Technologie "omics " a jejich využití jako prostředku personalizované medicíny u kriticky nemocných

Miroslav Průcha

Arch. Immunol. Ther. Exp. (2017) 65:37–49
DOI 10.1007/s00005-016-0415-9

REVIEW

Immunotherapy of Sepsis: Blind Alley or Call for Personalized Assessment?

Miroslav Prucha[1] · Roman Zazula[2] · Stefan Russwurm[3]

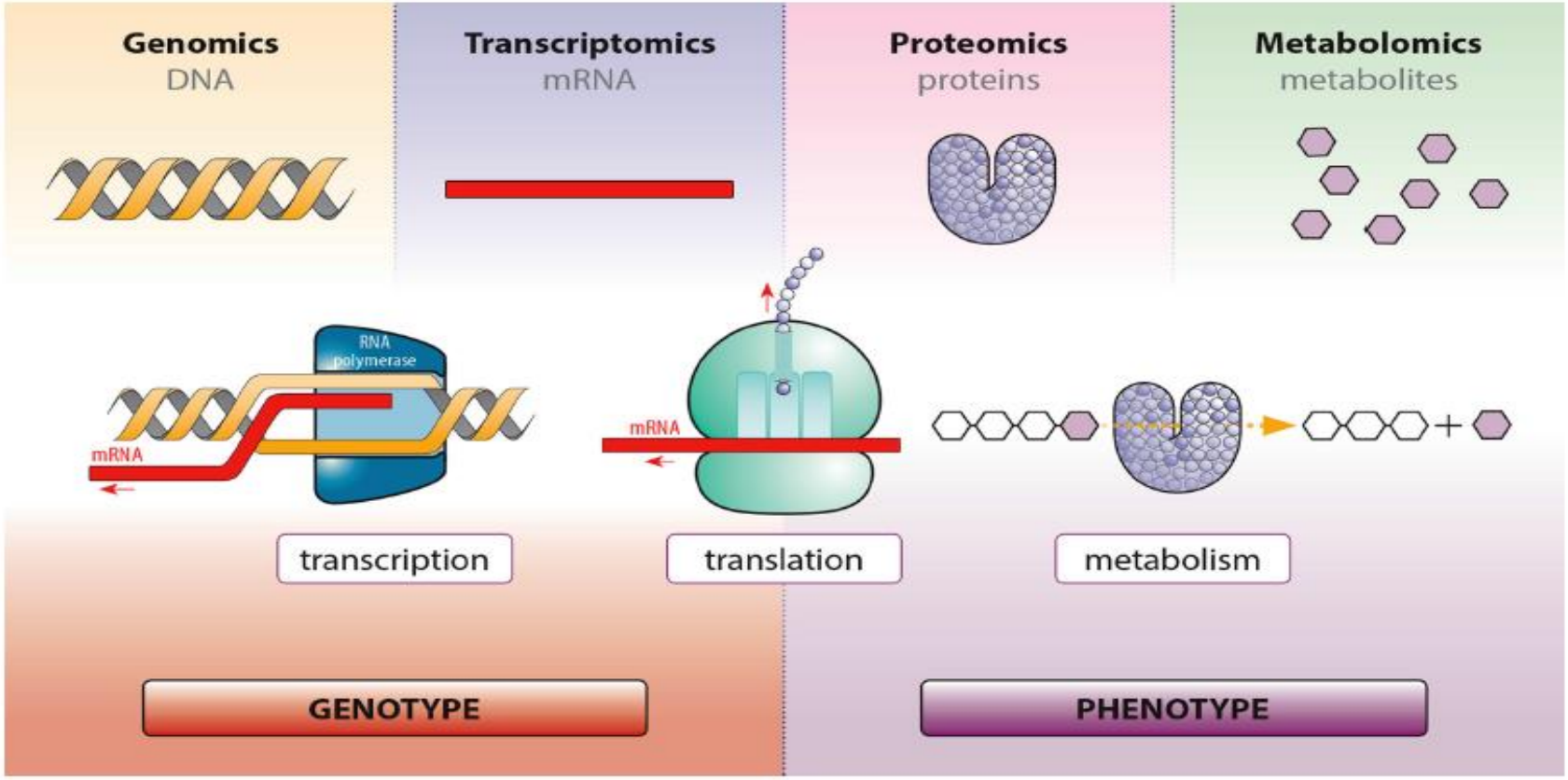


Fig. 2 The use of "omics" in critical care

Historie

Současnost

Genomika a epigenomika

Transkriptomika

Proteinomika

Metabolomika

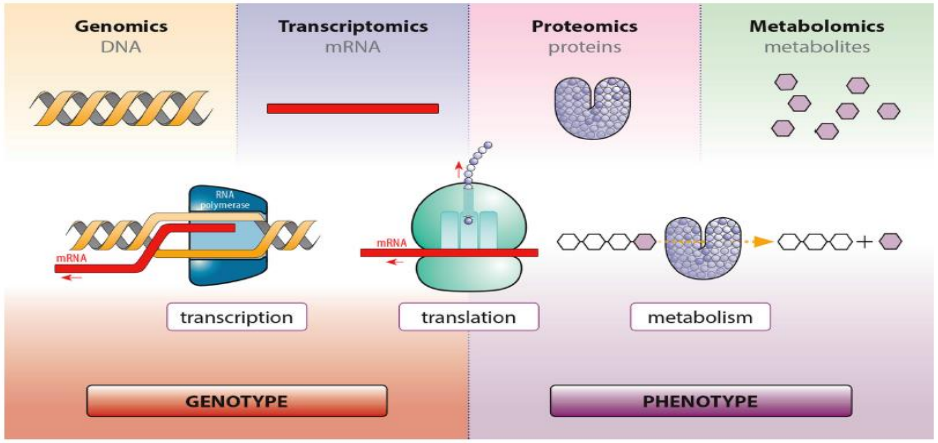
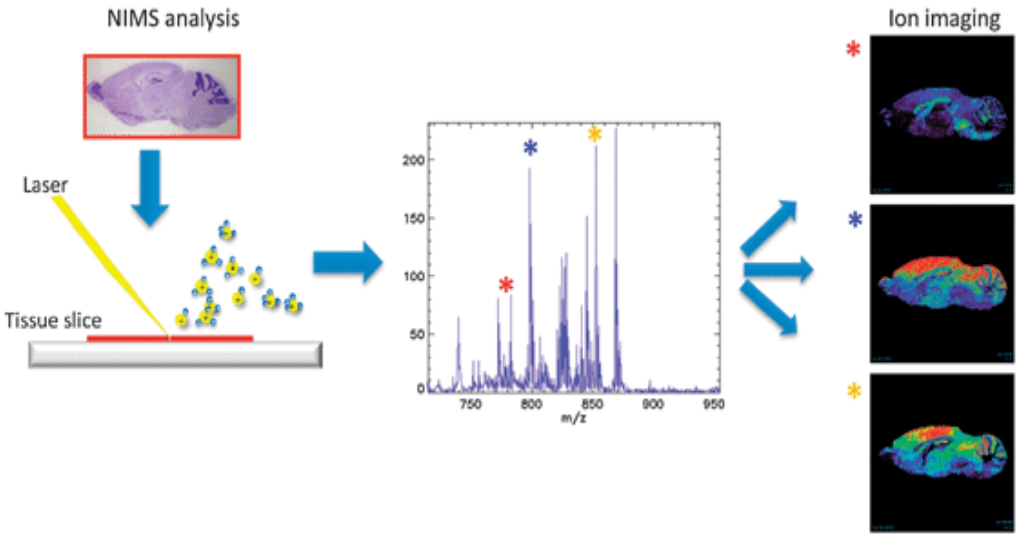


Fig. 2 The use of "omics" in critical care



equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).

[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astr* **5**, 285 (1949).

[3] Von Arx, W. S., Woods Hole Papers in Phy (3) (1950).

