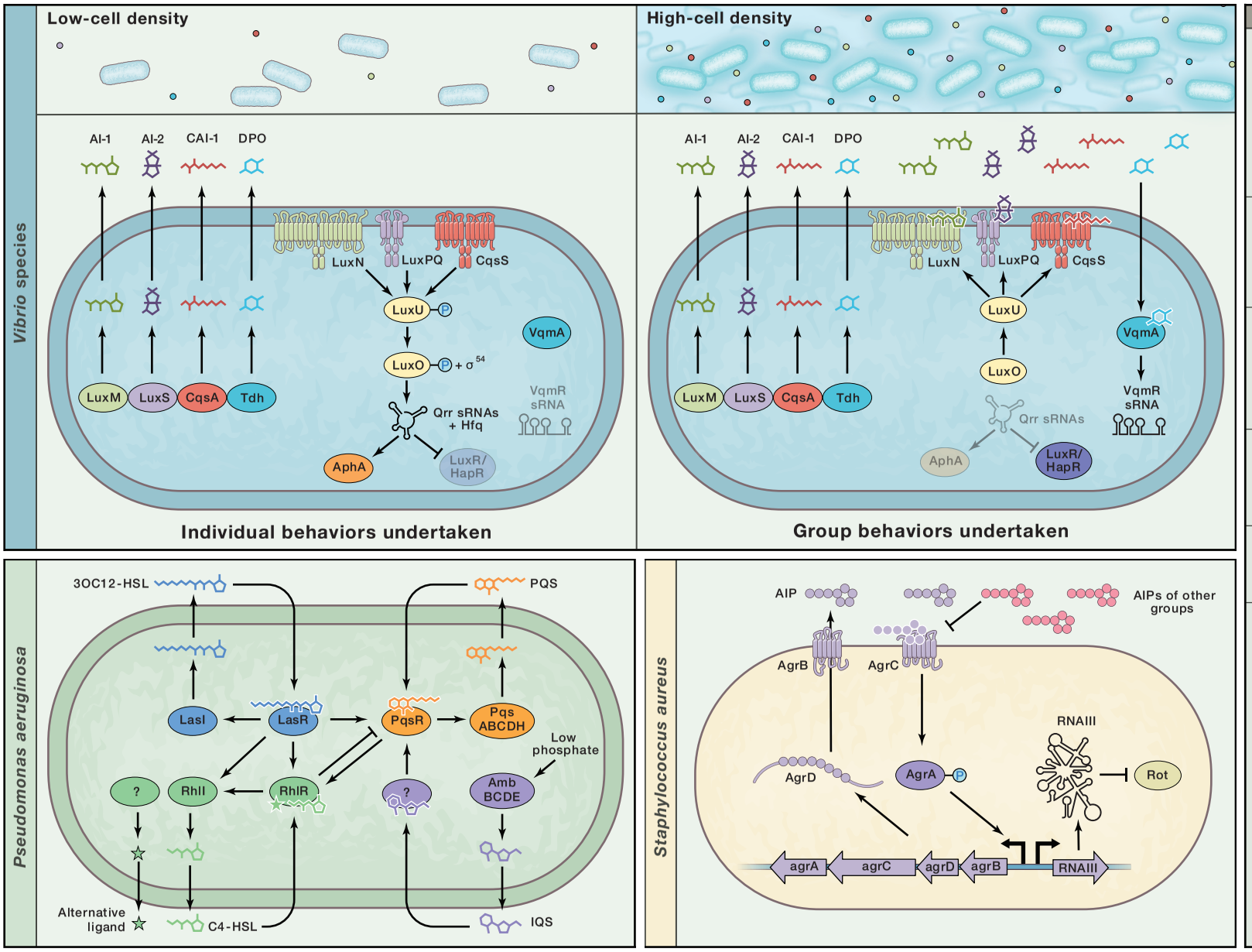
1328 Cell 174, August 23, 2018 © 2018 Elsevier Inc. DOI https://doi.org/10.1016/j.cell.2018.08.003

SnapShot: Bacterial Quorum Sensing

Michaela J. Eickhoff[1] and Bonnie L. Bassler[1,2]
[1]Department of Molecular Biology, Princeton University, Princeton, NJ, USA
[2]Howard Hughes Medical Institute, Chevy Chase, MD, USA

Cell



See online version for legends and references

SnapShot: Bacterial Quorum Sensing

Michaela J. Eickhoff[1] and Bonnie L. Bassler[1,2]
[1]Department of Molecular Biology, Princeton University, Princeton, NJ, USA
[2]Howard Hughes Medical Institute, Chevy Chase, MD, USA

