Journal of Exploratory Research in Pharmacology **2023** vol. 8(1) | 1–3
DOI: 10.14218/JERP.2022.00089

Editorial

Enolase-1 as a Prognostic Biomarker of Sepsis

Apostolos Zarros[1,2,3*]

[1]*Pharmacological Research Observatory, Glasgow, Scotland, UK;* [2]*College of Pharmacy, University of Babylon, Hillah, Iraq;* [3]*Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland, UK*

Received: November 28, 2022 | **Revised:** December 21, 2022 | **Accepted:** December 22, 2022 | **Published online:** January 29, 2023

Sepsis is characterized by high morbidity and mortality and is part of a complex clinical continuum (along with systemic inflammation and septic shock) that is associated with the dysregulation of the systemic immune response to an infection.[1] As is the case with other inflammatory syndromes, sepsis is also characterized by a complex pathophysiology and usually affects patients with multiple comorbidities, thereby complicating sepsis-focused trials with significant heterogeneity.[1] In this respect, the identification of biomarkers has become of paramount importance for the early detection, the classification, the therapeutic guidance, the prediction or the detection of complications, and the prognosis of sepsis.[1,2] Table 1 summarizes the most promising potential biomarkers of sepsis identified so far, as well as the nature of their function with regard to sepsis.[1]

In a study published in this journal, Xiao *et al*.[2] have undertaken a transcriptomic sequencing of mononuclear cells isolated from the peripheral blood samples of septic patients. The latter were divided into two groups based on the outcome of their hospitalization (i.e., survival or death), and the comparative analysis of the mononuclear cell transcriptomic sequences between these two groups has revealed a total of 475 differentially expressed genes (DEGs).[2] After employing a Gene Ontology-based functional annotation and a Kyoto Encyclopedia of Genes and Genomes-based pathway enrichment analysis, Xiao *et al*.[2] have revealed the DEGs exhibiting the most prominent differences within the pathways associated with metabolism. Amongst the identified genes, the relative expression of *ENO1* (the gene encoding enolase-1; ENO-1) was found to be significantly upregulated in the survival group, and a subsequent quantitative real-time polymerase chain reaction-mediated verification was able to confirm this finding.[2] Despite its limitations (small sample size and uneven groups), the study of Xiao *et al*.[2] represents a valuable contribution to the ongoing biomarker mapping of sepsis, as it essentially suggests that ENO-1 could be a prognostic biomarker of sepsis. This is particularly important in view of the fact that prognosis is the least accommodated function by the identified potential biomarkers of sepsis (Table 1).

ENO-1 is a metalloenzyme that is mainly known for its involvement in glycolysis, where it catalyzes the interconversion of 2-phosphoglycerate to phosphoenolpyruvic acid. However, ENO-1 is also known to exhibit other activities that strongly depend on its intra- or extracellular localization.[3] Qiao *et al*.[4] have recently characterized ENO-1 as a "moonlighting protein"; a justified characterization when one considers that ENO-1 can also display an array of DNA-binding capacity-related activities (resulting in the regulation of gene expression) as well as a critical role in plasmin-mediated pericellular proteolysis (when ENO-1 is anchored on the cellular membrane).[3] In fact, the cell surface-associated ENO-1 is known to play an important role in the regulation of pericellular proteolysis through the enhancement of plasmin formation; a role that has been well studied in the context of cancer cell migration and invasion.[5]

Interestingly, an increased expression of ENO-1 on the cell surface of blood monocytes and in alveolar space mononuclear cells of patients with pneumonia has been reported by Wygrecka *et al*.,[6] while Xiao *et al*.[2] recognize that the ability of ENO-1 to enhance monocytic invasion might be particularly relevant to the prognosis of sepsis. On the other hand, Lee *et al*.[7] have found that apolipoprotein B (apoB) can act as a specific ligand to ENO-1 (with an affinity that exceeds that of plasminogen) in the synovial fluid of patients with rheumatoid arthritis, while when mononuclear cells from these patients were exposed *in vitro* to apoB for 24 h, they were found to overexpress pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These findings suggest that the activation of the cell surface-bound ENO-1 of mononuclear cells can aggravate inflammation in rheumatoid arthritis.[7]

