Revista Prevenção de Infecção e Saúde
The Official Journal of the Human Exposome and Infectious Diseases Network

REVIEW

DOI: https://doi.org/10.26694/repis.v8i1.3066

An update on the role of Hfq RNA Chaperone in resistance and virulence of *Acinetobacter baumannii*

Uma atualização sobre o papel da chaperona de RNA Hfq na resistência e virulência de *Acinetobacter baumannii*

Una actualización sobre el papel de la chaperona de ARN Hfq en la resistencia y virulencia de *Acinetobacter baumannii*

Lilian Caroliny Amorim Silva [1], **Nilma Cintra Leal** [1], **Danilo Elias Xavier** [1]

How to cite this article:
Silva LCA, Leal NC, Xavier DE. An update on the role of Hfq RNA Chaperone in resistance and virulence of *Acinetobacter baumannii*. Rev Pre Infec e Saúde [Internet]. 2022;8:3066. Available from: http://periodicos.ufpi.br/index.php/repis/article/view/3066. DOI: https://doi.org/10.26694/repis.v8i.3066

[1] Microbiology Laboratory, Department of Microbiology, Instituto Aggeu Magalhães, Recife, Pernambuco, Brazil.

ABSTRACT

Introduction: The difficulty in treating *Acinetobacter baumannii* infections due to its high rate of resistance to antibiotics has led to the study of mechanisms inherent to the pathogen itself that can be used as effective targets in the treatment. Host Factor I Protein (Hfq) is an RNA chaperone generally necessary to assist in the connection between sRNAs and their mRNA target acting in the regulation of different genes, studies carried out in a range of bacterial species have shown that Hfq acts in a pleiotropic manner, contributing to virulence and response stress. **Aim:** To summarize current knowledge about the role of the Hfq RNA chaperone in the virulence and antibiotic resistance of *Acinetobacter baumannii*. **Outlining:** This is an integrative review developed from articles published in any language on Science Direct and PubMed platforms. Data collection and analysis were carried out between the period of April 2020 and February 2021. **Results:** Hfq shown to play important roles in cell growth, OMVs, metabolism of carbon sources, tolerance to physical and chemical stress, virulence through biofilm formation, fimbriae modulation, among others. **Implications:** Our work shows data that strengthen the role of Hfq in different aspects of virulence and environmental adaptation, including antimicrobial resistance of this pathogen, warning about the importance of Hfq as a possible future effective target in the treatment of these infections.

DESCRIPTORS

Virulence; Drug resistance; *Acinetobacter baumannii*; Review; Chaperone; Host Factor 1 Protein.

Corresponding author:
Lílian Caroliny Amorim Silva
Address: Instituto Aggeu Magalhães, Department of Microbiology, Av. Professor Moraes Rego, s/n.
CEP: 50740-465 Recife, Pernambuco, Brazil.
Telephone: + 55 (81) 99679-4922
E-mail: lilianamorim00@gmail.com

Submitted: 2022-09-23
Accepted: 2022-10-10
Published: 2022-10-19

INTRODUCTION

Acinetobacter baumannii is a Gram-negative bacillus recognized for its ability to cause serious nosocomial infections and has emerged as one one of the most relevant pathogens for health-associated infections worldwide. The high levels of resistance of this bacterium has been attributed to its great ability to adapt and survive under adverse conditions. Furthermore, *A. baumannii* is able to express virulence factors that facilitate bacterial infection and the expression of determinants that trigger resistance.[1-4]

The post-transcriptional regulation of protein translation by means of small RNAs (sRNAs), which function as small non-coding RNA molecules and are normally involved in the environmental stress response to preserve cellular response to environmental stress to preserve cellular homeostasis, have received increasing attention in bacterial studies. In Gram-negative bacteria, Hfq, an understudied RNA chaperone, is an important part of the interaction between mRNA and sRNA.[5-7] Hfq plays crucial roles in the regulatory mechanisms that occur after RNA transcription that occur between the sRNA and the target mRNA. It was first detected in *Escherichia coli* in the 1960s and is considered a regulator of RNA transcription involved in responses to stressful conditions, iron homeostasis, and outer membrane synthesis. This chaperone is typically responsible for modulating motility and promoting resistance to cellular stresses, however, *hfq* mutations result in a spread of species-dependent phenotypic changes.[8-11]

Studies on Hfq of bacterial pathogens, including *A.baumannii*, have detected, after deletion of the complete gene or part of it, disadvantages for the bacterium itself, including attenuation of virulence, defects in secretory sistems expression, reduction of invasion and dissemination through host mammal organs, defects of motility and decreased expression of several virulence factors.[11-14] It is very likely that the Hfq RNA chaperone is implicated in regulation of these important processes through sRNAs.[15] However, although the Hfq chaperone plays critical roles in cellular stress resistance, the correlation between its expression and stress-related molecules in *A. baumannii* still needs further studies.

This review summarizes the current knowledge on the role of the Hfq RNA chaperone in the virulence and antibiotic resistance of *A. baumannii*, an increasing important human opportunist pathogen.

