



香港中文大學
The Chinese University of Hong Kong



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MicroRNAs in Bacterial Infections: Roles, Mechanisms, and Therapeutic Potential

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Outline

1. Introduction
2. Mechanisms of Action
3. MicroRNAs and Bacterial Infections
4. Biomarkers and Therapeutic Potential
5. Challenges and Future Directions
6. Conclusion



Introduction

- Introduction to miRNA
- Discovery of miRNA
- Biogenesis of miRNA

microRNA (miRNA)

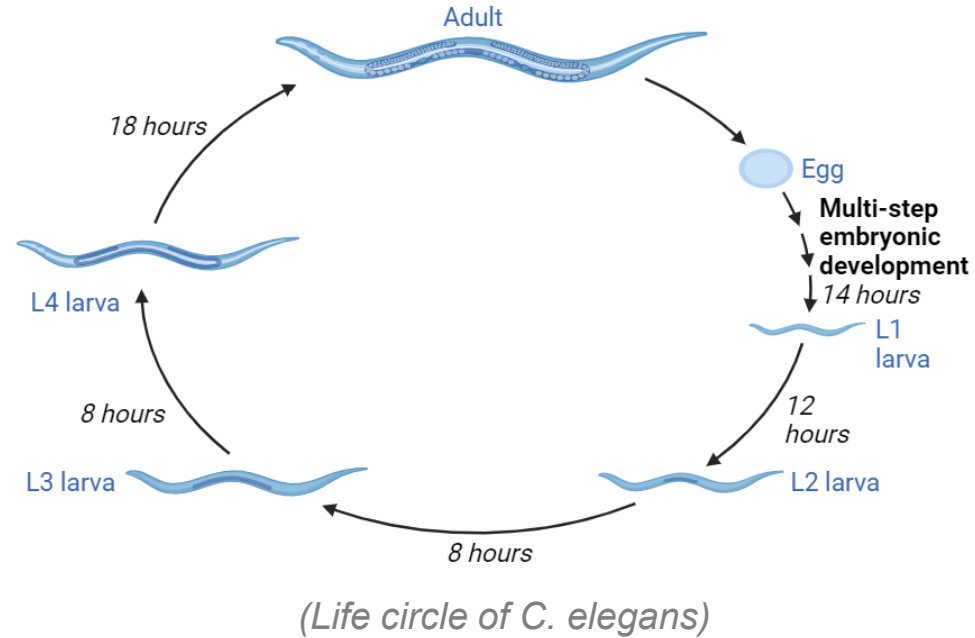
- Small, single-stranded non-coding RNA molecules containing ~22 nucleotides
- Involved in RNA silencing and post-transcriptional regulation of gene expression



(Example of miRNA stem-loop, with the mature miRNAs shown in red)