The study of Xiao *et al*.[2] is not the first to suggest a biomarker role for ENO-1. In fact, the expression levels of the latter have been found decreased in the serum of hepatitis B virus (HBV)-induced hepatic fibrosis patients as compared to those identified in the serum of HBV carriers,[8] thereby indicating their potential utility as a diagnostic biomarker of hepatic fibrosis. A fundamental difference between a diagnostic and a prognostic biomarker is that the latter is more likely to inform the clinical management of complex and life-threatening diseases such as sepsis. In that respect, the readers of our journal will likely ask themselves a simple question: can we pharmacologically enhance the expression of ENO-1 so as to improve the prognosis of sepsis? Xiao *et al*.[2] do not address this question. However, in a very interesting study by Zhu and McBride,[9] TRP120 (an effector of *Ehrlichia chaffeensis*) has been shown to interact with ENO-1 and to increase the ubiquitination and the degradation of the latter. Moreover, the knockdown

Abbreviations: apoB, apolipoprotein B; DEGs, differentially expressed genes; ENO-1, enolase-1; HBV, hepatitis B virus; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha.

***Correspondence to:** Apostolos Zarros, Pharmacological Research Observatory, 272 Bath Street, Glasgow, G2 4JR, Scotland, UK. ORCID: https://orcid.org/0000-0002-2868-1106. E-mail: azarros@pharmacolresobs.com

How to cite this article: Zarros A. Enolase-1 as a Prognostic Biomarker of Sepsis. *J Explor Res Pharmacol* 2023;8(1):1–3. doi: 10.14218/JERP.2022.00089.

Table 1. Potential biomarkers of sepsis based on data reviewed by von Groote and Meersch-Dini[1]

Biomarker(s)	Function of the biomarker(s) with regard to sepsis				
	Early detection	Classification	Therapeutic guidance	Prediction or detection of complications	Prognosis
Adrenomedullin			+		
Angiopoietin-1; Angiopoietin-2				+	
C-reactive protein	+	+			+
CD64 on neutrophils	+		+		+
Heparanase-1; Heparanase-2			+		
Human leukocyte antigen–DR isotype on antigen-presenting cells		+		+	+
IL-6	+	+			
Interleukin-8		+			
Lipopolysaccharide-binding protein		+			
Pathogen-associated molecular patterns	+				
Pentraxin-3				+	+
Presepsin	+	+	+		
Procalcitonin		+	+		
Soluble programmed death ligand 1			+	+	
Syndecan-1			+	+	
Thrombomodulin				+	

Note: The absence of a cross (+) underneath a specific function does not necessarily imply that the specific biomarker has been tested and was found to not be able to serve this function. The table summarizes the author's interpretation of a selection of data originally reviewed by von Groote and Meersch-Dini,[1] and it is not intended as a systematic or exhaustive overview of sepsis-associated biomarkers.

of *ENO1* (through the use of small interfering RNAs) was able to disrupt the glycolytic flux of human monocytic leukemia cells (THP-1 cells), thereby affecting their pyruvate and lactate metabolism and promoting ehrlichial infection.[9] Furthermore, in that same study, bortezomib (a proteasomal inhibitor) was shown to inhibit the TRP120-induced ENO-1 degradation.[9] Not surprisingly, in an earlier study by Han *et al*.,[10] bortezomib has been shown to reduce the expression of inflammatory cytokines (including those of TNF-α, IL-1β, and IL-6) in lipopolysaccharide-stimulated murine monocyte/macrophage-like RAW 264.7 cells, and to increase the survival in a murine model of sepsis involving cecal ligation and puncture-induced peritonitis.

