New biomarkers for sepsis

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[Abstract] There is a higher sepsis rate in the intensive care unit (ICU) patients, which is one of the most important causes for patient death, but the sepsis lacks specific clinical manifestations. Exploring sensitive and specific molecular markers for infection that accurately reflect infection severity and prognosis is very clinically important. In this article, based on our previous study, we introduce some new biomarkers with high sensitivity and specificity for the diagnosis and predicting the prognosis and severity of sepsis. Increase of serum soluble(s) triggering receptor expressed on myeloid cells-1 (sTREM-1) suggests a poor prognosis of septic patients, and changes of locus rs2234237 of sTREM-1 may be the one of important mechanisms. Additionally, urine sTREM-1 can provide an early warning of possible secondary acute kidney injury (AKI) in sepsis patients. Serum sCD163 level was found to be a more important factor than procalcitonin (PCT) and C-reactive protein (CRP) in prognosis of sepsis, especially severe sepsis. Moreover, urine sCD163 also shows excellent performance in the diagnosis of sepsis and sepsis-associated AKI. Circulating microRNAs, such as miR-150, miR-297, miR-574-5p, miR-146a, miR-223, miR-15a and miR-16, also play important roles in the evaluation of status of septic patients. In the foreseeable future, newly-emerging technologies, including proteomics, metabonomics and trans-omics, may exert profound effects on the discovery of valuable biomarkers for sepsis.

[Key words] sepsis; biological markers; triggering receptor expressed on myeloid cells-1 (TREM-1); antigens, CD163; microRNAs

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脓毒症：新兴生物学分子标志物初探

解立新

[摘要] 脓毒症在重症监护室患者中的发病率高，是最重要的致死病因之一，但缺乏特异性的临床表现。探寻能准确反映脓毒症感染程度并预测预后的特异、敏感的分子标志物，在临床工作中日趋重要。在既往研究的基础上，本文介绍了一些新的对脓毒症诊断、预后判断具有高度敏感性和特异性的分子标志物。可溶性髓样细胞诱发受体1(sTREM-1)的增加预示脓毒症患者的不良预后，而其中重要机制之一可能与rs2234237位点改变相关。血清sCD163水平在脓毒症，尤其是重症脓毒症的预后预测中，较降钙素原(PCT)和C反应蛋白(CRP)表现更为出色，尿sTREM-1和sCD163还可为脓毒症相关急性肾损伤的诊断提供有价值的实验室依据。循环miRNAs(如miR-150，miR-297，miR-574-5p，miR-146a，miR-223，miR-15a，miR-16)也在脓毒症患者的状态评价中发挥着重要作用。在可预见的未来，蛋白质组学、代谢组学和转录组学等新兴技术的发展将对脓毒症相关分子生物学标志物的发现历程有所裨益。

[关键词] 脓毒症；生物学标志；髓样细胞诱发受体1；抗原，CD163；微RNAs

Sepsis is the most important cause of morbidity and mortality in the intensive care unit (ICU), but it lacks specific clinical manifestations. As a result, sensitive and specific indicators of infection that can be easily collected and that accurately reflect infection severity and prognosis are anxious to have and are clinically important. Currently, commonly used clinical indicators of infection include pyrexia, white blood cell (WBC) counts, C-reactive protein (CRP), and procalcitonin (PCT). However, in clinical settings, the limited application of CRP and PCT in assessing the severity and in predicting the prognosis of sepsis may affect the evaluation of the change in septic patients' general condition. Therefore, looking for new biomarkers with high sensitivity and specificity is one of the main research fields in sepsis.

