香港中文大學
The Chinese University of Hong Kong

Quorum sensing in *Staphylococcus aureus*

Joint Graduate Seminar
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18th December, 2012

Outline

Ⅰ. Bacteria quorum sensing

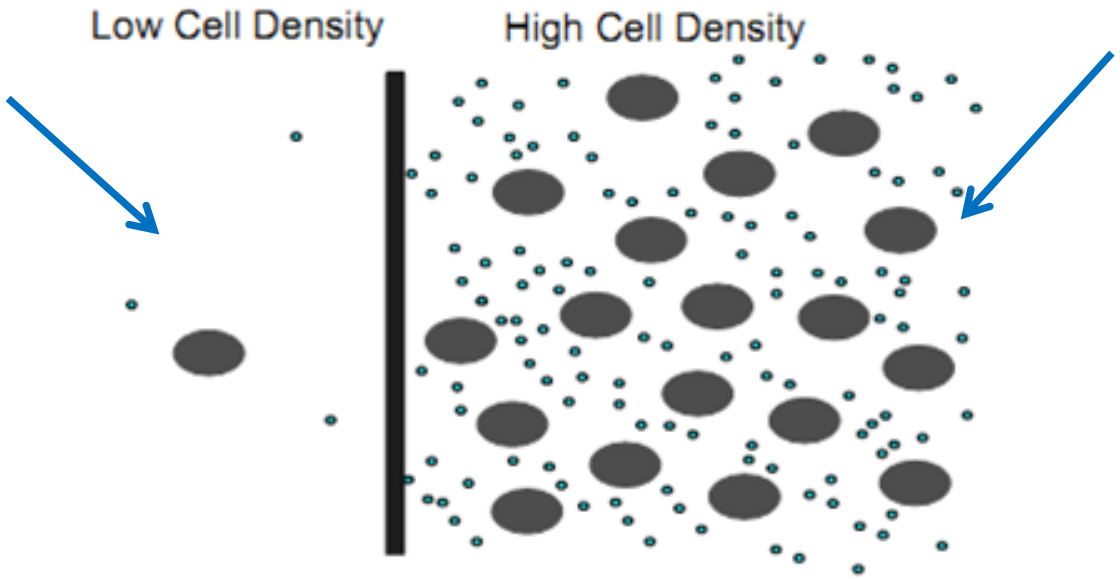
Ⅱ. Quorum sensing in *Staphylococcus aureus*

Accessory gene regulator (*agr*)

BACTERIA QUORUM SENSING

What is Quorum sensing?

- QS is a process that enables bacteria to communicate using secreted signaling molecules



