New strategies for combating multidrug-resistant bacteria

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Outline

- The crisis of antibiotic resistance
  - The emergence of ‘superbugs’
  - The decline of antibiotic development
- New strategies fights against resistant pathogens
  - Probiotics
  - Bacteriophage therapy
  - Anti-virulence strategies
The crisis of antibiotic resistance

Superbugs are on the rise
Antibiotic resistance is ancient
Long term persistence of antibiotics resistance

Antibiotic development is dwindling
Pharmaceutical firm abandon antibiotics development: economic and regulatory barriers.

Strategies to fight against resistant pathogens

- **Preserving available antibiotics**
  - Appropriate use of antibiotics
  - Inhibitors of resistant enzymes and antibiotic efflux
  - Silence resistant genes

- **New antibiotics**
  - Structural modification of existing drugs
  - New sources of antimicrobial chemicals-natural products, ocean

- **New strategies**
  - Probiotics
  - Bacteriophage therapy
  - Anti-virulence strategies
Probiotics: ‘good’ bacteria

Live microorganisms which when administered in adequate amounts confer a health benefit on the host. (Lactobacillus group: genera Lactobacillus, Enterococcus, Streptococcus, Lactococcus, Pediococcus, Bifidobacterium and Leuconostoc)

What’s new...

- The importance of gut microbiota
- 90%
- Break down food
- Clean the gut waste
- Suppress bad bacteria
- ...
- Imbalance and diseases
- Antibiotic associated infections
- Recurrent C. difficile infection

http://www.dfwchild.com/Fort-Worth/features/1014/Keeping-Kids-Healthy-With-Probiotics
Probiotics- ‘good’ bacteria fight against ‘bad’ ones

- Mechanism:
  - maintain microbial ecology
  - interspecific competition
- Probiotics
  - Dietary supplements
  - Microbiota transplantation
- Major concerns
  - Efficiency, safety, mechanism
  - Regulation

Probiotic *Escherichia coli* strain Nissle 1917 outcompetes intestinal pathogens during biofilm formation

Viktoria Hancock, Malin Dahl and Per Klemm
Bacteriophage therapy

- Bacteriophages, or simply 'phages', are viruses that infect and in some cases destroy bacterial cells.
- Phages are a natural part of the microbial ecosystem.
- Phage species are specific to particular bacterial species.
- The golden age in use of phage was in the 1930s.
- Phage ‘cocktail’

Mechanism of phage therapy

1. Attachment
2. Entry of phage DNA and degradation of host DNA
3. Synthesis of viral genomes and proteins
4. Assembly
5. Release
Phage assembly

Lytic cycle of a phage

Head Tail Tail fibers

http://cis.payap.ac.th/?p=3759
Bacteriophage therapy

Advantages

- Phage therapy is possible in all bacterial infections
- Phage coevolving with bacteria
- Specific - no effect on healthy microflora
- And so on...

Challenges

- Safety issue
- Precise and quick diagnosis are needed before prescribing a phage treatment
- Difficulties in getting the approval of phage ‘cocktail’ and intellectual property issue
Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy

Timothy K. Lu\textsuperscript{a,b} and James J. Collins\textsuperscript{b,1}

Engineered lexA3 bacteriophage enhances killing of wild-type \textit{E. coli} EMG2 bacteria by bactericidal antibiotics.
Bacteriophage endolysins

- Endolysins (or lysins) are highly evolved enzymes produced by phage to digest the bacterial cell wall for phage progeny release.
- Lysins exert their lethal effects by forming holes in the cell wall through peptidoglycan digestion.
- NO living viruses involved-
The development of ClyS ointment

1. Plasmid Transformation
2. Protein expression and purification
3. Ointment to apply to mouse skin infection model
A Novel Chimeric Lysin Shows Superiority to Mupirocin for Skin Decolonization of Methicillin-Resistant and -Sensitive Staphylococcus aureus Strains

Mina Pastagia, Chad Euler, Peter Chahales, Judilyn Fuentes-Duculan, James G. Krueger, and Vincent A. Fischetti

In vivo activity of ClyS ointment versus that of placebo or mupirocin on tape-stripped mice infected with S. aureus 8325-4 or MRSA MW2.

In vitro resistance studies of ClyS and mupirocin. MIC90 values for MRSA and MSSA remain the same for ClyS but increase for mupirocin
Staphefekt-the first endolysin available for human use on intact skin

Specific lysis of MRSA and MSSA by Staphefekt


Staphefekt™ effectively kills MRSA & MSSA without disturbing normal skin flora
What is virulence?

- Capacity to cause disease
  - Adhesins
  - Toxins, proteases
  - Secretion systems
  - And so on...
- Global regulation

Anti-virulence strategies

Colonization

Immune evasion

Resource acquisition

Host invasion

Anti-virulence strategies

- Block virulence factor induction, synthesis, or release
  - Singal
  - Transcription
  - Assemble
  - Delivery
- Inhibit the function
  - Neutralization
  - Host receptor antagonist

Anti-virulence strategies

Antibiotics VS Anti-virulence

Kill or inhibit cell growth

Interrupt infection

http://www.surface.mat.ethz.ch/research_old/functional_biointerface/GlycoSurf
http://www.smallerquestions.org/blog/2013/7/11/antibiotics-damage-human-cells.html
Anti-virulence strategies against MRSA

Alpha-hemolysin (α-toxin)

1. α-toxin is an essential virulence in SA
2. α-toxin form pore on cell membrane and lysis host cells
3. Metalloprotease 10 (ADAM10) is a cellular receptor for α-toxin
Anti-Virulence Strategies

1. Antibody: neutralize α-toxin
2. β-Cyclodextrin derivatives: block the pore formation
3. ADAM10 Inhibitor: inhibit binding of α-toxin to host cell

Prevention and Treatment of *Staphylococcus aureus* Pneumonia with a β-Cyclodextrin Derivative

Targeting *Staphylococcus aureus* α-Toxin as a Novel Approach to Reduce Severity of Recurrent Skin and Soft-Tissue Infections
Summary

- Antibiotic resistance pathogens continue to rise, while antibiotic development is dwindling
- Probiotics: ‘Good’ bacteria fight against ‘bad’ ones
- Bacteriophage therapy: ‘Viruse’ fight against pathogens
- Anti-virulence strategies: Strategies aim to interrupt pathogen-host interaction
References

- Antibiotics and the rise of superbugs
References


Thanks for your attention