1 Promising biomarkers

1.1 TREM-1 Triggering receptor expressed on myeloid cells-1 (TREM-1), expressing on polymorphonuclear granulocytes and mature monocytes, is a recently discovered member of the immunoglobulin superfamily. Bacterial or fungal infections may induce
MicroRNAs (miRNAs) are a type of endogenous non-coding small RNAs that are about 22 nucleotides in length\cite{15-18}. They play important biological roles by inhibiting the expression of messenger RNAs (mRNAs)\cite{19}. As with mRNAs, some miRNAs are differentially expressed among tissues or developmental stages. Unlike some widely expressed miRNAs, these tissue- or developmental stage-specific miRNAs are likely to play key roles in regulating specific processes involved in the development and function of individual tissues\cite{20}. A significant amount of miRNAs has been observed in various body fluids, and outside of the cells. These cell-free miRNAs in body fluids are stable under harsh conditions such as boiling, acidic environment (low pH) or basic environment (high pH), and multiple freeze-thaw cycles\cite{21-22}. Circulating miRNAs have been recently identified as biomarkers for sepsis. The level of miR-150, firstly identified as a prognostic marker for sepsis significantly varied in leucocytes between healthy controls and sepsis patients. In the plasma of sepsis patients, the level of miR-150 is correlated with the level of SOFA score, and the plasma level ratio for miR-150/interleukin-18 can be used to evaluate severity of sepsis\cite{23}. Sepsis is a complex disease that involves various tissues and organs. A simple screen for miRNAs differentially expressed in leucocytes may miss many miRNAs secreted by other type of cells. Hence, a genome-wide method is applied to screen for differentially expressed miRNAs.
between the surviving and non-surviving groups of sepsis patients. According to the results, two novel prognostic biomarkers, miR-297 and miR-574-5p, are identified by microarray screening and quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR). Moreover, miR-297 is found to be more closely correlated with survival from sepsis, whereas miR-574-5p is correlated with death from sepsis. Although being identified as diagnostic biomarkers for sepsis, the expression level of these markers are not only found to be differentially expressed between sepsis patients and healthy controls, but also between sepsis patients and SIRS patients.

The levels of miR-146a and miR-223 in sepsis patients’ sera significantly decreased when compared with that in SIRS patients and healthy controls, which are of higher sensitivity than IL-6 in the diagnosis of sepsis[24-25]. miR-15a and miR-16 are also newly identified as diagnostic markers for sepsis. The levels of these 2 miRNAs in sepsis and SIRS patients are both significantly higher than that in normal controls. And miR-15a may serve as marker to distinguish sepsis patients from SIRS patients, which is more valuable compared with CRP and PCT[26]. Although the function of these miRNAs has not been completely elucidated, their clinical value has been confirmed. New biomarkers also mean novel treatment targets. Hence, target genes of these miRNAs may emerge as potential treatment targets for sepsis patients.

2 Emerging technologies: proteomics, metabolomics and trans-omics

Recently, mass spectrometry (MS) technologies have made considerable progress and been used to search for new biomarkers. A large number of differentially expressed proteins and small molecule metabolites have been identified and reported as potential biomarkers for diagnosis and prognosis of several different diseases. Some researchers have put MS technique toward to unraveling new discoveries in the field of critical care medicine and draw some interesting conclusions[27]. Our results of serum proteomics of septic patients indicated that the most important changes in the coagulation-bradykinin and the complement system were noticed when sepsis occurred. The urine proteomics results suggested that cadherin-1 (CDH-1), haptoglobin (HPR), complement3 (C3), alpha-1-antitrypsin (SERPINA1) and ceruloplasmin (CP) may reflect the occurrence of sepsis; selenium binding protein-1 (SBP-1), heparan sulfate proteoglycan-2 (HSPG-2), alpha-1-B glycoprotein (A1BG), haptoglobin (HPR), lipocalin (LCN), lysosome-associated membrane proteins-1 (LAMP-1) and dipeptidyl peptidase-4 (DPP-4) may be able to predict the prognosis of sepsis. In addition, the results of metabolomics study prompted that glycerophospholipid metabolic products and arachidonic acid metabolites were the most important stuffs in the occurrence and development of sepsis. Currently, the results aforesaid are still under subsequent analysis and experimental verification.

With constant development of high-throughput technologies and improvement of the systems biology, it has been increasingly recognized that we can not simply take from only one perspective to learn and explain a complex biological phenomenon and essence. Therefore, the trans-omics have been put forward to solve this problem. Trans-omics is to explore how to integrate the genome, transcriptome, proteome and metabolomics data together and explain the function, pathogenesis of the disease and their relevant mechanisms. More and more researchers intend to combine the results of exon sequencing, miRNA sequencing, proteomics and metabolomics studies in order to elucidate the molecular mechanisms of sepsis. In theory, new discoveries and ideas in the pathogenesis of sepsis could be put forward with the help of the analysis methods of trans-omics.

3 Conclusion

In conclusion, in search of new biomarkers for determining the severity of sepsis patients and predicting the prognosis is a very important, interesting and challenging work, which may provide new insights to confront sepsis.

[References]


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