


LETTER TO THE EDITOR

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Regulation of soluble CD127 protein release and corresponding transcripts expression in T lymphocytes from septic shock patients

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To the Editor,

Sepsis is the leading cause of death for critically ill patients. Septic patients develop T lymphocyte dysfunctions associated with increased mortality and nosocomial infections [1]. Therefore, IL-7 has been recently evaluated in a clinical trial to reverse these alterations [2]. IL-7 receptor (IL-7R) is composed of an IL-7-specific chain (CD127) and a common receptor γ -chain [3]. IL-7R exists in a soluble form (sCD127) [4], resulting from shedding from the cell surface or transcriptional regulation [5, 6]. Several transcripts missing the exon 6, coding for the transmembrane domain have been identified, such as IL7R3 [4, 6] and IL7R7 (Ensembl). We recently showed that plasmatic sCD127 concentration and whole blood IL7R3 transcript expression were decreased in septic shock [7, 8]. However, sCD127 protein and transcripts regulations in survivor and non-survivor patients differed, with higher sCD127 concentration and lower IL7R3 expression in non-survivors. Therefore, the regulation of soluble IL-7R in sepsis remains not fully understood.

In this study, we evaluated sCD127 release and corresponding transcripts IL7R3 and IL7R7 expressions in purified T cells from septic shock patients. After approval by local ethics committee, T cells were isolated from 32 septic shock patients (Table 1) and 31 healthy volunteers (HV) (Additional file 1).

For clinical parameters, categorial data are presented as numbers of cases and percentages of the total population in brackets. Continuous data and biological parameters are presented as medians and interquartile ranges [Q1-Q3]. Simplified Acute Physiology Score II (SAPS II) and Mac Cabe score were calculated on admission. Sequential Organ Failure Assessment (SOFA) score was measured after 24 h of intensive care unit stay. mHLA-DR (AB/C): number of anti-HLA-DR antibodies bound per monocyte.

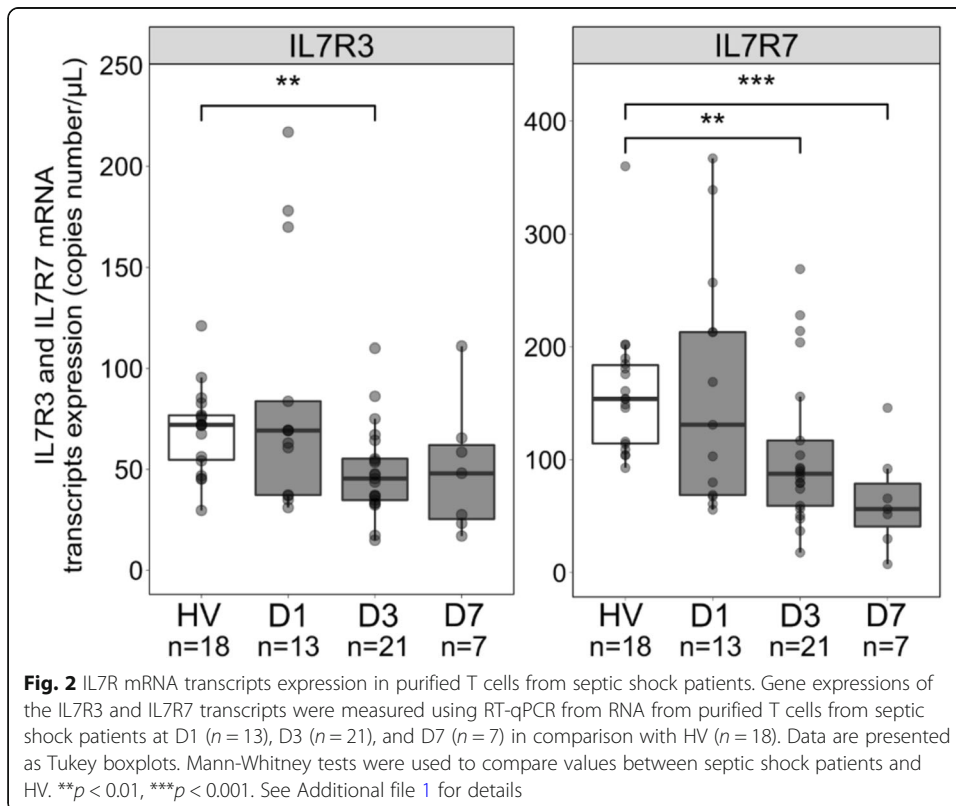
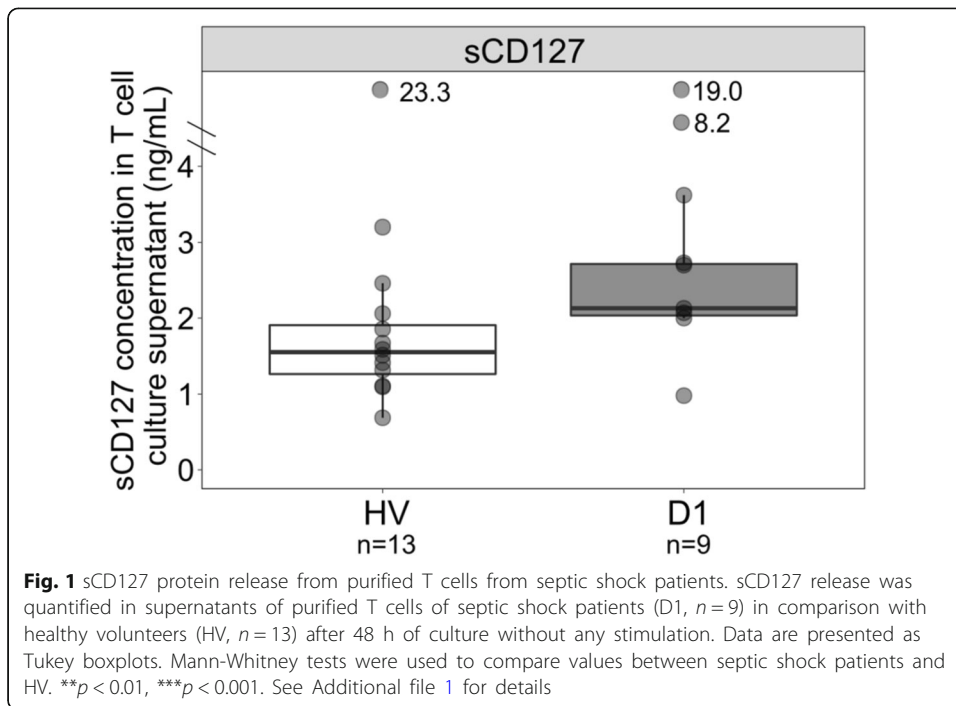
Interestingly, the sCD127 release tended to be higher in patients' T cells supernatant compared to HV (Fig. 1). This contrasts with the decreased plasmatic sCD127 concentration in septic shock patients [7], possibly impacted by lymphopenia. Both IL7R3 and IL7R7 transcripts expressions were decreased in septic shock patients' T cells (Fig. 2),