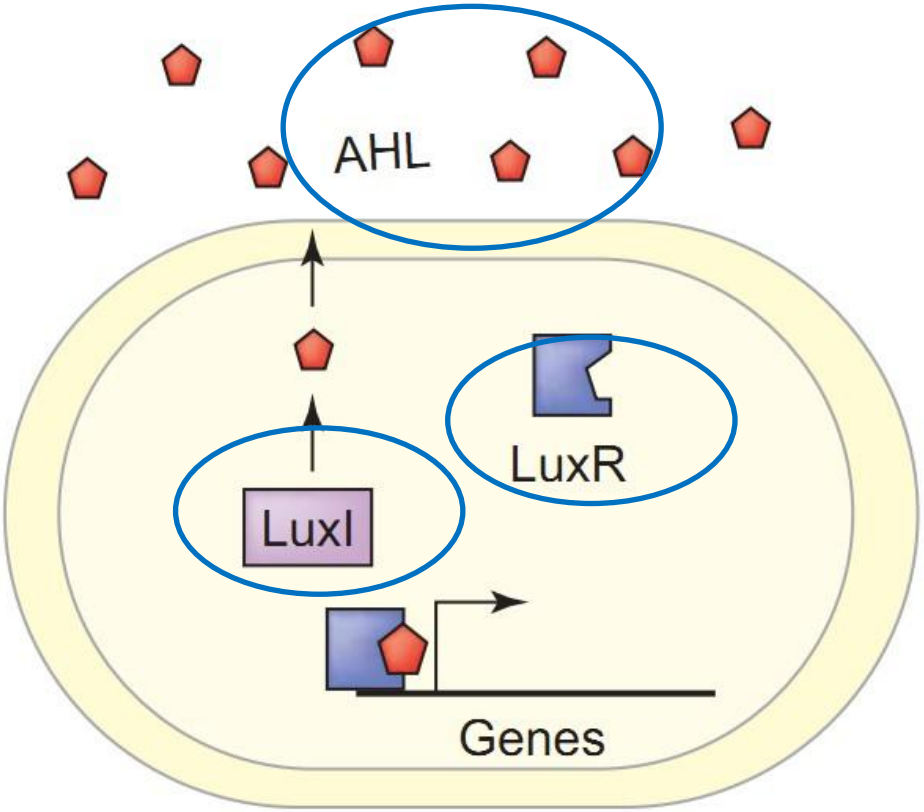
iBioSeminars: Bonnie Bassler, June 2008

Canonical quorum-sensing systems

- Gram-negative:LuxI/R
- Gram-positive:oligopeptide
- Hybrid

Gram-negative:LuxI/R

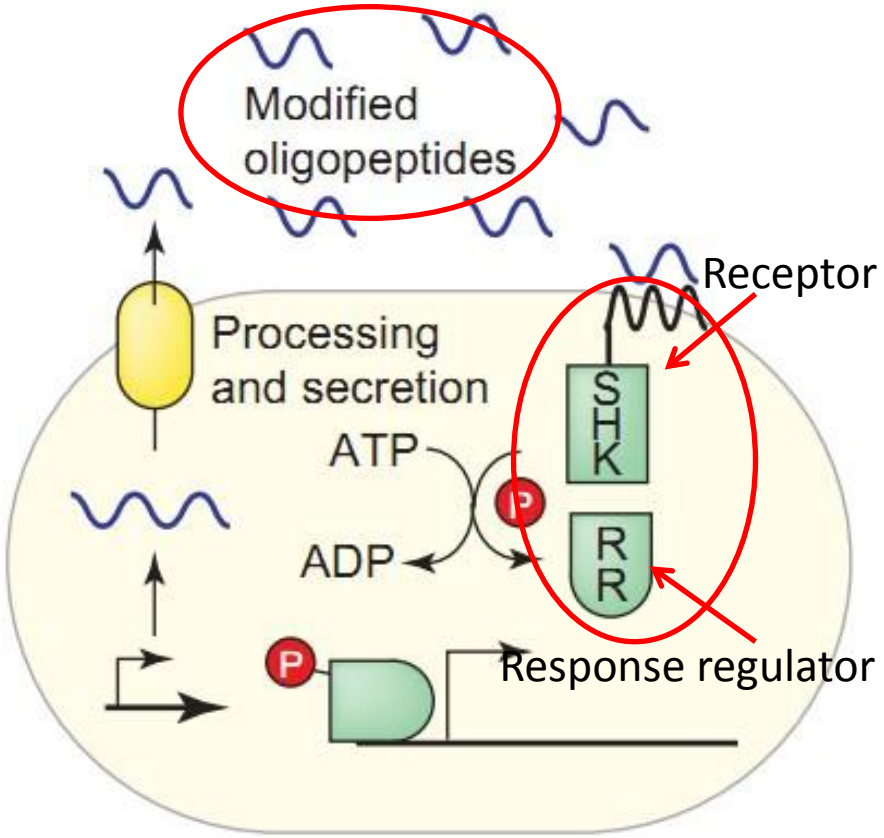
- Autorinducer: acyl-homoserine lactone (AHL)
- autoinducer synthase: LuxI
- Receptor : LuxR
- The LuxI/R system is a species specific system



Henke JM, Bassler BL.Trends Cell Biol. 2004 Nov;14(11):648-56.

