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LETTER

Sainath Raman
Nigel Klein
Antonia Kwan
Mike Hubank
Shamima Rahman
Asrar Rashid
Mark J. Peters

Oxidative phosphorylation gene expression falls at onset and throughout the development of meningococcal sepsis-induced multi-organ failure in children

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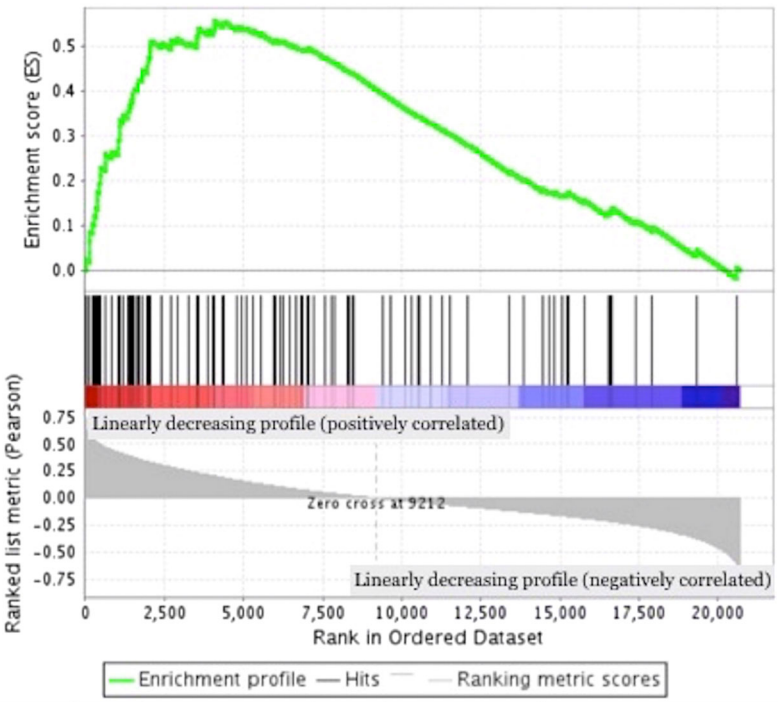
Dear Editor,

Sepsis-induced critical illness differs between adults and children. Children deteriorate more quickly and exhibit a 'cold shock' haemodynamic pattern more often. Organ failure scores characteristically peak earlier in septic children (<2 ICU days) than adults (days 3–4). A high proportion of deaths in children occur very early [1]. Yet, ICU stays are shorter and survival better in children [2]. Might these differences in clinical phenotype—more rapid onset and recovery—be due to differences in the underlying mechanisms of multi-organ failure (MOF)?

Acute mitochondrial dysfunction may contribute to MOF. Reduced mitochondrial oxygen utilisation and gene expression has been observed in established sepsis in adults and children [3]. There is an association between recovery of mitochondrial function and survival but the contribution to the onset of organ failure is less clear. We investigated whether mitochondrial oxidative phosphorylation gene expression (Oxphos) alters early enough in the clinical course of sepsis to remain a candidate element of MOF pathophysiology. To do this, we selected a population with the most rapid onset of profound sepsis-MOF: previously healthy children with acute meningococcal septicaemia. We investigated the time-course of gene expression in peripheral blood with gene set enrichment analysis (GSEA), at 0, 4, 8, 12, 24, and 48 h from time of admission to the emergency room. Extracted RNA was hybridised in Affymetrix microarrays. Methodological details are published elsewhere [4]. The dataset is available to download from the European Bioinformatics Institute database (ArrayExpress id: E-MEXP-3850). Emergency room venesection was designated time 0 as a pragmatic



Patient	NES	Nominal p value	FDR	RETC position	Gene sets with decreasing expression
Group	2.55	**<0.001**	0	75	1920

Fig. 1 Enrichment plot of the Respiratory Electron Transport Chain (RETC) gene set showing the normalised enrichment score (*NES*), the false discovery rate (*FDR*) and nominal *p* values for the gene set. Gene set enrichment analysis compares the variation in the gene expression in our overall dataset compared to a preselected gene set (RETC gene set) over the time-course. We have observed that RETC gene set expression is down-regulated more than would be expected by background variation in expression. The *top* portion of the plot shows the running enrichment score (*ES*) for the RETC gene set. The *middle* portion of the plot shows where the members of the gene set appear in the ranked list of genes. The *lower* portion of the plot shows the value of the ranking metric as you move down the list of ranked genes. The ranking metric measures a gene's correlation with a phenotype. For our continuous phenotype (time series), a *positive value* indicates correlation with the phenotype profile (decreasing profile)

reference time point while acknowledging that children may be at different stages of illness at presentation.

The GSEA ranks changes in single gene expression. It notes the distribution of elements of a predefined gene set in this overall ranked list. We focused on the Reactome TCA cycle and respiratory electron transport chain (RETC) genes within the 3655 included gene sets. GSEA describes the probability of a non-random distribution of RTEC elements within the ranked list [5].

On the group level analysis, with a false discovery rate (FDR) at <25 % and ranked according to their normalised enrichment score (NES), 1039 out of 3655 gene sets showed a decreasing profile with time. The RETC set was ranked 75th of the 1039 gene sets.

On the individual-level analysis and FDR <25 %, all five patients had a highly ranked fall in RETC set expression. Patient 1 showed a low correlation of RETC gene expression to a decreasing profile. This might be relevant as, unfortunately, this child died. Figure 1 shows the NES, FDR and nominal p values for the RETC set for the individual patients and the overall group.

Oxidative phosphorylation gene expression reduced early and continued to decrease for at least 48 h in septic critically ill children. These findings are consistent with mitochondrial dysfunction contributing to the development of organ failure in both adults and children despite the differences in sepsis phenotype in these groups.

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Conflicts of interest The authors do not have any competing interests.

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S. Raman (✉) · M. J. Peters
Respiratory, Critical Care and Anaesthesia Unit, University College London-Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
e-mail: sainath.raman@ucl.ac.uk

M. J. Peters
e-mail: mark.peters@ucl.ac.uk

N. Klein
Infectious Diseases and Immunology, University College London-Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
e-mail: n.klein@ucl.ac.uk

A. Kwan
Department of Pediatrics, University of California, San Francisco, CA, USA
e-mail: Antonia.Kwan@ucsf.edu

M. Hubank
Genetics and Genomic Medicine, University College London-Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
e-mail: m.hubank@ucl.ac.uk

S. Rahman
Genetics and Genomics Programme, University College London-Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

A. Rashid
EMBRACE, Sheffield Children's Hospital, Western bank, Sheffield S10 2TH, UK
e-mail: asrar@mac.com