regulator**	[84]
zigA	**ZigA**	**Zinc metallo-chaperone**	[85]
mumT	**MumT**	**Uptake of manganese**	[86]
pit	**PIT system**	**Low affinity phosphate uptake system**	[87]
pst operon	**PstS**	**High affinity phosphate uptake system**	[88]
phoB* and *phoR	**PhoB and PhoR**	**Two-component regulatory system for phosphate uptake**	[89]
hlyB, hlyD* and *tolC	**HlyB, HlyD and TolC (T1SS)**	**Secretion of proteins involved in biofilm formation and adhesion to pulmonary epithelia**	[12]
gsp genes	**T2SS**	**Secretion of proteins from the Sec or the Tat translocons**	[90]
***tra* locus**	**T4SS**	**Conjugative transfer of DNA, plasmids, and other mobile genetic elements**	[91]
AbfhaB* and *AbfhaC	**AbFhaB and C (T5bSS)**	**Adhesion to integrin and fibronectin**	[92]
***cdiA*$_1$, *cdiB*$_1$, *cdiA*$_2$ and *cdiB*$_2$**	**CdiA and B (T5bSS)**	**Killing of bacterial competitors**	[93]
ata	**Ata (T5cSS)**	**Adhesion to collagen I, III, IV, V and laminin**	[94]
Core, accessory and regulatory genes	**T6SS**	**Contact-dependent secretion of substrates into competitor bacterial or eukaryotic cells**	[95]
None	**OMVs**	**Long-distance delivery of multiple packaged virulence factors**	[96]

3.1. Survival Strategies

The environmental survival of *A. baumannii* depends on its ability to persist against desiccation, disinfection and oxidative stresses. Besides other important functions, the biosynthesis of capsular polysaccharide and biofilm formation support the viability of *A. baumannii* in dry conditions for over three months [18][43][97][98]. The K locus encompasses clustered genes needed for the biosynthesis of the capsule [44][99]. Despite strain-specific biosynthetic genes accounting for the wide diversity of capsule composition, the K locus commonly includes genes encoding initiating transferases (*itr*), glycosyltransferases (*gtr*), assembly/export proteins (*wzx*/*wzy*), and modification enzymes (*atr*/*ptr*) [13]. The polysaccharides composing the capsule act as water retainers that shield the bacterial body against desiccation [100]; however, although mutant strains within the K locus displayed lower resistance, the heterogeneous behavior of encapsulated bacteria in relation to desiccation led to the conclusion that the capsule plays a minor role [100]. The lipid composition of the outer membrane, more specifically the acylated level of the lipo-oligosaccharide (LOS), has been suggested to be involved in resistance to dryness, in that the appropriate fluidity retains water and nutrients inside the bacterial cell [45][101]. Indeed, in *A. baumannii,* the common bacterial lipopolysaccharide is replaced with the LOS, which is composed of lipid A with variable amounts of inner and outer core sugars but lacks the O-antigen [45]. The LOS outer sugars show diversity across strains, dependent on glycosyltransferases and nucleotide-sugar biosynthesis enzymes encoded in a highly variable outer core locus [13].

The ability to form biofilms extends the desiccation tolerance of *A. baumannii* under dryness [100]. Biofilm formation starts with bacterial adherence to a surface and it is further strengthened by bacterial attachment and aggregation. These sessile bacterial communities are surrounded by a blended matrix consisting of DNA, exopolysaccharides (capsular and non-capsular) and proteins which protect pathogens from desiccation, since the exopolysaccharide matrix can retain