Cell

Quorum sensing (QS) is a process of chemical communication that bacteria use to orchestrate group behaviors. QS involves the production, release, and population-wide detection of extracellular signaling molecules called autoinducers (AIs). QS-controlled behaviors are unproductive when undertaken by a single bacterium but become effective when performed in synchrony by the group. Such behaviors include bioluminescence, virulence factor production, biofilm formation, and release of public goods. In natural environments, bacteria live in heterogeneous populations and presumably encounter and integrate information from AIs produced by themselves, by related species, and by non-kin neighbors. Thus, blends of AIs allow bacteria to take a census of the overall cell density and species composition of the vicinal community. QS systems vary with respect to types of AIs, receptors, signal transduction mechanisms, and output regulatory responses (reviewed in Papenfort and Bassler, 2016).

Quorum Sensing in *Vibrio harveyi* and *Vibrio cholerae*

Vibrio harveyi, a model QS bacterium, uses three AIs. The LuxM, LuxS, and CqsA synthases produce AI-1 (3OHC4-homoserine lactone (HSL)), AI-2 ((2*S*,4*S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran-borate), and CAI-1 ((*Z*)-3-aminoundec-2-en-4-one), respectively. The three AIs are recognized by the receptors LuxN, LuxPQ, and CqsS, respectively. At low cell density (LCD), the receptors are kinases that transfer phosphate to LuxO via LuxU. Phospho-LuxO, with σ^{54}, activates transcription of genes encoding regulatory small RNAs (sRNAs). The sRNAs, called Qrr1-5 (Quorum Regulatory RNA), with the Hfq chaperone, activate or repress translation of target mRNAs. Importantly, they activate and repress translation of the LCD and high cell density (HCD) master regulators, AphA and LuxR, respectively. In this state, *V. harveyi* cells act as individuals. At HCD, AIs bind their receptors and phospho-flow through the circuit reverses. AphA is no longer activated, and LuxR is no longer repressed. Under this condition, *V. harveyi* cells enact collective behaviors. Hundreds of traits are controlled by this QS pathway. Most notably, bioluminescence is produced at HCD (reviewed in Papenfort and Bassler, 2016 and Svenningsen, 2018).

Vibrio cholerae, a species closely related to *V. harveyi*, uses a similar QS pathway but lacks LuxM/LuxN, CAI-1 is (*S*)-3-hydroxytridecan-4-one, there are only four Qrr sRNAs, and LuxR is called HapR. An additional QS system exists consisting of the Tdh AI synthase, an AI called DPO (3,5-dimethylpyrazin-2-ol), a cytoplasmic AI receptor called VqmA, and a sRNA called VqmR (Papenfort et al., 2017). QS activates and/or represses many genes in *V. cholerae*. Notably, at HCD, QS represses virulence factor production and biofilm formation, promoting dissemination from the host during disease.

With respect to *Vibrio* AIs, AI-1, CAI-1, and AI-2 promote intra-species, intra-genera, and inter-species communication, respectively. DPO is thought to broadly enable communication including with host microbiome bacteria.

Quorum Sensing in *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a human pathogen that uses QS to control biofilm formation and virulence factor production. There are four pathways all employing cytoplasmic AI receptors that, when liganded, act as transcription factors. The two major systems are LasI/LasR and RhlI/RhlR that produce and detect 3OC12-HSL and C4-HSL, respectively. Each receptor-ligand pair controls unique and overlapping subsets of genes. The systems function in series: LasR:3OC12-HSL activates *rhlI* and *rhlR* expression. RhlR also responds to an alternative ligand that is crucial for virulence but whose identity is unknown (Mukherjee et al., 2017). LasR:3OC12-HSL also activates expression of *pqs* genes, encoding the third QS circuit. PqsABCDH produces PQS (2-heptyl-3-hydroxy-4-quinolone), which is bound by the PqsR receptor. PqsR:PQS controls its own regulon and feeds back to activate expression of *rhlRI.* Feed-forward loops exist in all three pathways; each receptor-AI complex activates expression of its synthase gene. Additional feedback occurs through RhlR:C4-HSL inhibition of *pqsR* and *pqsABCDH.* The fourth system, AmbBCDE, produces IQS (2-(2-hydroxyphenyl)-thiazole-4-carbaldehyde) upon phosphate starvation. IQS activates the PQS system via an unknown receptor. Regulatory connections between QS systems are proposed to fine-tune the response (reviewed in Papenfort and Bassler, 2016).

