DATA NOTE

Blood transcriptome analysis of patients with uncomplicated bacterial infection and sepsis

Velma Herwanto1,2,3, Benjamin Tang1,2, Ya Wang1,2, Maryam Shojaei1,2, Marek Nalos1, Amith Shetty4,5, Kevin Lai5, Anthony S. McLean1 and Klaus Schughart6,7,8*

Abstract

Objectives: Hospitalized patients who presented within the last 24 h with a bacterial infection were recruited. Participants were assigned into sepsis and uncomplicated infection groups. In addition, healthy volunteers were recruited as controls. RNA was prepared from whole blood, depleted from beta-globin mRNA and sequenced. This dataset represents a highly valuable resource to better understand the biology of sepsis and to identify biomarkers for severe sepsis in humans.

Data description: The data presented here consists of raw and processed transcriptome data obtained by next generation RNA sequencing from 105 peripheral blood samples from patients with uncomplicated infections, patients who developed sepsis, septic shock patients, and healthy controls. It is provided as raw sequenced reads and as normalized log2 transformed relative expression levels. This data will allow performing detailed analyses of gene expression changes between uncomplicated infections and sepsis patients, such as identification of differentially expressed genes, co-regulated modules as well as pathway activation studies.

Keywords: Sepsis, Uncomplicated infection, Whole blood transcriptome

Objective

Sepsis is one of the most significant disease burdens in the world [1]. A better understanding of its disease mechanism is urgently needed to facilitate development of new therapy for sepsis. Several putative disease mechanisms have been suggested, including endothelial dysfunction, coagulation dysregulation and abnormal immune response [2]. Among these, abnormal immune response is thought to play the most critical role [3]. The abnormal immune response in sepsis is characterized by impaired innate and adaptive immune responses; both of which have been shown to strongly correlate with poor patient outcomes (e.g. increased secondary infection and reduced survival) [4, 5]. Recent studies aimed to determine pathways that are associated with impaired cellular metabolism in the immune cells of sepsis patients [6, 7]. These studies have identified several defective cellular pathways (e.g. inhibited mitochondrial complex activity and oxygen consumption, reduced ATP production) across different sepsis populations [8, 9] However, these studies share a common limitation—they were conducted in patients with established sepsis or in the late stage of sepsis. As a result, it is uncertain whether impaired cellular metabolism are also present in the immune cells of infected patients prior to the development of sepsis. Here, we report raw and processed transcriptome data obtained by next generation RNA sequencing from peripheral blood samples of patients with uncomplicated
infections, patients who developed sepsis and septic shock patients.

Data description

Patients with infection were recruited from the emergency department. Subjects were eligible if they aged 18 years or older; presented within the last 24 h with an infection, defined as either (1) positive pathogen identification in any body fluids sampled for microbiological culture, or (2) a suspicion of infection (as determined by the treating physician) and received antibiotics. Exclusion criteria: (1) decision not to actively treat or resuscitate the patient at admission; and (2) inability to consent the patient. The study participants were assigned into sepsis and uncomplicated infection groups, based on their Sequential Organ Failure Assessment (SOFA) score on admission ($\geq 2$ vs. $<2$), in accordance with the international consensus definition of sepsis (“Sepsis-3”)\[10\]. Septic shock subjects were recruited from the department of intensive care medicine of Nepean Hospital, New South Wales, Australia from December 2017 to February 2019. Recruited septic shock subjects had to fulfil the sepsis criteria as above with persisting hypotension requiring a vasopressor to maintain mean arterial pressure $\geq 65$ mmHg and having a serum lactate level $>2$ mmol/L despite adequate volume resuscitation as defined in Sepsis-3 [10]. Healthy volunteers, aged 18 or older, from different age groups were recruited at the Westmead Institute for Medical Research and in Magdeburg, Germany. Healthy subjects with recent (within prior 14 days) infection/under antimicrobial medication and subjects under immunosuppressive drugs were not included in the study.

Whole blood was collected on admission and another blood sample was collected 3–5 days later for follow up (FU samples). It was collected in PAXgene Blood RNA tubes and RNA was isolated using PAXgene Blood RNA Kit. Globin mRNA was depleted from total RNA and a strand-specific RNA sequencing library was generated. The library was sequenced with an average of 40 million reads per RNA sample. Reads were quality checked, then trimmed. Trimmed reads were mapped to the human genome and mapped reads were counted. Residual reads to beta-globin were set to 1000. Raw counts were then normalized and $\log_2$ transformed using DESeq2 (version 1.16.1, [11]). Sex was validated by gene expression for Y-specific genes and corrected if different from recorded sex.

Data are provided as raw sequence data and as normalized $\log_2$ transformed relative expression values. In addition, we provide a quality control report, a summary statistics for the patients, a detailed sample description for each patient with age, sex, and infection severity (40 Healthy $= \text{Hlty}$, 12 uncomplicated infections $= \text{Inf1}_P$, 20 sepsis $= \text{Seps}_P$, 19 septic shock $= \text{Shock}_P$, 4 follow-up sepsis $= \text{Seps}_\text{FU}$, 10 follow-up septic shock $= \text{Shock}_\text{FU}$), and a detailed material and methods description.

