5.6.3 Network of Excellence EuroPathoGenomics

CONTACT DETAILS

Professor Dr. rer. nat. Dr. h.c. mult. Jörg Hacker (Speaker)

Institut für Molekulare Infektionsbiologie
Bayerische Julius-Maximilians-Universität Würzburg
Röntgenring 11
97070 Würzburg
Tel.: 09 31 / 31-2575
Fax: 09 31 / 31-2578
E-mail: j.hacker@mail.uni-wuerzburg.de
www.noe-epg.uni-wuerzburg.de

Dr. rer. nat. Andreas Demuth (Office)
Dr. rer. nat. Gabriele Blum-Oehler (Office)
Tel.: 09 31 / 31-2126

General Information

Bacterial infections remain a major cause of disease and mortality in humans and animals throughout the world. Only the detailed understanding of their pathogenic processes will provide us with innovative tools for their prevention and treatment. The study of infectious disease needs a multidisciplinary approach that brings together the different disciplines of molecular biology, immunology, cell biology and structural biology. Although scientific collaborations within Europe have been established to some extent, there is a pressing need for more permanent links and structures between the different disciplines.

This task is accomplished by the Network of Excellence "EuroPathoGenomics" (NoE EPG) that is supported by the European Union with 6.7 million Euro for the duration of five years (July 2005 – June 2010). The NoE EPG, comprising 38 top level laboratories from 13 different nations, is co-ordinated by the University of Würzburg under the direction of Professor Jörg Hacker.

Major Research Interests

One of the major objectives in the field of research is to organise the mass of genomic information that has become available, regarding both microorganisms and their hosts, into schemes allowing one to decipher the cross talks between pathogens and commensals and their host cell and tissue targets. Innovation in diagnostic techniques and therapy, as well as the development of vaccines against pathogenic microorganisms, are expected to come out of the joint research activities of these top-level European research groups in the field of genomic research.

Accordingly, several topics are in the focus of the EPG project:

Comparative genomics/Biodiversity

Comparative genomics has been used to contribute to a better understanding of genome content and evolution of bacterial pathogens. Therefore, DNA-DNA hybridizations, sequencing as well as analysis of genes and complete genomes of different bacteria (e.g. *Vibrio, Rickettsia, Chlamydia, Listeria, Salmonella, Legionella, Bartonella, Escherichia, Staphylococcus, Helicobacter*) were performed in the NoE EPG. Broad comparative genome analysis of different *Vibrio* genomes for example allowed the establishment of a map of the overall genome plasticity in this bacterial group. Furthermore, preliminary results of the comparison of pathogenic *Legionella* species indicate major differences in the virulence gene repertoire and in secretion systems. Moreover, the genome sequence of *Staphylococcus carnosus*, a non-pathogenic *Staphylococcus* species has been completed and the genome has been annotated. Comparative genome analysis with the pathogenic *S. aureus* will give new insight into the core-genome of the species and new accessory genes that might contribute to the virulence of *S. aureus*. These data provide the basis for the application of new genomic approaches allowing the specific combat of pathogenic bacteria.

Antibiotic resistance

Lateral gene transfer through its implication in the development and spread of antibiotic resistance genes among bacterial pathogens is also a topic of major concern in the EPG network. Using Gram-negative and Gram-positive model systems, different aspects of the evolution and spread of antibiotic resistances were analysed by comparative genomics and functional studies. Furthermore, bacterial gene expression in response to exposure to antibiotics was investigated in order to get a deeper insight into the effect of antibiotics on gene regulation. These approaches will result in an improved understanding of the molecular mechanisms contributing to the development and spread of antibiotic resistances and