METHOD

This is an integrative review study, with the objective of gathering results obtained in previous studies, in a systematic and comprehensive way. The study was developed from the analysis of scientific reports published in scientific journals from Science Direct and PubMed databases. The articles were selected by applying the keywords: "Hfq and *Acinetobacter baumannii*", "Hfq and Gram-negative bacteria". The databases were accessed from April 2, 2020, to February 23, 2021.

The guiding questions we sought to answer were: does the RNA Hfq chaperone play roles in the resistance and virulence of *A. baumannii*? What are these roles and what are their impacts?

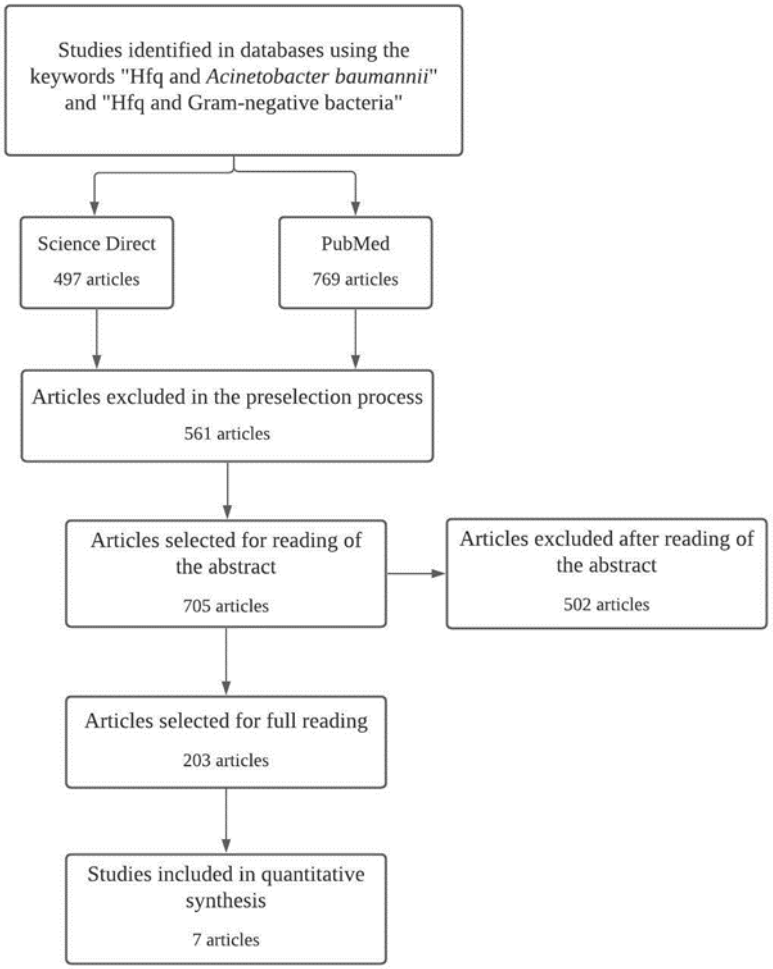
The inclusion criteria were studies available in full, in any language. As exclusion criteria: those that did not correspond to the object of the study were excluded.

The search results were filtered using the inclusion and exclusion criteria. The pre-selected studies went through the reading of titles and abstracts and then the full and carefully reading of the selected articles was carried out. After analyzing the results of the selected articles, our discussion was elaborated by considering their relationships with other available scientific references.

RESULTS

Seven studies were selected to compose the review, as they present results that are convenient to the guiding question (Figure 1).

Figure 1 – Flowchart for selecting the articles included in the study.



Source: Study data.

The analysis of the studies selected to compose the review is shown in chart 1, including the authors, year, journal and country where the study was carried out, as well as the objective and conclusions of each study. Three of the selected studies were carried out by a German group, two from the United States of America, one from a Indian and one from a Portuguese group. All articles were published in international journals, four were articles of review and three were original articles.

Chart 1 – Analysis of the seven studies selected to compose the review.

Authors	Year / Journal	Country	Aim	Conclusions
Vogel J, Luisi BF	2011 / Nature	Germany	Describe the structural and functional characteristics of Hfq and discuss possible ways in which this RNA chaperone can promote interactions to generate specific regulatory responses in vivo.	The main role of the Hfq chaperone is to act in bacterial regulation, however, the specific roles of this protein are still not fully understood, and further studies on its function are needed. Studies such as a global map of Hfq interaction sites in vivo could establish whether there is a variation in the concentration of Hfq in the bacterial cell, in addition to clarifying the interactions in the regulation of Hfq with other cellular factors.
Sharma A, Dubey V, Sharma R, Devnath K, Gupta VK,	2018 / Journal of Biological Chemistry	Indian	Understand the influence of the C-terminal tail of *A. baumannii* Hfq.	The flexible C-terminal tail present in *A. baumannii* Hfq is an integral functional part of this protein, being necessary for high-affinity RNA binding.

