Prédispositions Génétiques aux Infections Graves

Xème Journée de Réanimation de Picardie

Amiens, 4 Avril 2007
Pr. Jean-Paul Mira

Réanimation Médicale; CHU Cochin Port-Royal Paris
Institut Cochin, INSERM U 567, Paris
Completion of the Human Genome Project - April 2003 -

- 12.5 years
- $2.7 billion
- International cooperative effort
  - 6 countries
  - 20 sequencing centers
- Full & immediate data release

Odyssey to the Human Genome Project

1953  Watson & Crick: double helical structure of DNA
1960s  Role of RNA and Genetic Code
1970s  Recombinant DNA technology
1977  Sanger and Gilbert: DNA sequencing
1983  Mapping of disorders by linkage (Huntington disease)
1986  Polymerase Chain Reaction
1990  Human Genome Project
1995  *Haemophilus influenzae* genome
2003  Human and mice genome sequences
      SNPs Map
Genetic Polymorphisms

SNP

C G G T A C T T G A G G C T A Person 1
C G G T A C T T C G A G G C T A Person 2

→ Human SNP Map
How SNPs Influence Human Biology

SNP

Exon

rSNP (regulatory SNP)
iSNP (intron SNP)
cSNP

amino acid substitution
no amino acid substitution

Possible phenotype change

gSNP
Biodiversity: 0,1% of whole genome
Evidences for a genetic component to sepsis

Animal Studies

- Susceptibility/resistance to certain infection in mice
- Susceptibility/resistance phenotypes of knock-out mice
Intranasal challenge, $10^6$ cfu *S. pneumoniae* strain D39
Role of Genetic Resistance in Invasive Pneumococcal Infection: Identification and Study of Susceptibility and Resistance in Inbred Mouse Strains


Intranasal challenge, $10^6$ cfu S. pneumoniae strain D39
One phenotype may be due to different genotypes.

Despite the complexity of the immune defense, one missing element may have dramatic clinical consequences.
Evidences for a genetic component to sepsis

Animal Studies
- Susceptibility/resistance to certain infection in mice
- Susceptibility/resistance phenotypes of knockout mice

Human Studies
- Clinical Evidences
- Ethnic Differences
- Twin Studies
- Adoptee Studies
Recurrent Purpura Fulminans

2002/01: 15 yo girl admitted in ICU
- Temperature 40°C; HR 125; BP 74/45; RR 38
- Meningitis with purpura fulminans
- MOF (Shock, ARDS, ARF, DIC, Lactic acidosis)
- Meningococcus type N in the skin biopsy
- Survival with multiple finger amputations and skin grafting
- 6 month hospitalization

2003/02:
- Temperature 39°C; HR 125; BP 83/48; RR: 33
- Meningitis with purpura fulminans
- Lumbar punction → meningococcus type Y
- Shock and DIC
- Survival with new skin grafting
- 3 month hospitalization

Bohé J. Clin Infect Dis 2005
Pneumococcal Bacteremia by Ethnicity and Age

Monroe County, New York, 1985-1989

Bennet NM; Am J Public Health 1992;82:15
Twin Studies

dizygotic
- shared environment
- unique environment
- unique environment
- unique environment
- unique genes
- 0.5 shared genes

monozygotic
- shared environment
- unique environment
- unique environment
- unique genes
- shared genes
Twin Studies

• **Tuberculosis**
  Kallmann FJ, Am rev Tuber 1943.

• **Leprosis**
  Fine PE, Int J leprosy 1981

• **Helicobacter pylori**

• **Malaria**

• **AIDS**
Polymorphisms and Septic Shock
Genetic Polymorphisms and ICU

http://geneticassociationdb.nih.gov

### Genetic Association Database

**Search**

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

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## Genetic Polymorphisms and Severe Sepsis

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BRIEF REPORT

Inherited Deficiency of Mannan-Binding Lectin–Associated Serine Protease 2

• Opsonisation defect
  – C3 deficit
  – *H. influenzae* infections
  – *S. Pneumoniae* infections

• Membrane attack complex deficiency
  – C9, C7, properdin, C3...deficits
  – *N. meningitidis* infections
MBL Polymorphisms & the Risk of Infections

• Repeated bacterial and fungal infections
  Sumiya et al., Lancet 1991
  Summerfeld et al., Lancet 1995
  Garred et al., Lancet 1995
  Summerfeld et al., BMJ 1997

• Infections after chemotherapy
  Neth et al., Lancet 2001
  Peterslund et al., Lancet 2001

