butantan

"Quorum sensing"

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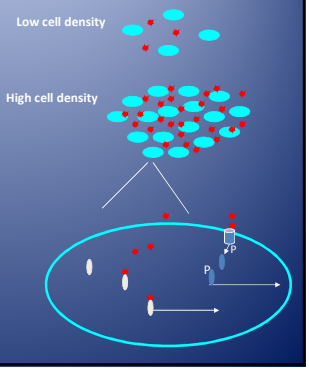
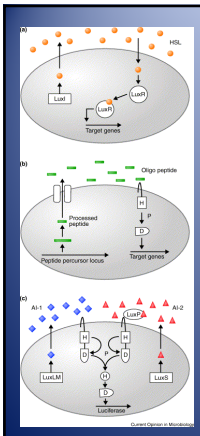
Quorum sensing PUBMED
1994- 2000 – 161 artigos
2001 – 108 artigos
2002- 147 artigos
2003 – 182 artigos
2004 – 211 artigos
2005 – 229 artigos
2006 – 312 artigos
2007 – 380 artigos
2008 - 396 artigos
2009 – 464 artigos
2010 – 458 artigos
2011 – 553 artigos
2012 – 576 artigos
2013 – 631 artigos
2014 – 652 artigos
2015 – 699 artigos
2016 - 334 artigos

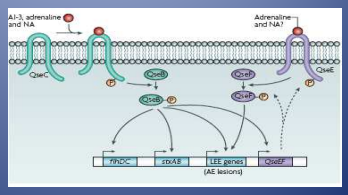
Quorum sensing

- Mecanismo pelo qual as bactérias comunicam-se umas com as outras.
- Bacterias produzem substâncias semelhantes a hormônios (autoindutores).
- Sensibilidade da população bacteriana e de outras espécies bacterianas no ambiente.
- Regulação da transcrição de diferentes genes.





Esquema ilustrativo mostrando os sistemas de quorum sensing descritos até agora na literatura. a) sistema *luxI/luxR* AI-1 descrito inicialmente em amostras de *Vibrio fischeri*. b) sistema de liberação de oligopeptídios, encontrado principalmente em amostras de bactérias Gram-positivas. c) sistema *luxS*/AI-2 descrito inicialmente em amostras de *Vibrio harveyi*. Nas amostras de *Vibrio harveyi*, além do sistema *luxS*/AI-2 ainda existe o sistema que produz AI-1 (XAVIER; BASSLER, 2003).



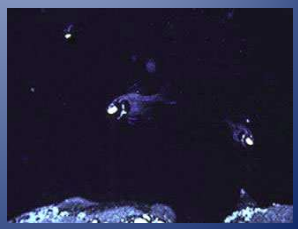
Sistema AI-3/ Epinefrina – composto aromático.

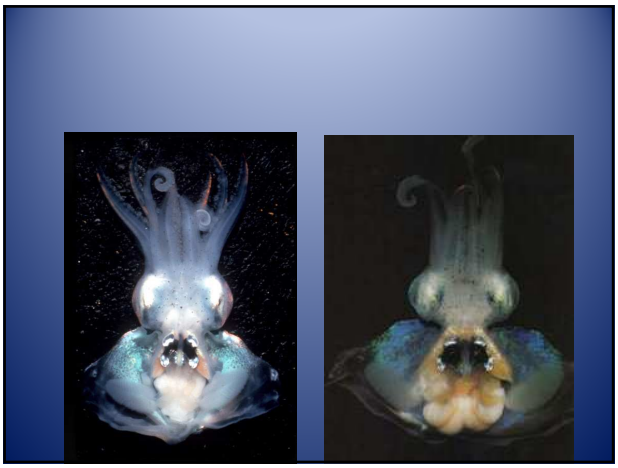
QS foi inicialmente descrito em amostras de *Vibrio fischeri*

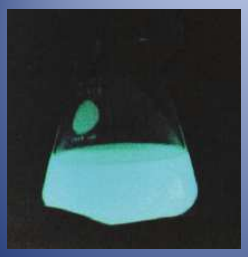
processo envolvido no controle da bioluminescência

Nealson , Platt & Hastings 1970

Quorum Sensing







Herring, P. (2002) Marine microlights: the luminous marine bacteria. *Microbiol. Today*, 29:174-176.

Cellular Control of the Synthesis and Activity of the Bacterial Luminescent System[1]

KENNETH H. NEALSON, TERRY PLATT, AND J. WOODLAND HASTINGS

Biological Laboratories, Harvard University, Cambridge, Massachusetts, 02138 and Marine Biological Laboratory, Woods Hole, Massachusetts 02534

Received for publication 30 April 1970

In bioluminescent bacteria growing in shake flasks, the enzyme luciferase has been shown to be synthesized in a relatively short burst during the period of exponential growth. The luciferase gene appears to be completely inactive in a freshly inoculated culture; the pulse of preferential luciferase synthesis which occurs later is the consequence of its activation at the level of deoxyribonucleic acid transcription which is attributed to an effect of a "conditioning" of the medium by the growing of cells. Although cells grown in a minimal medium also exhibit a similar burst of synthesis of the luminescent system, the amount of synthesis is quantitatively less, relative to cell mass. Under such conditions, added arginine results in a striking stimulation of bioluminescence. This is attributed to a stimulation of existing patterns of synthesis and not to induction or derepression per se.

Nealson, K.H.; Platt, T.; Hastings, J. W. (1970) Cellular control of the synthesis And activity of the bacterial luminescence system. *J. Bacteriol.*, 104:313–322.

1981 Structure of the signal determined

Biochemistry 1981 Apr 28;20(9):2444-9

Structural identification of autoinducer of *Photobacterium fischeri* luciferase.

Eberhard A, Burlingame AL, Eberhard C, Kenyon GL, Nealson KH, Oppenheimer NJ.

Synthesis of bacterial luciferase in some strains of luminous bacteria requires a threshold concentration of an autoinducer synthesized by the bacteria and excreted into the medium. Autoinducer excreted by *Photobacterium fischeri* strain MJ-1 was isolated from the cell-free medium by extraction with ethyl acetate, evaporation of solvent, workup with ethanol-water mixtures, and silica gel chromatography, followed by normal-phase and then reverse-phase high-performance liquid chromatography. The final product was greater than 99% pure. The structure of the autoinducer as determined by high-resolution 1H nuclear magnetic resonance spectroscopy, infrared spectroscopy, and high-resolution mass spectrometry was N-(3-oxohexanoly)-3-aminodihydro-2(3H)-furanone [or N-(beta-ketocaproyl)homoserine lactone]. The formation of homoserine by hydroly racemate, was prepared by coupling homoserine lactone to the ethylene glycol ketal of sodium 3-oxohexanoate, followed by mildly acidic removal of the protecting group; this synthetic material showed the appropriate biological activity.

1983 Genetic analysis and regulatory model

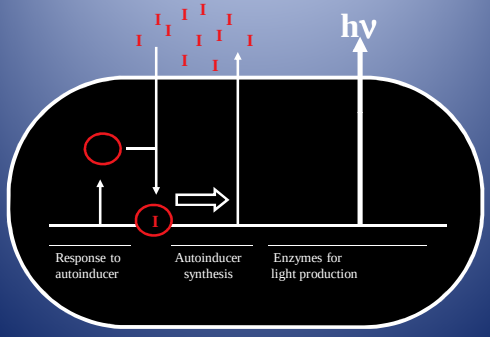
Cell 1983 March; 32:773-781

Bacterial bioluminescence: isolation and genetic analysis of functions from *Vibrio fischeri*.

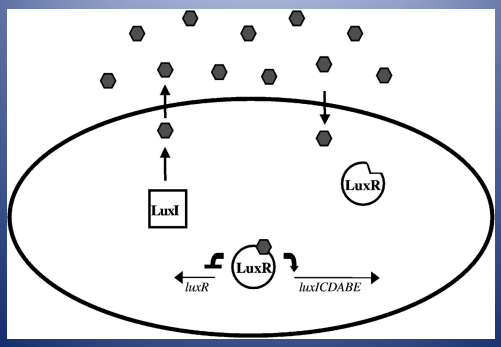
Engebrecht J, Nealson K, Silverman M.

Recombinant *E. coli* that produce light were found in a clone library of hybrid plasmids containing DNA from the marine bacterium *Vibrio fischeri*. All luminescent clones had a 16 kb insert that encoded enzymatic activities for the light reaction as well as regulatory functions necessary for expression of the luminescence phenotype (Lux). Mutants generated by transposons Tn5 and mini-Mu were used to define Lux functions and to determine the genetic organization of the *lux* region. Regulatory and enzymatic functions were assigned to regions of two *lux* operons. With transcriptional fusions between the *lacZ* gene or transposon mini-Mu and the target gene, expression of *lux* operons could be measured in the absence of light production. The direction of transcription of *lux* operons was deduced from the orientation of mini-Mu insertions in the fusion plasmids. Induction of transcription of one *lux* operon required a function encoded by that operon (autoregulation). From these and other regulatory relationships, we propose a model for genetic control of light production.

Regulatory Model from Engebrecht et al. 1983



Regulatory Model from Miller y Bassler 2002



1994: Primeiro trabalho abordando o tema. Primeira vez na literatura que aparece o termo quorum sensing

Fuqua, W.C.; Winans, S.C.; Greenberg, E.P. (1994) Quorum sensing in bacteria: the LuxR-LuxI family of cell density-responsive transcriptional regulators. *J. Bacteriol.*, 176:269-275.

