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Nex-Gen Biomarkers - A Genetic Model of Sepsis

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Abstract

Sepsis accounts for a major cause of morbidity and mortality in surgical and medical ICU. The current pharmacological management still hovers around early management of patients with antibiotics yet fails to adequately personalise the treatment on patient characteristics. Even today the severity of sepsis is assessed by a variety of biochemical and clinical markers that further helps to take a glimpse of the on-going metabolic structure of the disease and patient in-toto. Despite a huge list of proven and experimental markers, the ideal biomarker for sepsis remains elusive till today. Though a genetic basis of stress response has been previously formulated the study of the role of RNA in sepsis is still in its infancy. MicroRNAs (miRNAs) are a group of non-coding RNAs that regulate gene expression by affecting the target mRNAs. A recent development has shed some light on these miRNAs and their role amid different pathologic conditions like sepsis. Specific miRNAs that has been a target for research are miR-25, miR-133a, miR146, miR-150, and miR-150. While few of these have found to correlate with short-term and long-term prognosis, others have been investigated to have diagnostic value as well. In this article, we try to understand recent developments in this relatively new model of sepsis and its potential to be an ideal biomarker for sepsis in the future.

Keywords: MiRNA; Ideal biomarker; Genetic model

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In the late 1970s, it was evaluated that 164,000 instances of sepsis happened in the United States (US) [1]. From that point forward, rates of sepsis in the US and somewhere else have significantly expanded. A review of a worldwide database reported a worldwide occurrence of 437 for each 100,000 man years for sepsis and 270 for every 100,000 man years for extreme sepsis in the years 1995 and 2015, despite the fact that this rate did not reflect the true incidence in resource-limited nations [2].

The seriousness of sepsis seems, by all accounts, seems to be expanding [3]. In one review, the extent of patients with sepsis with maximum than single organ dysfunction expanded from 26 to 44 percent from 1993 to 2003 [4, 5]. The most widely recognized signs of so-called severe sepsis were ARDS, AKI, and DIC [6]. Be that as it may, it remains vague with respect to whether the rising frequency of serious sepsis and septic shock mirrors the generally expanded occurrence of sepsis or is due to changed definitions of sepsis over time.

A 2016 SCCM/EISCM [Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM)] task force has defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. On the other hand, Organ dysfunction was defined as the increase of two or more points in the SOFA (Sequential (Sepsis-related) Organ Failure Assessment) score. The term severe sepsis, which originally referred to sepsis that was associated with tissue hypoperfusion (e.g. elevated lactate, oliguria) or organ dysfunction (e.g. elevated creatinine, coagulopathy) [7], is no longer used since the 2016 sepsis and septic shock definitions include patients with evidence of tissue hypoperfusion and organ dysfunction. Finally, septic shock is defined as sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone [8]. Clinically, this includes patients who fulfil the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg and have a lactate >2 mmol/L (>18 mg/dL).

The current laboratory features are not only non-specific but also fail to predict the course of sepsis in the patient. Despite the pitfalls the list of experimental markers is endless. The biochemical

markers that have stood the test of time and are currently in vogue with the intensivists are, Leukocytosis (white blood cell [WBC] count >12,000 μL^{-1}) or leukopenia (WBC count <4000 μL^{-1}), Normal WBC count with greater than 10% immature forms, Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes, Plasma C-reactive protein more than two standard deviations above the normal value, Plasma procalcitonin more than two standard deviations above the normal value (not routinely performed in many centers), Arterial hypoxemia (arterial oxygen tension [PaO_2]/fraction of inspired oxygen [FiO_2] <300), Acute oliguria (urine output <0.5 mL/kg/h for at least two hours despite adequate fluid resuscitation), Creatinine increase >0.5 mg/dL or 44.2 µmol/L, Coagulation abnormalities (international normalized ratio [INR] >1.5 or activated partial thromboplastin time [aPTT] >60 s), Thrombocytopenia (platelet count <100,000 μL^{-1}), Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 µmol/L), Hyperlactatemia (higher than the laboratory upper limit of normal), Adrenal dysfunction (e.g. hypernatremia, hypokalemia)

Though biomarkers like interleukins do deserve a mention in this same context, recent advances have pointed out the role of miRNAs as better diagnostic and prognostic indicator in patients with sepsis. This articles implores the boundaries of this new revelation and also tries to understand the recent developments in the field of the genetic basis of sepsis. This new model may help in shifting in the current management guidelines from being micro-organism centred in a sepsis-septic shock model to host directed personalised treatment practices.

The genes encoding for miRNA accounting for less than 1% of the human genome have been purported to control around 60% of protein-coding genes [9]. One of the hypotheses suggests that a single miRNA could affect transcription of many other mRNAs by base pairing to specific regions and hence regulating gene expression in both health and disease. The role of miRNA has already been elucidated in various mechanisms of cell death and aging [10] and its effects on sepsis is current area of research [11].