Akhter J, et al.				
Kuo HY, Chao HH, Liao PC, Hsu L, Chang KC, Tung CH, et al.	2017 / Frontiers in Microbiology	United States	Clarify the role of *A. baumannii* Hfq in virulence and stress responses.	In this, which was the first study to illustrate the functional role of Hfq in *A. baumannii*, it was possible to observe that this chaperone plays a fundamental role in controlling environmental adaptation and bacterial virulence.
Felicinao JR, Grilo AM, Guerreiro SI, Sousa SA, Leitão JH.	2016 / Future Microbiology	Portugal	Review and gather understanding of the role of Hfq in regulating traits related to secretion systems, alternative sigma factors, outer membrane proteins, polysaccharides and iron metabolism in bacterial virulence.	The role of Hfq in the post-transcriptional regulation of genes involved in cellular processes in bacteria of clinical importance is critical, especially its role in the production of virulence factors.
Schilling D, Gerischer U.	2009 / Journal of Bacteriology	Germany	Study *Acinetobacter baylyi* Hfq, which, due to its elongated C-terminal tail, results in a protein almost twice the size of other gammaproteobacterial Hfqs.	A reduction in the growth of *A. baylyi* was observed after deletion of the complete *hfq* ORF. Additionally, the deletion or overexpression of the Hfq protein triggered the loss of bacterial cell chain assembly, however, the glycine-rich domain was not responsible for the observed changes.
Updegrove TB, Zhang A, Storza G.	2017 / Current Opinion in Microbiology	United States	Review the results of different studies in order to elucidate the role of Hfq in RNA base pairing, with a main focus on Gram-negative pathogens.	Hfq is a regulator that affects the stability of sRNAs, and acts by enabling the base pairing of sRNA with target mRNAs.
Chao Y, Vogel J.	2012 / Current Opinion in Microbiology	Germany	Gather knowledge about the functions of Hfq in bacterial pathogens and highlight some useful experimental approaches to study these roles.	Hfq is a global regulator responsible for interfering, beneficially or not, in gene expression in different bacterial pathogens.

Source: Study data.

DISCUSSION

The Hfq RNA Chaperone

The chaperone Hfq RNA (Host Factor I Protein) is a highly conserved protein present in Gram-negative and positive pathogens that collaborates in the efficiency of the regulatory functions of different sRNAs, affecting the responses to stress, virulence and impairment in the growth of several clinically important pathogens, being the best characterized bacterial protein for this role.[16-18]

Identified in the 1960s in *Esherichia coli*, the RNA-binding protein Hfq was initially presented as necessary for the replication of the bacteriophage Qß and in the 1970s it was biochemically characterized as an abundant nucleic acid-binding protein, showing resistance to high temperatures, with a high preference for RNA with high rates of AU. Hfq was characterized as a member of the Like-Sm RNA-binding proteins family, found in eukaryotes, bacteria and archaea.[17,19,20-21] Since the 1990s, when the hfq gene was initially identified and silenced in *E. coli*, studies have demonstrated the great advantages offered by the Hfq for the adaptation of the bacterium under stress conditions, where the *hfq* null mutant presented a pleiotropic phenotype that includes defective growth rates, change in cell size, susceptibility to stress, defective oxidation of carbon sources, reduced fitness, increased sensitivity, attenuated virulence, and difficulty responding to stress. Furthermore, the translation of several cellular mRNAs was found to be regulated by Hfq. Currently, it is known that Hfq acts as a chaperone of bacterial cells, facilitating base pairing between small sRNAs and their mRNA targets, so that Hfq interferes with the expression of different mRNAs, positively or negatively.[8,17,20,22-23]

Hfq is a highly conserved protein, approximately half of bacterial genomes have Hfq homologs. The N-terminal portion of this protein is generally highly conserved between amino acids 1

and 66 in most pathogens, a region responsible for RNA binding and protein interactions. However, the C-terminus of Hfq from different bacteria varies significantly in length and sequence (Figure 2). The largest Hfq proteins are present in members of the *Moraxellaceae* family of gammaproteobacteria. The length of the Hfq chaperone varies considerably in different species, in *Acinetobacter* species, Hfq has 168 to 174 amino acids, for *Psychrobacter* species its size is from 183 to 203 amino acids and up to 210 amino acids for *Moraxella catarrhalis*.[6,24]

Figure 2 - Multiple sequence alignment of Hfq amino acids from different bacterial species.

Source: The autors.
Caption: Multiple sequence alignment visualized with BioEdit Sequence Alignment Editor (v 7.0.5.3). Capital letters indicate amino acids. The numbers indicate the size of the Hfq protein sequence. Asterisks indicate the end of the amino acid sequence. The glycine-rich amino acid repetitive pattern of the *A. baumannii* Hfq sequence is marked by a red box.