Bortezomib (also known as PS-341 and being available as Velcade, Chemobort, and Bortecad) is a drug that has already been approved by the Food and Drug Administration for the treatment of multiple myeloma; therefore, the undertaking of preclinical studies should be prioritized in order to explore whether its repurposing for sepsis might be an option for the improvement of the prognosis of the latter.

Acknowledgments

The author would like to thank Dr. Christina Elliott (Newcastle University) for her useful remarks on a draft version of this editorial.

Funding

None.

Conflict of interest

Dr. Apostolos Zarros has been an editorial board member of the *Journal of Exploratory Research in Pharmacology* from August 2021 to December 2022. The author has no other conflicts of interest related to this publication.

References

[1] von Groote T, Meersch-Dini M. Biomarkers for the prediction and judgement of sepsis and sepsis complications: a step towards precision medicine? J Clin Med 2022;11(19):5782. doi:10.3390/jcm11195782, PMID:36233650.

[2] Xiao Y, Wang YJ, Xie JG, Wang XC. Transcriptomic identification of key genes in human peripheral blood mononuclear cells for the prognosis of sepsis. J Explor Res Pharmacol 2022;7(4):195–201. doi:10.14218/JERP.2022.00023.

[3] Didiasova M, Schaefer L, Wygrecka M. When place matters: shuttling of enolase-1 across cellular compartments. Front Cell Dev Biol 2019;7:61. doi:10.3389/fcell.2019.00061, PMID:31106201.

[4] Qiao G, Wu A, Chen X, Tian Y, Lin X. Enolase 1, a moonlighting protein, as a potential target for cancer treatment. Int J Biol Sci 2021;17(14):3981–92. doi:10.7150/ijbs.63556, PMID:34671213.

[5] Didiasova M, Zakrzewicz D, Magdolen V, Nagaraj C, Bálint Z, Rohde M, Preissner KT, Wygrecka M. STIM1/ORAI1-mediated Ca^{2+} influx regulates enolase-1 exteriorization. J Biol Chem 2015;290(19):11983–99. doi:10.1074/jbc.M114.598425, PMID:25805497.

[6] Wygrecka M, Marsh LM, Morty RE, Henneke I, Guenther A, Lohmeyer J, Markart P, Preissner KT. Enolase-1 promotes plasminogen-mediated recruitment of monocytes to the acutely inflamed lung. Blood 2009;113(22):5588–98. doi:10.1182/blood-2008-08-170837, PMID:19182206.

[7] Lee JY, Kang MJ, Choi JY, Park JS, Park JK, Lee EY, Lee EB, Pap T, Yi EC,

Song YW. Apolipoprotein B binds to enolase-1 and aggravates inflammation in rheumatoid arthritis. Ann Rheum Dis 2018;77(10):1480–9. doi:10.1136/annrheumdis-2018-213444, PMID:29997113.

[8] Zhang B, Wang Z, Deng B, Wu X, Liu J, Feng X. Identification of enolase 1 and thrombospondin-1 as serum biomarkers in HBV hepatic fibrosis by proteomics. Proteome Sci 2013;11(1):30. doi:10.1186/1477-5956-11-30, PMID:23845056.

[9] Zhu B, McBride JW. Alpha enolase 1 ubiquitination and degradation mediated by *Ehrlichia chaffeensis* TRP120 disrupts glycolytic flux and promotes infection. Pathogens 2021;10(8):962. doi:10.3390/pathogens10080962, PMID:34451426.

[10] Han SH, Kim JS, Woo JH, Jeong SJ, Shin JS, Ahn YS, Kim JM. The effect of bortezomib on expression of inflammatory cytokines and survival in a murine sepsis model induced by cecal ligation and puncture. Yonsei Med J 2015;56(1):112–23. doi:10.3349/ymj.2015.56.1.112, PMID:25510754.