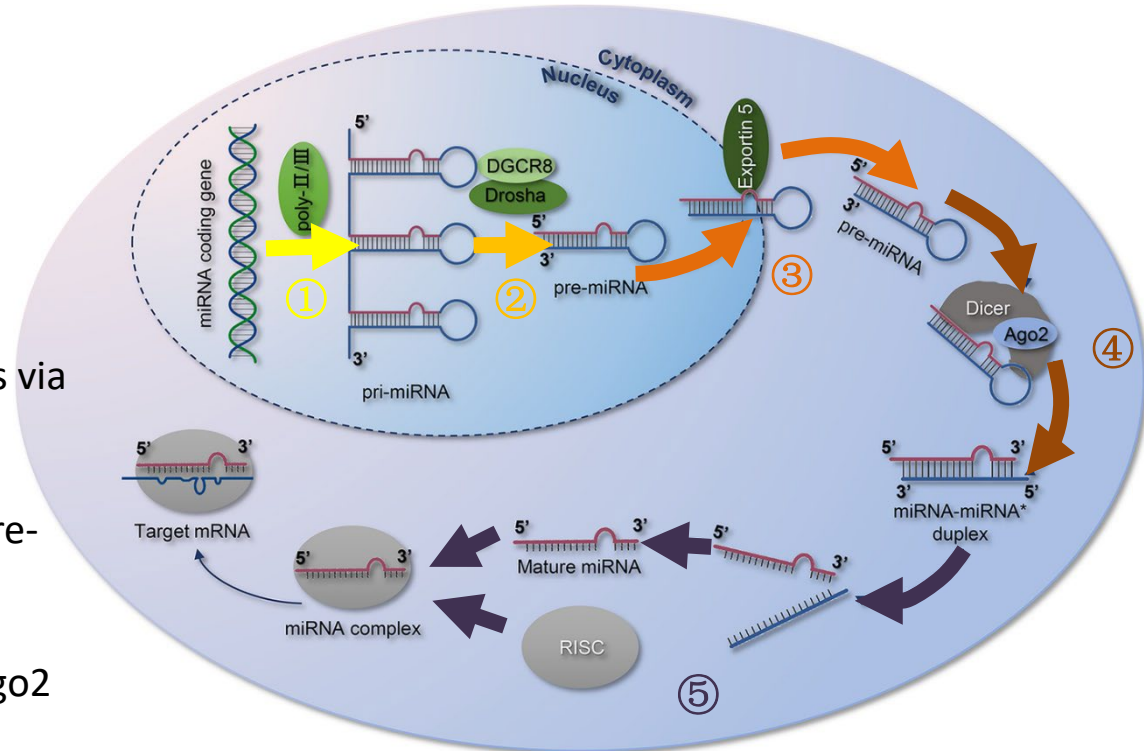
miRNA discovery

- First discovered in *C. elegans* in 1993
- (1993) *Lin-4* regulates *lin-14* mRNA translation via RNA-RNA interactions
- (2000) *Let-7* regulates several mRNAs, also found in other animals including flies and humans



miRNA biogenesis

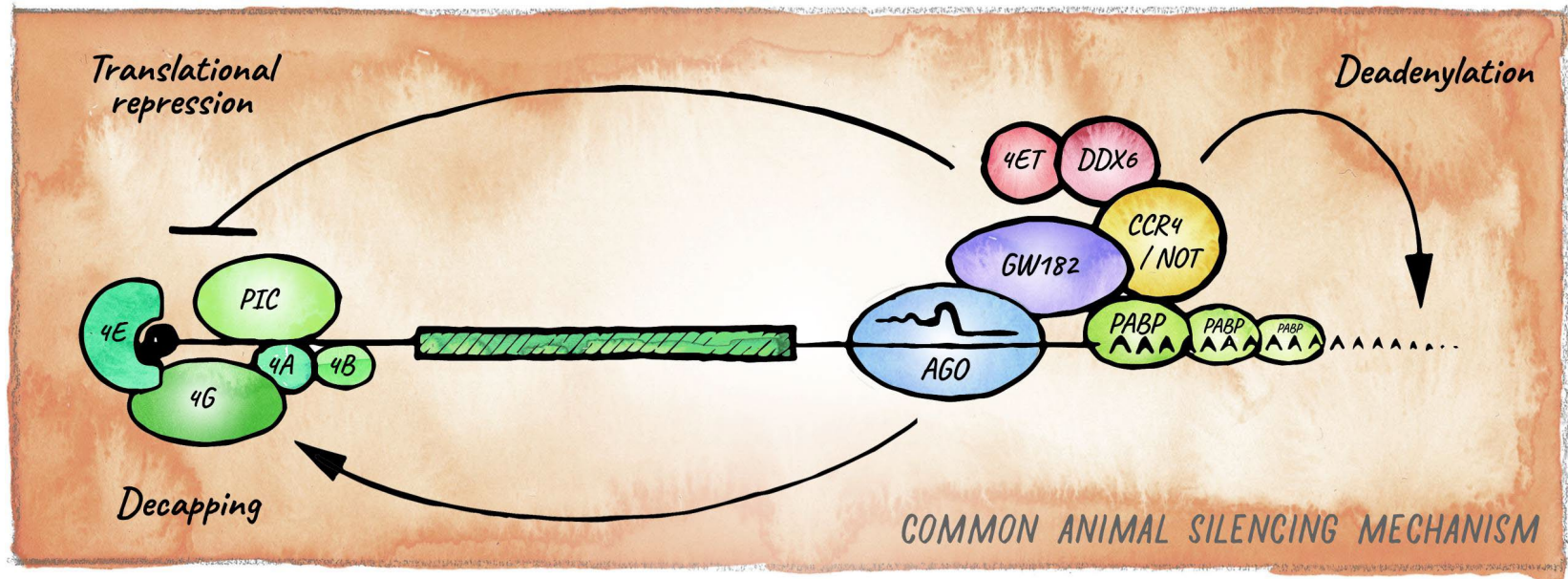
- ① Pri-miRNA transcript by RNA polymerase II & III
- ② DGCR8 and Drosha cleavage of pri-miRNA into pre-miRNA
- ③ Pre-miRNA export from the nucleus via Exportin-5 into the cytoplasm
- ④ RNase Dicer complex cleaves the pre-miRNA to its mature length
- ⑤ Mature miRNA is combined with Ago2 into RISC



