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Chapter 4

Cytokine Gene Polymorphism and Sepsis

Dablu Lal Gupta, Tejparkash Sinha, Sanjeev Bhoi and D.N. Rao

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Abstract

Trauma is a significant problem across the globe with mortality more than 50%. Despite the advancement of pre-hospital care to trauma patients, early resuscitation in the emergency department, surgical interventions and intensive care monitoring mortality rate has not improved yet. The higher rate of mortality in trauma patients is usually associated with development of complications such as sepsis, septic shock, and MOF which may occur due to hysterical immune inflammatory responses. Trauma patients who developed these complications in the ICU have comparatively higher chances of mortality. Cytokines are very important for host immune response against infections and play vital roles in the regulation of innate and adaptive immunity. The slanted expression of cytokines due to trauma may be involved in development of sepsis and related complications. The recently published work from various studies suggested that slanted expression of cytokines correlates with the variations in the promoter and structural regions of cytokine genes, which may be responsible for inter-individual differences in susceptibility to sepsis. Therefore, understanding the variations in cytokine genes and associated outcomes due to trauma would possibly contribute to the event of latest genetically changed diagnostic and therapeutic interventions that will improve the outcome in post-traumatic sepsis patients.

Keywords: trauma, cytokine, multiple organ failure, septic shock and inflammation

1. Introduction

Trauma remains a significant public health issue and is the fourth leading cause of death in persons younger than 40 years [1, 2]. Worldwide, about 16,000 people die every day as a result...
of an injury (5.8 million deaths per year), and the projections for 2020 show that 8.4 million deaths per year are expected [3]. Consequently, injury will be the second most common cause of disability adjusted years of life lost within the next 13 years (second only to cardiovascular disease). Undoubtedly, the major burden of injury is increasingly occurring in the developing world as it industrializes, adopts motorized transportation, and remains the major center for armed conflict [4, 5].

Despite advancement in primary care to trauma patients, early resuscitation in the emergency department, surgical interventions, and intensive care monitoring, mortality rate has not improved yet. The higher rate of mortality to trauma patients is usually associated with development of various complications such as sepsis, septic shock, and the development of the multiple organ dysfunction syndrome (MODS) [6, 7]. The outcome of trauma patients is not determined only by trauma but also by the impacts of immune-inflammatory insult. The inflammatory response is crucial for the host defense against infections, but hysterical immune inflammatory responses are generated due to imbalance in the production of inflammatory and anti-inflammatory cytokines which may lead to various complications and consequently unfavorable outcomes [8, 9].

According to the biphasic model of trauma etiology, dysregulations in the production of both inflammatory and anti-inflammatory cytokines primarily lead to the sepsis-associated mortalities and outcomes [10, 11]. Posttraumatic sepsis which may cause hysterical immune inflammatory responses is one of the leading sources of MODS in the ICU. Although there have been many advances in the development of broad and narrow spectrum of antibiotics and thoughtful care, sepsis remains a serious and deadly problem with high mortality rates across the globe. Therefore, prognostic biomarkers to identify high-risk trauma patients in the early stages are immediately needed for early detection and preventive care of sepsis.

The management of severely injured and multiple trauma patients who developed sepsis, septic shock, and MODS due to inflammatory insults is challenging for the physician in the ICU. Trauma leads to imbalance in production of pro-inflammatory and anti-inflammatory cytokines which may subsequently lead to the SIRS, sepsis, septic shock, and MODS which are shown in Figure 1.

1.1. SIRS

Systemic inflammatory response syndrome (SIRS) is a term that was developed in an attempt to describe the clinical manifestations that result from the systemic response to injury. The criteria of SIRS are considered as having at least two of the following four clinical parameters abnormal:

1. Temperature < 36°C or > 38°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or PaCO₂ < 32 mmHg
4. WBC count >12,000 cells/μL or < 4000 cells/μL, or > 10% immature forms

1.2. Sepsis

Sepsis is a common, deadly, and often underappreciated disease process in emergency departments. In the intensive care unit, if patients have SIRS along with documented cultures reports...
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Trauma has a multifactorial etiology, which can be divided into endogenous and exogenous factors [12]. The endogenous factors, such as genetic predisposition, form the basis of the patient's susceptibility for the development of organ failure. Recent studies have shown that genetic variations (e.g., TNF-α polymorphisms) are strongly associated with the development of organ failure [13]. The exogenous factors, such as injury itself (the "first hit" or "trauma load") and the resuscitation or surgical intervention (the "second hit" or "intervention load"), play a crucial role in the development of organ failure. Organ damage and subsequent organ failure are the result of dysfunctional immune system [11, 14].

3. Role of cytokines in development of sepsis-related complications

Cytokines are low molecular weight polypeptides, and pharmacologically active molecules possess autocrine, paracrine, and juxtracrine effects [15]. These molecules are classified into several classes (i.e., interleukins, interferons, colony-stimulating factors, tumor necrosis factors).
transforming growth factors, and chemokines), which are relevant to mediate the humoral and cellular immunity to protect the host against pathogens [16]. Cytokines are produced by a wide variety of lymphoid and nonlymphoid cells in the body, playing an important role in many physiological responses against infections and injury. In addition, cytokines exert important pleiotropic actions as cardinal effectors of injury [17]. They play vital roles in the regulation of host immune response, and distorted expression of cytokines is proven to be involved in development of complications such as sepsis, septic shock, and MODS. Many studies suggested that the genetic background of individuals determines the impacts of immune inflammatory response after trauma which may lead to differential cellular activations of immune cells, leukocyte migrations, and effector functions (Figure 2). Previous research suggests that the variations in the genes encoding cytokines are also involved in the inflammatory responses and also responsible for inter-individual differences in susceptibility to sepsis and in its severity [13, 18, 19]. Therefore, understanding the variations in cytokine genes and associated differences in response to trauma might contribute to the development of new genetically modified diagnostic and therapeutic interventions that may improve outcome in posttraumatic sepsis patients.