Structure of Hfq

Hfq, like the other members of the Sm/Lsm protein family, is characterized by its ring-shaped quaternary architecture that allows interactions with other macromolecules and acts by mediating the binding of sRNAs with their target mRNA.[8,20,25] Each Hfq subunit is composed of a short, variable N-terminal helix, which is generally four amino acids long, five highly twisted and curved antiparallel ß-strands, terminating in an unstructured C-terminal carboxy region. Hfq is a hexamer that has three RNA binding surfaces: proximal, distal, and lateral face, along with a C-terminal tail, necessary for contact between two RNA molecules.[23,26-27]

The proximal face of Hfq is extremely conserved and binds to uridines at the ends of the bacterial sRNA. The distal face binds to the 5'-UTR untranslated regions of mRNAs and sRNAs. The positively charged side of Hfq binds to a uridine-rich sequence of some sRNAs and mRNAs and plays a role in duplex structure formation and RNA exchange. The C-terminal tail varies substantially in sequence and size, being untidy and flexible. To date, studies investigating its cellular function of Hfq still yield conflicting conclusions. However, studies suggest that the C-terminal tail portion is important for interaction with some sRNAs.[23-25,27-29]

Bacterial Hfq and its functions

Several mechanisms of regulation mediated by Hfq has been proposed. This RNA chaperone can stabilize and promote interactions between sRNAs and mRNAs, these interactions can work by activating or preventing protein synthesis through alterations that will remodel the mRNA regions that contain the Ribosome Binding Site (RBS) and the start codon. Hfq can repress protein synthesis by binding to the 5' region of the target mRNA, making it unavailable for sRNA binding, preventing translation initiation. Hfq can also stimulate translation, helping to bind an sRNA to the 5' region of its target mRNA, this prevents the formation of a secondary structure that hinders and prevents binding to the ribosome. Hfq may also protect sRNAs from fragmentation by ribonucleases or cooperate in a way that promotes efficient mRNA fragmentation by associating with

RNase E and sRNA. Finally, Hfq can interact with the PAP I protein, stimulating its activity, making the 3' ends of the mRNA accessible for polyadenylation to promote RNA turnover. In previous studies, it was observed that when Hfq is absent, poly-A levels are reduced. In all cases, the information encoded in the RNA will be decisive to define the Hfq's mechanism of action.[8,27,30-31]

The most important portion for target recognition of an sRNA is its 5' end, which is normally small in Gram-negative bacteria, less than 10 nucleotides in length and triggering a low stability of duplex bonds as they are imperfectly complementary to the target mRNA. Hfq can work around the situation by creating more stable complexes that work by strengthening sRNA-mRNA bonds, allowing the sRNA to complete its regulatory activity. There are a few possible ways for Hfq to act as an aid in forming these bonds, either by increasing the sRNA recognition rate with its target mRNA or by making the sRNA-mRNA duplexes more stable due to their presence. It has also been shown that Hfq can induce alterations in the RNA structure to favor the formation of duplexes.[8,29]

In bacteria, most of the sRNAs that bind to Hfq are critical in stress responses. An example are the sRNAs that control the expression of RNA polymerase, sigma S (RpoS or σ38), which are regulatory proteins activated in response to environmental conditions and act in the regulation of genes expressionthat promotes bacterial survival under different stressors. Previous studies have shown that a loop formed in RpoS mRNA blocks the binding to RBS. Hfq can reverse the formation of this looping by binding to an upstream domain of RpoS mRNA, facilitating pairing and up-regulating RpoS expression. In previous studies, low expression of RpoS was observed in a mutant lacking the *hfq* gene (Δ*hfq*), and many of the observed phenotypic effects were attributed to defects in RpoS expression.[19,21-22,32]

Hfq also regulates the stress response mediated by RpoE (RNA polymerase, extracytoplasmic E), a sigma factor necessary for the response to extracytoplasmic stress, activated in situations such as heat shock (mutants with the silenced *rpoE* gene are unable to grow at temperatures above 42 degrees Celsius) and controls the expression of approximately 100 different genes. Hfq, together with other members of the RpoE regulon, controls the expression of OMPs and other components of the bacterial envelope, thus ensuring their integrity. The *hfq* deletion, in turn, causes severe activation of RpoE, along with uncontrolled OMP expression and increased envelope stress.[11,13,19]

The destabilization of the mRNA responsible for encoding *ompA* is also related to Hfq. OmpA is one of the main proteins that act and are found in large amounts in the outer membrane of Gram-negative bacteria, having important roles in pathogenicity, including invasion, adhesion and survival in the host organism, being even considered as target proteins for the creation of vaccines. The stability of the OmpA mRNA encoding is inversely proportional to the rate of cell growth. In the stationary phase of slow-growing cells, Hfq accumulates and competes with ribosomes for the 5' untranslated region of the mRNA, repressing ribosome binding and protecting against RNAseE degradation, resulting in mRNA degradation.[26]

The identification of the functions performed by the Hfq RNA chaperone during infectious processes is largely facilitated by the study of null-*hfq* mutants, since observing what happens to the organism in the absence of the gene of interest is the best way to discover its function. Studies of *Δhfq* mutants showed growth deficiency and increased susceptibility to stressful conditions. Hfq was also shown to be necessary for the suitability and virulence of almost all bacterial pathogens, especially in Gram-negative bacteria. *Δhfq* mutants tend to have a phenotype of sensitivity to host defense mechanisms and attenuated virulence, resulting in a failure to survive in the hostile and challenging environments

encountered in the host environment, e.g. oxidative stress.[33]