As mentioned before these 20 nucleotides long chain RNA regulates gene expression. Lee et al. [12] and group was one of the first credited researchers to have studied these molecules in nematodes and this initial discovery has led to the identification of 1881 miRNAs in the human genome today [13].

The biochemical origin of these molecules is quite complex and involves the formation of pri-miRNA transcript with the help of RNA polymerase II. These pri-miRNas are then cleaved by the ribonuclease III enzyme and DGCR8 (microprocessor complex) to form pre-miRNA. Next, this pre-miRNA is transported into the cytoplasm where it is further processed into ds-miRNA. This ds-miRNA finally unwinds to integrate with 3' or 5' UTR regions of target mRNAs (the binding points are termed as RISC complexes) leading to repression of degradation depending on the type of binding between the miRNA sequence and the RISC region in the target mRNA [14].

However that prime question at this point of time is, how would these seemingly innocuous, homeostatic molecules could correlate with the inflammatory cascade set ablaze by the septic insult and what's the need of measuring these complex intermediates instead of the much simpler assays of proteins like CRP or procalcitonin that have played a role of surrogate markers of sepsis till date. The first understanding regarding the use of miRNAs as biomarkers came when they were detected in the blood for the first time in 1990 [15, 16]. Further, it became apparent that due to short sequence structure not only these molecules were highly conserved in all of the human models of sepsis but are also remarkable stable in adverse physical conditions. The various hypothesis regarding association with RNA-binding proteins, lipoprotein complexes, and micro-particles have been put forward to explain this ability of miRNAs to withstand denaturation. Further, it has been shown in few studies the ability of miRNAs to perform intercellular communications that may form the basis of yet unknown systemic affection of localised infection [17].

The pathophysiology of sepsis in not easy to comprehend. With unmasking of molecules like TLR, TNF, STAT1, NF-κB and much more, participating at the core of the inflammatory model of sepsis, its becomes imperative to establish the relationship of miRNAs along with these proven inflammatory biochemical mediators. Atherosclerosis and rheumatoid arthritis were one of the first disorders that showed that miRNAs affects innate and adaptive immunity apiece [18]. Initially, the studies revolving around miR-155 showed its association with tumor necrosis factor (TNF) pathway where a positive correlation was noted in on stimulation of liver macrophages by lipopolysaccharides [19]. It was found that the severity of TNF-dependent endotoxic shock was greatly ameliorated by reduction of TNF receptor-1 expression on injecting miR-155 in a mice model of sepsis. The next target recognised by various models if TLRs and more specifically TLR-4 [20]. miR15a/16 deficiency has been studied to increase the transcription of TLR-4 resulting in enhanced phagocytosis shown by the macrophages in an *in vitro* model [21]. Another miRNA, miR-146a has been shown to repress TNF-alpha promoter thus blunting the effective inflammatory stimulation [22]. In a study assessing various adhesion molecules as markers of sepsis and inflammation miR-23b has been shown to inhibit expression of E-selectin, ICAM-1 and VCAM-1 [23]. What all these studies have shown that miRNAs are highly integrated with the inflammatory markers and it's quantitative and qualitative assessment can be the future for understanding the genetic model of sepsis.

As previously noted more than a 1500 different types of miRNAs have been identified in the human genome, but a handful of them has been studied as potential biomarkers for sepsis. We discuss the forerunners of this group in the present research arena, with a passing mention of other potential candidates of the future.

miR-150

This was one of the first miRNAs to be assessed in human volunteers with sepsis. It was noted that miR-150 was a part of a cluster of miRNAs including miR-155, miR-223, and miR-17-92 which were specifically downregulated in comparison to controls [24, 25]. A mice model showed that expansion of B cells to release specific immunoglobulin could specifically be upregulated by deletion of miR-150 gene. Overexpression in B-cells, however,

prevented these cells from transiting from pro-B cell stage to pre-B cell stage by affecting the c-Myb pathway [26].

A quantitative study revealed a correlation between miRNA serum levels with SOFA scores in a cohort of 16 patients with abdominal sepsis. A similar study also found that miR-150 levels achieved a lower nadir in sepsis model compared to patients with the autoimmune disease model. However later studies failed to show similar results and failed to achieve statistical significance when used as a diagnostic tool, but these articles also found that low miR-150 correlated with adverse outcomes thus affirming the prognostic role of this marker early in the disease process.

miR-133a

This represents one of the most versatile groups of miRNAs shown to be elevated in a myriad of disorders spanning from diabetes, liver cirrhosis, LVH and cancers themselves [27]. Its first correlation with septic cascade came from a mice model where the systemic response could be ascertained with a titrated rise of a cluster of miRNAs later classifies as miR-133a group [28]. Following this model a human cohort showed high serum levels correlated with poor survival and was reported to be an independent predictor of mortality in this group. In the current scenario, mi133a shows a lot of promise both as a diagnostic and prognostic tool.