4. Role of cytokine gene polymorphism in sepsis

Cytokine gene polymorphism, therefore, is advocated as the underlying reason to distinguish individual specific immune responses. The cytokine gene polymorphism studies may be considered as powerful biomarkers for the identification of trauma patients who have higher risk to develop sepsis complications in the ICU [20, 21]. Therefore, understanding the associations between genetic polymorphisms and sepsis or MODS may lead to the better understanding of sepsis. Nowadays the significance of genetic variations [particularly single-nucleotide polymorphisms (SNPs)] as key determinants of inter-individual variations in both inflammatory responses and clinical outcome in trauma patients is advocated [13, 22]. Single-nucleotide polymorphisms are the key factors to regulate the expressional variation of human genes and found to be associated with the disease susceptibility and progression. To understand the importance of cytokine gene polymorphism (CGP) while predicting the occurrence of sepsis, the SNPs in the promoter, coding, and noncoding regions of 13 cytokine genes with 22 loci are commonly used. Single-nucleotide polymorphisms of 13 cytokine genes including interleukin IL-1-α (T/C-889), IL-1-β (-511 C/T, T/C + 3962), IL-1 RA (T/C mspal 1100), IL-4 RA (G/A + 1902), IL-4 (T/G-1098, T/C-590, T/C-33), IL-6 (G/C-174, G/A nt560), IL-10 (G/C-1082, C/T-819, C/A-592), IL-12 (C/A-1188), γ IFN (+874 A/T), TGF-β1 (C/T codon 10, G/C codon 25), TNF-α (G/A -308, G/A-238), and IL-2 (T/G-330 G/T + 166), to investigate the susceptibility towards sepsis in trauma patients, are commonly used. All the cytokine genes and their polymorphic loci which are commonly used to investigate the genetic basis of susceptibility towards disease are shown in Table 1.

Various studies also showed the associations of these SNPs in the development of sepsis and outcomes. The polymorphic loci in the promoter region of TNF-α-308 and TNF-α-238 have been reported by various studies and showed susceptibility and resistance between
These two polymorphisms are well recognized and associated with susceptibility for tuberculosis, heart disease, and Graves' disease. The interleukin 6 is an important cytokine and plays a very important role in the activation of T17 cells. The polymorphisms in the promoter region of IL-6 (174 G/C) and structural region (+560) are well characterized in various diseases. However, the polymorphism in the promoter regions (174 G/C) showed significant association with celiac disease, bowel syndrome, cancer, and autoimmunity. Interestingly, the polymorphism in the promoter region of IL-6 (174 G/C) influenced the immunopathogenesis of sepsis and associated with outcomes in European population of trauma. We have also reported the association of IL-6 (174 G/C) polymorphism and susceptibility of sepsis in the Indian trauma patients. IL-10 is an important anti-inflammatory cytokine and plays a very crucial role in the inflammation, autoimmunity, and tolerance. Many studies suggested that elevated level of IL-10 activates the transcription factor Fox P3 which may subsequently lead to the production T regulatory cells. Polymorphism in the promoter regions of IL-10 gene (1082 G/A), (819 C/T), and (592 C/A) is well established and showed significant association with various infectious diseases, autoimmunity, cancer, and diabetic retinopathy. These IL-10 promoters, (1082 G/A), (819 C/T), and (592 C/A) polymorphisms, are associated with resistance to sepsis in the Caucasian population. Interleukin (IL-1) gene complex consists of IL-1α, IL-1β, IL-1R, and IL-RA genes with five potent polymorphic loci in the structural and promoter regions. These polymorphic loci are associated with susceptibility for sepsis in trauma patients of the Chinese population and also associated with other diseases, such as cancer and autoimmunity. In our study, we have reported the changes in alleles and genotype frequency at the promoter region of IL-1β (511) gene. We have also reported the significant association of this polymorphism with susceptibility for sepsis in Indian trauma patients. The recently published work by Gupta et al., 2016, showed that polymorphisms in the structural and promoter regions of TNF-α, IL-β, IL-6, and IL-10 are significantly associated with susceptibility to sepsis and outcomes in trauma patients (Figure 3).
5. Conclusion

The purpose of this chapter is to bring together currently available information of cytokine gene polymorphisms in pro-inflammatory and anti-inflammatory cytokine genes in the development of various complications such as sepsis, septic shock, and MODS in trauma patients. Specific emphasis is placed on the polymorphism of those cytokines which potentially contributed to the development of these complications and correlates with unfavorable outcomes.

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Conflict of interest

The authors have no conflicts of interest.

Author details

Dablu Lal Gupta 1, Tejparkash Sinha 2, Sanjeev Bhoi 2 and D.N. Rao 3

*Address all correspondence to: dablugupta10@gmail.com

1 Institute of Science, Nirma University, Ahmedabad, Gujarat, India
2 Department of Emergency Medicine, JPN Apex Trauma Center, All India Institute of Medical Sciences, New Delhi, India
3 Department of Biochemistry, All India Institute of Medical Science, New Delhi, India

References

[1] Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nature Reviews. Immunology. Oct. 2008; 8(10):776-787
[2] Moore K. Trauma mortality: Understanding mortality distribution to improve outcomes. Journal of Emergency Nursing. Jul. 2014; 40(4):405-406
[3] Mikkelsen R, Møller Hansen O, Brink O. Non-survivors after admission to trauma Centre. Danish Medical Journal. Oct. 2014; 61(10):A4928

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