[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik.* (St

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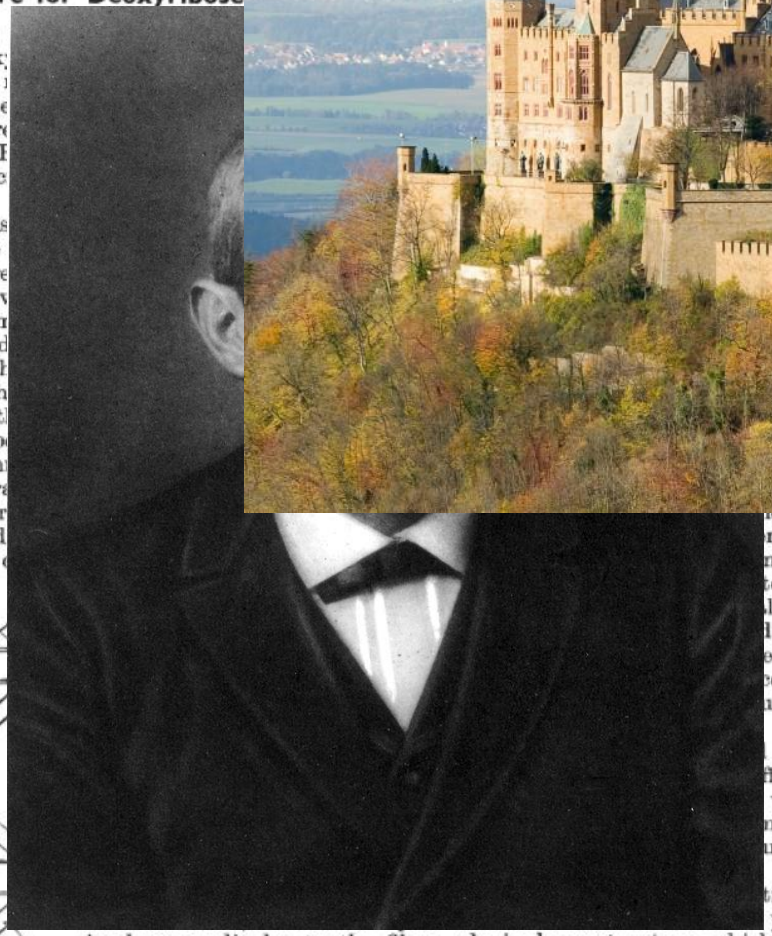

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Billionaire bought James Watson's Nobel prize medal in order to return it

Alisher Usmanov wants medal to remain with Watson and for money he paid for it to be donated to scientific research

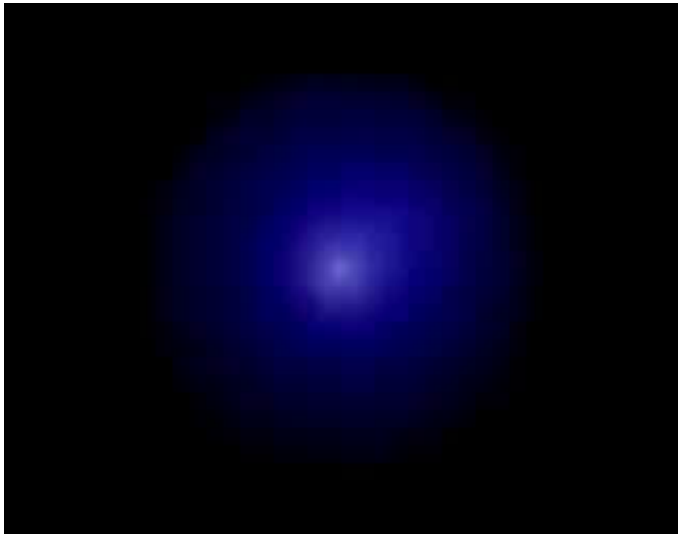
Alisher Usmanov: 'In my opinion, a situation in which an outstanding scientist has to sell a medal recognising his achievements is unacceptable.' Photograph: Sasha Mordovets/Getty Images

The richest man in Russia and a major shareholder in Arsenal football club has come forward as the buyer of James Watson's Nobel medal - declaring that he now plans to give the piece back.

Alisher Usmanov, the Russian entrepreneur, paid $4.1m (£2.6m) for the medal at

Systémová biologie

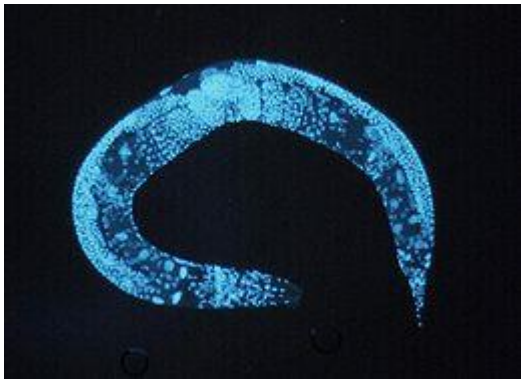
- je vědecký směr v biologii využívající přístupy dalších věd,především biochemie, chemie, informatiky a matematiky. Zabývá se studiem biologických funkcí a mechanizmů vzniklých následkem komplexních interakcí v biologických systémech
- Systémová biologie pracuje s velkým množstvím biologických dat a začala se prudce rozvíjet po roce 2000 následkem rozvoje technologií pro získávání genomických a proteomických dat a zvýšení výkonu počítačů.

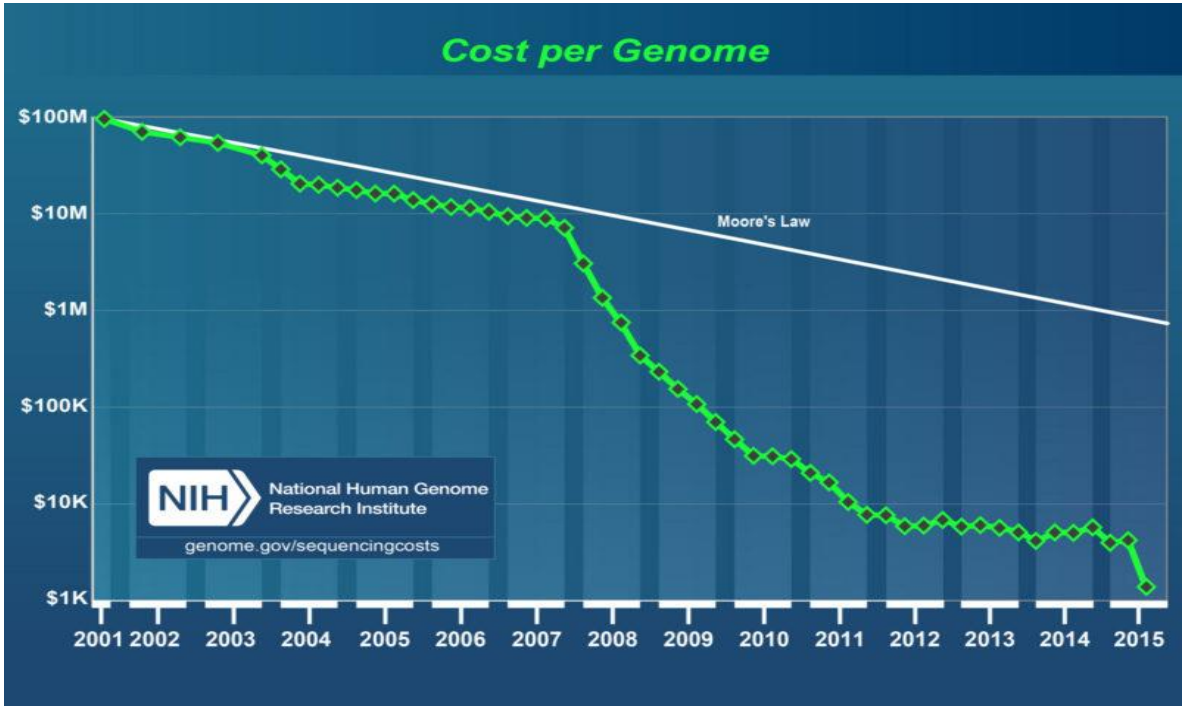


- 2003 – Human Genome Project a Celera Genomics
- ± 22 000 genů, 5-10x více proteinů
- 3,2 miliard párů bazí

Kukuřice 50 000 genů

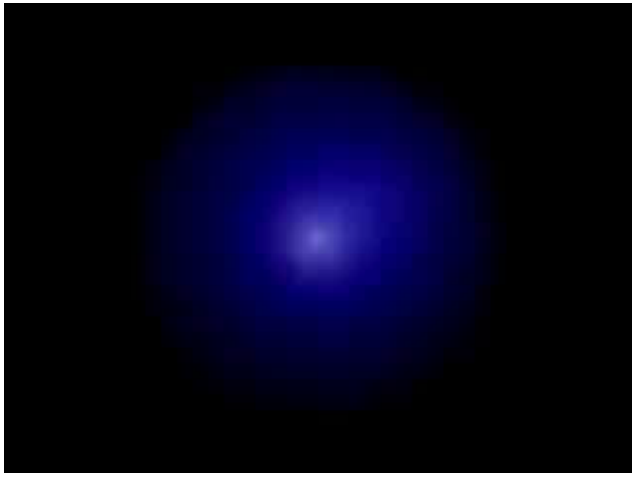
Caenorhabditis elegans
Háďátko obecné
20 000 genů





Cíle u pacientů v sepsi

- Nalezení nových biomarkerů indikující přítomnost infekčního zánětu, rizika a prognózu pacienta
- Nalezení mechanismů odpovědných za stav imunosuprese a v klinice obraz MOF
- Identifikace infekčního agens



Identifikace infekčního agens

Genome Med. 2016 Jul 1;8(1):73. doi: 10.1186/s13073-016-0326-8.