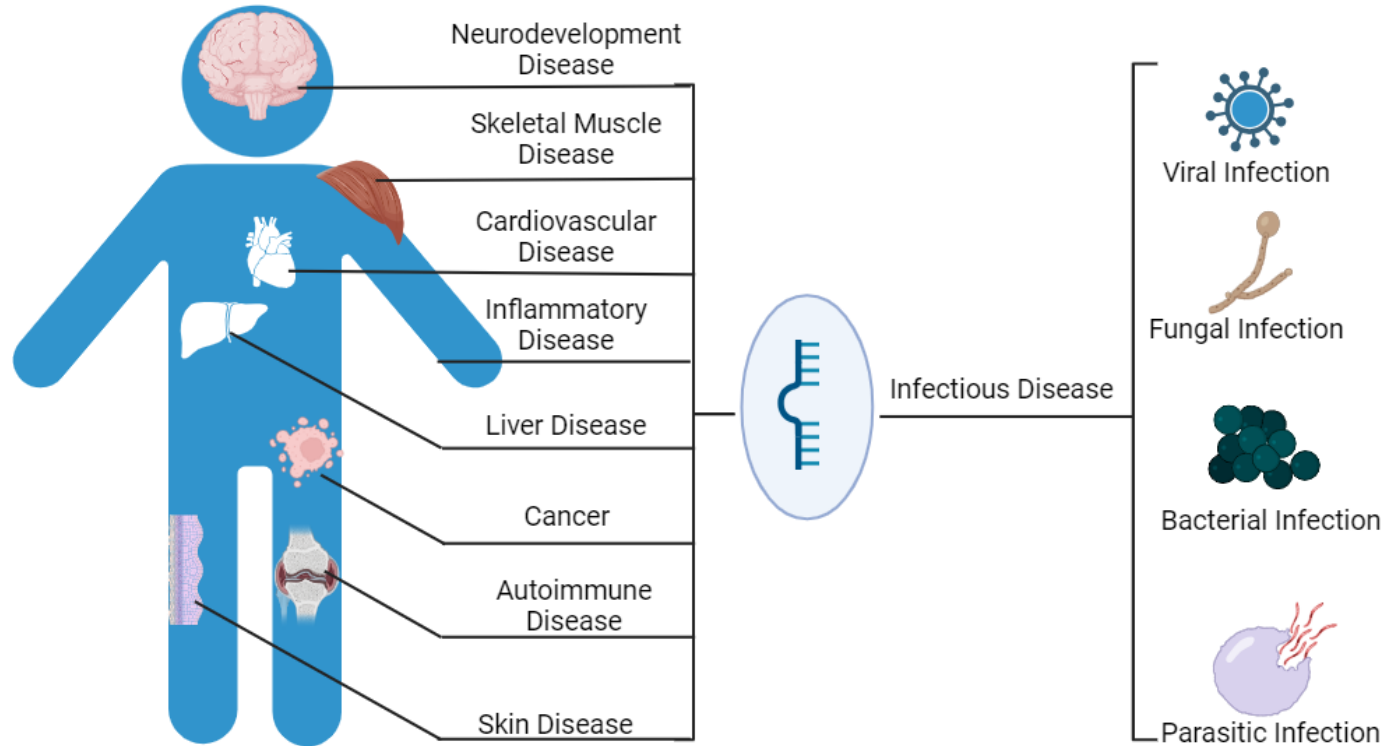


Mechanisms of Action

Translation inhibition & Deadenylation



miRNA associated with human diseases





MicroRNAs and Bacterial Infections

- MicroRNAs modulate immune and inflammatory responses

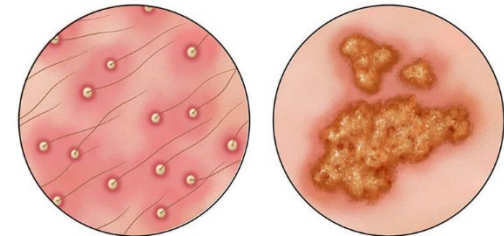
MiRNA regulates immune and inflammatory responses during *Staphylococcus aureus* infections

- Gram-positive bacterium
- Commonly colonizes the skin and nasal passages