Gram-positive:oligopeptide

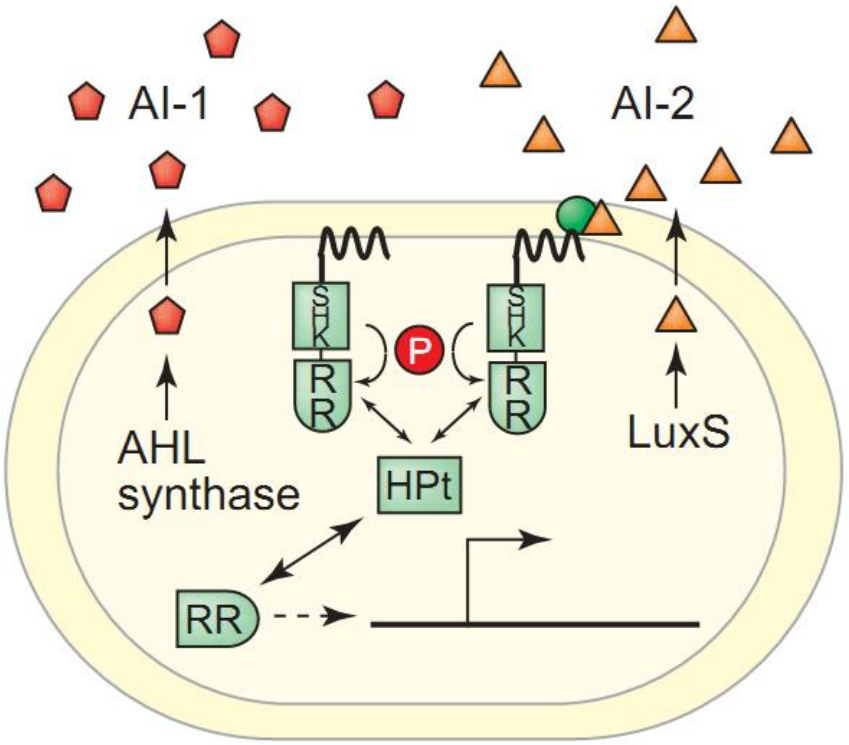
- Autorinducer: modified oligopeptides
- Receptor : membrane-bound sensor histidine kinases
- Response regulator :
  DNA-binding transcriptional
  regulatory protein



Henke JM, Bassler BL.Trends Cell Biol. 2004 Nov;14(11):648-56.

Hybrid system

- Autorinducer: AI-1 and AI-2
- Autoinducer synthase: AHL synthase and LuxS
- AI-2 is interspecies bacterial signals



Henke JM, Bassler BL.Trends Cell Biol. 2004 Nov;14(11):648-56.

Quorum sensing controlled Genes

- Bioluminescence *:V. harveyi* and *V. fischeri*
- Biofilm formation: *P.aeruginosa*
- Virulence gene expression: *S.aureus* and *P.aeruginosa*

Inhibitor of quorum sensing

Journal of Antimicrobial Chemotherapy (2004) **53**, 1054–1061
DOI: 10.1093/jac/dkh223
Advance Access publication 29 April 2004

JAC

Synthetic furanones inhibit quorum-sensing and enhance bacterial clearance in *Pseudomonas aeruginosa* lung infection in mice

H. Wu[1]*, Z. Song[1], M. Hentzer[2], J. B. Andersen[2], S. Molin[2], M. Givskov[2] and N. Høiby[1]

Introduction: Antibiotics are used to treat bacterial infections by killing the bacteria or inhibiting their growth, but resistance to antibiotics can develop readily. The discovery that bacterial quorum-sensing regulates bacterial virulence as well as the formation of biofilms opens up new ways to control certain bacterial infections. Furanone compounds capable of inhibiting bacterial quorum-sensing systems have been isolated from the marine macro alga *Delisea pulchra*.

Objectives: Two synthetic furanones were tested for their ability to attenuate bacterial virulence in the mouse models of chronic lung infection by targeting bacterial quorum-sensing without directly killing bacteria or inhibiting their growth.

Methods: Study I. Mice with *Escherichia coli* MT102 [*luxR-PluxI-gfp*(ASV)] lung infection were injected intravenously with *N*-acyl homoserine lactones with or without furanones to test the interference of furanones with quorum-sensing. Study II. Mice with lung infection by *Pseudomonas aeruginosa* PAO1 [*dsred, lasR-PlasB-gfp*(ASV)] were injected intravenously with furanones to evaluate their inhibiting effects on quorum-sensing. Study III. Mice with *P. aeruginosa* PAO1 lung infection were treated with different doses of furanones to evaluate the therapeutic effects of furanones on the lung infection.

Results: Furanones successfully interfered with *N*-acyl homoserine lactone and suppressed bacterial quorum-sensing in lungs, which resulted in decreases in expression of green fluorescent protein. Furanones accelerated lung bacterial clearance, and reduced the severity of lung pathology. In a lethal *P. aeruginosa* lung infection, treatment with furanone significantly prolonged the survival time of the mice.

Conclusion: Synthetic furanone compounds inhibited bacterial quorum-sensing in *P. aeruginosa* and exhibited favourable therapeutic effects on *P. aeruginosa* lung infection.