Exemplos de bacterias que utilizam acil homoserina lactonas

Bacteria	Function
Vibrio fischeri	luminescence
Aeromonas hydrophila	proteases
Agrobacterium tumefaciens	conjugation
Burkholderia cepacia	siderophores
Chromobacterium violaceum	antibiotics
Erwinia chrysanthemi	pectinase
Pseudomonas aereofaciens	phenazines
Pseudomonas aeruginosa	biofilms, etc
Rhizobium etli	number of nodules
Yersinia pseudotuberculosis	agreggation and motility

Applied and Environmental Microbiology, Apr. 2006, p. 2295–2297 Vol. 72, No. 4
0099-2240/06/$08.00+0 doi:10.1128/AEM.72.4.2295–2297.2006

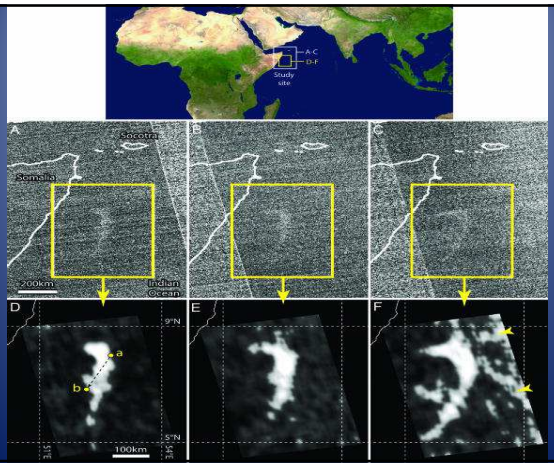
GUEST COMMENTARY

Quorum Sensing on a Global Scale: Massive Numbers of Bioluminescent Bacteria Make Milky Seas

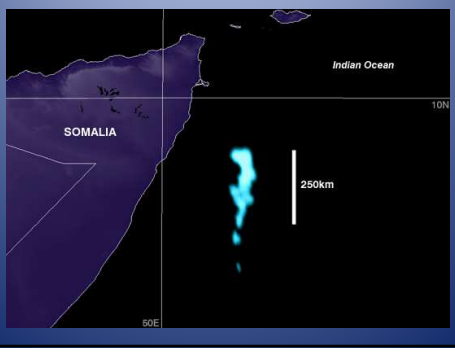
Kenneth H. Nealson[1] and J. Woodland Hastings[2]*

Detection of a bioluminescent milky sea from space

Steven D. Miller,*† Steven H. D. Haddock,‡ Christopher D. Elvidge,§ and Thomas F. Lee*
*Marine Meteorology Division, Naval Research Laboratory, 7 Grace Hopper Avenue, MS #2, Monterey, CA 93943; ‡Monterey Bay Aquarium Research Institute, 7700 Sandholdt Road, Moss Landing, CA 95039; and §National Geophysical Data Center, Boulder, CO 80303
† To whom correspondence should be addressed. E-mail: miller@nrlmry.navy.mil .
Proc Natl Acad Sci U S A. 2005 October 4; 102(40): 14181–14184



Tales of Milky Seas



JOURNAL OF BACTERIOLOGY,
0021-9193/97/$04.0010
June 1997, p. 4043–4045 Vol. 179, No. 12

Cross-Species Induction of Luminescence in the Quorum- Sensing Bacterium *Vibrio harveyi*

BONNIE L. BASSLER,1* E. PETER GREENBERG,2 AND ANN M. STEVENS3
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Microbiology, University of Iowa, Iowa City, Iowa 522422; and Department of Biology, Virginia Polytechnic
Institute and State University, Blacksburg, Virginia 240613
Received 29 January 1997/Accepted 16 April 1997

Different species of bacteria were tested for production of extracellular autoinducer-like activities that could stimulate the expression of the luminescence genes in *Vibrio harveyi*. Several species of bacteria, including the pathogens *Vibrio cholerae* and *Vibrio parahaemolyticus*, were found to produce such activities. Possible physiological

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 1639–1644, February 1999
Microbiology

Quorum sensing in *Escherichia coli*, *Salmonella typhimurium*, and *Vibrio harveyi*: A new family of genes responsible for autoinducer production

MICHAEL G. SURETTE*, MELISSA B. MILLER†, AND BONNIE L. BASSLER†‡
*Department of Microbiology and Infectious Diseases, University of Calgary, 3330 Hospital Drive, North West, Calgary, Alberta, T2N-4N1, Canada; and
†Department of Molecular Biology, Princeton University, Princeton, NJ 08544-1014
Communicated by M. J. Osborn, University of Connecticut, Health Center, Farmington, CT, December 21, 1998 (received for review

Quorum sensing controls expression of the type III secretion gene transcription and protein secretion in enterohemorrhagic and enteropathogenic Escherichia coli

Vanessa Sperandio, Jay L. Mellies, William Nguyen, Sooan Shin, and James B. Kaper*
Center for Vaccine Development and Department of Microbiology and Immunology, University of Maryland School of Medicine, 685 West Baltimore Street,
Baltimore, MD 21201
Communicated by Harley W. Moon, Iowa State University, Ames, IA, October 19, 1999 (received for review August 13, 1999)

Structural identification of a bacterial quorum-sensing signal containing boron

Xin Chen*, Stephan Schauder*, Noelle Potier[2], Alain Van Dorsselaer[2], IstvaÂn Pelczer[3], Bonnie L. Bassler* & Frederick M. Hughson*

* Department of Molecular Biology; and [3] Department of Chemistry, Princeton University, Princeton, New Jersey 08544-1014, USA
[2] Laboratoire de Spectrometrie de Masse Bio-Organique, Ecole de Chimie, Polymeres et Materiaux, 25 Rue Becquerel, 67087 Strasbourg, France

Bacteria–host communication: The language of hormones

Vanessa Sperandio*†, Alfredo G. Torres‡§, Bruce Jarvis¶, James P. Nataro§, and James B. Kaper‡§

*Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9048; Departments of ‡Microbiology and Immunology
and Pediatrics, and §Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD 21201; and ¶Department of Chemistry
and Biochemistry, University of Maryland, College Park, MD 20742
Edited by Harley W. Moon, Iowa State University, Ames, IA, and approved May 20, 2003 (received for review November 21, 2002)

Salmonella typhimurium Recognizes a Chemically Distinct Form of the Bacterial Quorum-Sensing Signal AI-2.

Molecular Cell, 2004 Volume 15, Issue 5, Pages 677-687
S. Miller, K. Xavier, S. Campagna, M. Taga, M. Semmelhack, B. Bassler, F. Hughson

Mol Microbiol. 1997 Jun;24(5):895-904.

Quorum sensing by peptide pheromones and two-component signal-transduction systems in Gram-positive bacteria.

Kleerebezem M, Quadri LE, Kuipers OP, de Vos WM.
Department of Biophysical Chemistry, NIZO, Ede, The Netherlands. kleerebe@nizo.nl

J Bacteriol. 2001 Jul;183(14):4210-6.

Indole can act as an extracellular signal in Escherichia coli.

Wang D, Ding X, Rather PN.
Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA.

Bull Math Biol. 2001 Jan;63(1):95-116.

A mathematical model for quorum sensing in Pseudomonas aeruginosa.

Dockery JD, Keener JP.
Department of Mathematics, Montana State University, Bozeman, MT 59718, USA.
umsfjdoc@math.montana.edu

The bacteria Pseudomonas aeruginosa use the size and density of their colonies to regulate the production of a large variety of substances, including toxins. This phenomenon, called quorum sensing, apparently enables colonies to grow to sufficient size undetected by the immune system of the host organism. In this paper, we present a mathematical model of quorum sensing in P. aeruginosa that is based on the known biochemistry of regulation of the autoinducer that is crucial to this signalling mechanism. Using this model we show that quorum sensing works because of a biochemical switch between two stable steady solutions, one with low levels of autoinducer and one with high levels of autoinducer.
PMID: 11146885 [PubMed - indexed for MEDLINE]

The QseC sensor kinase: A bacterial adrenergic receptor

Marcie B. Clarke*, David T. Hughes*, Chengru Zhu†, Edgar C. Boedeker†, and Vanessa Sperandio*‡
*Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9048; and †Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD 21201
Communicated by Steven L. McKnight, University of Texas Southwestern Medical Center, Dallas, TX, May 27, 2006 (received for review February 14, 2006)

Social cheating in *Pseudomonas aeruginosa* quorum sensing

Kelsi M. Sandoz*, Shelby M. Mitzimberg†, and Martin Schuster‡‡
Departments of *Biomedical Sciences and †Microbiology, Oregon State University, Corvallis, OR 97331
Edited by E. Peter Greenberg, University of Washington School of Medicine, Seattle, WA, and approved August 13, 2007 (received for review June 15, 2007)

Targeting QseC Signaling and Virulence for Antibiotic Development

David A. Rasko,1* Cristiano G. Moreira,1 De Run Li,2 Nicola C. Reading,1 Jennifer M. Ritchie,3 Matthew K. Waldor,3 Noelle Williams,2 Ron Taussig,4 Shuguang Wei,2 Michael Roth,2 David T. Hughes,1 Jason F. Huntley,1 Maggy W. Fina,4 John R. Falck,2,4 and Vanessa Sperandio1,2†