It was in the Gram-negative bacterium *Yersinia enterocolitica* that the role of Hfq in controlling virulence was first implicated due to its role in the production of enterotoxins from this microorganism. In other studies, Hfq has also been implicated in the production of exotoxin from *Pseudomonas aeruginosa* and the production of hemolysin from *Vibrio parahaemolyticus*, however the mechanisms that lead to these actions remain unknown. Hfq also controls virulence gene expression and synthesis of a crucial regulator to produce virulence factors in *Vibrio cholerae* and *Pseudomonas aeruginosa*.[6,11,14,33]

A study carried out with *Δhfq* mutants of pathogens belonging to thirty-four different species, mostly Gram-negative bacteria, showed that, in most cases, pleiotropic phenotypes are observed in the absence of Hfq in the bacterial organism, such phenotypes compromise pathogen survival under stress conditions, as well as impaired biofilm formation and decreased virulence.[22]

The Hfq RNA chaperone and *Acinetobacter baumannii*

The *A. baumannii hfq* gene encodes a protein of 168 amino acids, almost twice as long as other bacterial Hfqs, this is a consequence of an unusually elongated C-terminal portion rich in glycine residues that consists of a strictly repeated amino acid pattern unique to *Acinetobacter* species, in turn, the alignment of the *hfq* sequence of the N-terminus revealed a significant level of similarity with other bacterial species, with conserved regions of amino acids between 1 and 66 known to be involved in RNA binding.[6,24]

The C-terminal region of A. baumannii has a distinct repetitive pattern of amino acids GGFGGQ starting at amino acid 104 (Figure 1), which presented itself as an important component of Hfq for conferring flexibility and assisting these proteins in binding and interacting RNA with others protein partners, in addition, through experiments with truncated Hfq proteins it was possible to observe that the absence of the C-terminal portion rich in glycine brought disadvantages for the bacteria with respect to growth, tolerance to stress (oxidative, thermal, acid and osmotic), carbon metabolism, self-regulation of Hfq expression and virulence.[6]

Furthermore, the Hfq sequence reveals a relationship between its C-terminal portion and the family of eukaryotic glycine-rich proteins (GRP), the members of this family of proteins, as in *A. baumannii*, have an RNA recognition domain located in the In the N-terminal portion and a glycine-rich domain in the C-terminal portion, this glycine-rich tail confers flexibility and assists these proteins in binding RNA and interacting with other partner proteins. Interestingly, GRPs are recognized as central to RNA interaction and stress adaptation, as is Hfq, these observations may suggest an evolutionary relationship between prokaryotic and eukaryotic LSm proteins and considering the structure and function of Hfq, the presence of a C-Tail terminal that assists in interactions seems to be an obvious advantage.[6,34]

Experiments that silenced the *hfq* gene from strains of *A. baumannii* and *Acinetobacter baylyi*, a member of the same genus, also demonstrated that this chaperone has important functions for the bacterium itself. After deletion of *hfq*, defects and delays in cell growth of up to 7h, decreased levels of bacterial outer membrane vesicles (OMVs), deficiency in the metabolism of various carbon sources, including sugars, organic acids, amino acids, nucleosides, among others, were observed , drastic decrease in tolerance to physical and chemical stressors that can easily be found in hospital environments, such as temperature, pH, osmotic pressure and oxidative stress with consequent deficiency in the modulation of the expression of genes involved in stress tolerance, such as *basD*, *bauA*, *uspA*, among others.[6,7,24]

Hfq is also involved in the virulence of *A. baumannii*, being a vital factor for the survival of the pathogen under desiccation, for the formation of biofilms and in the modulation of fimbriae, which in the absence of the gene encoding this chaperone are reduced in compared to a wild-type strain. In addition, silencing the gene encoding Hfq led to a reduction of about 1 log in adhesion of *A. baumannii* cells to eukaryotic cell membranes.[6,7,24]

Hfq has also been involved in antibiotic resistance. A 2-fold reduction in the minimum inhibitory concentration (MIC) of nalidixic acid and gentamicin was observed after deletion of *hfq*, and the resistance was recovered after its complementation. On the other hand, there was an increase in resistance to meropenem in strains with *Δhfq* mutants when compared to wild cells.[6,7,24]

CONCLUSION

The data presented in this study gather evidence that implies Hfq as a central regulator of numerous functions of virulence and environmental adaptation in *A. baumannii*. The information exposed in this work allows this sRNA to be considered as a possible factor of significant virulence and resistance. Additional studies are needed in order to better characterize this molecule and its functioning mechanism so that its use is considered as a possible drug target effective against infections by *A. baumannii*.