Summary

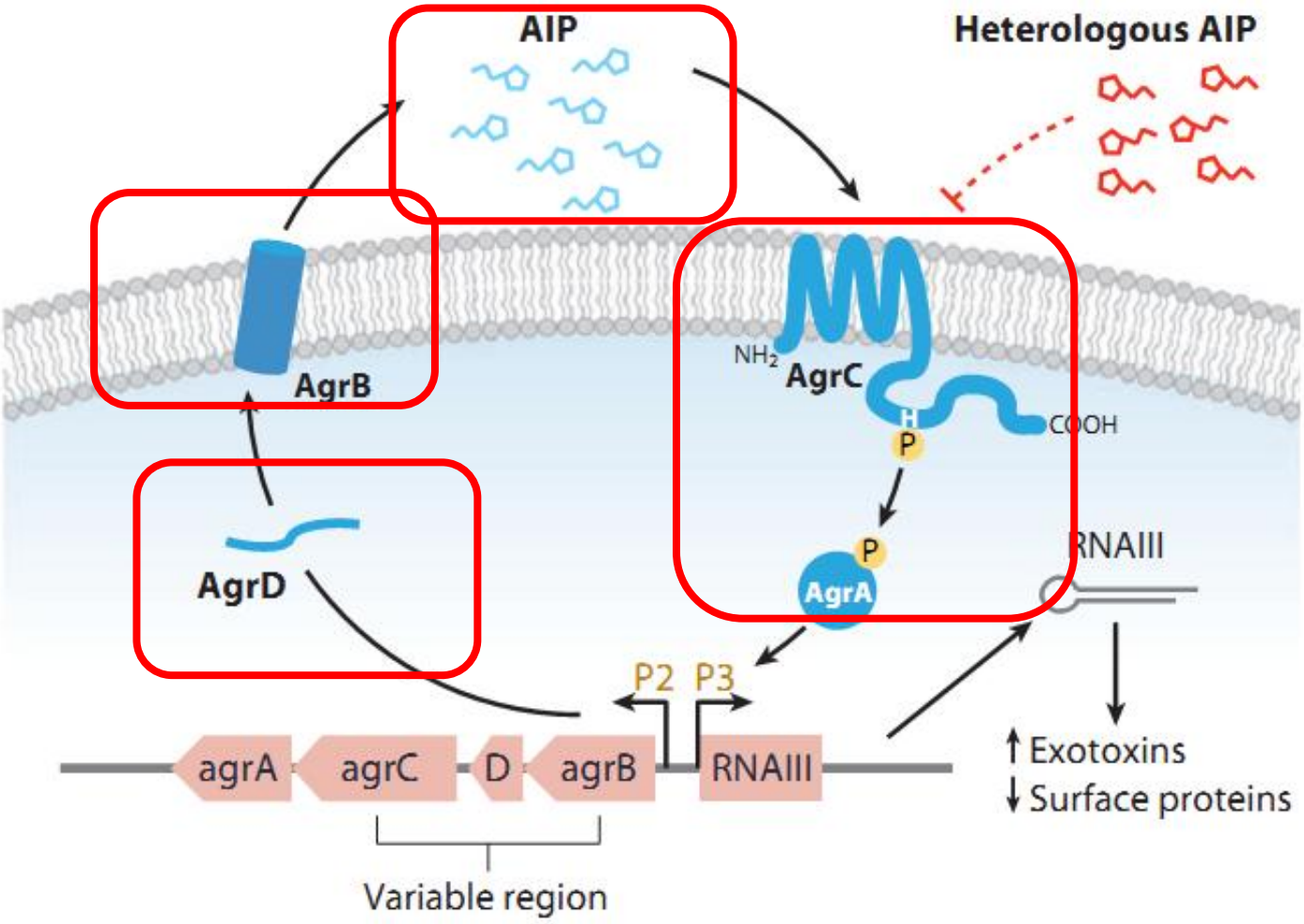
- Quorum sensing is a cell-cell communication process
- Bacteria use different architectures of chemical communication network
- Quorum sensing controls a wide spectrum phenotypes
- Quorum sensing is a attractive target for treating microbial infection

Staphylococcus aureus
Accessory gene regulator (*agr*)
quorum sensing,
two-component system