Science ,2008

Peroxisome Proliferator-Activated Receptors Mediate Host Cell Proinflammatory Responses to *Pseudomonas aeruginosa Autoinducer*

Aruna Jahoor,1 Rashila Patel,2 Amanda Bryan,1 Catherine Do,2 Jay Krier,2 Chase Watters,1 Walter Wahli,3 Guigen Li,4 Simon C. Williams,1* and Kendra P. Rumbaugh2*
Departments of Cell Biology and Biochemistry1 and Surgery,2 Texas Tech University Health Sciences Center, Lubbock, Texas 79430;

Center for Integrative Genomics and National Research Center Frontiers in Genetics, University of Lausanne, CH-1015 Lausanne,
Switzerland3; and Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 794094

JOURNAL OF BACTERIOLOGY, July 2008, p. 4408–4415

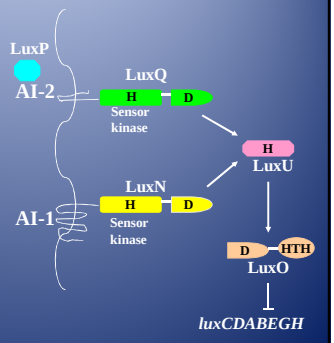
QS foi inicialmente descrito em amostras de *Vibrio fischeri*

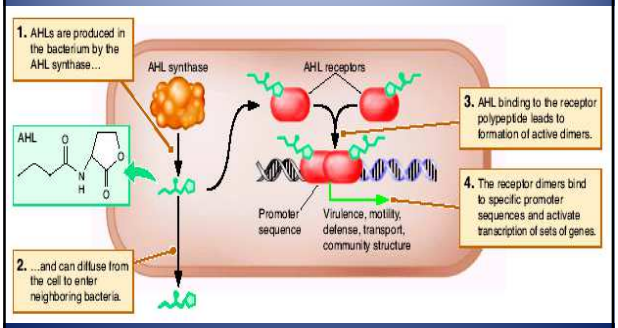
processo envolvido no controle da bioluminescência

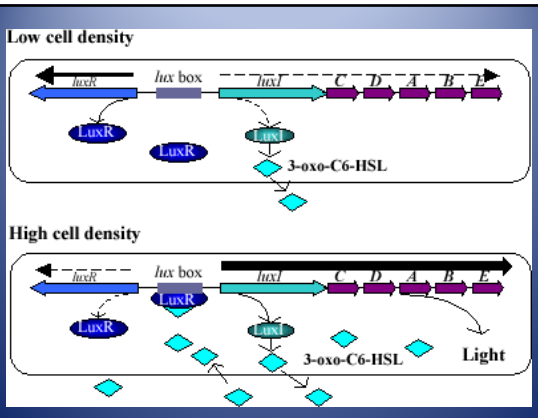
Nealson & Hastings 1970

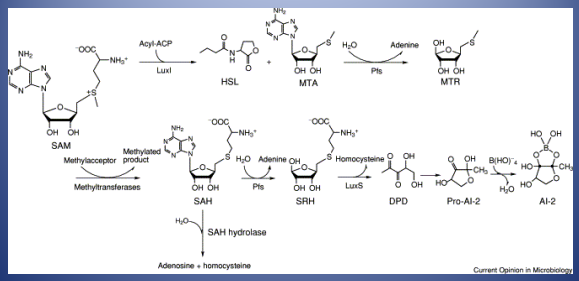
Vibrio harveyi quorum sensing systems

- **Sistema-1**
  - -Autoindutor-1 AI-1 (acil-homoserina-lactona)
  - -comunicação Intra-específica
- **Sistema-2**
  - -Autoindutor-2 AI-2
  - -comunicação interespecífica
  - -Presente em *E. coli, V. cholerae, Salmonella, Streptococci,* etc...
  - -Gene *luxS* responsável pela síntese de AI-2

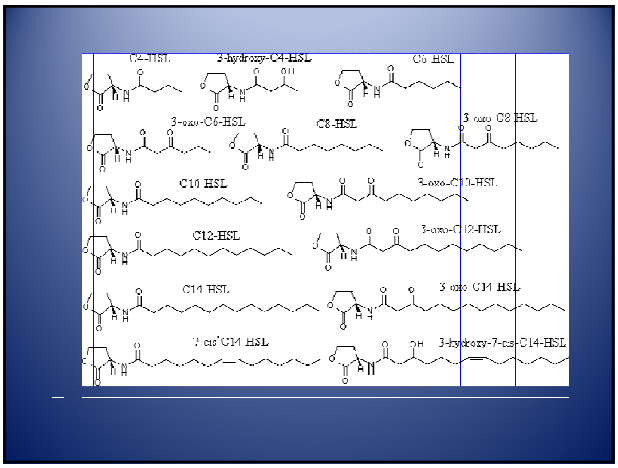




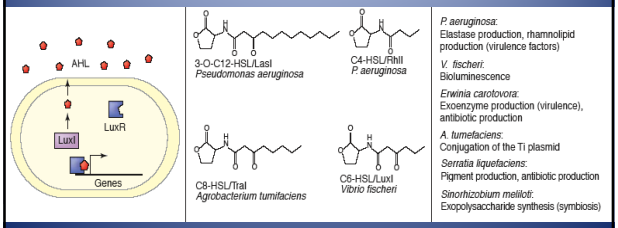




Via biossintetica para formação de homoserina lactona e AI-2. Tanto HSL como AI-2 são derivados de S- adenosil metionina (SAM) (XAVIER; BASSLER, 2003).



Outros exemplos



Henke, J.M. & Bassler, B.L. (2004) Bacterial social engagements. *Trends Cell Biol.*, 14:648-656.

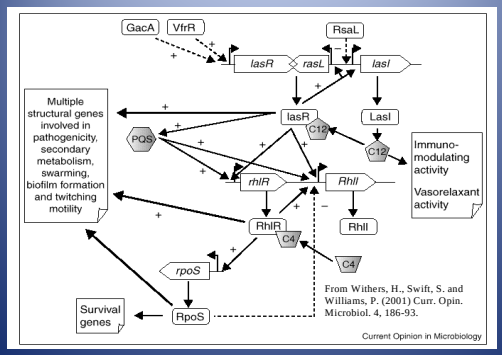
Bacterium	LuxR/I homologues with links to Swissprot	GenBank Accsession Number	Major AHL	Phenotype	Reference
Aeromonas hydrophila	AhyR, AhyI	X89469	C4-HSL	Extracellular protease, biofilm formation	Swift *et al* 1997, 1999b,c; Lynch *et al* 1999
Aeromonas salmonicida	AsaR, AsaI	U65741	C4-HSL	Extracellular protease	Swift *et al* 1997
Agrobacterium tumefaciens	TraR, TraI	L17024, L22207	3-oxo-C8-HSL	Conjugation	Fuqua *et al* 1994; Piper *et al* 1999;
Burkholderia cepacia	CepR, CepI	AF330018, AF330012	C8-HSL	Protease, siderophore	Lewenza *et al* 1999
Chromobacterium violaceum	CviR, CviI	no link available	C6-HSL	Antibiotics, violacein, exoenzymes, cyanide	McClean *et al* 1997; Chernin *et al* 1998
Enterobacter agglomerans	EagR, EagI	X74300	3-oxo-C6-HSL	Unknown	Swift *et al* 1993

Erwinia carotovora Subsp *carotovora*	CarR, ExpR ExpI, CarI	X74299 X80475 X72891	3-oxo-C6-HSL	Carbapenem antibiotic, exoenzymes	Bainton *et al* 1992, Swift *et al* 1993; Pirhonen *et al* 1993
Erwinia chrysanthemi	ExpR, ExpI (EchR, EchI)	X96440	3-oxo-C6-HSL	Pectinases	Nasser *et al* 1998
Escherichia coli	SdiA	AE005414	Unknown	Cell division	Sitnikov *et al* 1996
Nitrosomas europaea	Unknown	-	3-oxo-C6-HSL	Emergence from lag phase	Batchelor *et al* 1997
Obesumbacterium proteus	OprR, OprI	no link available	3-oxo-C6-HSL	Unknown	Swift *et al* 1999
Pantoea stewartii	EsaR, EsaI	L32183, L32184	3-oxo-C6-HSL	Exopolysaccharide	Beck von Bodman & Farrand 1995

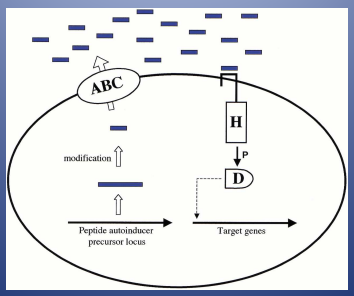
Pseudomonas aeruginosa	LasR, LasI	M59425	3-oxo-C12-HSL	Exoenzymes, Xcp, biofilm formation, RhlR, cell-cell spacing.	Chapon-Hervé *et al* 1997, Gambello & Iglewski 1991, Passador *et al* 1993, Glessner *et al* 1999
	RhlR, RhlI (VsmR, VsmI)	L08962, U11811, U15644	C4-HSL	Exoenzymes, cyanide, RpoS, lectins, pyocyanin, rhamnolipid, type 4 pili.	Latifi *et al* 1995, 1996; Winson *et al* 1995, Pearson *et al* 1997, Glessner *et al* 1999.
Pseudomonas aureofaciens	PhzR, PhzI	L32729, L33724	C6-HSL	Phenazine antibiotic	Pierson *et al* 1994, Wood *et al* 1997
Pseudomonas fluorescens	PhzR, PhzI	L48616	Unknown	Phenazine antibiotic	Shaw *et al* 1997
Pseudomonas syringae pv. *tabaci*	PsyR, PsyI	U39802	Unknown	Unknown	Swift *et al* 1999