- Cause a wide range of infections, from mild skin infections to severe invasive diseases



Abscesses and boils

Cellulitis



Folliculitis

Impetigo

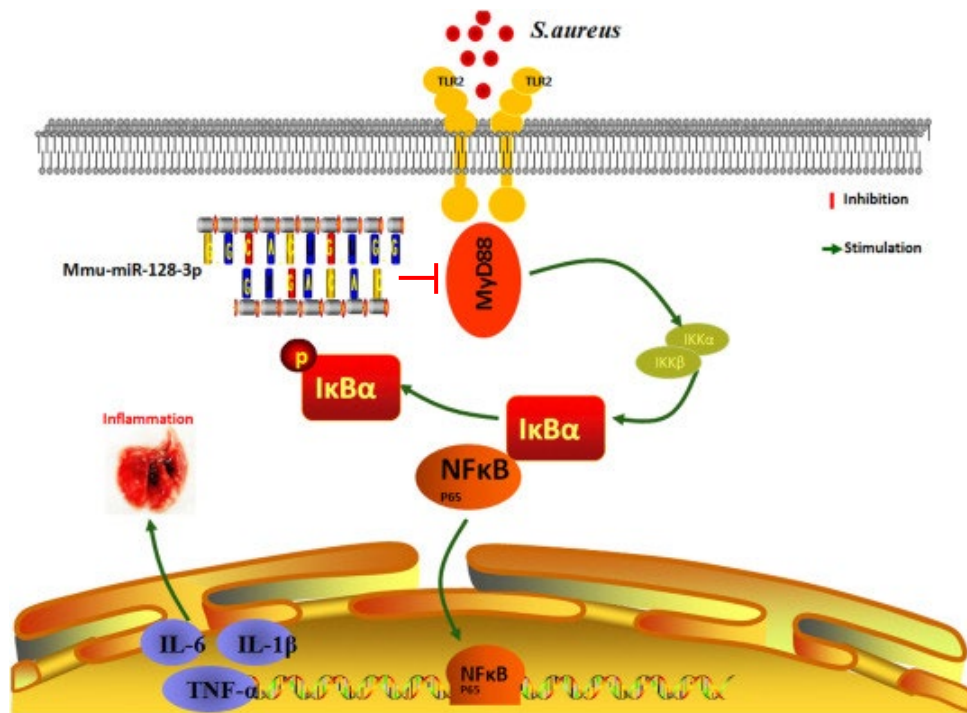
 Cleveland Clinic © 2021

(*S. aureus* cause skin infections)

(<https://my.clevelandclinic.org/health/diseases/21165-staph-infection-staphylococcus-infection>)

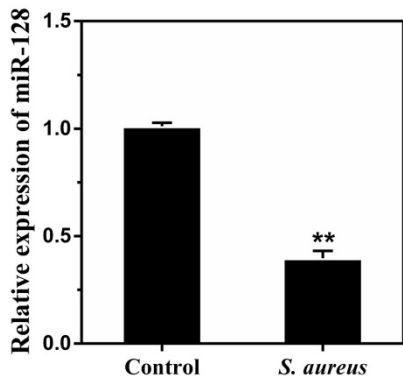
miRNA regulates immune and inflammatory responses during *Staphylococcus aureus* infections