Agr two-component system

- Components of the *agr* regulatory
- *agr* in *S.aureus* pathogenesis
- Relationship with other regulator systems in *S.aureus*

Agr two-component system

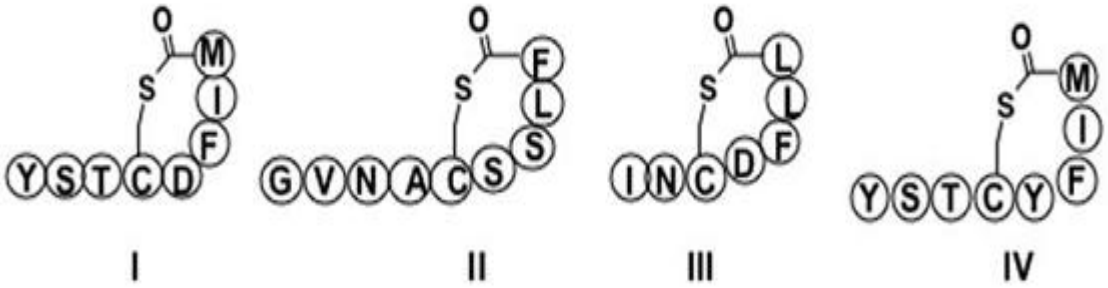


Richard P. Novick and Edward Geisinger, Annu. Rev. Genet. 2008. 42:541–64

agr two-component system

- *S. aureus* strains are classified according to the sequence of their autoinducing peptides.

