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Small non-coding RNAs in immunity of *Brucella*

Abstract

Brucella species are equipped with a variety of well-organized immune evasion strategies to establish chronic infection, including the use of small non-coding RNAs (sRNAs). In this review, the involvement of sRNAs in regulation of virulence and intracellular survival of *Brucella* is discussed. Further it highlights the role of sRNAs in modulation of innate and adaptive immune response mechanism of *Brucella*, which will improve our understanding of brucellosis and development of effective therapeutic approaches to treat this infectious disease.

Keywords: *Brucella*, small non-coding RNA, immunity, virulence

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Introduction

Bacterial small non-coding RNAs (sRNAs) have equipped with various mechanisms to balance their target gene expression and respond to environmental changes, stressful conditions and pathogenesis. These sRNAs are typically 50-200nt in length and act on independently expressed targets, do not encompass fully expressed open reading frames (ORFs).[1] These molecules are employing multiple molecular strategies to regulate gene expression, and divided into different classes such as cis-encoded sRNAs, trans-encoded sRNAs, CRISPR sRNAs and protein binding sRNAs. They modulate a variety of functions ranging from DNA maintenance or silencing, translation, transcription and mRNA stability.[2]

Brucella is Gram-negative, intracellular in nature, facultative, non-motile, non-spore-forming anaerobe which mainly causes infertility and abortion in wide range of animals and induces debilitating febrile diseases in humans. *Brucella* displays different strategies to modulate the immune response mechanism of its host to adapt the diverse environments through virulence factors or adaptation to structural components such as residing within phagocytic cells.[3,4] The activation and differentiation of innate and adaptive immune cells is associated with well-organized set of post-transcriptional and transcriptional events. sRNAs are linked directly or indirectly to regulate expression of gene related to virulence, quorum-sensing or adaptive stress-responses, which are essential for *Brucella* survival within host.[5] sRNAs critical roles in modulation of immune response mechanism upon *Brucella* infection is now growing. In this review, we summarize the role of sRNA in regulation of innate and adaptive immune response, host-pathogen interaction as well as implication of these modulations in the pathogenesis of brucellosis.

sRNA in modulation of virulence and intracellular survival of Brucella

sRNA plays critical roles in modulation of virulence and intracellular survival of *Brucella*. Caswell et al.[6] identified two highly conserved AbcR sRNAs (AbcR1 and AbcR2) that are essential for the ability of the *Brucella* to establish a chronic infection in mice.[6] Interestingly, AbcR sRNAs seem to be functionally redundant, as construction of a double abcR1 abcR2 (abcR1/2) deletion mutant strain leads to significant attenuation *in vitro* and *in vivo*.[6,7] Furthermore, AbcR sRNA plays key roles in regulation of ABC-transport system, such as B. abortus VtlR transcription regulator regulate several mRNAs that are directly targeted by AbcR sRNAs, and increased gene regulatory expression was observed with ΔAbcR sRNAs.[8]

In addition, they identified two M1 (CUCCCA) and M2 (GUUCCC) motifs in AbcR sRNA. These complementary motif sequences were identified in AbcR-regulated mRNA transcripts, suggesting that M1 and M2 motifs within the AbcR sRNAs are essential for direct binding and regulation of *Brucella* transcripts.[9] The conserved seed region of AbcR1 is responsible for regulating multiple target mRNAs belonging to transcriptional factor and two component response regulator of *Brucella* melitensis.[10] A BSR0602 sRNA directly target gntR mRNA and play important roles in bacterial adaptation to stress conditions and thus facilitates the intracellular survival of *Brucella*.[11] A large number of *Brucella* sRNA was identified using strand-specific RNA deep-sequencing approach, and BSR0441 was further characterized that involved in the virulence and stress adaptation of *Brucella*.[12]

A new cis-encoded sRNA, *Brucella* sRNA regulating HemH, BsrH , was considered to be first stress response related sRNA identified and functionally characterized.[13] Dong et al.[14] identified 129 sRNA of *Brucella* that plays significant roles in diverse biological processes ranging from physiology to virulence as well as in host-pathogen interaction.[14] In *Brucella* melitensis 16M ΔotpR, 877 cis-encoded and 99 trans-encoded sRNAs were identified and functionally characterized under acidic stress. These newly identified sRNAs are involved in various pathways including metabolism, lipids, carbohydrates, nucleotides transport, cell membrane biogenesis, quorum sensing, virulence and intracellular trafficking of *Brucella*.[15] Recent advancement in next-generation sequencing technologies have led to the identification of 33 sRNAs and 62 Hfq-associated mRNAs that play key roles in the pathogenesis and intracellular survival of *Brucella*.[16]

sRNA in regulation of innate and adaptive immune response of Brucella

MicroRNAs are integral constituent of small noncoding RNA plays significant role in modulation of immune response, gene expression, cellular mechanisms, signal transduction and apoptosis. Although knowledge and involvement of miRNAs in developing and regulating

immune response mechanism of *Brucella* is on initial stages, recent evidences found that miRNAs plays important function in modulation of immune mechanism. Zheng et al.[17] reported differential expression of miR-181b, miR-1981, miR-92a, let-7b and miR-93 in *Brucella* melitensis infected cells as compared with mock infected cells, suggesting the involvement of these miRNAs in apoptosis, autophagy and immune response mechanism.[17] miR-125b-5p down regulation was observed during *Brucella* abortus infection that result in higher expression of A20 protein, highlighting the role in inhibition of NF-κB activation as well as increasing *Brucella* intracellular survival.[18]

Recently, miRNA expression analysis of human CD8+ T cells revealed the involvement of miRNAs in cytokine-cytokine receptor interactions, regulation of actin cytoskeleton, MAPK signaling pathway, focal adhesion and endocytosis, suggesting miRNAs key roles in establishing chronic *Brucella* infection.[19] Furthermore, *Brucella* Omp25 prompts miR-21-5p, miR-23b and miR-155 to negatively modulate interleukin-12 production at posttranscriptional and transcriptional level through regulating PD-1 signaling pathway, which describe the novel mechanism underlying macrophage/monocyte dysfunction in *Brucella* chronic infection.[20] In contrast, inhibition of miR-351-5p, miR-146a, miR-181a and miR301a-3p reduced the inhibitory effects of Omp25 in RAW264.7 cells, while miR-351-5p, miR-146a, miR-181a and miR301a-3p leads to decrease in production of LPS-induced TNF-α in PAMs, indicating reduced intracellular bacteria number and higher TNF-α production in both cells.[21]

Conclusion and future perspectives

sRNA plays pivotal function in modulation of virulence gene expression and provides favorable environment to pathogenic bacteria to survive and proliferate within host. The incredible attention in sRNAs as watchdogs of bacterial gene expression keeps powering the inspiration of researchers in their interest for investigating novel strategies for identification and functional characterization of bacterial pathogens. sRNA plays critical roles in regulation of virulence and intracellular survival, as well as in modulation of innate and adaptive immune response mechanism of *Brucella*. However, further investigation are required to fully understand the involvement of miRNAs in modulation of innate and adaptive immune response such as how they monitor the TLR signaling pathway, miRNA based stealth strategies of *Brucella* for immune evasion. How do miRNAs participate in regulation of apoptosis and autophagy mechanism of *Brucella* is an open question.

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Conflict of interest

The author declared that no competing interest exists.

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