- *S. aureus* induced acute lung injury
- Lipopeptides engage with the TLR2 receptor
- Activate TLR2-MyD88-NF- κ B pathway
- miR-128 target on *MyD88*

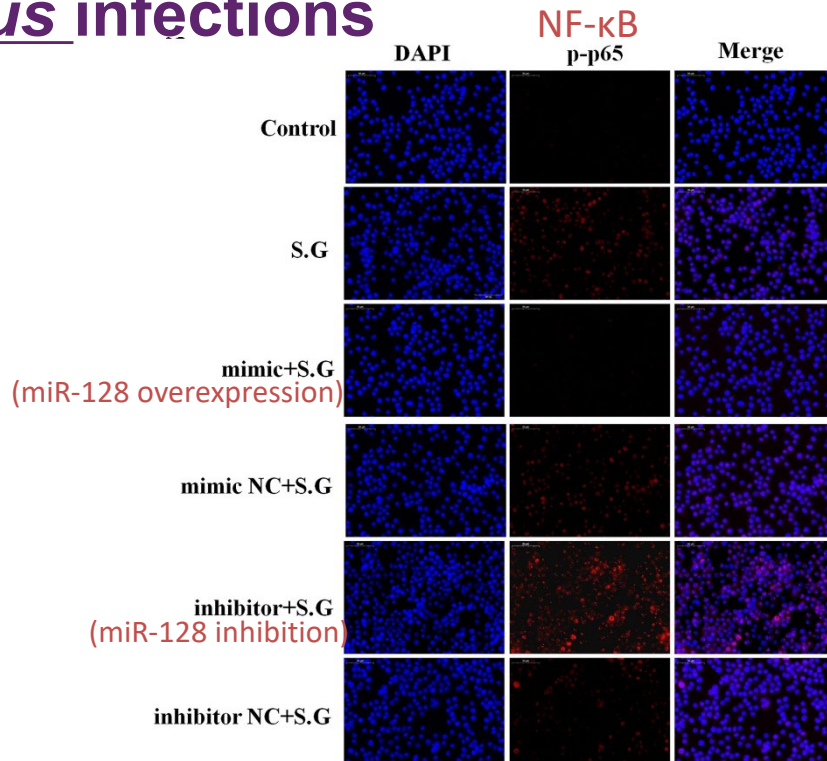


miRNA regulates immune and inflammatory responses during *Staphylococcus aureus* infections

- *S. aureus* down regulate miR-128
- miR-128 inhibits *S. aureus*-induced inflammatory cytokines production



(miR-128 expression level in lung tissues of *S. aureus* treated mice)



(miR-128 inhibits *S. aureus*-induced activation of NF-κB signaling in RAW264.7 cells)