Next-generation sequencing diagnostics of bacteremia in septic patients.

Grumaz S[1], Stevens P[2,3], Grumaz C[1], Decker SO[4], Weigand MA[4], Hofer S[4], Brenner T[4], von Haeseler A[3,5], Sohn K[6,7].

Author information

Abstract

BACKGROUND: Bloodstream infections remain one of the major challenges in intensive care units, leading to sepsis or even septic shock in many cases. Due to the lack of timely diagnostic approaches with sufficient sensitivity, mortality rates of sepsis are still unacceptably high. However a prompt diagnosis of the causative microorganism is critical to significantly improve outcome of bloodstream infections. Although various targeted molecular tests for blood samples are available, time-consuming blood culture-based approaches still represent the standard of care for the identification of bacteria.

METHODS: Here we describe the establishment of a complete diagnostic workflow for the identification of infectious microorganisms from seven septic patients based on unbiased sequence analyses of free circulating DNA from plasma by next-generation sequencing.

RESULTS: We found significant levels of DNA fragments derived from pathogenic bacteria in samples from septic patients. Quantitative evaluation of normalized read counts and introduction of a sepsis indicating quantifier (SIQ) score allowed for an unambiguous identification of Gram-positive as well as Gram-negative bacteria that exactly matched with blood cultures from corresponding patient samples. In addition, we also identified species from samples where blood cultures were negative. Reads of non-human origin also comprised fragments derived from antimicrobial resistance genes, showing that, in principle, prediction of specific types of resistance might be possible.

CONCLUSIONS: The complete workflow from sample preparation to species identification report could be accomplished in roughly 30 h, thus making this approach a promising diagnostic platform for critically ill patients suffering from bloodstream infections.

KEYWORDS: Circulating nucleic acids; Diagnostics; Next-generation sequencing; Sepsis

Genomika a epigenomika

- **22.000 genů kódující proteiny, 5-10x více proteinů**
- **1988 – Sorensen et al. – vliv genetických predispozic na mortalitu u infekce**

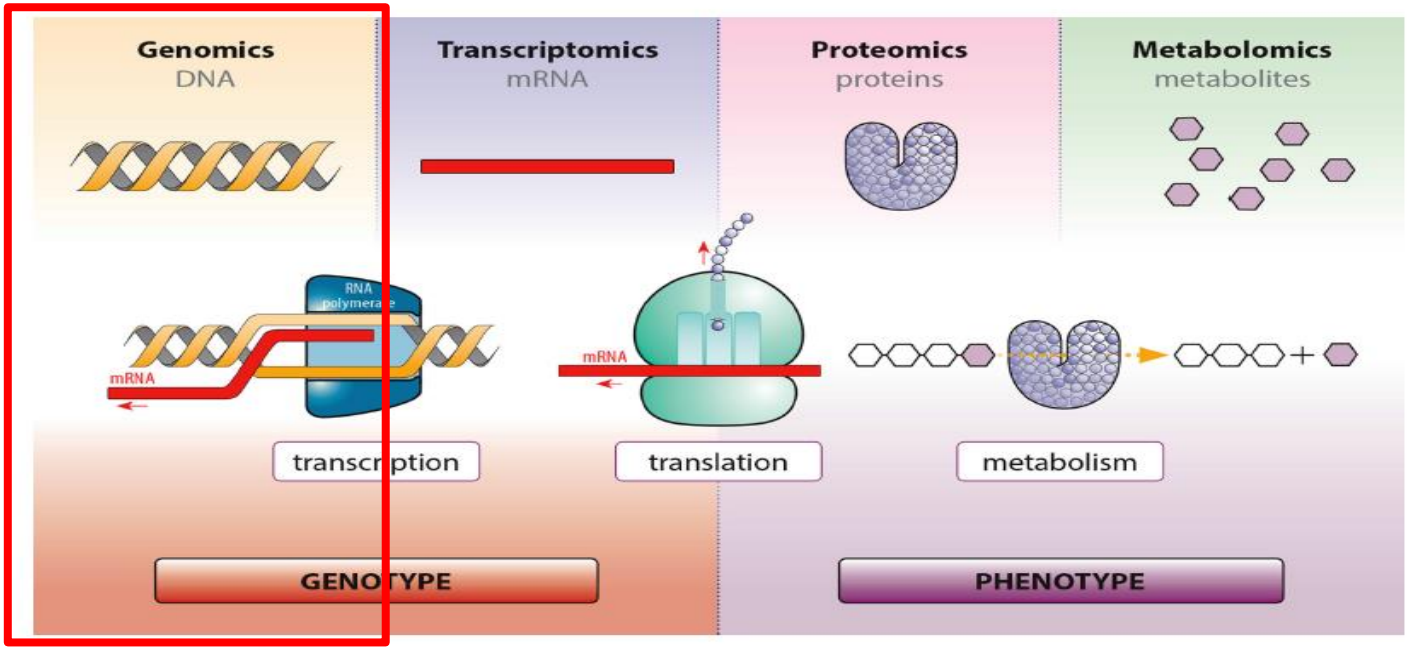


Fig. 2 The use of "omics" in critical care

Genomika a epigenomika

- SNPs – single nucleotide polymorphism
- Stuber et al 1996 – TNF – α
- Hubacek et al 2001 – CD14

- Epigenomika - genetická informace a změny její exprese bez změny v DNA sekvenci. Mechanismy - methylace bazí, acetylace histonů

- Bierne H et al 2012 – **bakterie jako epigenetický faktor**

Genomika – prognóza
Genomové asociační studie – GWAS
Zjišťování genetických predispozic u multifaktoriálních onemocnění

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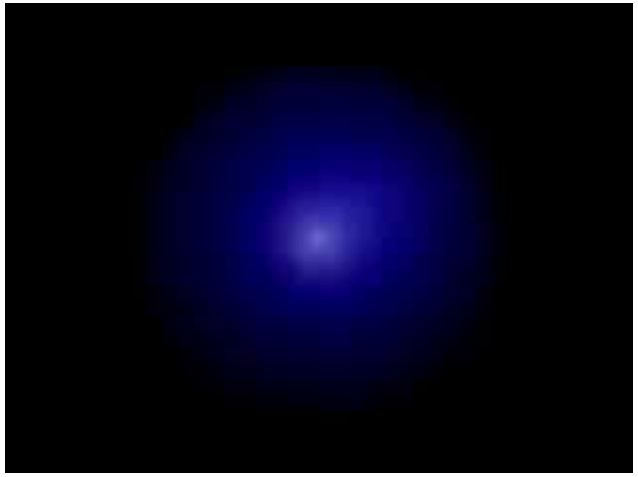
Research Paper

Genetic Factors of the Disease Course after Sepsis: A Genome-Wide Study for 28 Day Mortality

André Scherag [a,b,*,1], Franziska Schöneweck [a,b,1], Miriam Kesselmeier [a,b], Stefan Taudien [a,c], Matthias Platzer [c], Marius Felder [c], Christoph Sponholz [a,c,d], Anna Rautanen [e,2], Adrian V.S. Hill [e,2], Charles J. Hinds [f,2], Hamid Hossain [g,3], Norbert Suttorp [h,3], Oliver Kurzai [a,i,j], Hortense Slevogt [a,j], Evangelos J. Giamarellos-Bourboulis [a,k,4], Apostolos Armaganidis [l], Evelyn Trips [m], Markus Scholz [n,o,1], Frank M. Brunkhorst [a,p,q,1]

Autoři nalezli 3 loci associované s 28 denní mortalitou (VPS13A, CRISPLD2 a chromozome 13



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ABSTRACT

Sepsis is the dysregulated host response to an infection which leads to life-threatening organ dysfunction that varies by host genomic factors. We conducted a genome-wide association study (GWAS) in 740 adult septic patients and focused on 28 day mortality as outcome. Variants with suggestive evidence for an association ($p \leq 10^{-5}$) were validated in two additional GWA studies ($n = 3470$) and gene coding regions related to the variants were assessed in an independent exome sequencing study ($n = 74$).

In the discovery GWAS, we identified 243 autosomal variants which clustered in 14 loci ($p \leq 10^{-5}$). The best association signal (rs117983287; $p = 8.16 \times 10^{-8}$) was observed for a missense variant located at chromosome 9q21.2 in the *VPS13A* gene. *VPS13A* was further supported by additional GWAS ($p = 0.03$) and sequencing data ($p = 0.04$). Furthermore, *CRISPLD2* ($p = 5.99 \times 10^{-6}$) and a region on chromosome 13q21.33 ($p = 3.34 \times 10^{-7}$) were supported by both our data and external biological evidence.