water [100]. The Csu pili or Csu fimbriae are encoded by six-segmented operon, *csuA/BABCDE*, and are assembled by the chaperone–usher (CU) pathway [46]. Together with the biofilm-associated proteins (Bap), Csu pili are crucial for the formation and maintenance of biofilms on abiotic surfaces [11][16][18][46][47][102]. Some recent reviews describe the detailed network controlling biofilm formation [11][18][44][103][104][105]. Other important factors involved in biofilm formation are an effector protein encompassing a Repeats-in-Toxin (RTX)-like domain, poly-β (1-6)-N-acetyl-glucosamine (PNAG), the capsule, and autotransporter systems that will be discussed below [3][11][12][13][48]. Despite the remarkable desiccation tolerance of *A. baumannii* during environmental persistence, the restricted water availability could lead to DNA damages, osmotic and oxidative stresses [18][44][100]. *A. baumannii* copes with DNA damages, comprising alkylation, base omission, cross-linking, oxidation and strand breaks, with the RecA protein, which is recognized as an essential enzyme for homologous recombination [18][49][106]. Oxidative stress can be overcome by overexpression of genes encoding catalases. Indeed, *A. baumannii* is a catalase-positive bacterium; despite the genomic presence of four catalase genes, *katA*, *katE*, *katG*, and *katX,* only KatG and KatE defend the bacterium from oxidative stress [50][100]. Interestingly, both *katG* and *katE* genes are overexpressed through the upstream insertion of IS*Aba1* promoter sequences, thereby providing full protection from hydrogen peroxide (H_2O_2) [50][100]. Moreover, DNA damages as consequence of water stress, as well as other environmental stresses in clinical settings, generate base-pair substitutions in a number of different bacterial targets, thereby contributing to the acquisition of additional antibiotic resistances in *A. baumannii* (i.e., rifampin-resistance) [7][18][107]. Conversely, the osmoregulatory mechanism adopted by *A. baumannii* aims to increase the uptake of glycine betaine or synthesize glutamate and mannitol; without interfering with the general bacterial metabolism, these compounds, known as compatible solutes, stabilize proteins and membranes, thereby protecting bacteria from cell damage [18][100]. Osmotic stress, desiccation and resistance to antibiotics and disinfectants also involve efflux pumps, three-component protein systems (an outer membrane channel, a periplasmic lipoprotein, and an inner membrane transporter) that extrude disturbing or toxic molecules/compounds from inside the cell to the extracellular milieu. *A. baumannii* possesses several classes of efflux pumps, including major facilitator superfamily (MFS), resistance nodulation-division (RND), small multidrug resistance (SMR) family, and multidrug and toxic efflux (MATE), ATP binding cassette (ABC), and the proteobacterial antimicrobial compound efflux (PACE) family [53][55][108][109]. Apart from their role in antibiotic resistance, the RDN AdeABC, the MFS EmrAB efflux pumps as well as the RND-type AbeD transporter contribute to osmotic stress resistance [52][53][54][100][109]. Moreover, AbuO, a TolC-like protein, is involved in the oxidative stress response [54][109]. AmvA and AceI, belonging to the MFS and PACE efflux pumps respectively, were shown to be associated with the extrusion of disinfectants [54][55][56][109][110]. It is worth mentioning that the great adaptability of *A. baumannii* to such a variety of different stressful environments relies on several additional proteins that guarantee cellular homeostasis, such as GroEL, GroES, DnaJ, DnaK, ClpX, ClpB, OxyR, as well as Lon protease and other numerous chaperones [111][112][113][114]. Complex regulatory networks overlook these stress defense mechanisms, including two-component systems, the second messenger cyclic-di-GMP, the RNA chaperone Hfq, alternative sigma factors of the general stress response, and quorum sensing (QS) regulators [51][54][100][103][105][109][110][115].