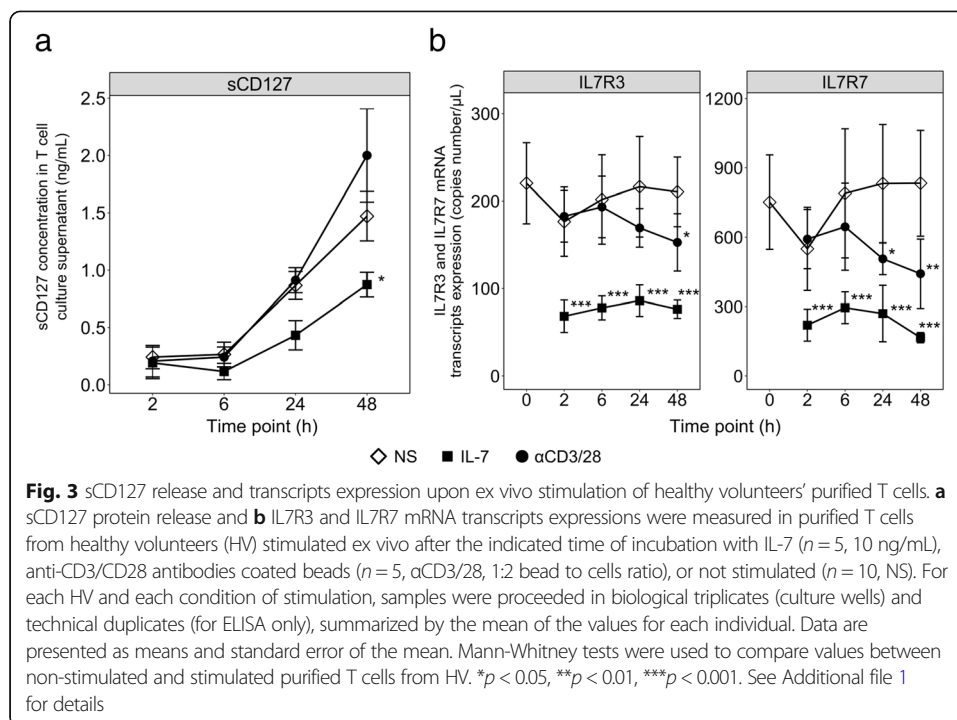
Table 1 Clinical characteristics of septic shock patients