We found 14 loci with suggestive evidence for an association with 28 day mortality and found supportive, converging evidence for three of them in independent data sets. Elucidating the underlying biological mechanisms of *VPS13A*, *CRISPLD2*, and the chromosome 13 locus should be a focus of future research activities.

Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study

Anna Rautanen, Tara C Mills, Anthony C Gordon, Paula Hutton, Michael Steffens, Rosamond Nuamah, Jean-Daniel Chiche, Tom Parks, Stephen J Chapman, Emma E Davenport, Katherine S Elliott, Julian Bion, Peter Lichtner, Thomas Meitinger, Thomas F Wienker, Mark J Caulfield, Charles Mein, Frank Bloos, Ilona Bobek, Paolo Cotogni, Vladimir Sramek, Silver Sarapuu, Makbule Kobilay, V Marco Ranieri, Jordi Rello, Gonzalo Sirgo, Yoram G Weiss, Stefan Russwurm, E Marion Schneider, Konrad Reinhart, Paul A H Holloway, Julian C Knight, Chris S Garrard, James A Russell, Keith R Walley, Frank Stüber, Adrian V S Hill*, Charles J Hinds*, for the ESICM/ECCRN GenOSept Investigators*

Summary

Background Sepsis continues to be a major cause of death, disability, and health-care expenditure worldwide. Despite evidence suggesting that host genetics can influence sepsis outcomes, no specific loci have yet been convincingly replicated. The aim of this study was to identify genetic variants that influence sepsis survival.

Methods We did a genome-wide association study in three independent cohorts of white adult patients admitted to intensive care units with sepsis, severe sepsis, or septic shock (as defined by the International Consensus Criteria) due to pneumonia or intra-abdominal infection (cohorts 1–3, n=2534 patients). The primary outcome was 28 day survival. Results for the cohort of patients with sepsis due to pneumonia were combined in a meta-analysis of 1553 patients from all three cohorts, of whom 359 died within 28 days of admission to the intensive-care unit. The most significantly associated single nucleotide polymorphisms (SNPs) were genotyped in a further 538 white patients with sepsis due to pneumonia (cohort 4), of whom 106 died.

Findings In the genome-wide meta-analysis of three independent pneumonia cohorts (cohorts 1–3), common variants in the *FER* gene were strongly associated with survival ($p=9\cdot7\times10^{-8}$). Further genotyping of the top associated SNP (rs4957796) in the additional cohort (cohort 4) resulted in a combined p value of $5\cdot6\times10^{-8}$ (odds ratio 0·56, 95% CI 0·45–0·69). In a time-to-event analysis, each allele reduced the mortality over 28 days by 44% (hazard ratio for death 0·56, 95% CI 0·45–0·69; likelihood ratio test $p=3\cdot4\times10^{-9}$, after adjustment for age and stratification by cohort). Mortality was 9·5% in patients carrying the CC genotype, 15·2% in those carrying the TC genotype, and 25·3% in those carrying the TT genotype. No significant genetic associations were identified when patients with sepsis due to pneumonia and intra-abdominal infection were combined.

Interpretation We have identified common variants in the *FER* gene that associate with a reduced risk of death from sepsis due to pneumonia. The *FER* gene and associated molecular pathways are potential novel targets for therapy or prevention and candidates for the development of biomarkers for risk stratification.

Funding European Commission and the Wellcome Trust.

Lancet Respir Med 2015; 3: 53–60

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See Comment page 7

*These authors supervised this work equally

Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK (A Rautanen PhD, T C Mills DPhil, T Parks MB, S J Chapman DM, E E Davenport MBiochem, K S Elliott PhD, Prof J C Knight DPhil, Prof A V S Hill DPhil); **Imperial College London, London, UK** (A C Gordon MD, P A H Holloway PhD); **John Radcliffe Hospital, Oxford, UK** (P Hutton PG Cert, C S Garrard MD); **William Harvey Research Institute, Barts and The London School of Medicine Queen Mary University of London, London, UK** (R Nuamah BSc, C Mein PhD, Prof C J Hinds FRCP, Prof M J Caulfield MD); **Hospital Cochin, Paris, France** (Prof J-D Chiche MD), **School**

FER gen

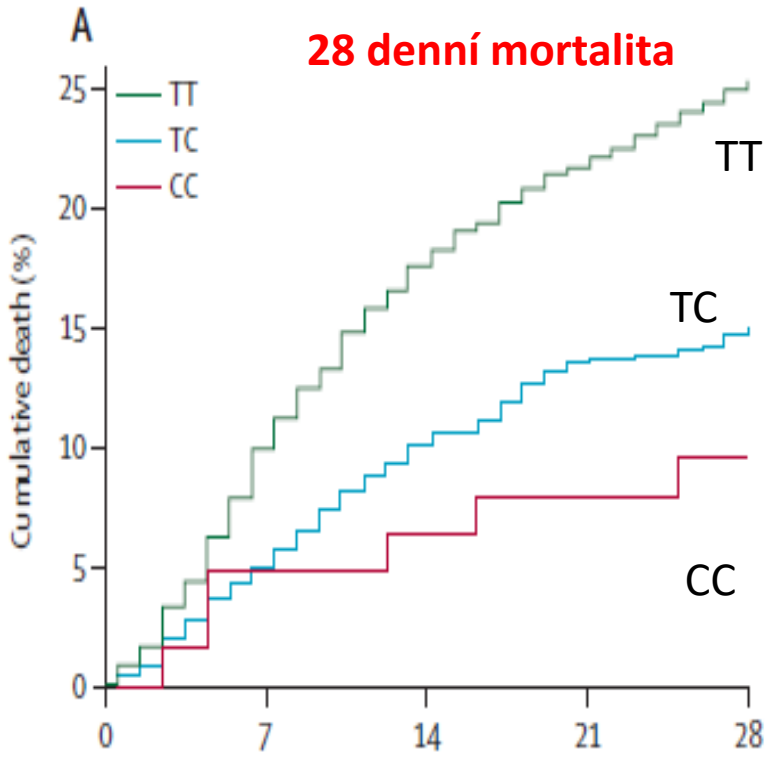
FER gen kóduje nereceptorový protein tyrozinkinázu

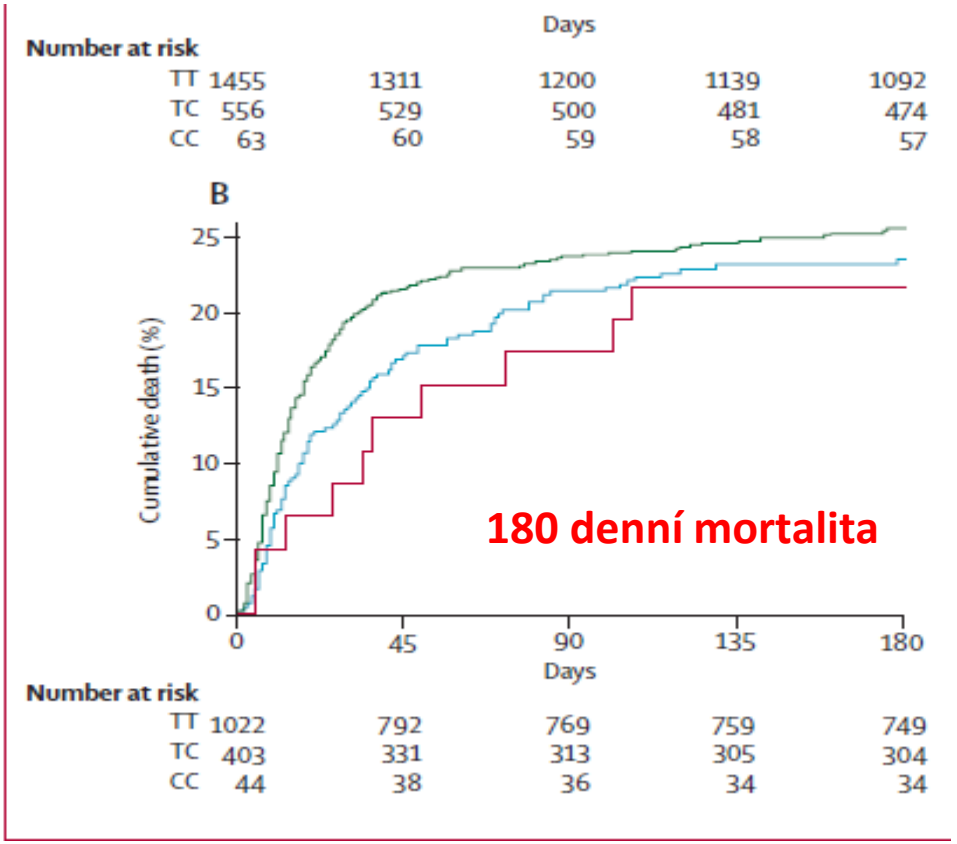
Tyrozinkináza je enzym ze skupiny proteinkináz, který katalyzuje přenos fosfátové skupiny (fosforylace) z nukleosidtrifosfátů (většinou ATP) na aminokyselinu tyrozin v proteinech

Nereceptorové tyrozinkinázy vykonávají své funkce v cytoplazmě a vedou signály uvnitř buňky až do jádra

FER ovlivňuje recruitment leukocytů a střevní bariérovou dysfunkci po účinku LPS

Interpretation We have identified common variants in the *FER* gene that associate with a reduced risk of death from sepsis due to pneumonia. The *FER* gene and associated molecular pathways are potential novel targets for therapy or prevention and candidates for the development of biomarkers for risk stratification.