miR-25

With the knowledge of the intricate behaviour of miRNAs in various models of sepsis, it became clear that these markers had prognostic significance. But as noted in various critical care units, a diagnostic tool portends much significance in today's practice. The result of this conscious effort was the identification of miR-25. For the first time, a marker was identified that could differentiate between SIRS and sepsis [29]. Low serum levels further correlated with poor prognosis. An ROC curve analysis showed that miR-25 had much higher diagnostic accuracy for sepsis as compared to currently accepted markers like procalcitonin and C-reactive peptide. Thus, miR-25 is a molecule worth investigating to assess for external validation of results pending which it could well be the biomarker for identification and assessment of sepsis.

miR-122

Wang et al. and the group were the first proponents of miR-122 as a marker in critical illness following their report on 214 patients with sepsis [30]. However, it was found that the correlation between rising miR-122 levels and severity of sepsis was spuriously associated due to increasing liver damage in this subgroup of patients. miR-122 is now propagated as a liver-specific miRNA and subsequent studies on chronic liver disease and hepatocellular carcinoma further strengthened the association [31]. Another study found the correlation between elevated miR-122 levels and poor neurological outcomes due to impaired perfusion following a cardiac arrest. The current consensus on this molecule stands to describe as a highly sensitive marker of liver damage and its role in the identification of early organ dysfunction in various models of sepsis is an active area of research [32].

miR-223

STAT3, Mef2c, IGFR1, Artemin, Rougin, and Stathmin are just a few of the genes that are known to be responsible for various immune responses that are supposedly affected by this single miRNA, miR-223, which suggests that this may be a key modulator in various inflammatory processes [33]. This molecule is known to be a key determinant of hematopoietic lineage differentiation, but later studies have shown it to be a pretty handy biomarker for sepsis also. In a study by Essandoh et al, it was noted that lack of miR-223 was associated with severe sepsis and was an independent predictor of mortality due to sepsis [34]. In another study, it was noted that serum levels of miR-122 were unaffected in a cohort of non-sepsis induced SIRS though this was not found to be replicable by other authors citing difference in assessment methods and normalization procedures that might have affected the results [35]. Elevated levels have been noted in patients with autoimmune arthritis and miR223 knockout model showed suppressed effects in the affected mice [36]. In another study increased response to candida was noted along with the rapid destruction of tissue in the presence of LPS in a miR223 mutant mice model. Thus, we conclude by stating, that the results in human cohorts of the relevance of miR-223 in various sepsis models are still in infancy and requires further studies before a statistically significant recommendation is made.

miR-574-5p

The interest in this molecule was developed after an article commented over the predictive power of miR-574-5p in patients prognosis by combining it with SOFA score that showed better correlation with patient outcome that either predictor alone suggesting its role to be a part of an enhanced clinical scoring system to may help with crucial management decisions [37]. In the study, it was noted that lower serum levels were associated with poorer prognosis and hence the authors concluded its value as an important prognostic asset in an intensivist armamentarium.

miR-4772

This miRNA has been known to be released by monocytes as a reaction to circulating LPS stimulation in a sepsis model. However, the role of miR-4772 in differentiating patients with sepsis and with non-sepsis SIRS is highly debated. A study using parallel sequencing of miRNAs and real-time PCR confirmed higher levels of miR-4772 in patients with sepsis compared to healthy counterparts [38].

Other miRNAs

A recent study in 2015 explored the new miRNA in setting of neonatal sepsis including miR-16 and miR-15a and found an important correlation with sepsis models thus strengthening the genetic model of sepsis [39]. Another novel study involving urosepsis explored the role of let-7a found a negative correlation between let-7a and increasing the severity of sepsis [40]. These new studies and much more in current trials further impress upon us the improving understanding and possible future of miRNAs as the biomarkers of sepsis

A potential role yet not explored of this biomarker is its ability

to differentiate gram-positive to gram-negative sepsis. A study by Wu et al. [41] noted that levels of miR219b, miR-1889, miR-205, miR-133b and miR-122 positively correlated with gram-positive sepsis compared to miR-20a, miR-451, miR-16, miR-106a and miR-106b that were upregulated in gram-negative sepsis; thus opening entirely new methods of approach a case of sepsis. Another interesting concluding remark had been made by Benz et al. [42] where they listed a number of studies showing correlation between miRNAs and specific microorganisms, they stated, "Analysis of circulating miRNA bear the potential to serve as point of care diagnostic tests allowing rapid initiation of directed treatment by circumventing time intensive microbiological confirmation of sepsis and infection." Though as of today we have ample of data to suggest the potential benefits of miRNA as biomarkers of sepsis what remains to be answered is the external validity of the various experimental trials to analyse the inter-study variations that may arise due to lack of standardisation, normalization, and analysis of outcomes. Thus, a lot remains unanswered at the end of this exciting journey, nevertheless, we have embarked a new era of a genetic model of sepsis in humans and its role in the management of sepsis, and its least to say that it holds the promise to bring us next generation of biomarkers in sepsis.

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