Molecular Subclasses of Sepsis

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Canada Critical Care Forum
November 7, 2018
Disclosures

• Funding from National Institute of General Medical Sciences and Eunice Kennedy Shriver National Institute of Child Health and Human Development:
  • R35GM126943
  • R21HD092869
  • R01GM108025
  • T32GM008478
  • R43GM125418.

• Sepsis biomarker-related patents issued and pending.

• Scientific advisory board:
  • *Inflammatix*
  • *Eccrine Systems*
  • *Endpoint Health*
“Molecular Subclasses of Sepsis”

“Subgroup”  “Subclass”  “Subtype”

“Subphenotype”  “Endotype”
“Molecular Subclasses of Sepsis”

“Subgroup” “Subclass” “Subtype”

“Subphenotype” “Endotype”

“Gene expression-based subgroups of sepsis”
Gene Expression Based Subgroups of Sepsis

**Approach**

- **Microarray-based, whole genome expression profiling**
- **Whole blood-derived mRNA**

**Statistics to identify genes differentially regulated**

**Validation**

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

Emma E Davenport, Katie L Burnham, Jayashrand Raadhakrishnan, Peter Humbug, Paula Hutton, Tara C Mills, Anna Rautanen, Anthony C Gordon, Christopher Garrard, Adrian V S Hill, Charles J Hinds, Julian C Knight

- UK Genomic Advances in Sepsis (GAinS) study
- Adults with sepsis 2° CAP

- 2 subgroups: “Sepsis Response Signature (SRS) 1 & 2
- SRS1 with features of immune suppression:
  - Endotoxin tolerance
  - T cell exhaustion
  - ↓ expression of HLA class II
- SRS1: greater 14-day mortality
Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

Brendon P Scicluna, Lonneke A van Vught, Aeliko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium*

- Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project
- Adults with sepsis

- 4 subgroups: Mars 1, 2, 3, and 4
- Mars1 characterized by ↓ expression of genes corresponding to innate and adaptive immunity
- Mars1: greater 28-day mortality
Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters

Clustering of all publically available transcriptomic data from patients with sepsis; adults and children

- 3 subgroups:
  - Inflammopathic
  - Adaptive
  - Coagulopathic

- Coagulopathic group: higher mortality
Children with septic shock

- 2 subgroups: endotypes A and B
- Endotype A: ↓ expression of genes reflecting adaptive immunity and GCR signaling
- Higher mortality and organ failure burden among endotype A patients
- Corticosteroid prescription independently associated with increased mortality risk in endotype A
Important nuance(s)...

- All of these studies report important outcome differences between subgroups.
- But, this is not the main goal of these efforts.
- The main goal is identifying subgroups with biological commonalities, having the potential to inform therapy: *Predictive Enrichment*.
- The differences in outcome strengthen (perhaps) the clinical relevance of the subgroups.
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Lancet Respir Med. 4:259, 2016

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Lancet Respir Med. 5:816, 2017

Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters

Timothy E. Sweeney, MD, PhD1,2; Tej D. Azad1;2; Michele Donato, PhD1;1; Winston A. Haynes1;2; Thannwar M. Perunath, PhD; Ricardo Henao, PhD2; Jesus E. Bermejo-Martin, MD, PhD; Raquel Almansa, PhD2; Eduardo Tamayo, MD, PhD;2; Judith A. Hoory Shak, MD; Augustine Choi, MD2; Grant P. Parnell, PhD; Benjamin Tang, MD3;4; Marshall Nichols, MS; Christopher W. Woods, MD3;4; Geoffrey S. Ginsburg, MD, PhD; Stephen F. Kingsmore, MD, DSc;1; Larsson Omberg, PhD2; Lara M. Mangravite, PhD3; Hector R. Wong, MD1;2; Ephraim L. Tsalik, MD4;1;4; Raymond J. Langley, PhD3; Purvesh Khatri, PhD1;2

Crit Care Med. 46:915, 2018

Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong1;2, Natalie Z. Cvijanovich3, Nick Anas4, Geoffrey L. Allen5, Neal J. Thomas6, Michael T. Bigham7, Scott L. Weiss8, Julie Fitzgerald6, Paul A. Cechcia9, Keith Meyer10, Thomas P. Shanley11, Michael Quasney11, Mark Hall12, Rainer Gedeit13, Robert J. Freishtat14, Jeffrey Nowak15, Raj S. Shekhar16, Shira Gertz17, Emily Dawson18, Kelli Howard1, Kelli Harmon1, Eileen Beckman1, Erin Frank1, and Christopher J. Lindsell18

Nonsense?

All are saying the same thing, but through different gene signatures?

We don’t yet know what all this means?
Commonalities Across the Four Strategies

• Generated using whole genome transcriptomic data and discovery-oriented clustering algorithms: “unbiased” subgroup discovery.

• All describe a subgroup with gene expression patterns corresponding to the adaptive immune system.
Immune “enhancing” therapies are actively being considered for sepsis...