Transkriptomika

- Kvantifikace mRNA v tkáních, buňkách
- Monitorace aktivity genů a jejich regulací
- Rozlišení infekčního a neinfekčního zánětu
- Prognóza pacienta a patogenetické mechanismy

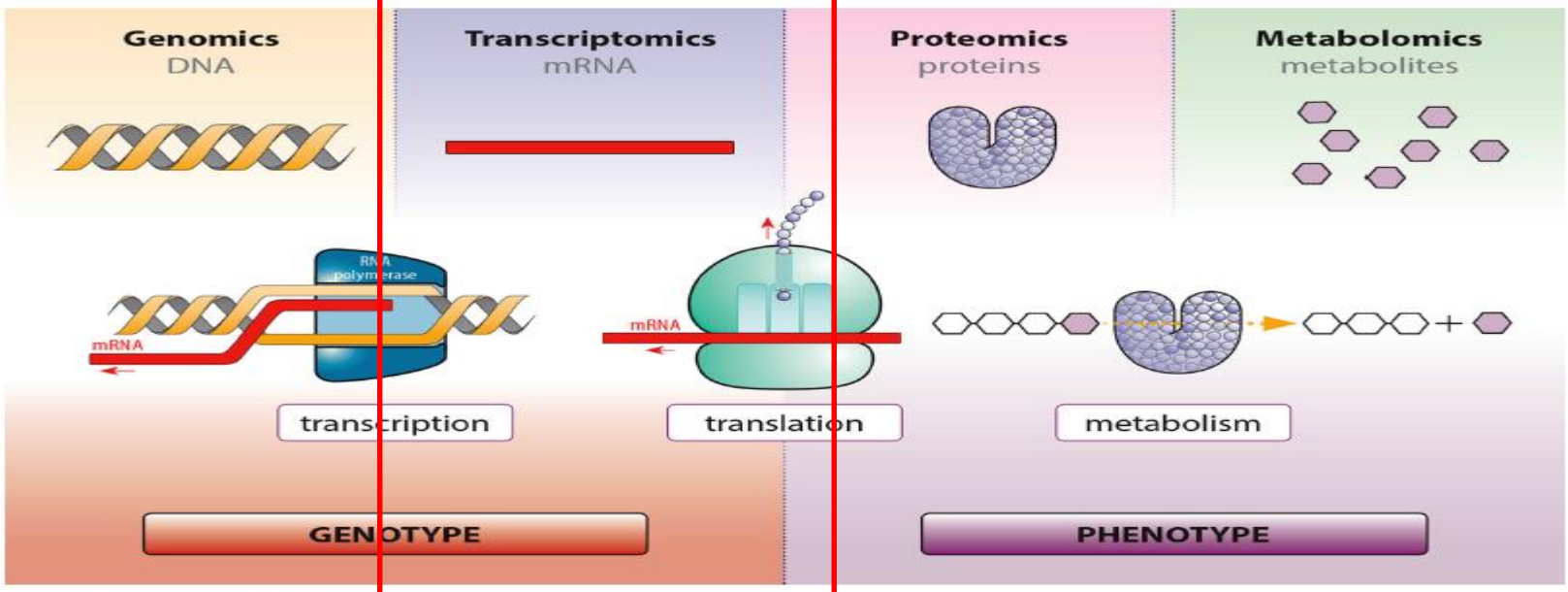
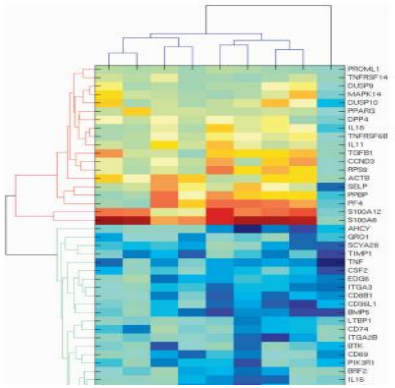


Fig. 2 The use of "omics" in critical care

Rozdílná genová exprese u infekčního a neinfekčního SIRSu



Shock. 2004 Jul;22(1):29-33.

Expression profiling: toward an application in sepsis diagnostics.

Prucha M[1], Ruryk A, Boriss H, Möller E, Zazula R, Herold I, Claus RA, Reinhart KA, Deigner P, Russwurm S.

Author information

Abstract

Sepsis is a common and serious health problem whereby improvements in diagnosis are crucial in increasing survival rates. To test whether profiling transcription is applicable to sepsis diagnosis, we analyzed whole blood using a microarray containing probes for 340 genes relevant to inflammation. The patient's gene expression pattern was highly homogenous, resulting in 69% of differentially expressed genes. With a positive predictive value of 98%, a list of 50 differentially expressed genes was compiled, and randomly chosen transcripts were confirmed by PCR. Here, we present the first evidence that microarrays can identify typical gene expression profiles in the blood of patients with severe sepsis. Regardless of the heterogeneity of the patients, we observed a striking correlation between the conventional diagnostic classification and our approach. The unity of responses suggests that the principle of this multiparameter approach can be adapted to early stage sepsis diagnosis.

Lancet Respir Med. 2016 Apr;4(4):259-71. doi: 10.1016/S2213-2600(16)00046-1. Epub 2016 Feb 23.

Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study.

Davenport EE[1], Burnham KL[1], Radhakrishnan J[1], Humburg P[1], Hutton P[2], Mills TC[1], Rautanen A[1], Gordon AC[3], Garrard C[2], Hill AV[1], Hinds CJ[4], Knight JC[5].

Author information

Abstract

BACKGROUND: Effective targeted therapy for sepsis requires an understanding of the heterogeneity in the individual host response to infection. We investigated this heterogeneity by defining interindividual variation in the transcriptome of patients with sepsis and related this to outcome and genetic diversity.

METHODS: We assayed peripheral blood leucocyte global gene expression for a prospective discovery cohort of 265 adult patients admitted to UK intensive care units with sepsis due to community-acquired pneumonia and evidence of organ dysfunction. We then validated our findings in a replication cohort consisting of a further 106 patients. We mapped genomic determinants of variation in gene transcription between patients as expression quantitative trait loci (eQTL).

FINDINGS: We discovered that following admission to intensive care, transcriptomic analysis of peripheral blood leucocytes defines two distinct sepsis response signatures (SRS1 and SRS2). The presence of SRS1 (detected in 108 [41%] patients in discovery cohort) identifies individuals with an immunosuppressed phenotype that included features of endotoxin tolerance, T-cell exhaustion, and downregulation of human leucocyte antigen (HLA) class II. SRS1 was associated with higher 14 day mortality than was SRS2 (discovery cohort hazard ratio (HR) 2·4, 95% CI 1·3-4·5, p=0·005; validation cohort HR 2·8, 95% CI 1·5-5·1, p=0·0007). We found that a predictive set of seven genes enabled the classification of patients as SRS1 or SRS2. We identified cis-acting and trans-acting eQTL for key immune and metabolic response genes and sepsis response networks. Sepsis eQTL were enriched in endotoxin-induced epigenetic marks and modulated the individual host response to sepsis, including effects specific to SRS group. We identified regulatory genetic variants involving key mediators of gene networks implicated in the hypoxic response and the switch to glycolysis that occurs in sepsis, including HIF1α and mTOR, and mediators of endotoxin tolerance, T-cell activation, and viral defence.

INTERPRETATION: Our integrated genomics approach advances understanding of heterogeneity in sepsis by defining subgroups of patients with different immune response states and prognoses, as well as revealing the role of underlying genetic variation. Our findings provide new insights into the pathogenesis of sepsis and create opportunities for a precision medicine approach to enable targeted therapeutic intervention to improve sepsis outcomes.