RESUMO

Introdução: A dificuldade no tratamento das infecções por *Acinetobacter baumannii* devido ao seu alto índice de resistência aos antibióticos tem levado ao estudo de mecanismos inerentes ao próprio patógeno que podem ser utilizados como alvos eficazes no tratamento. A proteína do fator I do hospedeiro (Hfq) é uma chaperona de RNA geralmente necessária para auxiliar na conexão entre sRNAs e seu mRNA alvo atuando na regulação de diferentes genes, estudos realizados em uma variedade de espécies bacterianas têm demonstrado que o Hfq atua de forma pleiotrópica, contribuindo para a virulência e a resposta estresse. **Objetivo:** Resumir o conhecimento atual sobre o papel da chaperona Hfq RNA na virulência e resistência a antibióticos de *Acinetobacter baumannii*. **Delineamento**: Esta é uma revisão integrativa desenvolvida a partir de artigos publicados em qualquer idioma nas plataformas Science Direct e PubMed. A coleta e análise de dados foram realizadas entre o período de abril de 2020 a fevereiro de 2021. **Resultados:** Hfq mostrou desempenhar papéis importantes no crescimento celular, OMVs, metabolismo de fontes de carbono, tolerância ao estresse físico e químico, virulência através da formação de biofilme, modulação de fímbrias, entre outros. **Implicações:** Nosso trabalho mostra dados que fortalecem o papel do Hfq em diferentes aspectos da virulência e adaptação ambiental, incluindo a resistência antimicrobiana desse patógeno, alertando sobre a importância do Hfq como um futuro possível alvo eficaz no tratamento dessas infecções.

DESCRITORES

Virulência; Resistência a Medicamentos; *Acinetobacter baumannii*; Revisão; Chaperona; Fator Proteico 1 do Hospedeiro.

RESUMEN

Introducción: La dificultad en el tratamiento de las infecciones por *Acinetobacter baumannii* debido a su alta tasa de resistencia antibiótica ha llevado al estudio de mecanismos inherentes al propio patógeno que puedan ser utilizados como dianas efectivas en el tratamiento. La proteína del factor I del huésped (Hfq) es una chaperona de ARN generalmente necesaria para ayudar en la conexión entre los ARNs y su ARNm objetivo que actúa en la regulación de diferentes genes, los estudios realizados en una variedad de especies bacterianas han demostrado que Hfq actúa en una diferente forma pleiotrópica, que contribuye a la virulencia y la respuesta al estrés. **Objetivo:** Resumir el conocimiento actual sobre el papel de la chaperona de ARN Hfq en la virulencia y la resistencia a los antibióticos de *Acinetobacter baumannii*. **Delineación:** Esta es una revisión integradora desarrollada a partir de artículos publicados en cualquier idioma en las plataformas Science Direct y PubMed. La recopilación y el análisis de datos se llevaron a cabo desde abril de 2020 hasta febrero de 2021. **Resultados:** se ha demostrado que Hfq desempeña un papel importante en el crecimiento celular, las OMV, el metabolismo de las fuentes de carbono, la tolerancia al estrés físico y químico, la virulencia a través de la formación de biopelículas, la modulación de fimbrias, entre otros. **Implicaciones:** Nuestro trabajo muestra datos que fortalecen el papel de Hfq en diferentes aspectos de la virulencia y adaptación ambiental, incluyendo la resistencia antimicrobiana de este patógeno, alertando sobre la importancia de Hfq como posible diana efectiva futura en el tratamiento de estas infecciones.

DESCRIPTORES

Virulencia; Resistencia a Medicamentos; *Acinetobacter baumannii*; Revisión; Proteína de Factor 1 del Huésped.

REFERENCES

1. Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin. Infect. Dis [Internet] 2008. [cited 2022 Jan 02];46(8):1254-1263. Available from: https://pubmed.ncbi.nlm.nih.gov/18444865/

2. Nwugo CC, Gaddy JA, Zimbler DL, Actis LA. Deciphering the iron response in *Acinetobacter baumannii*: A proteomics approach. J Proteomics [Internet] 2011. [cited 2022 Jan 02]; 74(1):44-58. Available from: https://pubmed.ncbi.nlm.nih.gov/20692388/

3. Giamarellou H, Antoniadou A, Kanellakopolou K. *Acinetobacter baumannii*: a universal threat to public health? Int J Antimicrob Agents [Internet] 2008. [cited 2022 Jan 02];32(2):106-119. Available from: https://pubmed.ncbi.nlm.nih.gov/18571905/

4. Gordon NC, Wareham DW. Multidrug-resistant *Acinetobacter baumannii*: mechanisms of virulence and resistance. Int J Antimicrob Agents [Internet] 2010. [cited 2022 Jan 02];35(3):219-226. Available from: https://pubmed.ncbi.nlm.nih.gov/20047818/

5. Storz G, Vogel J, Wassarman KM. Regulation by Small RNAs in Bacteria: Expanding Frontiers. Mol Cell [Internet] 2011. [cited 2022 Jan 02];43(6):880-891. Available from: https://pubmed.ncbi.nlm.nih.gov/21925377/