Ralstonia solanacearum	SolR, SolI	AF021840	C8-HSL	Unknown	Flavier *et al* 1997
Rhizobium etli	RaiR, RaiI	U92713	Unknown	Restriction of nodule number	Gray *et al* 1996, Rosemeyer *et al* 1998
Rhizobium leguminosarum	RhiR	M98835	3-hydroxy-7-*cis*-C14-HSL	Nodulation, bacteriocin, stationary phase survival	Gray 1997, Rodelas *et al* 1999, Thorne and Williams 1999
Rhodobacter sphaeroides	CerR, CerI	AF016298	7-*cis*-C14-HSL	Community escape	Puskas *et al* 1997
Serratia liquefaciens	SwrR, SwrI	U22823	C4-HSL	Swarming, protease	Eberl *et al* 1996, Givskov *et al* 1997, Lindum *et al* 1998

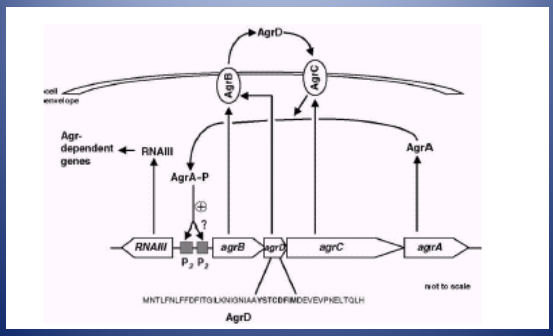
Vibrio anguillarum	VanR, VanI	U69677	3-oxo-C10-HSL	Unknown	Milton *et al* 1997
Vibrio fischeri	LuxR, LuxI	M19039 M96844 M25752	3-oxo-C6-HSL	Bioluminescence	
Xenorhabdus nematophilus	Unknown	-	3-hydroxy-C4-HSL or an agonist	Virulence, bacterial lipase	Dunphy *et al* 1997
Yersinia enterocolitica	YenR, YenI	X76082	C6-HSL	Unknown	Throup *et al* 1995
Yersinia pestis	YpeR, YpeI	AF071401	Unknown	Unknown	Swift *et al* 1999a,b
Yersinia pseudotuberculosis	YpsR, YpsI	AF079973	3-oxo-C6-HSL	Motility, clumping	Atkinson *et al* 1999
	YtbR, YtbI	AF079136	C8-HSL	Unknown	Atkinson *et al* 1999
Yersinia ruckeri	YukR, YukI	AF079135	Unknown	Unknown	Atkinson *et al* 1999



Quorum Sensing in Gram(+): The Signals are Peptides



Quorum sensing e a virulência de *Staphylococcus aureus*



Podbielski, A. & Kreikemeyer, B. (2004) Cell density - dependent regulation: basic principles and effects on the virulence of Gram-positive cocci. *Int. J. Infect. Dis.*, 8:81-95.

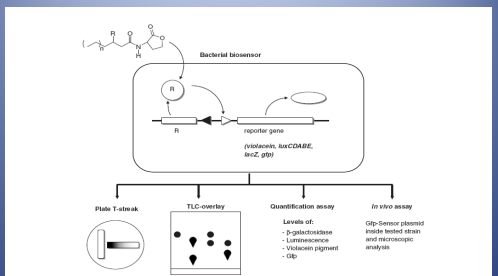
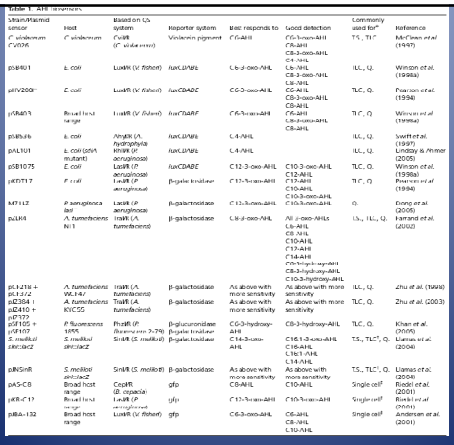


Fig. 1. Construction and use of a bacterial AHL biosensor. At the top of the diagram, the structure of AHLs is shown. The letter 'R' refers to the moiety at position C3, which can be either unmodified or carries an oxo- or hydroxyl group. The letter 'n' refers to the length of the acyl chain, which is most commonly from 4 to 12 and in some cases bacteria can produce AHLs having chains of 14 to 18 carbons. The exogenous AHL interacts with a LuxR family protein inside the bacterial biosensor (non-AHL producer), which results in the transcription of a reporter gene(s) from a LuxR family-AHL regulated promoter as shown by the open triangle. The LuxR family gene is usually expressed from a constitutive promoter as shown with a filled triangle. The AHL biosensor can then be used in (i) a plate 'T' streak assay, resulting in the expression of the reporter phenotype in a gradient near the tested strain as indicated, (ii) a TLC overlay technique after separation of AHLs from a bacterial extract resulting in the detection of the reporter phenotype at the place where AHLs are found, (iii) a quantification assay by measuring levels of the reporter phenotype upon exposure to spent bacterial supernatants or bacterial organic extracts and (iv) an *in vivo* assay using gfp-based biosensors. See text for all details.



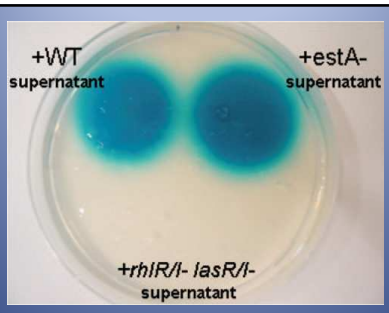


FIG. 3. *Agrobacterium tumefaciens*-based bioassay for autoinducer (AI) detection in culture supernatants of *P. aeruginosa*. Tested were wild-type (WT) *P. aeruginosa* PAO1 and the *estA*-negative mutant for the presence of AIs, and an AI-deficient mutant (*rhlRI* and *lasRI* deficient) served as a negative control. Shown is the *A. tumefaciens*based bioassay, where the formation of blue halos confirmed the presence of AI molecules

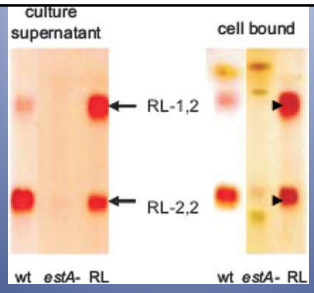
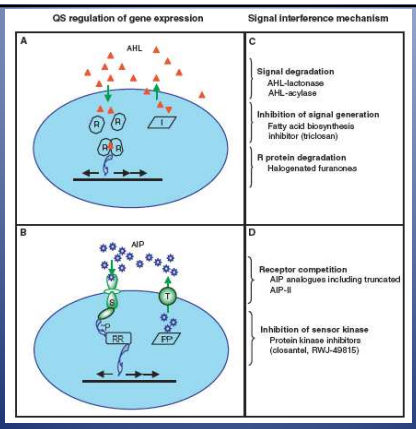


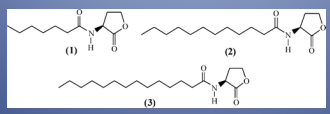
FIG. 2. TLC separation of extracellular and cell-bound rhamnolipids from *P. aeruginosa*. *P. aeruginosa* PAO1 (wild type [wt]) and the *estA*-negative mutant (*estA*-) were examined for rhamnolipid production. Rhamnolipids were extracted from cultures which were grown for 48 h in PPGAS medium. The rhamnolipid standard (RL) was purified from *P. aeruginosa*. Rhamnolipids were separated by TLC and stained with a reagent containing orcinol and sulfuric acid in ethanol.



Zhang, L.H. and Dong, Y.H. (2004) Quorum sensing and signal interference: diverse implications. *Mol. Microbiol.*, 53:1563-1571.

N-acyl-homoserine lactones from Enterobacter sakazakii (Cronobacter spp.) and their degradation by Bacillus cereus enzymes.

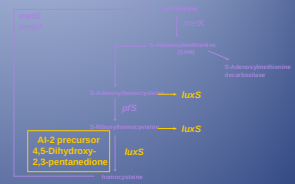
Araújo FD, Esper LM, Kuaye AY, **Sircili MP**, Marsaioli AJ.
J Agric Food Chem. 2012 Jan 18;60(2):585-92.

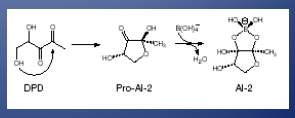


(*S*)-*N*-Acyl-homoserine lactones identified in *E. sakazakii* (*Cronobacter* spp.) extracts: (*S*)-*N*-heptanoyl-HSL (**1**), (*S*)-*N*-dodecanoyl-HSL (**2**) and (*S*)-*N*-tetradecanoyl-HSL (**3**).

