UNIVERSITE PARIS DESCARTES
Les Sciences de l'Homme et de la Santé

Equipe 2

Université Paris Descartes
Faculté de Médecine
Paris Descartes (site Necker)

Unité de Pathogénie
des Infections Systémiques
UMR 1002

Directeur: Prof Xavier Nassif
156, rue de Vaugirard
75730 Paris Cedex 15
FRANCE

Equipe 2: Coordonnateur Alain Charbit

Génomique fonctionnelle des échanges intra-cellulaire des bactéries pathogènes

Notre objectif général est de comprendre les bases moléculaires du parasitisme intracellulaire et la diffusion des bactéries pathogènes intracellulaires humains. Jusqu'à présent nous avons utilisé la bactérie Listeria monocytogenes, une bactérie pathogène responsable de méningo-encéphalite et des infections mortelles chez l'homme, comme un organisme modèle unique. Nous avons récemment entrepris l'étude d'un agent pathogène humain seconde intracellulaire, Francisella tularensis, responsable de la tularémie maladies zoonotiques. La virulence extrême de F. tularensis, sa capacité à infecter sous la forme d'aérosols et de persister dans l'environnement, en font une classe potentielle Un agent de bioterrorisme.
L. monocytogenes a développé des stratégies bien caractérisés pour rapidement s'échapper de la vacuole des cellules infectées, de multiplier activement dans le cytosol et de répandre par le passage direct de cellule à cellule. Notre travail sur Listeria monocytogenes, qui se concentre exclusivement sur les mécanismes de captation du fer, est réalisée en étroite collaboration avec le laboratoire de Phillip Klebba (Université d'Oklahoma).
F. tularensis, qui reproduit in vivo principalement à l'intérieur des macrophages, inhibe la fusion tphagolysosomal et s'échappe rapidement de phagosomes acidifiés à se multiplier activement dans le cytosol de la cellule hôte. La bactérie diffuse finalement à des cellules adjacentes en détruisant sa cellule hôte par apoptose et pyroptosis. Les mécanismes moléculaires sous-jacents de son cycle de vie intra-cellulaires sont à présent largement inconnus.
Notre équipe développe deux axes de recherche principaux:
i) la réponse de stress F. tularensis. Nous spécifiquement le rôle des protéines Hfq liant l'ARN et des petits ARN dans la régulation de l'expression génique.
ii) F. tularensis contraintes nutritionnelles. Nous souhaitons comprendre les mécanismes de l'acquisition intra-cellulaire des nutriments et leur relation à la virulence.
L. monocytogenes se multiplier dans le cytosol des macrophages infectés (microscopie confocale).

F. tularensis dans un phagosome (Thin microscopie électronique section)

Alain Charbit (DR1, CNRS)

Monique Barel (DR2, Inserm)
Jennifer Dieppedal (doctorant, Université Paris Descartes)
Iharilalao Dubail (TR, Université Paris Descartes)
Marion Dupuis (TR, Inserm)
Gaël Gesbert (M2, Université Paris Descartes)
Karin Meibom (CR1, Inserm)
Guillaume Postic (doctorant, Université Paris Descartes)
Aurélie Ramond (Doctorant, Université Paris Descartes)

The unraveling panoply of Francisella tularensis virulence attributes. Meibom KL, Charbit A. Curr Opin Microbiol. 2009 Dec 22. [Epub ahead of print]

Meibom KL, Barel M, Charbit A. 2009. Loops and networks in control of Francisella tularensis virulence. Future Microbiol.

Bigot A., and Charbit A. 2008. Genetic Manipulations In Handbook of Listeria monocytogenes (D. Liu, Ed.), ch 9, (Taylor & Francis CRC press). (book chapter).

Bigot A., and Charbit A. 2008. Genetic Manipulations In Handbook of Nucleic Acids (D. Liu, Ed.), ch 9, (Taylor & Francis CRC press). (book chapter), in press.

Kayal S. and Charbit A. 2006. Listeriolysin O: a key protein of Listeria monocytogenes with multiple functions. FEMS Microbiol. Rev., 30: 514-529.

N. Autret and A. Charbit. 2005. Lessons from signature-tagged mutagenesis on the infectious mechanisms of pathogenic bacteria. FEMS Microbiology Rev., 29: 703-717.

Grall N, Livny J, Waldor M, Barel M, Charbit A, Meibom KL. 2009. Pivotal role of the Francisella tularensis heat-shock sigma factor RpoH. Microbiology. 155(Pt 8):2560-72.