6. Sharma A, Dubey V, Sharma R, Devnath K, Gupta VK, Akhter J, et al. The unusual glycine-rich C terminus of the *Acinetobacter baumannii* RNA chaperone Hfq plays an important role in bacterial physiology. J Biol Chem [Internet] 2018. [cited 2022 Jan 02];293(35):13377-13388. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6120210/

7. Kuo HY, Chao HH, Liao PC, Hsu L, Chang KC, Tung CH, et al. Functional characterization of *Acinetobacter baumannii* Lacking the RNA chaperone Hfq. Front Microbiol [Internet] 2017. [cited 2022 Jan 02];8:1-12. Available from: https://pubmed.ncbi.nlm.nih.gov/18444865/

8. Vogel J, Luisi BF. Hfq and its constellation of RNA. Nat Rev Microbiol [Internet] 2011. [cited 2022 Jan 02];9(8):578-589. Available from: https://pubmed.ncbi.nlm.nih.gov/21760622/

9. Chao Y, Vogel JA. A 3' UTR-Derived Small RNA Provides the Regulatory Noncoding Arm of the Inner Membrane Stress Response. Mol Cell [Internet] 2016. [cited 2022 Jan 02];61(3):352-363. Available from: https://pubmed.ncbi.nlm.nih.gov/26805574/

10. Bohn C, Rigoulay C, Bouloc P. No detectable effect of RNA-binding protein Hfq absence in *Staphylococcus aureus*. BMC Microbiol [Internet] 2007. [cited 2022 Jan 02];7:1-9. Available from: https://pubmed.ncbi.nlm.nih.gov/17291347/

11. Sittka A, Pfeiffer V, Tedin K, Vogel J. The RNA chaperone Hfq is essential for the virulence of *Salmonella typhimurium*. Mol Microbiol [Internet] 2007. [cited 2022 Jan 02];63(1):193-217. Available from: https://pubmed.ncbi.nlm.nih.gov/17163975/

12. Sonnleitner E, Hagens S, Rosenau F, Wilhelm S, Habel A, Jäger KE, et al. Reduced virulence of a hfq mutant of *Pseudomonas aeruginosa* O1. Microb Pathog [Internet] 2003. [cited 2022 Jan 02];35(5):217-228. Available from: https://pubmed.ncbi.nlm.nih.gov/14521880/

13. Ding Y, Davis BM, Waldor MK. Hfq is essential for *Vibrio cholerae* virulence and downregulates σEexpression. Mol Microbiol [Internet] 2004. [cited 2022 Jan 02];53(1):345-354. Available from: https://pubmed.ncbi.nlm.nih.gov/15225327/

14. Chiang MK, Lu MC, Liu LC, Lin CT, Lai YC. Impact of Hfq on global gene expression and virulence in *Klebsiella pneumoniae*. PLoS ONE [Internet] 2011. [cited 2022 Jan 02];6(7):e22248. Available from: https://pubmed.ncbi.nlm.nih.gov/21779404/

15. Amin SV, Roberts JT, Patterson DG, Coley AB, Allred JA, Denner, et al. Novel small RNA (sRNA) landscape of the starvation-stress response transcriptome of *Salmonella enterica* serovar typhimurium. RNA Biol [Internet] 2016. [cited 2022 Jan 02];13(3):331-342. Available from: https://pubmed.ncbi.nlm.nih.gov/26853797/

16. Berry KE, Hochschild A. A bacterial three-hybrid assay detects *Escherichia coli* Hfq-sRNA interactions in vivo. Nucleic Acids Res [Internet] 2018. [cited 2022 Jan 02];46(2):1-12. Available from: https://pubmed.ncbi.nlm.nih.gov/29140461/

17. Andrade JM, Santos RF, Chelysheva I, Ignatova Z, Arraiano CM. The RNA -binding protein Hfq is important for ribosome biogenesis and affects translation fidelity. EMBO J [Internet] 2018. [cited 2022 Jan 02];37(11):1-13. Available from: https://pubmed.ncbi.nlm.nih.gov/29669858/

18. Zhang L, Yu W, Tang Y, Li H, Ma X, Liu Z. RNA chaperone hfq mediates persistence to multiple antibiotics in *Aeromonas veronii*. Microb Pathog [Internet] 2019. [cited 2022 Jan 02];132:124-128. Available from: https://pubmed.ncbi.nlm.nih.gov/31054368/

19. Kulesus RR, Diaz-Perez K, Slechta ES, Eto DS, Mulvey MA. Impact of the RNA chaperone Hfq on the fitness and virulence potential of uropathogenic *Escherichia coli*. Infect Immun [Internet] 2008. [cited 2022 Jan 02];76(7):3019-3026. Available from: https://pubmed.ncbi.nlm.nih.gov/18458066/

20. De Lay N, Schu DJ, Gottesman S. Bacterial small RNA-based negative regulation: Hfq and its accomplices. J Biol Chem [Internet] 2013. [cited 2022 Jan 02];288(12):7996-8003. Available from: https://pubmed.ncbi.nlm.nih.gov/23362267/