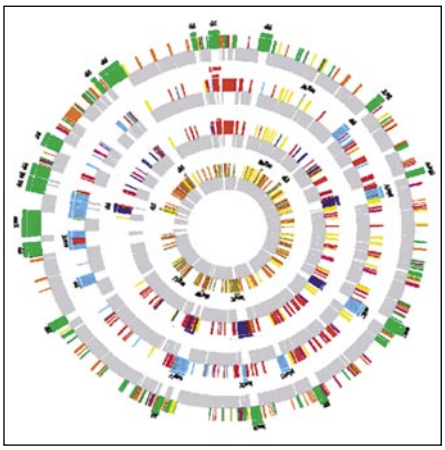

Fig.1: Comparison of different E. coli genomes. Circles represent complete E. coli genomes. From inside to outside: E. coli K-12 strain MG1655, uropathogenic E. coli strain 536, uropathogenic E. coli strain CFT073, enterohemorrhagic E. coli strain EDL 933.

to the discovery of novel anti-infectious agents and their targets.

Cellular microbiology

The analysis of factors influencing the virulence of bacterial pathogens is one of the cornerstones of experimental infection biology. Therefore, extensive analysis of regulatory networks involved in the production of virulence factors and survival of pathogens (e.g. *Mycobacteria, Pseudomonas, Listeria, Legionella, Salmonella, Neisseria*) in vitro and within the host was carried out in the EPG project. Whole genome expression and comparative gene profiling were performed to allow the identification and quantitative analysis of network components that are parts of signalling pathways.

Microbe-microbe interaction

Microbial communities such as biofilms are involved in many infections in humans often resulting in chronic states that are very difficult to combat. Therefore, to develop new strategies for diagnosis, prevention and control of microbial infections it is aimed to identify specific factors expressed within biofilms (e.g. *Escherichia, Legionella, Pseudomonas, Staphylococcus*). The collaboration of some EPG network partners already showed that the presence of specific genes (e.g. *cupB/cupC* and *flp/tad/rcp* gene cluster) and surface proteins is important for biofilm formation of *Pseudomonas aeruginosa*.

Pathogen-host cell interactions

Microbial diseases are the result of the interaction of the parasite and its host. Therefore, analysis of the interactions between bacterial pathogens and eukaryotic cells were accomplished in various cell culture and animal models and corresponding adhesion assays as well as screening tests were established. For example, a library of small organic molecules was screened for their inhibitory capacities on microbial specific structures that induce Toll-like receptor activated signal transduction cascades. This screen resulted in 20 substances classified as inhibitors that could not only help to understand the stimulation of cascades but also serve as therapeutic agents.

Teaching

One of the main activities of the EPG project is related to the education and training of students in the field of pathogenomics. Therefore, the so-called "EuroPathoGenomics Graduate Academy" (EGA) has been established. The EGA provides young scientists a broad-based interdisciplinary study programme with a wide range of seminars, summer schools and practical workshops. Furthermore, participants of the implemented exchange programme have the opportunity to visit the laboratory of project partners in order to exchange expertise and to gain new insights into particular areas of interest.

SELECTED PUBLICATIONS

Brzuszkiewicz E, Brüggemann H, Liesegang H, Emmerth M, Olschläger T, Nagy G, Albermann K, Wagner C, Buchrieser C, Emody L, Gottschalk G, Hacker J, Dobrindt U. (2006) How to become a uropathogen: comparative genomic analysis of extraintestinal pathogenic Escherichia coli strains. Proc Natl Acad Sci U S A. 103:12879-84.

Nougayrède JP, Homburg S, Taieb F, Boury M, Brzuszkiewicz E, Gottschalk G, Buchrieser C, Hacker J, Dobrindt U, Oswald E. (2006) Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science 313:848-51.

Fournier PE, Vallenet D, Barbe V, Audic S, Ogata H, Poirel L, Richet H, Robert C, Mangenot S, Abergel C, Nordmann P, Weissenbach J, Raoult D, Claverie JM. (2006) Comparative genomics of multidrug resistance in Acinetobacter baumannii. PLoS Genet. 2:e7.

Josenhans C, Beier D, Linz B, Meyer TF, Suerbaum S. (2007) Pathogenomics of helicobacter. Int J Med Microbiol. 297: 589-600.