Bigot A, Raynaud C, Dubail I, Dupuis M, Hossain H, Hain T, Chakraborty T, Charbit A. 2009. lmo1273, a novel gene involved in Listeria monocytogenes virulence. Microbiology. 155(Pt 3):891-902.

Meibom KL, Forslund AL, Kuoppa K, Alkhuder K, Dubail I, Dupuis M, Forsberg A and Charbit A. 2009. Hfq, a novel pleiotropic regulator of virulence-associated genes in Francisella tularensis.Infect Immun. 77(5):1866-80.

Alkhuder K, Meibom KL, Dubail I, Dupuis M and Charbit A. 2009. Glutathione provides a source of cysteine essential for intracellular multiplication of Francisella tularensis. PLoS Pathog., 5(1):e1000284.

Barel M, Hovanessian AG, Meibom K, Briand JP, Dupuis M and Charbit A. 2008. A novel receptor - ligand pathway for entry of Francisella tularensis in monocyte-like THP-1 cells: interaction between surface nucleolin and bacterial elongation factor Tu. BMC Microbiol., 8:145.

Meibom K, Dubail I, Dupuis M, Monique Barel, Juraj Lenco, Jiri Stulik, Igor Golovliov, Anders Sjostedt, and Charbit A. 2008. The heat-shock protein ClpB of Francisella tularensis is involved in stress tolerance and is required for multiplication in target organs of infected mice. Mol. Microbiol. 67: 1384-1401.

Peixoto A, Evaristo C, Munitic I, Monteiro M, Charbit A, Rocha B, Veiga-Fernandes H. 2007. CD8 single-cell gene coexpression reveals three different effector types present at distinct phases of the immune response. J Exp Med. 204:1193-1205.

Le Monier A., Autret N., Join-Lambert, O. F., Jaubert, F., Charbit A. , Berche, P. and Kayal S. 2007. ActA is required for the crossing of the feto-placental barrier byListeria monocytogenes. Infect. Immun. 75: 950-957

Raynaud C., Meibom K. L, Lety M. A., Dubail I., Candela T., Frapy E., Charbit A. 2007. The wbt locus of Francisella tularensis: role in LPS antigen biogenesis and pathogenicity. Infect. Immun. 75: 536-541.

Bigot A., Botton E., Dubail I,. and Charbit A. 2006. A homolog of Bacillus subtilis Trigger Factor in Listeria monocytogenes is involved in stress tolerance and bacterial virulence. Appl. Environ. Microbiol. 72: 6623-6631.

Lety M. A., Frehel C., Raynaud C., Dupuis M., and Charbit A. 2006. Exploring the role of the CTL epitope region of listeriolysin O in the pathogenesis of Listeria monocytogenes. Microbiology, 152: 1287-1296.

Jin B., Newton S. M., Shao Y., Jiang X., Charbit A and Klebba PE. 2006. Iron acquisition systems for ferric hydroxamates, haemin and haemoglobin in Listeria monocytogenes. Mol. Microbiol. 59: 1185-1198.

Le Monnier A., Join-Lambert O., Jaubert F., Berche P., and Kayal, S. 2006. Invasion of placenta during murine listeriosis. Infect. Immun. 74: 663-672.

Dubail I., Bigot A., Lazarevic V., Soldo B., Euphrasie D., Dupuis M., and Charbit A. 2006. Identification of an essential gene of Listeria monocytogenes involved in teichoic acids biogenesis. J. Bacteriol. 188 : 6580-6591.

Bigot A., Pagniez H., Botton E., Frehel C, Dubail I., Jacquet C., Charbit A. and C Raynaud. 2005. Role of FliF and FliI of L. monocytogenes in flagellar assembly and pathogenicity. Infect. Immun. 73: 5530-5539.

Raynaud C. and Charbit A. 2005. Regulation of Type I Signal Peptidases expression in Listeria monocytogenes. Microbiology, 151: 3769-3776.

O. Join-Lambert, S. Ezine, A. Le Monnier, F. Jaubert, M. Okabe, P. Berche, S. Kayal, S. 2005. Listeria monocytogenes infected bone marrow myeloid cells promote bacterial invasion of the central nervous system. Cell. Microbiol., 7:167-180.

S. M. C. Newton, P. E. Klebba, C. Raynaud, Y. Shao, X. Jiang, I. Dubail, C. Archer, C. Frehel 1 and A. Charbit. 2005. The svpA-srtB locus of Listeria monocytogenes: Fur-mediated iron regulation and effect on virulence. Mol. Microbiol. 55:927-940.

Bonnemain, C., Raynaud, C., . Reglier-poupet, H., Dubail, I., Frehel, C., Lety, M. A., Berche, P. and Charbit, A. 2004. Differential roles of multiple signal peptidases in the virulence of Listeria monocytogenes. Mol. Microbiol., 51 : 1251-1266.