Rozdílný transkriptom imunitní odpovědi (leukocytů) u pacientů se sepsí s vlivem na výsledný outcome. Východisko pro predikci pacientů profitujících z cílené imunomodulační terapie

Proteomika

- **Expresní proteomika – identifikace biomarkerů specifických pro sepsi**
- **Funkční proteomika – identifikace proteinů a jejich funkce na molekulární úrovni**

Arch. Immunol. Ther. Exp. (2017) 65:37–49

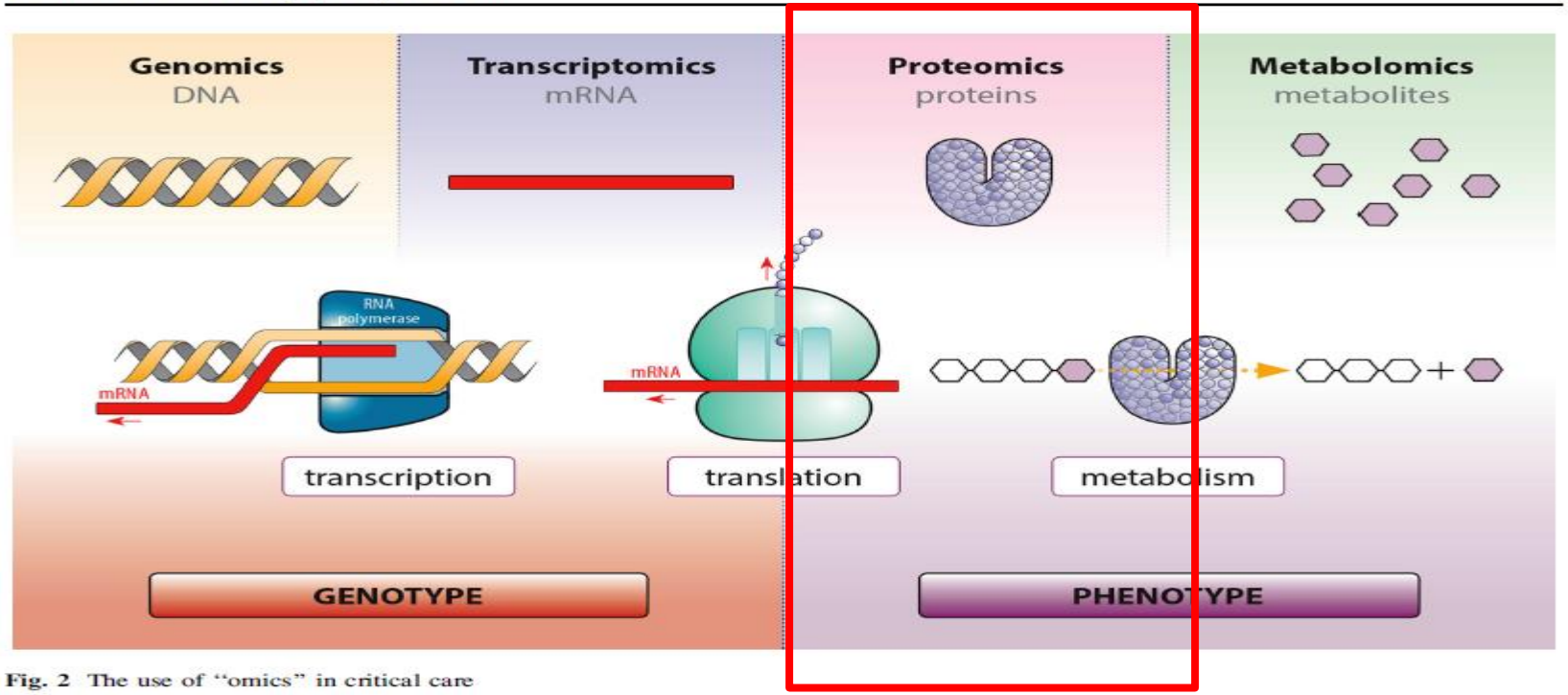


Fig. 2 The use of "omics" in critical care

PLoS One. 2011;6(10):e26111. doi: 10.1371/journal.pone.0026111. Epub 2011 Oct 10.

Proteomics mapping of cord blood identifies haptoglobin "switch-on" pattern as biomarker of early-onset neonatal sepsis in preterm newborns.

Buhimschi CS[1], Bhandari V, Dulay AT, Nayeri UA, Abdel-Razeq SS, Pettker CM, Thung S, Zhao G, Han YW, Bizzarro M, Buhimschi IA.

Author information

Abstract

BACKGROUND: Intra-amniotic infection and/or inflammation (IAI) are important causes of preterm birth and early-onset neonatal sepsis (EONS). A prompt and accurate diagnosis of EONS is critical for improved neonatal outcomes. We sought to explore the cord blood proteome and identify biomarkers and functional protein networks characterizing EONS in preterm newborns.

METHODOLOGY/PRINCIPAL FINDINGS: We studied a prospective cohort of 180 premature newborns delivered May 2004-September 2009. A proteomics discovery phase employing two-dimensional differential gel electrophoresis (2D-DIGE) and mass spectrometry identified 19 differentially-expressed proteins in cord blood of newborns with culture-confirmed EONS (n=3) versus GA-matched controls (n=3). Ontological classifications of the proteins included transfer/carrier, immunity/defense, protease/extracellular matrix. The 1(st)-level external validation conducted in the remaining 174 samples confirmed elevated haptoglobin and haptoglobin-related protein immunoreactivity (Hp&HpRP) in newborns with EONS (presumed and culture-confirmed) independent of GA at birth and birthweight (P<0.001). Western blot concurred in determining that EONS babies had conspicuous Hp&HpRP bands in cord blood ("switch-on pattern") as opposed to non-EONS newborns who had near-absent "switch-off pattern" (P<0.001). Fetal Hp phenotype independently impacted Hp&HpRP. A bayesian latent-class analysis (LCA) was further used for unbiased classification of all 180 cases based on probability of "antenatal IAI exposure" as latent variable. This was then subjected to 2(nd)-level validation against indicators of adverse short-term neonatal outcome. The optimal LCA algorithm combined Hp&HpRP switch pattern (most input), interleukin-6 and neonatal hematological indices yielding two non-overlapping newborn clusters with low (≤20%) versus high (≥70%) probability of IAI exposure. This approach reclassified ~30% of clinical EONS diagnoses lowering the number needed to harm and increasing the odds ratios for several adverse outcomes including intra-ventricular hemorrhage.

CONCLUSIONS/SIGNIFICANCE: Antenatal exposure to IAI results in precocious switch-on of Hp&HpRP expression. As EONS biomarker, cord blood Hp&HpRP has potential to improve the selection of newborns for prompt and targeted treatment at birth.

PMID: 22028810 [PubMed - indexed for MEDLINE] PMCID: PMC3189953 Free PMC Article

Anesthesiology. 2010 Apr;112(4):926-35. doi: 10.1097/ALN.0b013e3181d049f0.

Plasma proteome to look for diagnostic biomarkers of early bacterial sepsis after liver transplantation: a preliminary study.

Paugam-Burtz C[1], Albuquerque M, Baron G, Bert F, Voitot H, Delefosse D, Dondero F, Sommacale D, Francoz C, Hanna N, Belghiti J, Ravaud P, Bedossa P, Mantz J, Paradis V.

Author information

Abstract

BACKGROUND: While outcome continuously improves after liver transplantation, sepsis remains the leading cause of early postoperative mortality. Diagnosis of infections remains particularly difficult in these patients. This study used plasma profiling coupling Proteinchip array with surface-enhanced laser desorption ionization time-of-fly mass spectrometry to search for biomarkers of postoperative sepsis in patients who underwent liver transplantation.

METHODS: Diagnosis of sepsis at day 5 relied on widely accepted clinical signs and positive culture of microbiologic samples. Profiles of day 5 plasma were obtained from SELDI-TOF CM10 chip (BioRad, Marnes-la-Coquette, France) analysis. Mean peak intensity of proteins was compared between septic and nonseptic plasma by U test followed by analysis of the area under the receiver-operating characteristic for the significant peaks. Diagnostic performance of significant proteins was established in a derivation set and in a validation set.

RESULTS: In the derivation set of 31 patients with and 30 without infection, 23 plasma protein peaks were differentially expressed between patients with and without sepsis. Combination of five peaks allowed sepsis diagnosis with a positive likelihood ratio of 12.5 and a C-statistics of 0.72, 95% CI 0.57-0.85. In the validation set of 31 patients with infection and 34 without infection, the five peaks were differentially expressed as well and allowed day 5 sepsis diagnosis with a positive likelihood ratio of 5.1 and C-statistics of 0.74 (0.58-0.85).