• Increased severity of lung disease and low survival in cystic fibrosis

• Meningococcal disease
  Hibberd et al., Lancet 1999

• Increased risk and severity of severe sepsis
  Roy, Lancet 2002
  Garred JID 2003
MBL genotype and risk of invasive pneumococcal disease


Odds ratio 3.48 (1.51 – 8.01); p=0.003
MBL Polymorphisms, SIRS, and Sepsis

272 ICU Pts with SIRS

A: Wild Type
O: Structural polymorphism associated with low MBL levels

Garred P. J Infect Dis 2003;188:1394
Clinical potential of mannose-binding lectin-replacement therapy

J.A. Summerfield¹

Division of Medicine, Faculty of Medicine, Imperial College London, St Mary’s Campus, London W2 1NY, U.K.
IRAK-1 Haplotype Increases NF-κB Activation

IRAK-1 gene located on X chromosome

2 haplotypes: htSNP = IRAK-1 532L→S

Arcoli J. Am J Respir Crit Care Med 2006;175:1335
IRAK-1 Haplotype Increases Morbidity of Sepsis

155 septic Caucasians patients

A

\[ p = 0.03 \]

\[ VFD \]

\[ \text{Variant IRAK-1 Haplotype} \]

\[ \text{Wildtype IRAK-1 Haplotype} \]

\[ OR: 2.6 \ (95\% \ CI, 1.1-7.7) \]

B

\[ p = 0.02 \]

\[ VFD \]

\[ \text{Variant IRAK-1 Haplotype} \]

\[ \text{Wildtype IRAK-1 Haplotype} \]

\[ OR: 2.9 \ (95\% \ CI, 1.06-7.7) \]

Arcoli J. Am J Respir Crit Care Med 2006;175:133
IRAK-1 Haplotype Increases Mortality of Sepsis

Arcoli J. Am J Respir Crit Care Med 2006;175:133
Cytokine Polymorphisms
Association of TNF2 with TNF levels in Septic Shock

![Graph showing the association of TNF2 with TNF levels in Septic Shock](image)

*Appoloni O. Am J Med 2001; 110:486*
TNF2 polymorphism and septic shock outcome

JAMA 1999;282:561-8
TNF Locus Polymorphisms and SDRA Mortality

TNFA adjusted OR: 3.5; 95% CI: 1.4-8.6; p=0.007

<67 years adjusted OR: 14.9; 95% CI: 3.0-74; p<0.001

>67 years p=0.3

Gong MN Eur Respir J 2005;26:
## TNF-308 Polymorphism and ICU Patients

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The TNF-308 G→A Promoter Polymorphism
- Genetic Determinant of Sepsis Outcome?

- 591 adult caucasians with septic shock
- 584 age- & sex-matched control patients
  - ICU patients
  - No sepsis
  - No vasopressors / inotropes
  - No comorbidities

- Phenotyping
  - Septic shock
  - Comorbidities
    - Heart failure (NYHA class III/IV) n=113
    - Liver cirrhosis n=63
    - Cancer n=119
    - Treatment with immunosuppressive agents n=104

- Genotyping
TNF2 & Mortality of Septic Shock

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P <0.001

P =0.27

% Mortality

n: 440, 151, 212, 88, 228, 63
Genetics of Coagulation
4G/5G PAI-1 Polymorphism

Transcriptional activator

Regulatory region

Promoter

- 675

GGGGG

Transcriptional activator

GGGGG

Repressor protein

Low plasma PAI-1 concentration

Transcription

Exon1-9

PAI-1 gene

High plasma PAI-1 concentration
4G/5G promoter polymorphism in the PAI-1 gene and severe trauma patients

Menges, Lancet 2001;357:1096
4G/5G promoter polymorphism in the PAI-1 gene and severe trauma patients

Menges, Lancet 2001;357:1096

- % Sepsis
  - 4G/4G: 19
  - 4G/5G: 29
  - 5G/5G: 13

- % MOF
  - 4G/4G: 80
  - 4G/5G: 80
  - 5G/5G: 1

- % Fatal Outcome
  - 4G/4G: 60
  - 4G/5G: 30
  - 5G/5G: 10
4G/5G PAI-1 Polymorphism and Meningococcal Disease

% Predicted Mortality

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P = 0.02

% Observed Mortality

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P = 0.005

% Vascular Complications

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P = 0.03

Survivors

Haralambous E. Crit Care Med 2003;31:27
Conclusions & Perspectives - 2

- Identification of markers of susceptibility and severity
  - Evaluation of the individual risk
  - Prevention, immunization
  - Pharmacogenomics
  - Personalized physiopathology
Recurrent Purpura Fulminans