3.2. Sensing the Quorum

Bacterial QS is a cell-to-cell communication system based on specific signaling molecules called ‘auto-inducers’ that allow bacteria to sense population densities. QS systems have a crucial role in the expression of virulence factors, motility, conjugation, biofilm formation and interactions with eukaryotic host cells [16][104][116][117][118]. To date, only one QS system was found in *A. baumannii*, consisting of the two *abaI* and *abaR* genes, acquired from *Halothiobacillus neapolitanus* through horizontal gene transfer. AbaI is the autoinducer synthase and AbaR is its cognate receptor, which belong to the typical LuxI/LuxR family members found in other Gram-negative bacteria. AbaI synthesizes N-(3-hydroxydodecanoyl)-1-homoserine lactone (Acyl Homo-serine Lactones, AHLs); upon binding of AHL to AbaR, the complex recognizes *lux*-box sequences on QS target promoters, thereby regulating their expression [57][119]. Indeed, QS molecules affect *A. baumannii bfmS* and *bfmR* genes by upregulating their expression leading to strong biofilm formation on abiotic surfaces [16][58]. Limited concentrations of iron also upregulate QS signaling molecules, enhancing *A. baumannii* persistence and virulence [16][119][120].

3.3. The Power of Pilus Retraction

Despite the name of this genus, *A. baumannii* is able to perform twitching motility through type IV pili. Encoded by the *pil* operon genes, these pili are cytoplasmic ATPase dependent projections that extend and retract to keep the bacterium going, mainly on wet surfaces [102]. It has been shown that the C-terminus of the major subunit of type IV pili, PilA, is glycosylated by O-oligo-saccharyl-transferases [59]. Interestingly, there is a high degree of variability both in amino acid sequence as well as in glycosylation of PilA proteins among *A. baumannii* isolates, most probably to evade the host immune system [121]. Although a clear link between twitching motility and virulence has not yet been established, several studies showed an upregulated biogenesis of type IV pili when grown in serum with respect to sputum, highly suggestive

of a key role of twitching motility during bacteremia [13][18][44]. However, the role of type IV pili is not restricted to twitching motility but also to biofilm formation, virulence and DNA uptake [13][18][44][59]. Indeed, it has been reported that type IV pili promote host-cell adhesion to both pharynx and lung carcinoma cells in vitro [121]. In addition to twitching motility, some isolates of *A. baumannii* can move by surface-associated motility [13][18][44]. This motility seems to be independent from type IV pili and relies on the biosynthesis of polyamine 1,3-diaminopropane, LOS and QS [13][18][44]. Although the precise mechanism of surface-associated motility remains to be elucidated, the signaling network of cyclic-di-GMP, the second messenger molecule involved in adaptation to various stress responses, was shown to upregulate biofilm formation and downregulate surface associated motility [105].