CONCLUSION: A combination of five plasma protein peaks may provide material for useful diagnostic biomarkers of postoperative sepsis in patients undergoing liver transplantation. However, these proteins remain to be identified.

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Metabolomika

- **Komplexní analýza metabolomu za konkrétního fyziologického nebo patologického stavu organismu, tkáně či buňky**
- **Poskytuje cenné informace jak z hlediska diagnostiky, tak výsledného outcome a identifikace rizikových pacientů**

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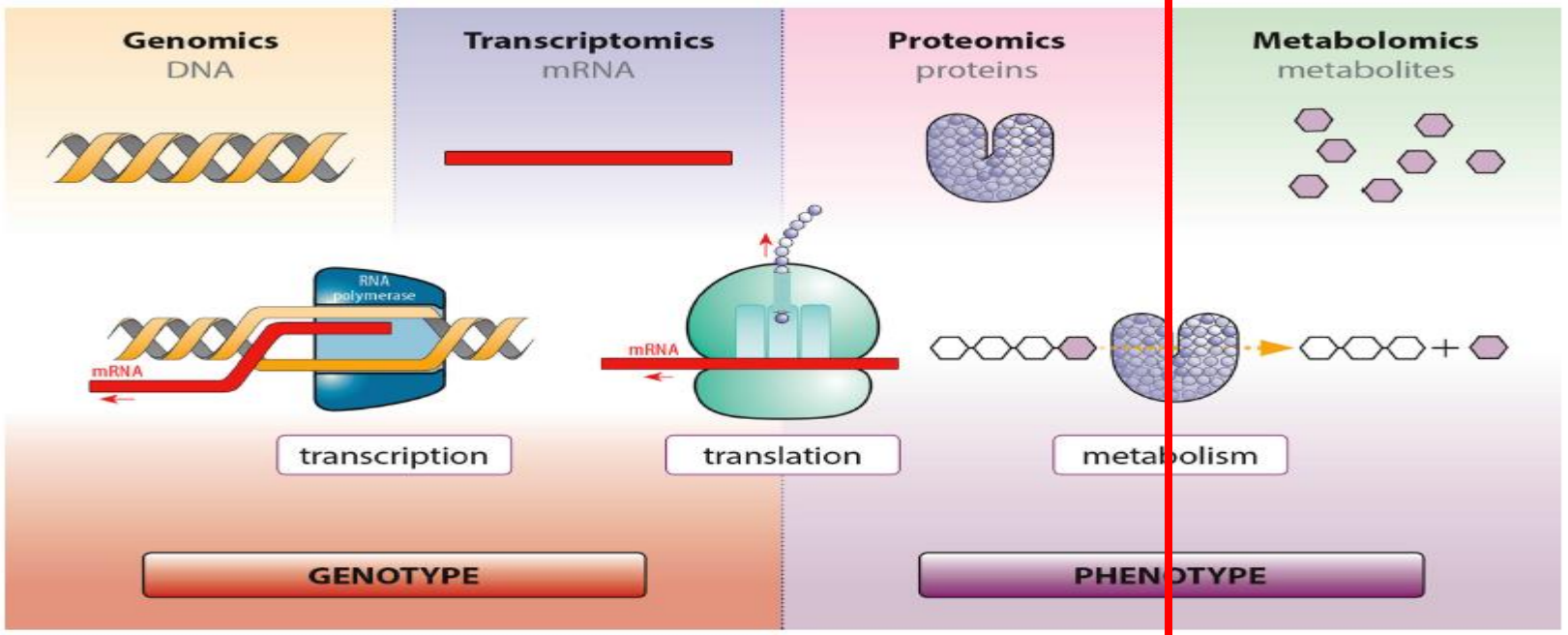

Fig. 2 The use of "omics" in critical care

PLOS | ONE

DIAGNOSTIKA

6 metabolitů
Kyselina myristová
Sensitivita 1,0 !!
Specificita 0,95

RESEARCH ARTICLE

Metabolites in Blood for Prediction of Bacteremic Sepsis in the Emergency Room

Anna M. Kauppi[1], Alicia Edin[1], Ingrid Ziegler[2], Paula Mölling[3], Anders Sjöstedt[1], Åsa Gylfe[1], Kristoffer Strålin[4], Anders Johansson[1]*

1 Department of Clinical Microbiology, Clinical Bacteriology, the Laboratory for Molecular Infection Medicine Sweden and Umeå Centre for Microbial Research, Umeå University, Umeå, Sweden, **2** Department of Infectious Diseases, Örebro University Hospital, Örebro, Sweden, **3** Department of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, **4** Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

* anders.f.johansson@umu.se

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Abstract

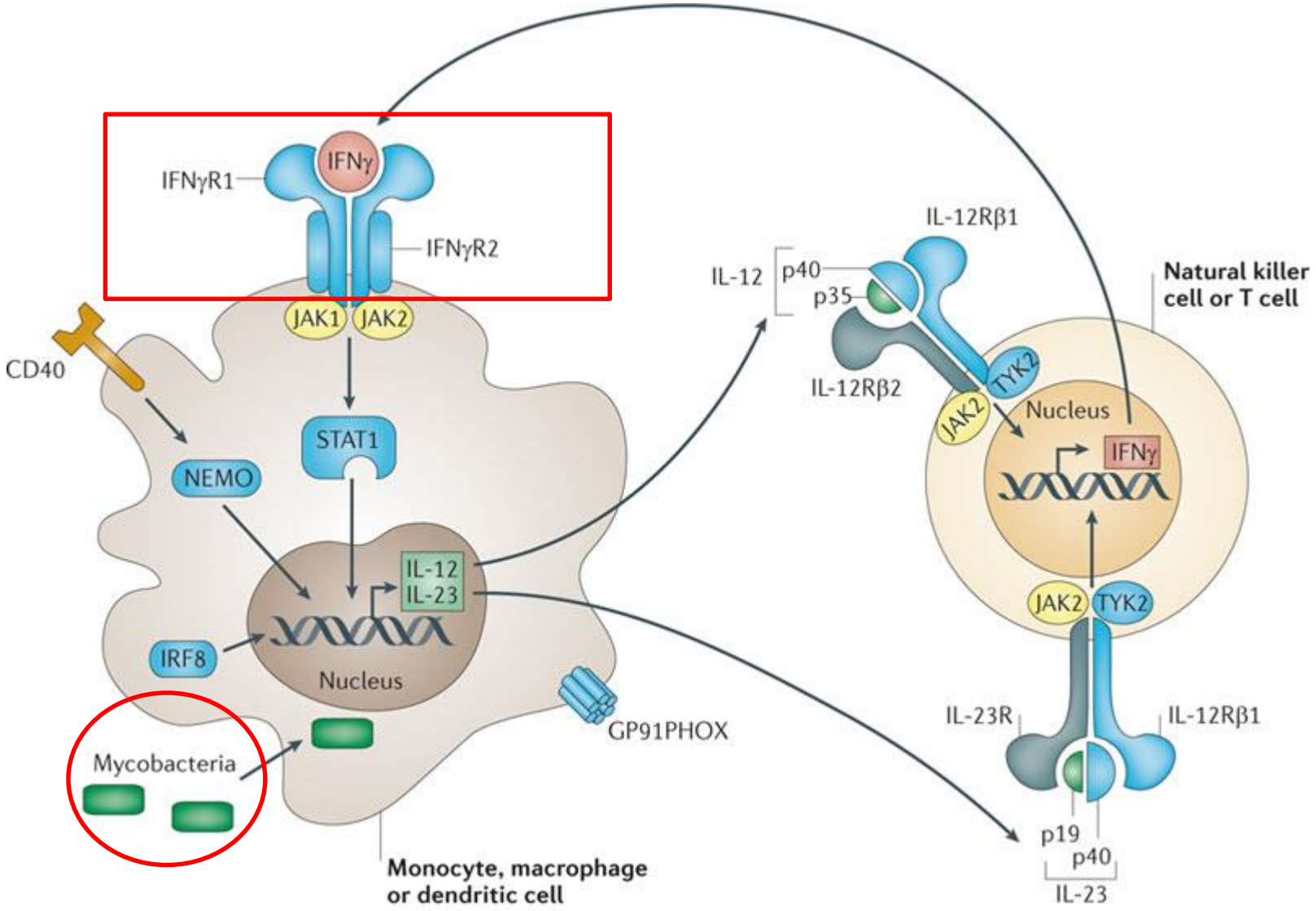
A metabolomics approach for prediction of bacteremic sepsis in patients in the emergency room (ER) was investigated. In a prospective study, whole blood samples from 65 patients with bacteremic sepsis and 49 ER controls were compared. The blood samples were analyzed using gas chromatography coupled to time-of-flight mass spectrometry. Multivariate and logistic regression modeling using metabolites identified by chromatography or using conventional laboratory parameters and clinical scores of infection were employed. A predictive model of bacteremic sepsis with 107 metabolites was developed and validated. The number of metabolites was reduced stepwise until identifying a set of 6 predictive metabolites. A 6-metabolite predictive logistic regression model showed a sensitivity of 0.91 (95% CI 0.69–0.99) and a specificity 0.84 (95% CI 0.58–0.94) with an AUC of 0.93 (95% CI 0.89–1.01). Myristic acid was the single most predictive metabolite, with a sensitivity of 1.00 (95% CI 0.85–1.00) and specificity of 0.95 (95% CI 0.74–0.99), and performed better than various combinations of conventional laboratory and clinical parameters. We found that a metabolomics approach for analysis of acute blood samples was useful for identification of patients with bacteremic sepsis. Metabolomics should be further evaluated as a new tool for infection diagnostics.