H. Bierne, C. Garandeau, M. G. Pucciarelli, C. Sabet, S.Newton, F. Garcia-Del Portillo, P. Cossart and A. Charbit. 2004. Sortase B, a New Class of Sortase in Listeria monocytogenes. Journal of Bacteriology, 186: 1972-1982.

Lety, M. A., Frehel, C., Beretti, J. L., Berche, P., and Charbit, A. 2003. Modification of the signal sequence cleavage site of listeriolysin O does not affect protein secretion but impairs the virulence of Listeria monocytogenes. Microbiology , 149: 1249-1255.

Reglier-Poupet, H., Frehel, C., Dubail, I., Beretti, J. L., Berche, P., Charbit, A., and Raynaud C. 2003. Maturation of Lipoproteins by Type II Signal Peptidase is Required for Phagosomal Escape of Listeria monocytogenes. J. Biol. Chem., 278: 49469-49477.

Autret, N., Raynaud, C., Dubail, I., Berche, P., and Charbit A. 2003. Identification of the agr locus of Listeria monocytogenes: role in bacterial virulence. Infect. Immun. 71:4463-71.

Reglier-Poupet, H., Pellegrini, E., Charbit, A. and Berche, P. 2003. Identification of LpeA, a PsaA-like membrane protein that promotes cell entry by Listeria monocytogenes. Infect. Immun. 71:474-482.

Frehel, C., Lety, M. A., Autret, N., Beretti, J. L., Berche, P. and Charbit, A. 2003. Capacity of ivanolysin O to replace listeriolysin O in phagosomal escape and in vivo survival of Listeria monocytogenes. Microbiology,149 :611-620.

Garandeau C., Reglier-Poupet H., Dubail I., Beretti J.-L., Berche P. and Charbit A. 2002. The sortase SrtA of Listeria monocytogenes is involved in processing of internalin and in virulence. Infection and Immunity, 70: 1382-1390.

Kayal S., Lilienbaum A., Join-Lambert O, Li X., Israel A. and Berche P. 2002. Listeriolysin O secreted by Listeria monocytogenes induces NF-kappaB signalling by activating the IkappaB kinase complex. Molecular Microbiology, 44:1407-1419.

Merino D., Reglier-Poupet H., Berche P. and Charbit A. 2002. A hypermutator phenotype attenuates the virulence of Listeria monocytogenes in a mouse model. Molecular Microbiology, 44: 877-887

Lety, M. A., Frehel, C., Berche, P., and Charbit, A. 2002. Critical role of the N-terminal residues of listeriolysin O in phagosomal escape and virulence of Listeria monocytogenes. Molecular Microbiology, 46: 367-379

Pron B., Boumaila C., Jaubert F., Berche P., Milon G., Geissmann F. and Gaillard J.-L. 2001. Dendritic cells are early cellular targets of Listeria monocytogenes after intestinal delivery and are involved in bacterial spread in the host. Cellular Microbiology, 3: 331-340.

Gaillot O., Bregenholt S., Jaubert F., Di Santo J.-P. and Berche P. 2001. Stress-induced ClpP serine protease of Listeria monocytogenes is essential for induction of listeriolysin O-dependent protective immunity. Infection and Immunity, 69: 4938-4943.

Milohanic E., Jonquières R., Cossart P., Berche P. and Gaillard J.-L. 2001. The autolysin Ami contributes to the adhesion of Listeria monocytogenes to eukaryotic cells via its cell wall anchor. Molecular Microbiology, 39:1212-1224.

Lety M.A., Frehel C., Dubail I., Beretti J.-L., Kayal S., Berche P. and Charbit A. 2001. Identification of a PEST-like motif in listeriolysin O required for phagosomal escape and for virulence of Listeria monocytogenes. Molecular Microbiology, 39: 1124-1139.

Autret N., Dubail I., Trieu-Cuot P., Berche P. and Charbit A. 2001. Identification of new genes involved in the virulence of Listeria monocytogenes by signature-tagged transposon mutagenesis. Infection and Immunity, 69: 2054-2065.

Borezee E., Pellegrini E. and Berche P. 2000. OppA of Listeria monocytogenes, an oligopeptide-binding protein required for bacterial growth at low temperature and involved in intracellular survival. Infection and Immunity, 68: 7069-7077.

Nair S., Milohanic E. and Berche P. 2000. ClpC ATPase is required for cell adhesion and invasion of Listeria monocytogenes. Infection and Immunity, 68: 7061-7068.