3.4. Exploring Surface Proteins

Outer membrane proteins (Omps) embedded within the outer membrane (OM) are cornerstone proteins involved in cellular permeability and virulence in *A. baumannii*. These monomeric or trimeric β-barrel proteins, also known as porins, connect the external environment to the periplasmic space, allowing the diffusion of nutrients as well as small molecules, antibiotics, and disinfectants [18][40][41][44][51]. To date, identified Omps in *A. baumannii* are OmpA, CarO, OprD-like, Omp33-36 kDa, OmpW, AbuO, TolB, DcaP, Oma87/BamA, NmRmpM, CadF, OprF, LptD [18][41][44]. Besides its role in antibiotic-resistance, OmpA plays a central role in *A. baumannii* virulence, including, serum resistance, biofilm formation, host-interaction, cytotoxicity, and apoptosis [11][18][60][61][62][63][64][65][66][67][122]. OmpA has eight- antiparallel β-barrel strands embedded within the OM at the N-terminus while the C-terminus is bound to a peptidoglycan-derived pentapeptide, thereby performing also a structural role [123]. The amino acid sequence of this protein is highly conserved among *A. baumannii* clinical isolates; its involvement in antibiotic-resistance was revealed by the use of *ompA* mutants [41][62]. However, the increase in antibiotic-susceptibility of these mutants could be related to a broader membrane permeability as a consequence of membrane alterations [61]. Nevertheless, several studies demonstrated that OmpA acts as a specific and selective channel for small antibiotics [41][61][62][124]. However, multiple data indicate that OmpA is associated with efflux pump systems located in the inner membrane to counteract the influx of antibiotics [62]. Due to its key role, several proteins control *ompA* expression such as the global repressor H-NS and an anti-repressor (i.e., gene locus A1S_0316), the RNA chaperone Hfq as well as the two-component system BfmSR [41][125][126]. Its high amino acid conservation among isolates, crucial structural role and strong immunogenicity make OmpA the ideal target for the development of an *A. baumannii* vaccine [124]. Additionally, several studies have addressed the role of CarO or carbapenem susceptibility porin in *A. baumannii* [13][41][68][69][70]. Limansky et al. first demonstrated that resistance to carbapenems among clinical isolates, specifically to imipenem, was due to the loss of CarO [127]. CarO is the channel for the transport of small amino acids such as glycine and ornithine, but it was shown to mediate the influx of imipenem into the bacterial cells [13][41]. While this may seem very harmful, CarO physically interacts with the most widespread carbapenemase OXA-23 in *A. baumannii* so that imipenem is hydrolyzed immediately upon entry into the bacterial periplasm [128]. Additionally, five porins orthologous to OprD from *P. aeruginosa* were identified in carbapenem-resistant *A. baumannii* isolates; they belong to the Occ class (OccAB1–5) [129]. Structural studies of OccAB1–4 showed that they are 18-stranded β-barrel proteins characterized by different pore diameters; OccAB1 has the largest channel and was the most efficient in the uptake of carbapenems [70][73][74][75][76][129]. Formerly known as porinD or OprD, this protein was showed to be involved in the transport of different molecules including amino acids, sugars and antibiotics such as meropenem and Fosfomycin [129]. Moreover, OprD together with OmpW were linked to iron uptake in *A. baumannii* [77]. OmpW is an eight-stranded OM β barrel protein that shares several features with OmpA; its amino acid sequence is highly conserved among *A. baumannii* isolates, it is greatly immunogenic, highly concentrated in OM vesicles (OMVs) and it has cytotoxic activity against host cells [63][77][130]. OMVs are micro-spherical vesicles of 20-200 nm in diameter that are secreted by the secretory system independently from conventional systems [11][42][63][96][131][132]. These vesicles are composed of LOS, Omps, phospholipids, periplasmic proteins, as well as DNA and RNA molecules; OMVs are a means through which bacteria deliver a number of bacterial virulence factors to other bacteria or host cells, thereby inducing host cell damage and innate immune responses [7][11][13][19][42][63]. Another important Omp in *A. baumannii* is Omp33-36 kDa or Omp34 or Omp33 [41][71][72]. Its resolved crystal structure showed that Omp33 has 14 antiparallel β-strands connected by 7 loops extending outside and 6 turns protruding into the periplasmic side; recently, it was reported that two of these periplasmic turns block the aqueous channel [41]. Interestingly, it was found that Omp33 plays an important role in fitness and virulence in *A. baumannii*; this cytotoxic protein triggers apoptosis via caspase activation while modulating autophagy to enhance its persistence within host cells [71][72].

3.5. Micronutrients Hunger

Micronutrients are fundamental for bacterial survival and growth. *A. baumannii* possesses different metal uptake systems for scavenging zinc, iron and manganese as well as other valuable and essential nutrients. Iron bioavailability is scarce both in the environment and in hosts. To acquire free iron, *A. baumannii* produces and secretes siderophores, low