21. Peng Y, Curtis JE, Fang X, Woodson SA. Structural model of an mRNA in complex with the bacterial chaperone Hfq. Proc Natl Acad Sci U S A [Internet] 2014. [cited 2022 Jan 02];111(48):17134-17139. Available from: https://pubmed.ncbi.nlm.nih.gov/25404287/

22. Felicinao JR, Grilo AM, Guerreiro SI, Sousa SA, Leitão JH. Hfq: A multifaceted RNA chaperone involved in virulence. Future Microbiol [Internet] 2016. [cited 2022 Jan 02];11(1):137-151. Available from: https://pubmed.ncbi.nlm.nih.gov/26685037/

23. Morita T, Aiba H. Mechanism and physiological significance of autoregulation of the *Escherichia coli* HFQ gene. Rna [Internet] 2019. [cited 2022 Jan 02];25(2):264–276, 2019. Available from: https://pubmed.ncbi.nlm.nih.gov/30487269/

24. Schilling D, Gerischer U. The *Acinetobacter baylyi* hfq gene encodes a large protein with an unusual C terminus. J Bacteriol [Internet] 2009. [cited 2022 Jan 02];191(17):5553–5562. Available from: https://pubmed.ncbi.nlm.nih.gov/19561130/

25. Yamada J, Yamasaki S, Hirakawa H, Hayashi-Nishino M, Yamaguchi A, Nishino K. Impact of the RNA chaperone HFQ on multidrug resistance in *Escherichia coli*. J Antimicrob Chemother [Internet] 2010. [cited 2022 Jan 02];65(5):853–858. Available from: https://pubmed.ncbi.nlm.nih.gov/20211861/

26. Murina VN, Nikulin AD. Bacterial Small Regulatory RNAs and Hfq Protein. Biochemistry (Mosc) [Internet] 2015. [cited 2022 Jan 02];80(13):1647–1654. Available from: https://pubmed.ncbi.nlm.nih.gov/26878571/

27. Updegrove TB, Zhang A, Storza G. Hfq: the flexible RNA matchmaker. Curr Opin Microbiol [Internet] 2017. [cited 2022 Jan 02];25(5):1032–1057. Available from: https://pubmed.ncbi.nlm.nih.gov/26907610/

28. Dimastrogiovanni D, Fröhlich KS, Bandyra KJ, Bruce HA, Hohensee S, Vogel J, Luisi BF. Recognition of the small regulatory RNA RydC by the bacterial Hfq protein. Elife [Internet] 2014. [cited 2022 Jan 02];3:1–19. Available from: https://pubmed.ncbi.nlm.nih.gov/25551292/

29. Santiago-Frangos A, Jeliazkov JR, Gray JJ, Woodson SA. Acidic C-terminal domains autoregulate the RNA chaperone Hfq. Elife [Internet] 2017. [cited 2022 Jan 02];6:1–25. Available from: https://pubmed.ncbi.nlm.nih.gov/28826489/

30. Mikulecky PJ, Kaw MK, Brescia CC, Takach JC, Sledjeski DD, Feig AL. *Escherichia coli* Hfq has distinct interaction surfaces for DsrA, rpoS and poly(A) RNAs. Nat Struct Mol Biol [Internet] 2004. [cited 2022 Jan 02];11(12):1206–1214. Available from: https://www.nature.com/articles/nsmb858

31. Andrade JM, Pobre V, Matos AM, Arraiano CM. The crucial role of PNPase in the degradation of small RNAs that are not associated with Hfq. RNA [Internet] 2012. [cited 2022 Jan 02];18(4):844–855. Available from: https://pubmed.ncbi.nlm.nih.gov/22355164/

32. Peterson CN, LrhA regulates *rpoS* translation in response to the Rcs phosphorelay system in *Escherichia coli*. J Bacteriol [Internet] 2006. [cited 2022 Jan 02];188(9):3175–3181. Available from: https://pubmed.ncbi.nlm.nih.gov/16621809/

33. Chao Y, Vogel J. The role of Hfq in bacterial pathogens. Curr Opin Microbiol [Internet] 2012. [cited 2022 Jan 02];13(1):24–33. Available from: https://pubmed.ncbi.nlm.nih.gov/20080057/

34. Sachetto- Martins G, Franco LO, Oliveira DE. Plant glycine-rich proteins: a family or just proteins with a common motif? Biochim Biophys Acta [Internet] 2000. [cited 2022 Jan 02];1492(1):1-14. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0167478100000646

COLLABORATIONS

LCAS, NCL and DEX: substantial contributions in the conception or design of the work; in the analysis and interpretation of data; and article's writing or in its critical review. **All authors agree and are responsible for the content of this version of the manuscript to be published.**

ACKNOWLEDGMENTS

Not applicable.

AVAILABILITY OF DATA

Not applicable.

FUNDING SOURCE

Instituto Aggeu Magalhães, Recife - PE, Brazil.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.