AIPs of each *S. aureus* agr group



George EA,et al. Chembiochem. 2007 May 25;8(8):84

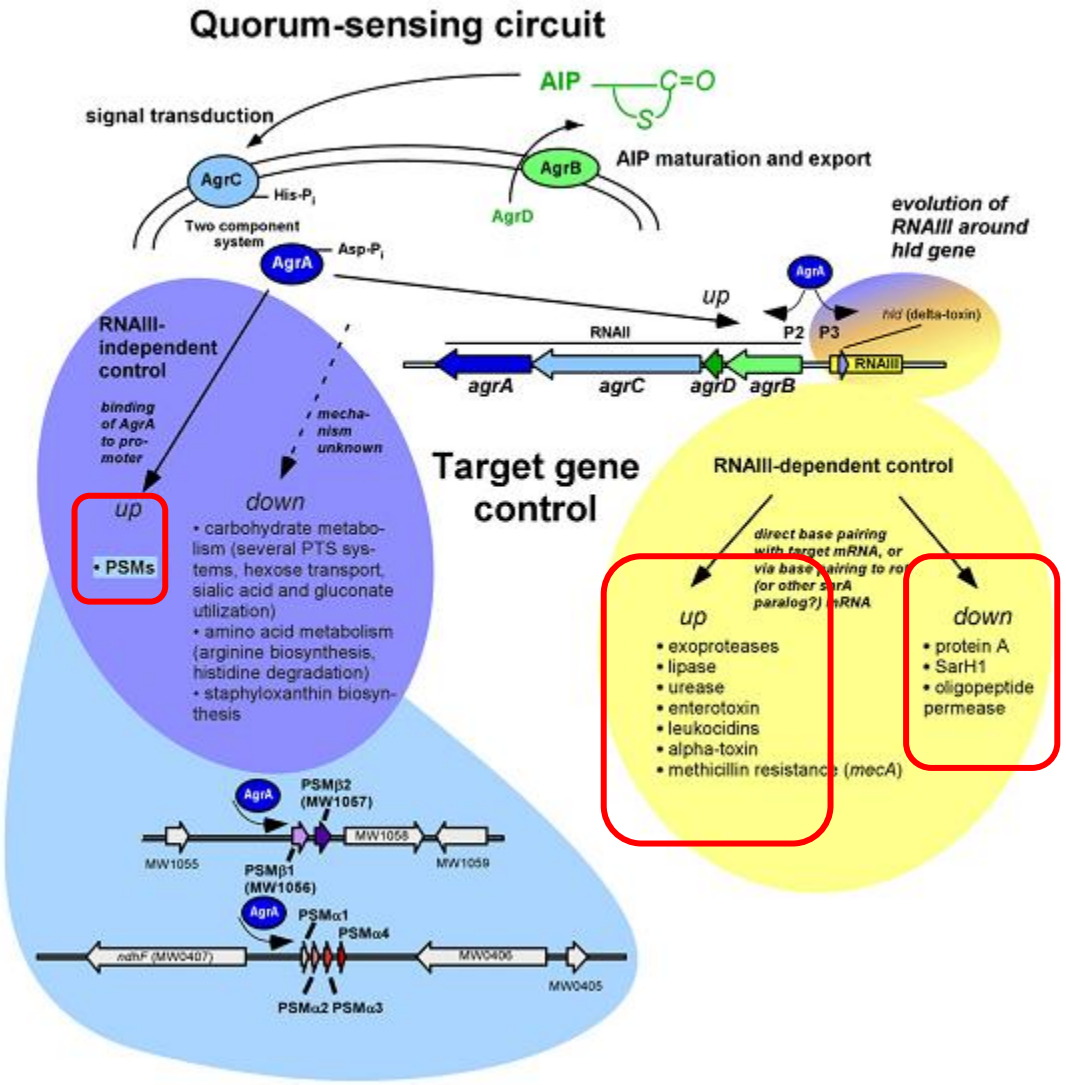
agr two-component system

- AIP of *S.aureus* altered *agr* controlled gene expression within its group and inhibits gene alteration in all the other groups
- Quorum sensing molecules of other staphylococci and other species(*P. aeruginosa*) can interference *agr* in *S.aureus*

--Harraghy N,et al.Anal Bioanal Chem. 2007 Jan;387(2):437-44

Inhibitor of *agr* to fight against *S.aureus* infections

Virulence regulation by *agr*



- > 70 virulence factors are under control by *agr*
- Down-regulation of surface virulence
- Up-regulation of secreted proteins expression
- PSM are upregulated by binding *AgrA* to *psm* promoter regions.

Shu Y. et al,. Mol Cell. 2008 October 10; 32(1): 150–158.

Agr in biofilm formation

- Recently, a report reveal that PSMs production remained constant to ascertain biofilm homeostasis, and PSMs represent key molecular factors contributing to biofilm structuring and detachment in *S. aureus*

- They also pointed out that the observed excessive biofilm thickness of *agr* mutants is the result of abnormal biofilm development, which is caused by the lack of PSM dependent biofilm structuring and control of biofilm expansion.

- Thus, Agr not only controls biofilm detachment, but also biofilm structuring.

---Boles BR, Horswill AR.PLoS Pathog. 2008 Apr 25;4(4):e1000052

Agr in biofilm formation

Treatment of *Staphylococcus aureus* Biofilm Infection by the Quorum-Sensing Inhibitor RIP[▽]

Naomi Balaban,[1]* Oscar Cirioni,[2] Andrea Giacometti,[2] Roberto Ghiselli,[3] Joel B. Braunstein,[4] Carmela Silvestri,[2] Federico Mocchegiani,[3] Vittorio Saba,[3] and Giorgio Scalise[2]

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Received 30 August 2006/Returned for modification 25 January 2007/Accepted 7 March 2007

The quorum-sensing inhibitor RIP inhibits staphylococcal TRAP/*agr* systems and both TRAP- and *agr*-negative strains are deficient in biofilm formation in vivo, indicating the importance of quorum sensing to biofilms in the host. RIP injected systemically into rats has been found to have strong activity in preventing methicillin-resistant *Staphylococcus aureus* graft infections, suggesting that RIP can be used as a therapeutic agent.

Agr in the intracellular milieu

- *agr* was shown to be active after cell internalization and to be required for endosome escape and for induction of apoptosis, therefore, *agr* is important for the intracellular survival of *S. aureus*

  --HaslingerL. B, et al. 2005. Cell Microbiol. 7:1087–97

Agr in *S.aureus* animal infections

- *agr* system of *S. aureus* is an important virulence determinant in the induction and progression of septic arthritis, osteomyelitis, endocarditis in animal model.