molecular weight iron scavengers (400–1000 kDa) able to chelate it at high affinity. The catechol-hydroxy-mate siderophores including acinetobactin, fimsbactins A-F, baumannoferrin A and B are examples of *A. baumannii* iron chelators [78]. However, acinetobactin is the most conserved and recognized siderophore in *A. baumannii* [7][11][18][133]. According to genomic studies, bacterial siderophore biosynthetic genes are usually clustered and under the transcriptional control of the ferric uptake regulator Fur encoded by the *fur* gene [11][79][114]. Due to the importance of iron in *A. baumannii* physiology, the expression of a huge number of genes is under the control of iron availability, including those encoding for efflux pumps belonging to MFS, MATE, and ABC families, QS, Bap, phospholipases C and D, catalase and superoxide dismutase [51][54][55][80][81][108][109][110][134]. Indeed, to overcome the high reactivity of iron via the Fenton reaction, iron acquisition and metabolism is associated with the expression of OxyR and SoxR, responsible for reactive oxygen species (ROS) detoxification and for super oxide response, respectively [11][18][82][83][111][135][136]. *A. baumannii* phospholipases C and D are potent virulence factors characterized by hydrolytic and lipolytic activities; these enzymes showed hemolytic activities by targeting red blood cells in order to provide iron for *A. baumannii* growth during the infection process [7][11][18][133][136]. In addition, iron receptors or transport proteins that bind directly ferrous (Fe^{2+}) ions are located on the bacterial cell surface [11]. In addition to iron, zinc (Zn) and manganese (Mn) are important micronutrients for growth and virulence in *A. baumannii*. Being a cofactor of metalloproteins, e.g., metalloproteases, *A. baumannii* employs an ABC transporter system, ZnuABC that works together with the OM TonB-dependent receptor ZnuD for the uptake of zinc; the whole system is under the control of the transcriptional zinc uptake regulator Zur [84][137]. Thereafter, the Zn metallochaperone ZigA seems to assist the transfer of the precious metal to metalloproteins, although more studies are required to elucidate the precise mechanism [11][18][85][136]. Mn is the redox-active cofactor for enzymes that protect the bacteria from ROS, such as superoxide dismutase and ribonucleotide reductase [11][42]. Like other pathogens, *A. baumannii* has a high-affinity Mn transmembrane transporter, MumT, belonging to the resistance-associated macrophage protein (NRAMP) family, that uses the proton motive force as an energy source for the uptake of exogenous manganese [86][111][138]. Being involved in several biochemical reactions, phosphate has two dedicated transport systems in *A. baumannii*, a low- and a high-affinity transport system, encoded by the *pit* gene and the *pst* operon (*pstA*, *pstB, pstC, pstS*, and *phoU*), respectively [87][88]. In this latter, the periplasmic phosphate-binding protein PstS controls the system by sensing phosphate levels and by transferring it to its specific transporter; the whole operon is transcriptionally activated by the two-component system PhoB/R under phosphate deficiency [89][139]. Interestingly, it was recently reported that PstS plays an important role in *A. baumannii* virulence during microaerobic conditions; indeed, the *pstS* deletion mutant showed reduced adhesion to and invasion of human alveolar type II cells (A549 cell line, see below), whereas its overexpression enhances pathogenesis [88]. Supported also by in vivo results, it was concluded that PstS is important for *A. baumannii* pathogenicity and spread within the host [88].