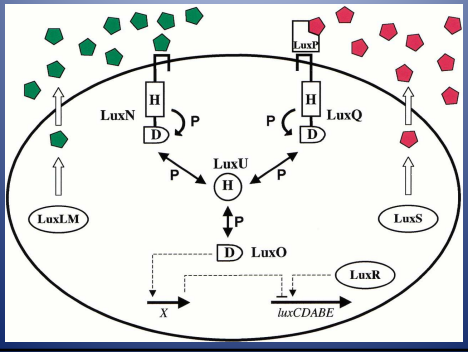
SISTEMA LuxS /AI-2

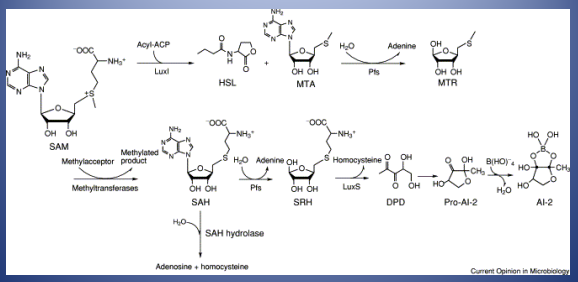
- Amplamente distribuído em espécies bacterianas, tanto gram- negativas, como gram-positivas.
- AI-2 é uma molécula de furanosil diester com um átomo de boro
- Sintetizada pela enzima LuxS (envolvida na detoxificação de S-adenosil-metionina)





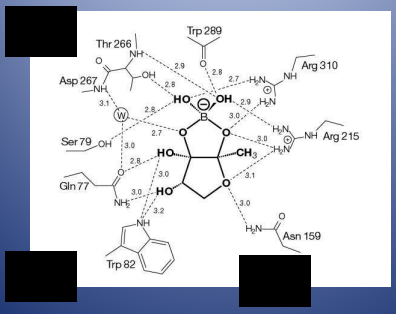
Variations and Complications : *Vibrio harveyi*

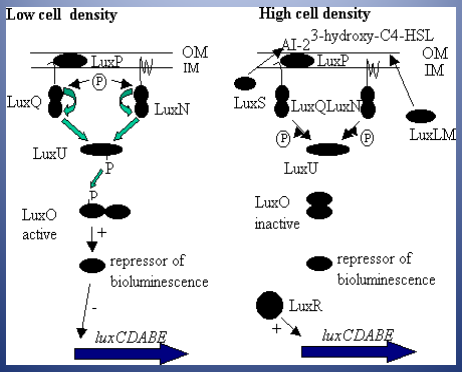


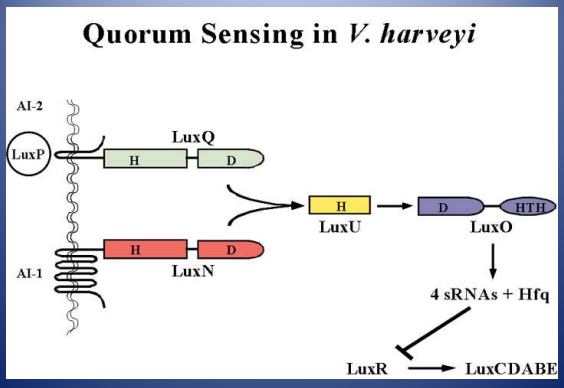


Via biossíntetica para formação de homoserina lactona e AI-2. Tanto HSL como AI-2 são derivados de S- adenosil metionina (SAM) (XAVIER; BASSLER, 2003).

LuxS is “quasiuniversal”







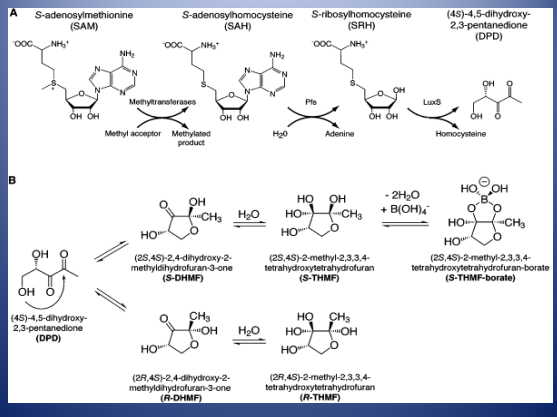


Table 1. Genes and functions controlled by LuxS in bacteria.

Species	Functions regulated by *luxS*	Genes regulated by *luxS*	References
Actinobacillus actinomycetemcomitans	Virulence factors: leukotoxin, iron acquisition	*sigA*	[28•]
Borrelia burgdorferi	Expression of many putative cell-membrane-associated lipoproteins including OspA, -B and -N proteins		[15•]
Campylobacter jejuni	Motility		[21]
Clostridium perfringens	Virulence factors: alpha, kappa and theta toxins	*pfo*	[14••]
Escherichia coli W2110	Cell division, DNA processing, cell shape and morphology	242 genes (microarray)	[22••]
Escherichia coli EHEC (O157:H7)	Virulence factors: type III secretion, Shiga toxin, flagella, motility, cell division	LEE operon, *stx*, *grlrA*, *ambA*, *fliD*, *fliA*, *flhC*, *envZ*, *qseA*, *qseBC* 40% genes (microarray)	[23–25]
Escherichia coli EPEC (O127:H6)	Motility (flagella expression)		[26]
Neisseria meningitidis	Bacteraemic infection		[27]
Photorhabdus luminescens	Cytotoxin biosynthesis	*cpsx*	[4•]
Porphyromonas gingivalis	Virulence factors: protease, hemagglutinin activities, lactic acid production	*mfa1*, *hagA*	[29•,28,29]
Salmonella typhi	Biofilms		[30]
Salmonella typhimurium	AI-2 ABC transport system	*lsrACDBFGE*	[19••]
Shigella flexneri	Transcription factor involved in controlling virulence	*virB*	[31]
Streptococcus pyogenes	Virulence factors: secreted protease, hemolysin	*speB* and *sagA*	[32••]
Vibrio cholerae	Virulence Factors: Cholera toxin, toxin-coregulated pilus	*tcpP*, *tcpA*, *aphB*	[9••,33•]
Vibrio harveyi	Light production, colony morphology, siderophore production	~70 virulence genes (quiescent) *luxCDABE*	[12,13,34]

EHEC, enterohemorrhagic *E. coli*; EPEC, enteropathogenic *E. coli*.

Bacterial species	QS system	Autoinducer(s)	Regulated phenotype(s)
EHEC and EPEC	Qse/LuxS	AI-3	TTS, flagella, and motility
	Lsr/LuxS	AI-2 (*R*-THMF)[a]	AI-2 uptake by Lsr
	SdiA	AHLs (not self-produced)	?
Salmonella sp.	Qse/LuxS	AI-3	?
	Lsr/LuxS	AI-2 (*R*-THMF)	AI-2 uptake by Lsr; biofilm formation?
	SdiA	AHLs (not self-produced)	Resistance to human complement (Rck)
Vibrio cholerae	System 1 (CqsA/CqsS)	CAI-1	TCP, CT, HA protease, biofilm
	System 2 (LuxS)	AI-2 (furanosyl-borate diester?)	TCP, CT, HA protease, biofilm
	System 3	?	?
EAEC	Qse/LuxS	AI-3	?
	Lsr/LuxS	AI-2 (*R*-THMF)	?
	SdiA	AHLs (not self-produced)	?
	Other?	?	AggR-regulated virulence genes

Enterococcus faecalis	CylS	CylLs	Cytolysin production
	FsR	Peptide	Gelatinase, serine protease
	LuxS	AI-2	?
Yersinia sp.	Qse/LuxS	AI-3	?
	Lsr/LuxS	AI-2	?
	YenR/I	AHLs	?
	YpsR/I	AHLs	Flagella and motility
	YtbR/I	AHLs	Flagella and motility
Shigella flexneri	Qse/LuxS	AI-3	Expression of VirB?
	Lsr/LuxS	AI-2	Expression of VirB?
Campylobacter jejuni	LuxS	AI-2	Motility
Vibrio vulnificus	LuxS	AI-2 (furanosyl-borate diester?)	Protease, hemolysin
	SmrC	?	Protease, hemolysin, virulence
Vibrio parahaemolyticus	LuxM, LuxR (OpaR)	AI-1 (AHL?)	TTS
	LuxP, LuxQ, LuxS	AI-2 (furanosyl-borate diester?)	?