Quorum Sensing in *Staphylococcus aureus*

Staphylococcus aureus uses the Agr QS system and a peptide AI called AIP (for autoinducing peptide) to control pathogenesis. AgrD is a precursor peptide for AIP. AgrB processes and exports the mature AIP, depending on the strain, into a seven to nine amino acid peptide with a five amino acid thiolactone ring. AIP activates AgrC, an autokinase receptor that transduces phosphate to AgrA. Phospho-AgrA activates expression of genes encoding the phenol-soluble modulins (a family of peptide toxins) and a gene encoding a regulatory RNA, RNAIII (reviewed in Le and Otto, 2015). RNAIII blocks translation of mRNAs encoding cell-adhesion proteins and the Rot (repressor of toxin) protein. Inhibition of Rot derepresses genes encoding exoproteins and toxins. RNAIII also activates translation of the Hla alpha-toxin. Thus, at HCD, *S. aureus* is invasive and pathogenic (reviewed in Svenningsen, 2018). Allelic variation among the AIPs enables *S. aureus* strains that activate the Agr pathway within a group to inhibit the Agr response of other groups. Interference is proposed to allow *S. aureus* strains to outcompete other invading *S. aureus* strains. A truncated AIP lacking the tail is an inhibitor of all groups (Lyon et al., 2000).

Conclusion

QS is the norm in the bacterial world and the process underpins diverse collective behaviors. Exciting questions remain concerning the diversity of QS molecules, the precise information encoded in each AI, and how bacteria decode the information contained in blends of AIs made by bacteria with whom they cooperate versus those with whom they compete. Challenges facing the field include learning how QS operates in natural environments, which are heterogeneous and fluctuate in time, space, and bacterial species composition. Future studies in 3-dimensional contexts, in the presence of flow (Kim et al., 2016), and that include other bacterial species (Thompson et al., 2015), viruses (Erez et al., 2017), and eukaryotic hosts (Ismail et al., 2016) should further transform our understanding of Earth's most ancient communication relays.

REFERENCES

Erez, Z., Steinberger-Levy, I., Shamir, M., Doron, S., Stokar-Avihail, A., Peleg, Y., Melamed, S., Leavitt, A., Savidor, A., Albeck, S., et al. (2017). Communication between viruses guides lysis-lysogeny decisions. Nature *541*, 488–493.

Ismail, A.S., Valastyan, J.S., and Bassler, B.L. (2016). A host-produced Autoinducer-2 mimic activates bacterial quorum sensing. Cell Host Microbe *19*, 470–480.

Kim, M.K., Ingremeau, F., Zhao, A., Bassler, B.L., and Stone, H.A. (2016). Local and global consequences of flow on bacterial quorum sensing. Nat. Microbiol. *1*, 15005.

Le, K.Y., and Otto, M. (2015). Quorum-sensing regulation in staphylococci-an overview. Front. Microbiol. *6*, 1174.

Lyon, G.J., Mayville, P., Muir, T.W., and Novick, R.P. (2000). Rational design of a global inhibitor of the virulence response in Staphylococcus aureus, based in part on localization of the site of inhibition to the receptor-histidine kinase, AgrC. Proc. Natl. Acad. Sci. USA *97*, 13330–13335.

Mukherjee, S., Moustafa, D., Smith, C.D., Goldberg, J.B., and Bassler, B.L. (2017). The RhlR quorum-sensing receptor controls Pseudomonas aeruginosa pathogenesis and biofilm development independently of its canonical homoserine lactone autoinducer. PLoS Pathog. *13*, e1006504.

Papenfort, K., and Bassler, B.L. (2016). Quorum sensing signal-response systems in Gram-negative bacteria. Nat. Rev. Microbiol. *14*, 576–588.

Papenfort, K., Silpe, J.E., Schramma, K.R., Cong, J.-P., Seyedsayamdost, M.R., and Bassler, B.L. (2017). A Vibrio cholerae autoinducer-receptor pair that controls biofilm formation. Nat. Chem. Biol. *13*, 551–557.

Svenningsen, S.L. (2018). Small RNA-based regulation of bacterial quorum sensing and biofilm formation. Microbiol. Spectr. *6*, 10.1128/microbiolspec.RWR-0017-2018.

Thompson, J.A., Oliveira, R.A., Djukovic, A., Ubeda, C., and Xavier, K.B. (2015). Manipulation of the quorum sensing signal AI-2 affects the antibiotic-treated gut microbiota. Cell Rep. *10*, 1861–1871.

  DOI https://doi.org/10.1016/j.cell.2018.08.003