Our dataset represents a highly valuable resource to study the biology of sepsis and to evaluate biomarkers for severe sepsis in humans which may allow prognoses of development of severe disease. It will allow to perform more detailed analyses of the gene expression changes between uncomplicated infections and sepsis patients, such as identification of differentially expressed genes, co-regulated modules as well as pathway activation studies. Furthermore, our data provides a valuable resource to replicate and validate findings from other studies (Table 1).

| Table 1 | Overview of data files/data sets |
| ------- | ------------------------------- |
| Label   | Name of data file/data set     | File types (file extension) | Data repository and identifier (DOI or accession number) |
| Data file 1 | Raw sequence files | Fastq | Sequence Read Archive https://identifiers.org/ncbi/insdc.sra:SRP273118 |
| Data file 2 | Normalized expression values | Text (txt) | Gene Expression Omnibus (https://identifiers.org/geo:GSE154918) |
| Data set 3 | ST1_QC_Sepsis_080221.xlsx | Excel | Figshare https://doi.org/10.6084/m9.figshare.13740400.v1 |
| Data set 4 | ST2_summary_table_080221.xlsx | Excel | Figshare https://doi.org/10.6084/m9.figshare.13740400.v1 |
| Data set 5 | ST3_Patients_characteristics_080221.xlsx | Excel | Figshare https://doi.org/10.6084/m9.figshare.13740400.v1 |
| Data set 6 | ST4_Material_Methods_080221.docx | Word | Figshare https://doi.org/10.6084/m9.figshare.13740400.v1 |
Acknowledgements

We would like to thank Joey Lai for checking the quality control of the RNA and Sally Teoh for recruiting the healthy volunteers, and Tracy Chew for her input in the analysis. We thank Jennifer Fricke for excellent technical assistance. Next generation sequencing was performed by Novogene, Sacramento, CA.

Authors’ contributions

BT, VH, AM conceived and designed the study. VH, YW, MN, AS, KL performed samples collection. VH, YW, MS processed the samples. VH and KS analyzed the data. KS, VH and BT wrote the manuscript. All authors read and approved the final manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL. This work was supported by intra-mural grants from the Helmholtz-Association (Program Infection and Immunity), a start-up grant from the University of Memphis Tennessee Health Science Center, and NIH Research Grants 2-U19-AI100625-06 REVISED and SU19A100625-07 awarded to KS. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data materials

Raw transcriptome data are available in Sequence Read Archive: https://identifiers.org/ncbi/sra:SRP273118 [12]. Processed transcriptome data are available in Gene Expression Omnibus: https://identifiers.org/geo:GSE154918 [13]. The quality control report, a detailed sample description for each patient with age, sex, and sepsis status, and detailed description of Material and Methods are available in the figshare repository: https://doi.org/10.6084/m9.figshare.13740400.v1 [14].

Ethics approval and consent to participate

Written, informed consent from all study participants and ethical clearance to conduct this study was obtained from the Human Research Ethics Committee at Westmead Hospital (approval number LNR/17/NEPEAN/71) for sepsis patients, and for healthy control samples collected in Germany from the Ethics Committee of the Otto-von-Gericke-University (No 36/14, date 2.4.2014).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1 Department of Intensive Care Medicine, Nepean Hospital, Sydney, Australia. 2 Centre for Immunology and Allergy Research, The Westmead Institute for Medical Research, Sydney, Australia. 3 Faculty of Medicine, Universitas Tarumanagara, Jakarta, Indonesia. 4 Centre for Infectious Diseases and Microbiology, the Westmead Institute for Medical Research, Sydney, Australia. 5 Department of Emergency Medicine, Westmead Hospital, Sydney, Australia. 6 Department of Infection Genetics, Helmholtz Centre for Infection Research, Braunschweig, Germany. 7 University of Veterinary Medicine Hannover, Hannover, Germany. 8 Department of Microbiology, Immunology and Biochemistry, University of Tennessee Health Science Center, Memphis, TN, USA.

References

1. Rudd KE, Kissoon N, Limmathurosatsuk D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: barriers and potential solutions. Crit Care. 2018;22(1):232.
2. Gots JF, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016;353:i586.
3. Delano MJ, Ward PA. The immune system’s role in sepsis progression, resolution, and long-term outcome. Immunol Rev. 2016;274(1):330–53.
4. Jensen IU, Sjastad FV, Griffith TS, Badovinac VP. Sepsis-Induced T cell immunoparalysis: the ins and outs of impaired T cell immunity. J Immunol. 2018;200(5):1543–53.
5. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? J Clin Invest. 2016;126(1):23–31.
6. Garrabou G, Morén C, López S, Tobias E, Cardellach F, Miró O, Casademont J. The effects of sepsis on mitochondria. J Infect Dis. 2012;205(3):392–400.
7. Japiassú AM, Santiago AP, d’Avila JC, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, Bozza FA, Oliveira MF. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1F0 adenosine-5’-triphosphate synthase activity. Crit Care Med. 2011;39(5):1056–63.
8. Merz TM, Pereira AJ, Schürch R, Scheufeld JC, Jakob SM, Takala J, Djaifarzadeh S. Mitochondrial function of immune cells in septic shock: a prospective observational cohort study. PLoS ONE. 2017;12(6):e0178946.
9. Shalova IN, Lim JY, Chittezhath M, Zinkernagel AS, Beasley F, Hernández-Jiménez E, Toleldano Y, Cubillos-Zapata C, Rapisarda A, Chen J, et al. Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1α. Immunity. 2015;42(3):484–98.
10. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):802–10.
11. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 2014;15(12):550.
12. Schuchhart K. RNAseq analysis of blood from sepsis patients and healthy controls. NCBI Sequence Read Archive https://identifiers.org/ncbi/sra:SRP273118. 2020.
13. Schuchhart K. RNAseq analysis of blood from sepsis patients and healthy controls. Gene Expression Omnibus https://identifiers.org/geo:GSE154918. 2020.
14. Schuchhart K. Supplements: Blood transcriptome analysis of patients with uncomplicated bacterial infection and sepsis. Figshare https://doi. org/10.6084/m9.figshare.13740400.v1. 2021.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.