2002/01: 15 yo girl admitted in ICU
- Temperature 40°C; HR 125; BP 74/45; RR 38
- Meningitis with purpura fulminans
- MOF (Shock, ARDS, ARF, DIC, Lactic acidosis)
- Meningococcus type N in the skin biopsy
- Survival with multiple finger amputations and skin grafting
- 6 month hospitalization

2003/02:
- Temperature 39°C; HR 125; BP 83/48; RR: 33
- Meningitis with purpura fulminans
- Lumbar punction → meningococcus type Y
- Shock and DIC
- Survival (Xigris) with new skin grafting
- 3 month hospitalization

Bohé J. Clin Infect Dis 2005
Recurrent Purpura Fulminans

Genetic predisposition?
Innate immunity
Inflammation
Coagulation

**Innate Immunity**  
- TLR4  
- CD14  
- FcγRIIa  
- FcγRIII  
- MBL  
- Complement  
- C7 deficiency

**Inflammation**  
- TNFα  
- LTα  
- IL-1  
- IL-6  
- IL-10  
- ACE

**Coagulation**  
- Tissue Factor  
- Prothrombin  
- Factor V  
- Factor VII  
- Factor XIII  
- PAI-1

Bohé J. Clin Infect Dis 2005
Conclusions & Perspectives

- Identification of markers of susceptibility and severity
  - Evaluation of the individual risk
  - Prevention, immunization
  - Pharmacogenomics
  - Personalized physiopathology

- Inclusion criteria in clinical trials
  - Interventional studies (i.e. anti-TNF)
  - Severity scores: SAPS IV, APACHE IV?
The « challenge »

From Genetics to Rationale Therapeutics
Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial

Elliot Israel, Vernon M Chinchilli, Jean G Ford, Homer A Boushey, Reuben Cherniack, Timothy J Craig, Aaron Deykin, Joanne K Fagan, John V Fahy,

Lancet 2004; 364: 1505 - 12

**Interpretation** Genotype at the 16th aminoacid residue of the β₂-adrenergic receptor affects the long-term response albuterol use. Bronchodilator treatments avoiding albuterol may be appropriate for patients with the Arg/Al genotype.
Protein C -1641A/G SNP and Severity of Severe Sepsis

402 White Severe Sepsis Patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>AA (n = 142)</th>
<th>AG (n = 195)</th>
<th>GG (n = 64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age^6</td>
<td>44/55/68</td>
<td>47/63/72</td>
<td>45/60/70</td>
<td>.17</td>
</tr>
<tr>
<td>Male sex</td>
<td>61%</td>
<td>66%</td>
<td>66%</td>
<td>.62</td>
</tr>
<tr>
<td>APACHE II^6</td>
<td>17/24/29</td>
<td>18/23/31</td>
<td>18/24/30</td>
<td>.94</td>
</tr>
<tr>
<td>Medical/surgical (% surgical)</td>
<td>20%</td>
<td>24%</td>
<td>27%</td>
<td>.58</td>
</tr>
</tbody>
</table>

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**Survival (%)**

- -1641 GG/GA (66%; N=260)
- -1641 AA (58%; N=142)

Walley KR. Crit Care Med 2006;35
PUTTING SCIENCE RIGHT TO WORK!

Social Security #

DNA

Retina Scan

Hologram

Hair Sample

Denial Records

ID Badge to Badger
Conclusions & Perspectives

- Identification of markers of susceptibility and severity
  - Evaluation of the individual risk
  - Prevention, immunization
  - Pharmacogenomics
  - Personalized physiopathology

- Inclusion criteria in clinical trials
  - Interventional studies (i.e. anti-TNF)
  - Classification of diseases, SAPS IV, APACHE IV

- LIMIT: Doctor’s education and training
Education and Training

Case-control studies in the genomic era: a clinician’s guide

Daniel G Healy

- Human genetic code
- Human genome project
- Candidate-gene and genome-wide approaches
- What is linkage disequilibrium?
- How to judge a case-control study?

Lancet Neurol 2006; 5:701-707
Current Genetic Association Studies in Sepsis

- Large cohorts
- Homogeneous populations (ethnies, age, gender, infections)
- Well-defined phenotypes:
  - severe sepsis ≠ septic shock, ALI ≠ ARDS, …
  - importance of comorbidities