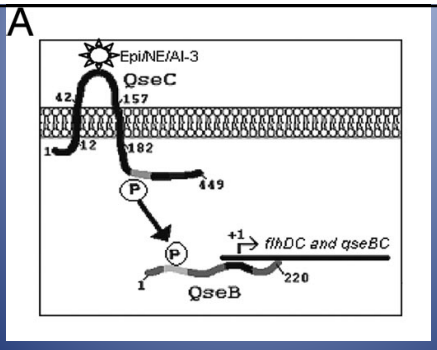
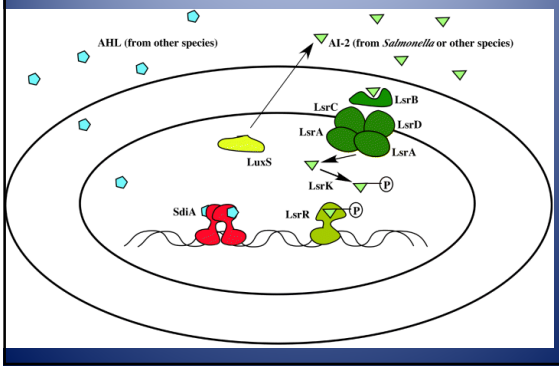
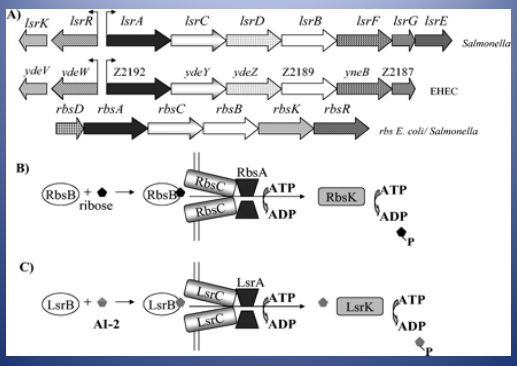


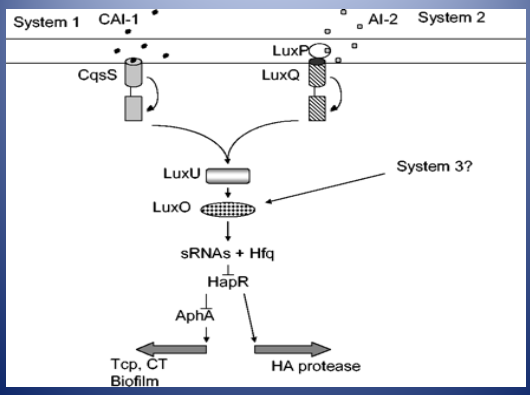
Fig. 3. QseBQseC is a functional two-component system. (*A*) Model of signaling begins with QseC responding to epiNE and AI-3. QseC increases its autophosphorylation and transfers its phosphate to QseB. Phosphorylated QseB then activates both its own transcription and that of *flhDC*.

Table S1. List of QseC homologs in other bacteria compared to EHEC QseC.
Shigella flexneri 2a str. 301
Citrobacter koseri ATCC BAA-895
Enterobacter sp.
Salmonella typhimurium LT2
Salmonella enterica subsp. *enterica* serovar Typhi str.
Yersinia mollaretii ATCC 43969
Klebsiella pneumoniae subsp. *pneumoniae* MGH 78578
Haemophilus influenzae PittGG
Pasteurella multocida subsp. *multocida* str.
Coxiella burnetii RSA 493
Burkholderia phymatum STM815
Ralstonia eutropha H16
Legionella pneumophila str. Paris
Bordetella parapertussis 12822
Francisella tularensis subsp. *tularensis* SCHU S4
Pseudomonas aeuriginosa
Pseudomonas fluorescens Pf-5
Vibrio sp.
Erwinia carotovora subsp. *atroseptica*
Actinobacillus pleuropneumoniae serovar 1 str. 4074
Yersinia pestis CO92
Yersinia pseudotuberculosis IP 32953
Yersinia enterocolitica subsp. *enterocolitica* 8081
Chromobacterium violaceum ATCC 12472

Fig. 4. Diagram of the SdiA and AI-2 systems of *Salmonella*. *Salmonella* detects AHLs synthesized by other species using the SdiA protein and increases the expression of *argE* and the *rck* operon based on results obtained with other LuxR homologues. It is likely that SdiA binds AHL directly and activates transcription of target genes. AI-2 is synthesized by LuxS. AI-2 is imported by the LsrACD transport system, which is a member of the ATP-binding cassette family. LsrB is the periplasmic binding component that presumably binds AI-2 directly. LsrK is a kinase that phosphorylates AI-2 at an unknown position. LsrR represses the *lsr* operon unless AI-2 is present.







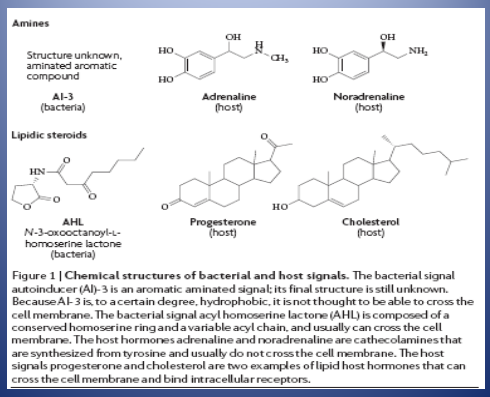


Figure 1 | **Chemical structures of bacterial and host signals.** The bacterial signal autoinducer (AI)-3 is an aromatic aminated signal; its final structure is still unknown. Because AI-3 is, to a certain degree, hydrophobic, it is not thought to be able to cross the cell membrane. The bacterial signal acyl homoserine lactone (AHL) is composed of a conserved homoserine ring and a variable acyl chain, and usually can cross the cell membrane. The host hormones adrenaline and noradrenaline are cathecolamines that are synthesized from tyrosine and usually do not cross the cell membrane. The host signals progesterone and cholesterol are two examples of lipid host hormones that can cross the cell membrane and bind intracellular receptors.

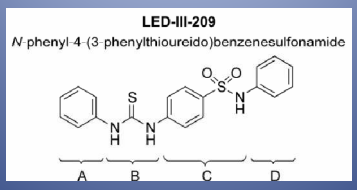


Table 1 | **Hormonal signals, receptors and biological functions**

Signal	Prokaryotic receptor	Prokaryotic function	Eukaryotic receptor	Eukaryotic function	Refs
Prokaryotic					
Providencia stuartii autoinducer (AI)	Unknown	Peptidoglycan modifications	Unknown	Unknown	10,11
AI-3	QseC	Type III secretion system (T3SS) activation, motility, toxin expression, iron uptake and virulence	Unknown	Unknown	5,19–25
Acyl homoserine lactones	LuxR, TraR, LasR and others	Virulence, T3SS regulation, biofilm formation, motility, antibiotic production and others	Unknown	Immunomodulation, intracellular calcium signalling and apoptosis	65–94
Eukaryotic					
Adrenaline and noradrenaline	QseC	T3SS activation, motility, toxin expression, iron uptake, virulence, growth and quorum sensing (QS)	Adrenergic receptors	Cyclic AMP levels, phospholipase C activation, stress, cell proliferation, enzyme production and ion channels	5,6, 12–25
Peptide (epidermal growth factor (EGF))	Unknown	Unknown	EFG receptor	Cell proliferation, growth and development	6,8
Dynorphin	Unknown	QS and virulence	υ dynorphin opiate receptor	Stress responses	63
Steroid hormones	Unknown	Unknown	Nuclear receptors	Reproduction and regulated metabolism	6

Pathogen	Signal source	Bacterial receptor	Host receptor	Effects in bacteria	Effects in the host
Pseudomonas aeruginosa	3OC12-HSL bacterial	LasR	PPARβ/δ PPARγ	Production of virulence factors (elastase, exotosin A), biofilm, regulation of *rhl* QS system	PPARβ/δ: energy, homeostasis, cell proliferation and differentiation PPAR(: anti-inflammatory
EHEC *Salmonella Francisella*	AI-3 bacterial	QseC	?	Activation of motility, T3SS, Shiga-toxin	?
EHEC *Salmonella Francisella*	Adrenaline Norepinephrine Host	QseC	Adrenergic receptors	Activation of motility, T3SS, Shiga-toxin	Stress responses Electrolyte balance Intestinal motility

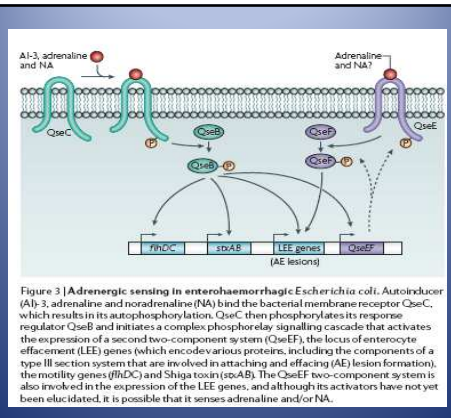


Figure 3 | **Adrenergic sensing in enterohaemorrhagic *Escherichia coli*.** Autoinducer (AI)-3, adrenaline and noradrenaline (NA) bind the bacterial membrane receptor QseC, which results in its autophosphorylation. QseC then phosphorylates its response regulator QseB and initiates a complex phosphorelay signalling cascade that activates the expression of a second two-component system (QseEF), the locus of enterocyte effacement (LEE) genes (which encode various proteins, including the components of a type III section system that are involved in attaching and effacing (AE) lesion formation), the motility genes (*flhDC*) and Shiga toxin (*stxAB*). The QseEF two-component system is also involved in the expression of the LEE genes, and although its activators have not yet been elucidated, it is possible that it senses adrenaline and/or NA.

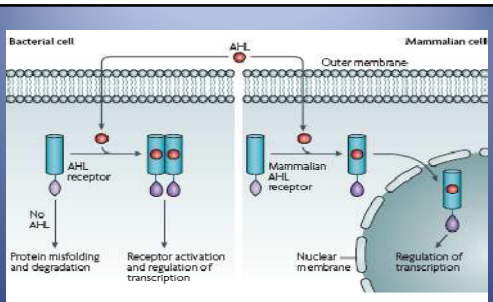


Figure 4 | **AHL inter-kingdom signalling.** In bacteria, acyl homoserine lactones (AHLs) cross the cell membrane and interact with cytoplasmic receptors of the LuxR family. Binding the AHL to the LuxR-type receptor allows proper folding of this protein, which allows the receptor to dimerize and bind to its target sequence on DNA to regulate genes expression. In the absence of signal, LuxR-type proteins misfold and are targeted for degradation. In mammalian cells, AHLs also gain access to the cytoplasm by crossing the plasma membrane. The identity of the mammalian receptor (or receptors) for AHLs in mammalian cells is unknown. However, if there are intracellular receptors, it is proposed that the interaction with the AHL ligand activates these receptors and thereby allows their transportation into the nucleus, where they could control gene expression.