Nair S., Derre I., Msadek T., Gaillot O. and Berche P. 2000. CtsR controls class III heat shock gene expression in the human pathogen Listeria monocytogenes. Molecular Microbiology, 35: 800-811.

Dubail I., Berche P. and Charbit A. 2000. Listeriolysin O as a reporter to identify constitutive and in vivo inducible promoters in the pathogen Listeria monocytogenes. Infection and Immunity, 68: 3242-3250.

Gaillot O., Pellegrini E., Bregenholt S., Nair S. and Berche P. 2000. The ClpP serine protease is essential for the intracellular parasitism and virulence of Listeria monocytogenes. Molecular Microbiology, 35: 1286-1294.

Nair S., Frehel C., Nguyen L., Escuyer V. and Berche P. 1999. ClpE, a novel member of the HSP100 family, is involved in cell division and virulence of Listeria monocytogenes. Molecular Microbiology, 31: 185-196.

Kayal S., Lilienbaum A., Poyart C., Memet S., Israel A. and Berche P. 1999. Listeriolysin O-dependent activation of endothelial cells during infection with Listeria monocytogenes: activation of NF-kappa B and upregulation of adhesion molecules and chemokines. Molecular Microbiology, 31: 1709-1722.

Pron B., Boumaila C., Jaubert F., Sarnacki S., Monnet J.-P., Berche P. and Gaillard J.-L. 1998. Comprehensive study of the intestinal stage of listeriosis in a rat ligated ileal loop system. Infection and Immunity, 66:747-755.

Rouquette C., De Chastellier C., Nair S. and Berche P. 1998. The ClpC ATPase of Listeria monocytogenes is a general stress protein required for virulence and promoting early bacterial escape from the phagosome of macrophages. Molecular Microbiology, 27: 1235-1245.

Sirard J.-C., Fayolle C., De Chastellier C., Mock M., Leclerc C. and Berche P. 1997. Intracytoplasmic delivery of listeriolysin O by a vaccinal strain of Bacillus anthracis induces CD8-mediated protection against Listeria monocytogenes. Journal of Immunology, 159:4435-4443.

Gaillard J.-L., Jaubert F. and Berche P. 1996. The inlAB locus mediates the entry of Listeria monocytogenes into hepatocytes in vivo. Journal of Experimental Medecine, 183: 359-369.

Rouquette C., Ripio M.-T., Pellegrini E., Bolla J.-M., Tascon R.-I., Vazquez-Boland J.-A. and Berche P. 1996. Identification of a ClpC ATPase required for stress tolerance and in vivo survival of Listeria monocytogenes. Molecular Microbiology, 21: 977-987.

De Chastellier C. and Berche P. 1994. Fate of Listeria monocytogenes in murine macrophages: evidence for simultaneous killing and survival of intracellular bacteria. Infection and Immunity, 62: 543-553.

Other selected publications of A. Charbit : 1994- 2007.

Berkane E., Orlik F., Charbit A., Danelon C., Fournier D., Benz R., and Winterhalter M. 2005. Nanopores: maltoporin channel as a sensor for maltodextrin and lambda-phage. J. Nanobiotechnol. 3: 3-8.

Berkane E., Orlik F., Stegmeier J. F., Charbit A., Winterhalter M., and Benz R. 2006. Interaction of bacteriophage lambda with its cell surface receptor: an in vitro study of binding of the viral tail protein gpJ to LamB (Maltoporin). Biochemistry. 45: 2708-2720.

Charbit A. 2003. Maltodextrin transport through LamB. Frontiers in Biosciences, 8: 265-274.

Charbit A., Andersen C., Wang J., Schiffler B., Michel V., Benz R. and Hofnung M. 2000. In vivo and in vitro studies of transmembrane beta-strand deletion, insertion or substitution mutants of the Escherichia coli K-12 maltoporin. Molecular Microbiology, 35:777-790.

Andersen C., Bachmeyer C., Tauber H., Benz R., Wang J., Michel V., Newton S.-M., Hofnung M. and Charbit A. 1999. In vivo and in vitro studies of major surface loop deletion mutants of the Escherichia coli K-12 maltoporin: contribution to maltose and maltooligosaccharide transport and binding. Molecular Microbiology, 32:851-867.

Charbit A., Reizer J. and Saier M.-H. Jr. 1996. Function of the duplicated IIB domain and oligomeric structure of the fructose permease of Escherichia coli. Journal of Biological Chemistry, 271: 9997-10003.

Klebba P.-E., Hofnung M. and Charbit A. 1994. A model of maltodextrin transport through the sugar-specific porin LamB, based on deletetion analysis. EMBO Journal, 13: 4670-4675.