3.6. The Versatility of Secretion Systems

Bacteria secrete proteins to adapt more easily to environmental conditions and host-interactions. To date, five secretion systems have been identified in *A. baumannii*, comprising type 1 secretion system (T1SS), T2SS, T4SS, T5SS, and T6SS [11][18][44]. T1SS is composed by an inner membrane (IM) ATPase protein (hemolysin secretion protein B, HlyB), a periplasmic adaptor (hemolysin secretion protein D, HlyD), and an Omp (TolC); this system contributes to exporting proteins involved in biofilm formation and maintenance and assisting also to adhesion with pulmonary epithelia, i.e., Bap and Blp1, as well as the RTX-serra-lysin-like toxin [12][140]. Conversely, the T2SS involves 12–15 proteins including cytoplasmic ATPases, IM platform assembly, OM secretins and periplasmic pseudo-pili; the pseudo-pilus works as a sort of piston that extrudes substrates out of the bacterial cells though OM secretins. Genes encoding the proteins composing T2SS are referred to as general secretory pathway (Gsp) [90][141]. T2SS accommodates proteins with an export signal from the Sec or the Twin-arginine (Tat) translocons before delivering them outside the cell; important virulence factors such as lipases (LipA and LipH), zinc-dependent metallo-endopeptidase (CpaA), elastase, alkaline phosphatase, and phospholipases are secreted by T2SS [3][13]. Interestingly, T2SS and type IV pili share the pilin peptidase PilD/GspO that processes pre-pseudo-pilins and pre-pilins before assembly into the T2SS and type IV pilus, respectively, revealing their evolutionary relatedness [141][142]. T4SS (type F) is devoted to conjugative transfer of DNA, plasmids, and other mobile genetic elements; therefore, this system is thought to be responsible for the spread of antibiotic-resistance genes among *A. baumannii* clinical isolates and particularly OXA- 23 [44][91][143]. Conversely, the T5SS, also known as autotransporters, represents the simplest and most widespread secretion system in Gram-negative bacteria; the name is due to the ability of these proteins to cross the OM autonomously [144][145]. T5SS is composed of five subgroups, T5aSS, T5bSS, T5cSS, T5dSS and T5eSS [145]. This classification is based on the specific features of the passenger/translocation domains, quaternary structure (i.e., monomeric or trimeric), and the terminal residues of proteins exposed on the surface (N- or C-terminus) [145]. Only the T5bSS (AbFhaB/C and CdiA/B) and T5cSS (Ata) subgroups were found in *A. baumannii* [11][92][93]. In the T5bSS subclass, also termed the two-partner secretion (TPS) system, passenger and translocation domains (TpsA and TpsB, respectively) are allocated onto two distinct proteins whose genes are transcriptionally linked [11]. The 16-stranded β barrel AbFhaC protein recognizes and translocates to the cell surface its partner protein, AbFhaB, via two

specific periplasmic polypeptide transport-associated domains; AbFhaB has the arginine-glycine-aspartic acid (RGD) motif that was shown to be associated with eukaryotic integrin and fibronectin attachment [92]. The contact-dependent inhibition (CDI) systems are strategies that *A. baumannii* uses to kill bacterial competitors; the OM pore CdiB allows the secretion of the CdiA toxin that kills bacterial cells that do not have the antitoxin or the immunity protein CdiI [3]. *A. baumannii* has two CDI loci, Cdi1 and Cdi2, each composed of the transporter, the toxin and the immunity proteins [42]. On the other hand, *Acinetobacter* trimeric autotransporter, or Ata, belongs to the T5cSS; each monomer of this large homo-trimeric protein consists of a C-terminal domain that forms a 4 β-strand hydrophilic pore within the OM through which it extrudes the N-terminal passenger domain of each monomer [94]. The passenger domain contains four pentameric collagen binding consensus sequences (SVAIG) and one RGD motif able to bind extracellular matrix and basal proteins (i.e., collagen I, III, IV, and V and laminin) and to participate to biofilm formation [94]. Finally, several *A. baumannii* strains carry a genetic locus for T6SS; this contact-dependent multi-component apparatus is encoded by 13 core structural proteins together with accessory (i.e., TagF, TagN, PAAR, and TagX) and regulatory proteins (i.e., VgrG1, TetR) [95]. Indeed, due to the high-demanding energy costs, T6SS is activated upon stressful stimuli, including nutrient limitation, cell damage and competing bacteria [146]. Accordingly, the T6SS enables *A. baumannii* to inject into other bacteria toxic proteins, including peptidoglycan hydrolases, nucleases, or those effectors targeting the cell membrane, to outcompete neighboring bacteria [147].

It is important to note that in the past, *A. baumannii* was considered a commensal, and a relatively low-grade opportunistic pathogen; the main features of *A. baumannii* virulence factors highlighted the great pathogenic potential of this bacterium. Nevertheless, it should be taken into account that the immune status of the human host plays a big role in the infective success of *A. baumannii.* In the following paragraphs, the components of *A. baumannii* virulome important for the interaction with host cells and evasion of the host immune response will be discussed.

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