Farmakogenomika

Tomek et al: Impact of CYP2C19 Polymorphisms on Clinical Outcomes and Antiplatelet Potency of Clopidogrel in Caucasian Post- Stroke Survivors

- Clopidogrel
- Warfarin CYP2C9 (CYP2C9*1 , *2 a *3(90% redukce) 2-6% prevalence Caucasian a VKOR1
- Pradaxa – CES1 – RS2244613
- Imuran – TPMT (Thiopurinmethyltransferaza)

MSMD – Mendelian susceptibility to mycobacterial disease
detekce vlastního genomu



MSMD

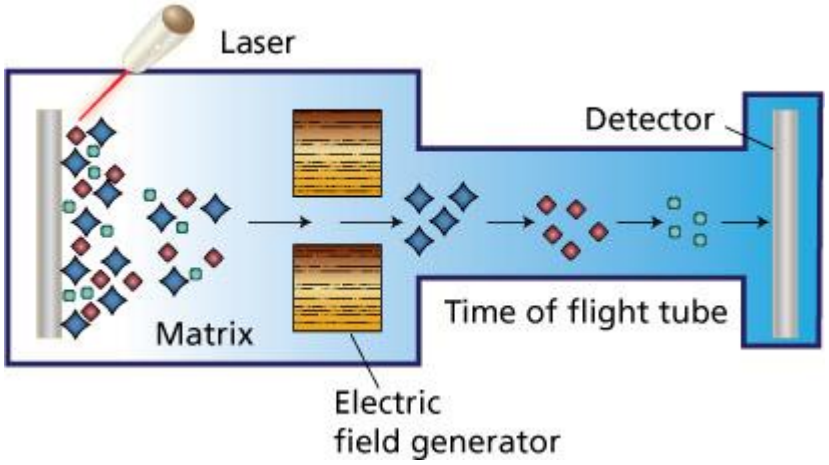
- 42 letá pacientka
- BCG vakcinace bez problémů, v 5 letech TBC uzlin,v 18 letech erythema nodosum – povazováno mylně za sarkoidozu a léčeno KS asi rok…exacerbace – postižení kostí, měkkých tkání, nosní přepážky…M. avium, lentiflavum…
- NGS (Next Gene Sequencing) parciální defekt genu pro receptor pro IFN ɣ
- Léčba - Imukin

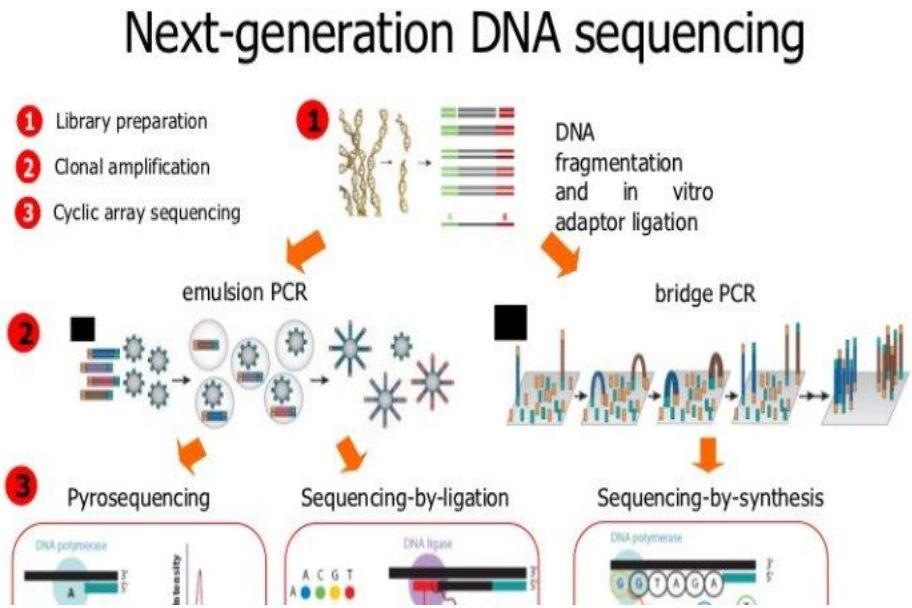
Detekce cizího genomu

- 40 letý muž
- Orální sex
- Zduření lymfatických uzlin , výtok, otok….
- Neúspěšná kultivace včetně PCR (chlamydie, sexuálně přenosné choroby
- Neúspěšná léčba ATB a podpůrná imunomodulační terapie
- NGS – Prevotella spp.

Závěry

- **Nové technologie – MALDI TOF, Next Generation Sequencing, Nukleární magnetická rezonance a jejich uplatnění v kontextu personalizované mediciny**





Závěry

- Diagnostika infekčního agens
- Nalezení nových biomarkerů, jejich role v prognóze a predikci odpovědi na léčbu
- Diagnostika aktuální imunokompetence pacienta a nové poznatky o patogenezi sepse

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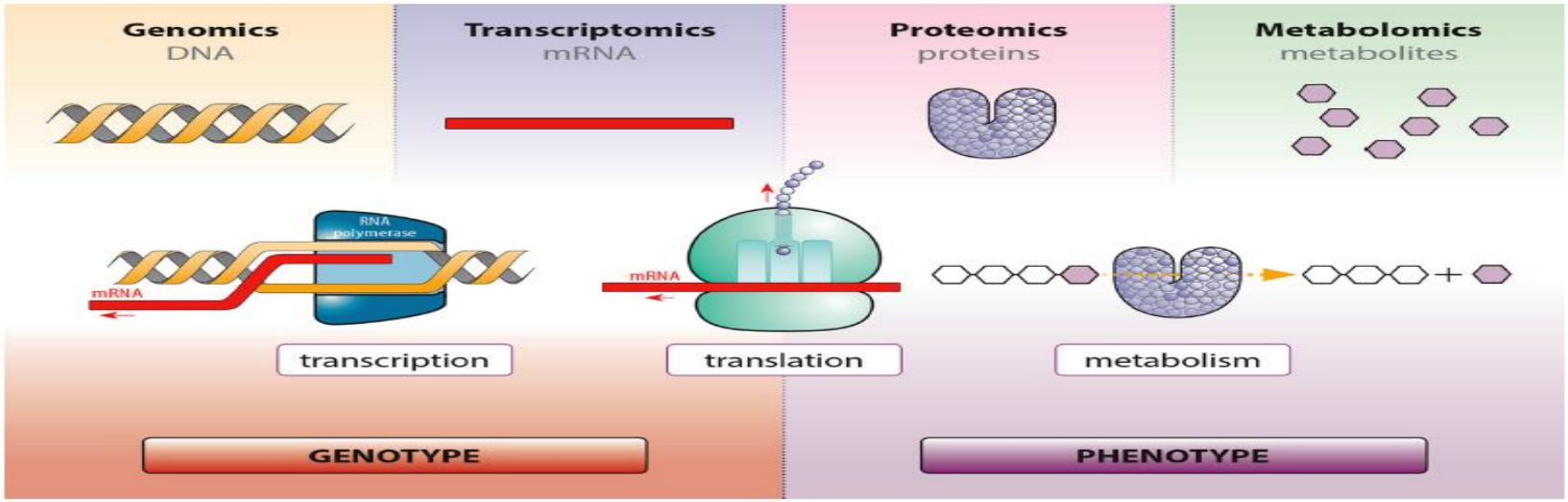

Fig. 2 The use of "omics" in critical care

Závěry

- **Nejdůležitější je lékař u lůžka pacienta – s jeho vědomostmi, technologiemi a „uměním“ medicíny**