Quorum sensing em *E. coli*

Indol – Crescimento e divisão celular

SdiA AI-1 homólogo de LuxI / LuxR

LuxS/AI-2 Receptor homólogo de Lsr

AI-3- epinefrina / norepinefrina

Sistema de peptideos ?

Escherichia coli diarreiogênica: seis patotipos

EPEC - *E. coli* Enteropatogênica

EHEC - *E. coli* Enterohemorragica

ETEC - *E. coli* Enterotoxigênica

EAEC - *E.coli* Enteroagregativa

EIEC - *E.coli* Enteroinvasiva

DAEC - *E.coli* de aderência difusa

EPEC faz parte de um grupo de patógenos entéricos que são capazes de formar um tipo de lesão em células epiteliais intestinais denominada de lesão "attaching and effacing" (AE).

Lesão A/E

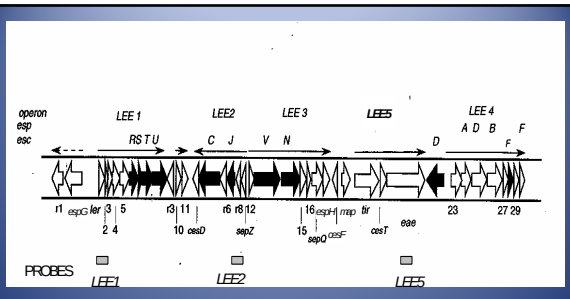
Aderência íntima

Destruição das microvilosidades

Rearranjo do citoesqueleto

Polimerização de actina

Formação de pedestal



Representação esquemática da ilha de patogenicidade LEE("locus of enterocyte effacement"). A região LEE contém 41 fases abertas de leitura; a maioria está contida em 5 operons (*LEE1-5*). As sondas utilizadas nos experimentos de slot blot estão mostradas em cinza.

EPEC típica- plasmídio EAF ("EPEC adherence factor") envolvido na formação do padrão de aderência localizada.

EPEC atípica -não possui o plasmídio EAF.

A transcrição dos genes da região LEE em EPEC é regulada por:

Ler (“LEE encoded regulator”)

Per (Plasmid encoded regulator)

IHF “Integration Host factor”

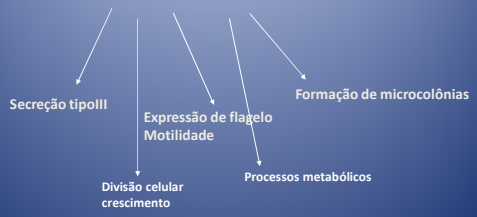
BipA

GadX

GrolRA

“quorum sensing” através do sistema AI-3/epinefrina.

Quorum sensing em EPEC
sistema AI-3/ epinefrina



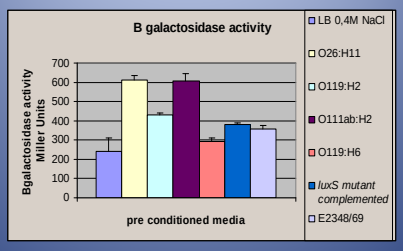
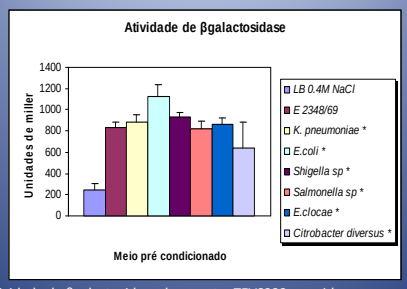


Gráfico mostrando ativação da fusão *LEE1*::*lacZ* pelos meios pré-condicionados com amostras de EPEC e EPEC atípicas. As barras representam a média dos experimentos realizados em triplicata.



Atividade de βgalactosidase de amostra TEVS232 crescida em meios pré condicionados com amostras de enterobactérias presentes na flora normal além outros patógenos e amostra de EPEC como controle positivo e meio sem pré condicionamento como controle negativo.

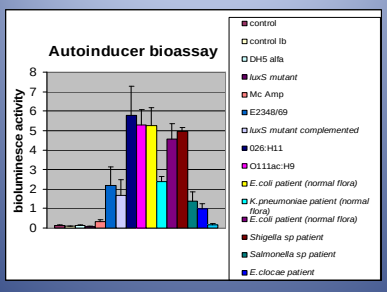
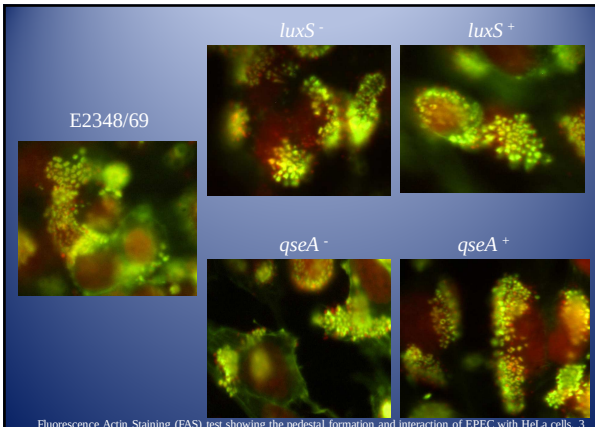
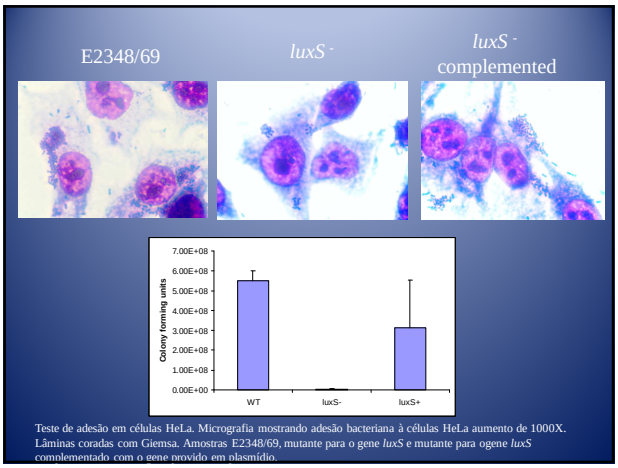


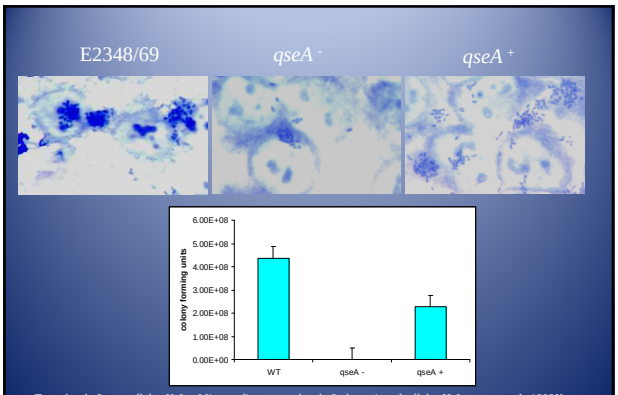
Gráfico mostrando indução de bioluminescência em amostra de *Vibrio harveyi* reporter por meios pré condicionaods com amostras de *E. coli* e algumas enterobactérias presentes na flora normal.



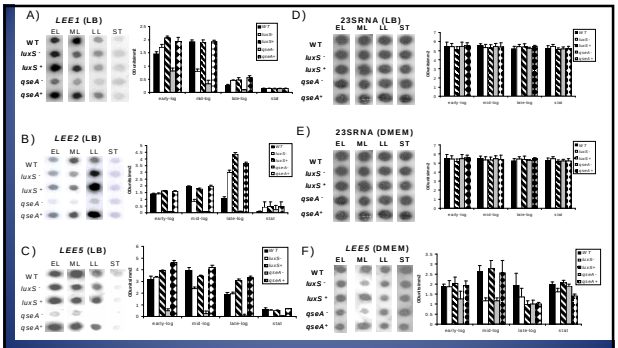
Fluorescence Actin Staining (FAS) test showing the pedestal formation and interaction of EPEC with HeLa cells. 3 hours of infection. Bacteria are stained in red with propidium iodide and actin stained in green with FITC phalloidin.



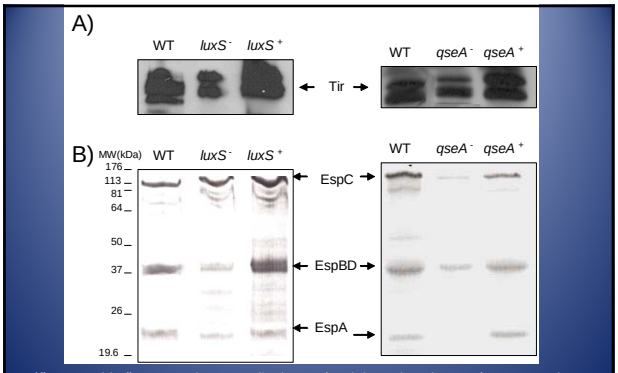
Teste de adesão em células HeLa. Micrografia mostrando adesão bacteriana à células HeLa aumento de 1000X. Lâminas coradas com Giemsa. Amostras E2348/69, mutante para o gene *luxS* e mutante para ogene *luxS* complementado com o gene provido em plasmídio.