--Cheung, A. L.et al,. 1994. Infect. Immun. 62:1719-1725

--Gillaspy, A. F et al,. 1995.Infect. Immun.63:3373-3380

--Nilsson, I. M, et al,.1996. Infect. Immun. 64:4438-4443

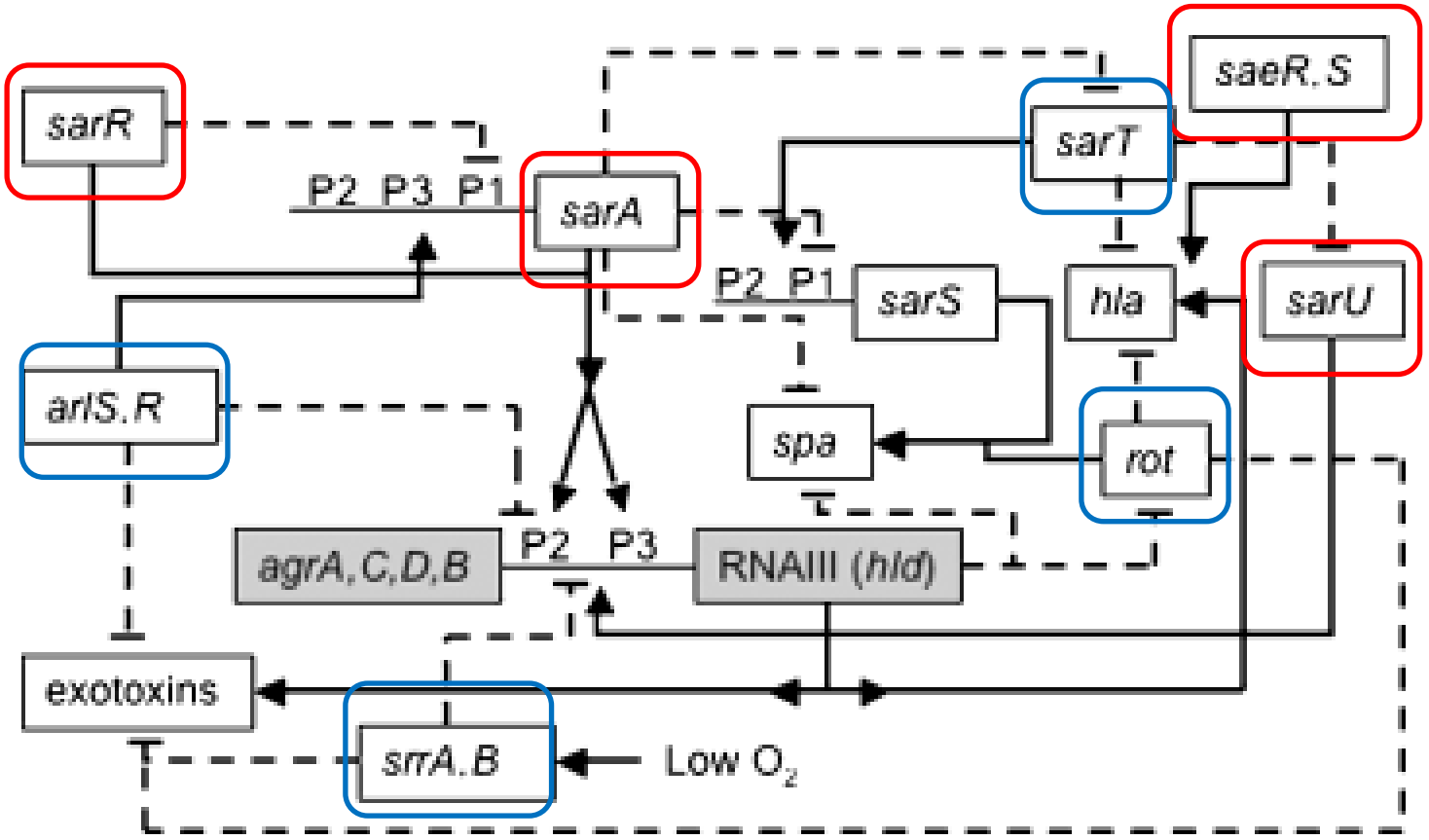
Clinical importance of *agr*

- Most clinical isolates are *agr+* strains

- *agr-* strains less pathogenic than those *agr+* strains

--Katrina E.et al,. Microbiology (2008), 154, 2265–2274

Regulator network in *S. aurues*



George EA,et al. Chembiochem. 2007 May 25;8(8):84

sarA↑, sarR↑, sarU↑ ,seaR.S ↑,sarT ↓ rot↓ arlRS↓and srrAB↓

Conclusion

- *Agr* is the most important two-component system in *S.aureus*
- *Agr* plays a crucial role in the pathogenesis of *S.aureus* infections and biofilm formation
- Inhibitor of *agr* system to treat *S.aureus* infection is promising

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Thanks for your attention