Parameters	Septic shock patients (n = 32)
Sex, male	26 (68%)
Age, years	70 [62–76]
SAPS II score	61 [51–82]
SOFA score (n = 31)	9 [8–12]
Charlson co-morbidity score (n = 30)	
0	3 (10%)
1	14 (47%)
> 1	13 (43%)
Mac Cabe score (n = 31)	
Non-fatal diseases	21 (68%)
Ultimately fatal diseases	9 (29%)
Rapidly fatal diseases	1 (3%)
Initial infection	
Abdominal infection	16 (50%)
Pneumopathy	4 (12.5%)
Urinary infection	4 (12.5%)
Other	8 (25%)
Type of admission	
Medical	13 (41%)
Emergency surgery	18 (56%)
Elective surgery	1 (3%)
Microbiological documentation	
Gram negative	10 (31%)
Gram positive	7 (22%)
Other	1 (3%)
Non-documented	14 (44%)
Mortality at D28	9 (28%)
Lactate at D1 (mmol/L)	2.8 [1.7–5.6]
Lymphocytes at D3 (10 ⁹ /L)	1.05 [0.6–1.35]
mHLA-DR at D3 (AB/C)	8199 [3076–12,171]

as we previously observed in whole blood [8]. While whole blood IL7R3 and IL7R7 expressions may be impacted by sepsis-induced lymphopenia, these transcripts are also intrinsically regulated in T cells.

To delineate soluble IL-7R regulation in sepsis, we aimed to reproduce *ex vivo* its expression pattern observed in patients, by stimulating T cells from HV with IL-7 or TCR activation, known to regulate CD127 expression [9]. sCD127 was spontaneously released from non-stimulated T cells (Fig. 3a). During IL-7 stimulation, sCD127 protein release and transcripts expression decreased. In contrast, TCR activation induced an opposite regulation of sCD127 and corresponding transcripts (Fig. 3b): sCD127 concentration increased, as previously described [10], while IL7R7 and IL7R3 transcripts expressions decreased. This suggests that these transcripts are not the main source of sCD127 in this context, and that other mechanisms, such as shedding of membrane CD127, might occur. Overall, *ex vivo* TCR activation partly reproduced soluble IL-7R





expression pattern observed in septic shock, suggesting that the initial T cell activation shown to occur in sepsis [11, 12] could participate to soluble IL-7R regulation, both at the transcriptional and protein levels.

Altogether, we report here an intrinsic downregulation of IL-7R soluble transcripts in septic shock patients' T cells, independently of lymphopenia, in parallel with an increased sCD127 protein release. Ex vivo experiments in cells from HV suggest that initial T cell activation after sepsis might participate in this regulation, although this remains to be formally demonstrated.

Additional file

Additional file 1: Methods. (PDF 352 kb)

Abbreviations

HV: Healthy volunteer; IL-7R: IL-7 receptor; sCD127: Soluble CD127; α CD3/28: Anti-CD3/CD28 antibodies coated beads

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JM, CA, FV, and EP designed the experiments. JM and CA performed the experiments and the statistical analyses. All authors discussed the data, drafted or revised critically the manuscript for important intellectual content, and read and approved the final manuscript.

Ethics approval and consent to participate

Septic shock patients: this project was approved by our Institutional Review Board for ethics ("Comité de Protection des Personnes Sud-Est II"), which waived the need for informed consent, because this study was observational and performed on residual blood after completion of routine follow-up (#IRB 11236). This study is registered at the French Ministry of Research and Teaching (#DC-2008-509), at the Commission Nationale de l'Informatique et des Libertés and on clinicaltrials.gov (NCT02803346). Non-opposition to inclusion in the study was registered for each patient. Healthy volunteers: peripheral blood from healthy volunteers was provided by the "Etablissement Français du Sang" from Lyon. According to the standardized procedure for blood donation, written informed consent was obtained from healthy volunteers and personal data were anonymized at time of blood donation and before blood transfer to our research lab.

Consent for publication

Not applicable.

Competing interests

JM, JT, and EP are employees of bioMérieux. BD, FV, GM, EP, and JT are co-inventors on three patent families covering IL-7 receptor biomarkers. This work was supported by Association Nationale de la Recherche et de la Technologie (JM, Convention Industrielle de Formation par la Recherche convention 2015/060).

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