Biomarkers and Therapeutic Potential

MiRNA as biomarkers



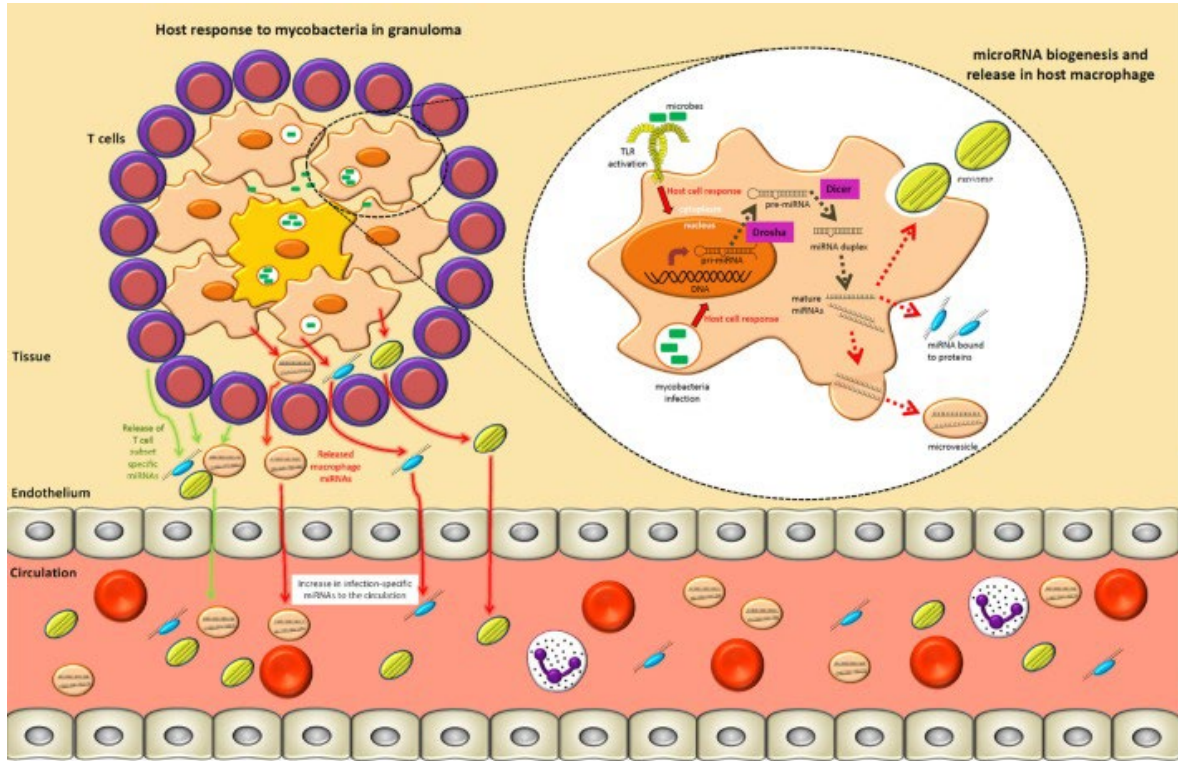
Properties of an ideal biomarker

- Has high specificity and sensitivity
- Detectable by minimally invasive sampling procedures

MiRNA as biomarkers

Circulating miRNAs

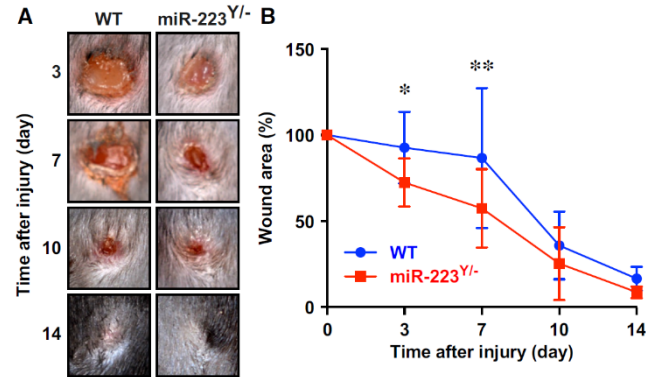
- Mycobacterial pathogens activate miRNAs in immune cells
- Extracellular miRNA enter the circulation system
- Still viable after long-term storage of frozen samples



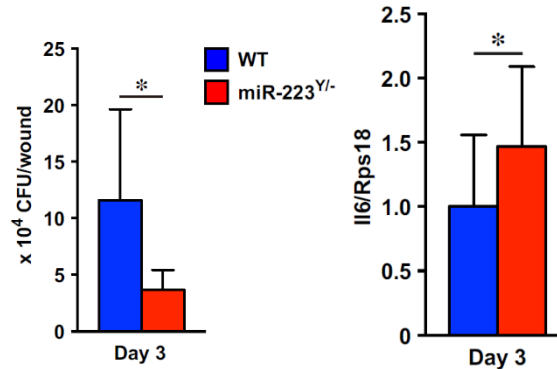
(A tuberculosis lung granuloma demonstrates how specific circulating miRNAs may arise during an infection process)

miRNA as infection therapy

- miR-223 was highly expressed in *S. aureus*-infected wound sites
- miR-223 targets IL-6
- miR-223 deleted neutrophils contribute to improved healing of *S. aureus*-infected wounds