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Immuno-suppression in sepsis: A novel understanding of the disorder and a new therapeutic approach

Richard S. Hotchkiss, Guillaume Moncarn, Elvis Poyen

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The new normal: immunomodulatory agents against sepsis immune suppression

Noelle A. Hutchins¹, Jacqueline Unsinger², Richard S. Hotchkiss², and Alfred Ayala¹

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Invited review

Immunotherapy: A promising approach to reverse sepsis-induced immunosuppression

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¹ Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA
² Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA
Commonalities Across the Four Strategies

• Generated using whole genome transcriptomic data and discovery-oriented clustering algorithms: “unbiased” subgroup discovery.
• All describe a subgroup with gene expression patterns corresponding to the adaptive immune system.
• But, adaptive immune dysfunction is inferred from gene expression, rather than shown directly.
• All show an association between subgroup membership and outcome.
Subgroup Overlaps?

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

Emma E Davenport, Katie L Burnham*, Joyachandran Radhakrishnan*, Peter Hemburg, Paula Hutton, Tara C Mills, Anna Routanne, Anthony C Gordon, Christopher Garrard, Adrian V S Hill, Charles J Hinds, Julian C Knight

Lancet Respir Med. 4:259, 2016

Is SRS1 similar to pediatric septic shock endotype A?

Overlap in signaling pathway enrichment (adaptive immunity)

Minimal overlap in subgroup-defining genes
Subgroup Overlaps?

Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

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Overlap between Mars3 and SRS2

Mars3 not detected among children with septic shock
Subgroup Overlaps?

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Crit Care Med. 46:915, 2018

Overlap between SRS1/2, pediatric septic shock endotype A/B, and inflammopathetic/adaptive clusters
# Pediatric Sepsis Endotypes Among Adults With Sepsis

Hector R. Wong, MD\textsuperscript{1,2}; Timothy E. Sweeney, MD, PhD\textsuperscript{3,4}; Kimberly W. Hart, MA\textsuperscript{5}; Purvesh Khatri, PhD\textsuperscript{3,4}; Christopher J. Lindsell, PhD\textsuperscript{5}

*Crit Care Med. 45:e1289, 2017*

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**GAinS Study**

**Pediatric Septic Shock**

**Nomenclature**

- SRS1/2

**Biological Features**

- Endotoxin tolerance, T-cell exhaustion, and repression of HLA class II in SRS1

**Clinical Association**

- Increased mortality in SRS1
Pediatric endotypes among adults with sepsis

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<th>Endotype B</th>
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<tr>
<td>SRS1</td>
<td>18</td>
<td>127</td>
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<tr>
<td>SRS2</td>
<td>112</td>
<td>114</td>
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Phi coefficient = 0.36, P < 0.001
There is statistically significant association between endotype assignment and SRS membership, but there is insufficient overlap to conclude redundancy.
Interaction Between Endotype, SRS, and Age
Interaction Between Endotype, SRS, and Age
Data harmonization and “consensus” gene expression based subgroups forthcoming...
Precedent for consensus molecular subgroups

The consensus molecular subtypes of colorectal cancer

Justin Guinney1,21, Rodrigo Dienstmann1,2,21, Xin Wang3,4,21, Aurélien de Reyniès5,21, Andreas Schlicker6,21, Charlotte Soneson7,21, Laetitia Marisa5,21, Paul Roepman8,21, Gift Nyamundanda9,21, Paolo Angelino7, Brian M Bot1, Jeffrey S Morris10, Iris M Simon8, Sarah Gerster7, Evelyn Fessler3, Felipe De Sousa E Melo3, Edoardo Missiaglia7, Hena Ramay7, David Barras7, Krisztian Homicsko11, Dipen Maru10, Ganiraju C Manyam10, Bradley Broom10, Valerie Boige12, Beatriz Perez-Villamil13, Ted Laderas1, Ramon Salazar14, Joe W Gray15, Douglas Hanahan11, Josep Taberner02, Rene Bernards0, Stephen H Friend1, Pierre Laurent-Puig16,17,22, Jan Paul Medema3,22, Anguraj Sadanandam9,22, Lodewyk Wessels6,22, Mauro Delorenzi7,18,19,22, Scott Kopetz10,22, Louis Vermeulen3,22 & Sabine Tejpar20,22

Colorectal cancer (CRC) is a frequently lethal disease with heterogeneous outcomes and drug responses. To resolve inconsistencies among the reported gene expression–based CRC classifications and facilitate clinical translation, inspection of the published gene expression–based CRC classifications2–9 revealed only superficial similarities. For example, all of the groups identified one tumor subtype enriched for microsatellite instability (MSI) and one subtype characterized by high expression
Take home messages...

• Four independent research groups have recently reported and validated gene expression-based subgroups of sepsis.

• All share the common theme of immune dysfunction, adaptive immunity in particular.

• All report associations with subgroup membership and risk of mortality, but this is not the main point.

• The main point is subgroups with biological commonalities, which could potentially be targeted therapeutically.

• It is unclear whether the four groups are describing the same thing, albeit via different gene signatures.

• The opportunity exists for harmonizing these subgroup classification systems and reaching a consensus for defining clinically relevant, molecular subgroups of sepsis.
Thank You