Teste de adesão em células HeLa. Micrografia mostrando adesão bacteriana à células HeLa aumento de 1000X. Lâminas coradas com Giemsa. Amostras E2348/69, mutante para o gene *qseA* e mutante para o gene *qseA* complementado com o gene provido em plasmídio.



Resultados ilustrativos exemplificando os experimentos de RNA "slot blot"e gráficos baseados na densidade óptica de cada slot para uma estimativa quantitativa da transcrição do respectivo gene. A) *LEE1* meio LB, B) *LEE2* meio LB, C) *LEE5* meio LB, D) 23S RNA meio LB, E) 23S RNA meio DMEM e F) *LEE5* meio DMEM . As barras representam uma média e desvio padrão das densidades ópticas obtidas em experimentos realizados em triplicata.



A)"Western blot" mostrando expressão de Tir. B) Gel de acrilamida proteínas secretadas em amostras de EPEC selvagens e mutantes para os genes *luxS* e *qseA*.

Formação de microcolônias em EPEC

-Fímbria Tipo IV : Bundle Forming Pilus (BFP): Interação bacteria-bacteria.

(Giron et al., 1991 Science 254:710-3; Donnenberg et al., 1992 Mol. Microbiol. 6:3427-37)

-Plasmid-encoded-regulator (PerABC): ativa transcrição dos genes que codificam BFP

(Gomez-Duarte and Kaper, 1995 Infect. Immun. 63:1767-76; Tobe et al., 1996 Mol. Microbiol. 21:963-75)

-Tanto *bfp* como *per* estão localizados no plasmídio EAF

-Envolvimento de flagelo no processo de adesão e formação de microcolônias

(Giron et al., 2002 Mol. Microbiol. 44:361-79)

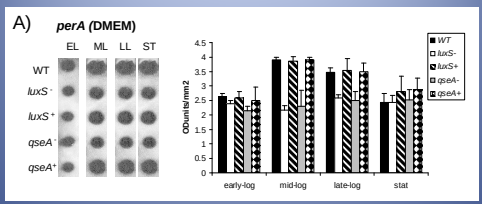
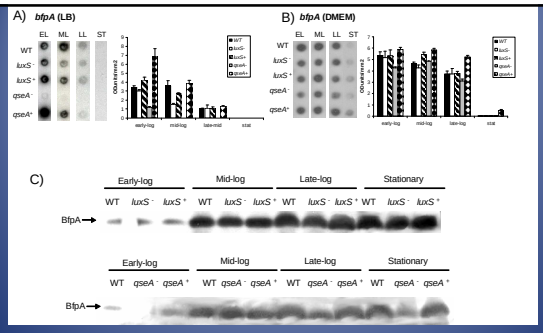
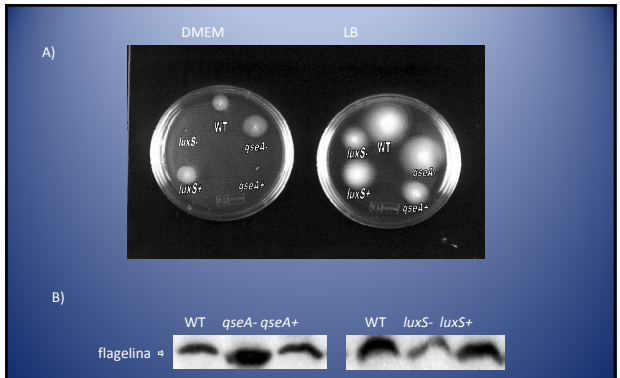


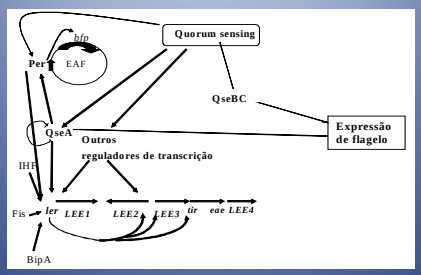
Ilustração de RNA "slot blot" e gráfico quantitativo da transcrição do gene *perA*.



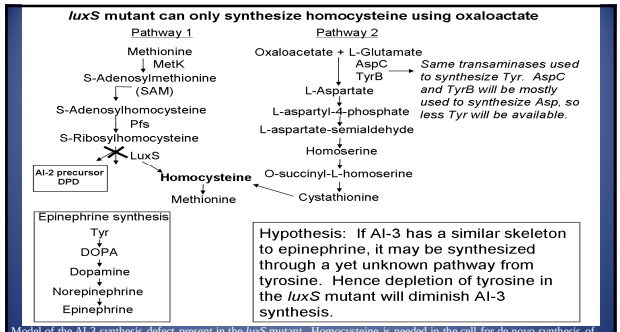
A) Estudo da transcrição de bfp em meio LB, B)estudo da transcrição de BFP em meio DMEM. C)"Western blot" para verificação da expressão de BFP.



A) Ensaios de motilidade com amostras selvagem e mutantes para os genes *luxS* e *qseA* e seus respectivos mutantes complementados em meios DMEM e LB. B) Western blot com soro anti flagelina H6.



Representação esquemática da regulação de genes de virulência em amostra de EPEC.



Model of the AI-3 synthesis defect present in the *luxS* mutant. Homocysteine is needed in the cell for de novo synthesis of methionine, and methionine is required for the production of the vital metabolic enzyme *S*-Adenosylhomocysteine (SAM). The *luxS* mutant cannot produce homocysteine through *S*-Ribosylhomocysteine (SRH) hydrolysis and may upregulate an alternative pathway involving the use of oxaloacetate to generate methionine. Activation of this pathway may lead to decreased levels of tyrosine because the AspC and TryB transaminases are being used to synthesize more aspartate. Since epinephrine/norepinephrine and AI-3 seem to share a common receptor, they may have similar structures. Synthesis of epinephrine/norepinephrine begins with a tyrosine molecule. If activation of the oxaloacetate-homocysteine pathway leads to a decrease in cellular tyrosine levels and tyrosine is involved in the production of AI-3, a reduction in tyrosine levels in the *luxS* mutant would lead to reduced AI-3 synthesis.

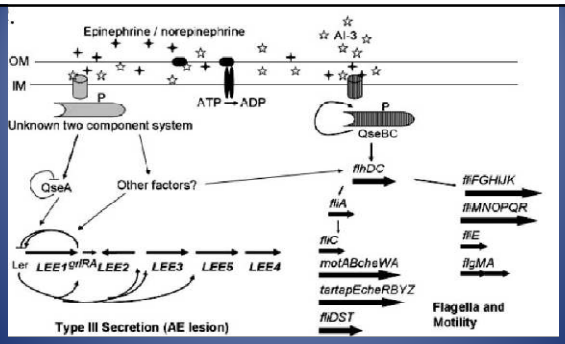
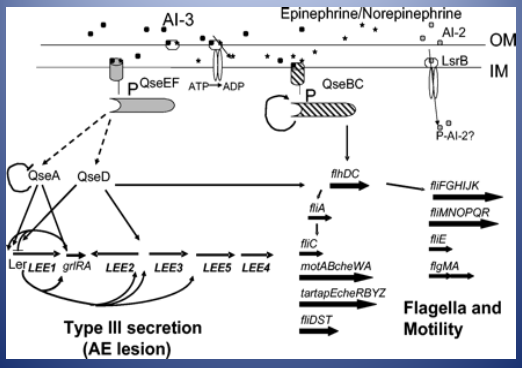
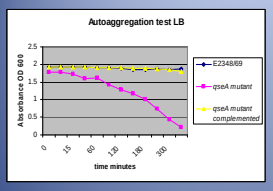
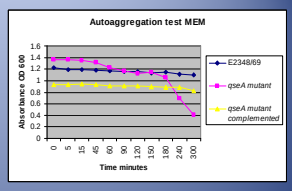


FIG. 1.. (C) Model of AI-3-mediated QS signaling cascade in EHEC. AI-3 and epinephrine/norepinephrine seem to be recognized by the same receptor and interact with sensor kinases once inside the periplasm. The QseC sensor kinase is part of the QseBC two-component system that regulates the flagellum regulon. Another two-component system is hypothesized to recognize the signal and activate transcription of the LEE. QseA regulates the LEE by activating transcription of *LEE1*.

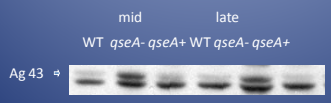


A)



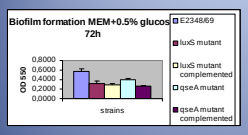


B)

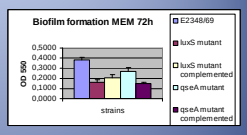


A) O mutante de *qseA* apresenta o fenótipo de autoagregação tanto em meio LB como em meio DMEM B) Western Blot utilizando with soro anti Ag43 mostrando que está proteína está presente na amostra mutante.

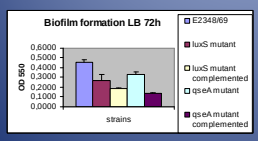
A)



B)



C)



Formação de biofilme (72 horas de incubação) nas amostras selvagem, mutantes para *luxS*, e *qseA* e respectivos mutantes complementados. A) DMEM + 0.5% glucose. B) DMEM. C) LB.

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