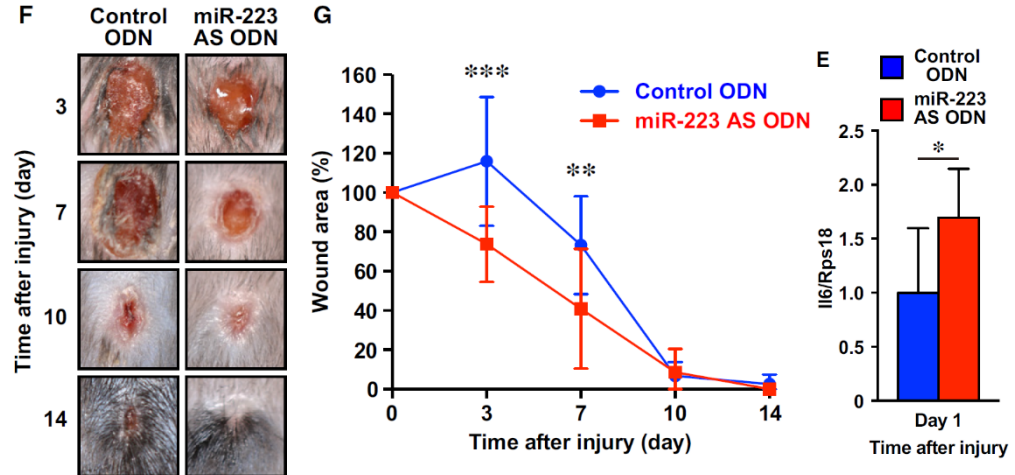
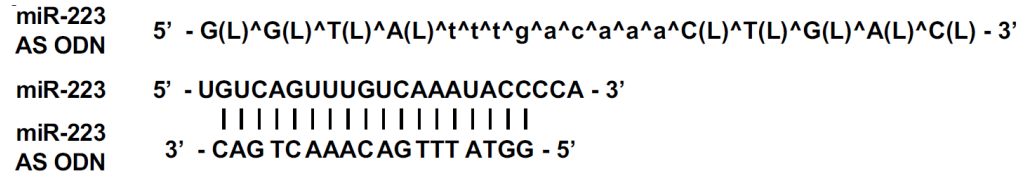
(Wound area of *S. aureus*-infected wounds)



(Bacterial load and IL-6 expression of *S. aureus*-infected wounds)

miRNA as infection therapy

- miR-223 antisense oligodeoxynucleotides (AS ODNs)
- miR-223 AS ODNs markedly improved wound healing in *S. aureus*-infected wild-type wounds
- Use miR-223 AS ODNs as potential therapy



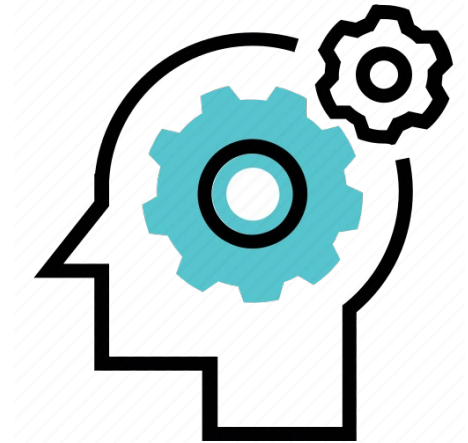
(Wound area and IL-6 expression of *S. aureus*-infected wounds treated with ODN)



Challenges and Future Directions

Challenges...

- Sample processing **methods** affect the quality of RNA extraction
- Accurate **transcriptional profiling** and **quantification** of miRNAs
- **Specificity** and design of miRNAs



Future Directions

- Sample processing methods affect the quality of RNA extraction
- Accurate transcriptional profiling and quantification of miRNAs

Standardized assays for sample processing and miRNAs measurement

- Specificity and design of miRNAs

Precise gene editing by single miRNA without **off-target** effects



Conclusion

Conclusion

- miRNAs are small non-coding RNAs involved in **gene expression** regulation
- miRNAs as key regulators of **host immune responses** to bacterial infections
- miRNAs as **potential biomarkers** and **therapeutic targets** for infectious diseases

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Thank you!