Genetic Polymorphisms and Trauma Precision Medicine

Wei Gu and Jianxin Jiang

Abstract Major trauma is the leading cause of death in young adults. Post traumatic complications, especially sepsis and MODS, are the main causes of death of trauma patients in hospital. Recent advances in researches have showed a close relationship between genetic background and outcomes of trauma patients. The emerging field of precision medicine is expected to provide the best available care for every patient based on accurate clinical information and evidences at an individual level or at a community level. The further studies on genetics of trauma patients will certainly lead to a better understanding of post-trauma complications and personality treatment of trauma patients in the future.

Keywords Trauma · Precision medicine · Polymorphisms · Sepsis · MODS

1 Background

1.1 Precision Medicine

The core concept of precision medicine is the consideration of individual variability during the prevention and treatment of patients. It is believed to be an innovative approach to disease treatment, disease prevention and health promotion. The main purpose of precision medicine is to integrate basic science, diagnostic tests and the best evidence-based knowledge to conduct personalized health education, counseling, and prevention. This advanced approach will take the man's genetic profile and predisposition, environment, emotional and psychological state, and lifestyle choices into account when make a medicine care plan. In addition, it is the time for us health care providers to embrace and increase our knowledge to develop and

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X. Fu and L. Liu (eds.), *Advanced Trauma and Surgery*,
DOI 10.1007/978-981-10-2425-2_13

manage the best health care system that provides safe, patient-centered, transparent, and quality health care based on those big data sets of population health and genomics.

There are many favorable condition for the propose of precise medical. The cost of sequencing a genome has dramatically dropped since 2001, when the first draft of the human genome sequence was published. Besides of that, the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. It could image that precision medicine's more individualized, molecular approach to disease will certainly encourage and support the next generation of scientists to develop creative new approaches for detecting, measuring, and analyzing a wide range of biomedical information, including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters.

1.2 The Application of Precision Medicine in Trauma

Trauma is a major public health problem worldwide, ranking as the fourth leading cause of death. In 2010, there were 5.1 million deaths from injuries, and the total number of deaths from injuries was greater than the number of deaths from HIV/AIDS, tuberculosis, and malaria combined (3.8 million) [1, 2]. With the promotion of emergency technology and the advent of new medical treatment, the early mortality of trauma was effectively reduced [3]. However, the late complications, especially infectious complications, such as sepsis and multiple organ dysfunction syndromes (MODS) are serious threats to the trauma patients, and dramatically increase the burden of cost to society. The cause of sepsis and MODS are numerous, including age, sex and injury. However, it is still not well known why some patients may develop sepsis, while others consulting similar injury not. Growing evidences show that the interaction between gene and host or gene and environment may play an important role in it.

The results from an early animal experiment supporting the role of genetic background in trauma outcomes. Radojicic et al. [4] observed a difference of survival rates among four inbred strains of mice (AKR, CBA, BALB/c and C57BL/6) after suffering mechanical, radiation and thermal injuries. Our results also demonstrated a significant differences of mortality between C57BL/6 and BALB/c mice after blast wave injury [5]. Another strong evidence comes from an early epidemiological study. Sorensen et al. [6] reported a close relationship between death from infection in adoptee and his/her biological, instead of adoptive parents, indicating a role of genetic background in risk of infectious outcomes. Besides of these initial findings, more and more studies indicated that genetic factors may influence the reaction and susceptibility of complications in trauma patients.

Genetic polymorphism refers to the occurrence of two or more alleles at one locus in the same population, each with a distinct frequency, where the minimum frequency is typically 1 %. This word is now used to describe the differences among individual DNA sequence that make each human genome unique. There are generally two types of genetic polymorphisms, DNA site polymorphisms and length polymorphisms. DNA site polymorphisms refer to those alleles at specific sites on the DNA sequence differences, also different genome scattered in the base, including point mutation (transition and transversion) and single base substitution, deletion and insertion. DNA length polymorphisms refer to the polymorphisms of DNA fragment length difference between the alleles of the same gene locus, including VNTR (variable number of tandem repeats), STR (short tandem repeats) and MVR (minisatellite variant repeat mapping). Among them, single nucleotide polymorphisms (SNPs), known as DNA sequence polymorphism caused by variation of a single base pair of nucleotide at the genome level, have been extensively studied.

In association studies, SNP markers have more advantages than microsatellite markers. (1) For SNP markers, there are always two alleles or three alleles in the population. Therefore, the allele frequencies can be easily estimated. (2) SNPs' distribution in the genome, with minor allele frequency >0.1 occur once every 600 kb, is much wider than that of microsatellite markers. (3) SNPs are highly stable compared with tandem repeat microsatellite loci, especially in the coding region of SNP (cSNP). (4) Researches have found that some SNPs, especially those exist in the coding region of a gene, may directly affect the structure or expression level of encoded protein. (5) It is easy to carry out automatic and high-throughput genotyping analysis for SNPs, which shortens the research periods. In addition, compared with protein biomarkers that are always transiently expressed in the disease course, SNPs do not alter in response to underlying disease, and may be the most suitable predictors for disease susceptibility research.

Since genotyping can be easily carried out using a small amount of peripheral blood, it is attractive to assess individual reaction after major trauma in a genetic approach. Identifying patients at risk of developing complications may improve their outcome by precise and targeted treatments such as antibiotic prophylaxis, substitution therapy, or plasma transfusions.

2 Relationship Between Genetic Polymorphisms and the Outcomes of Trauma Patients

Sepsis and MODS are among the most severe traumatic complications burdened with high mortality. Although a number of investigations have been conducted, the underlying pathogenesis is still not very clear, mainly due to its complex and multiple influencing factors. In the middle of 1980s, sepsis was considered as an excessive inflammatory response to infection, characterized by large number of

pro-inflammatory cytokines released by immune cells. However, subsequent so-called "anti-inflammatory therapies" were all failed. Later, Bone et al. [7] proposed the "compensatory anti-inflammatory response syndrome" (CARS) Hypothesis in 1996. It points out that the inflammatory response induced by early stage of sepsis can induce immune suppression in the later stage. Nowadays, it has become more clear that infection can trigger a much more complex, variable and prolonged host response, in which both pro-inflammatory and anti-inflammatory mechanisms are existing at the same time, contributing to clearance of infection and tissue repair on the one hand and organ damage and secondary infections on the other [8]. In order to determine the patients' risk of developing infectious complications after major trauma, a number of genes have been studied, including pattern recognition receptors (PPRs), signal transducing adaptors, inflammatory cytokines, complement system and coagulation system related genes.

2.1 Pattern Recognition Receptors and Complexes

Pattern recognition receptors are proteins mainly expressed on the surface of innate immune cells, with the role of identify two classes of molecules. The first is pathogen-associated molecular patterns (PAMPs), derived from microorganisms. The other one is damage-associated molecular patterns (DAMPs), which are cell-derived and released during cell damage or death. Among them, Toll-like receptors (TLRs), homologues of the Drosophila Toll gene, plays a critical role in early innate immunity to recognize invading pathogens by sensing microorganisms [9, 10]. TLRs are considered as bridges that connect both innate immunity and adaptive immunity, so they are widely studied. There are totally ten human and nine murine TLRs have been characterized so far, which can be divided into two groups. One group of TLRs are all expressed on the surface of immune cells, in charge of the recognition of microbial cell walls components or microbial proteins. TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11 all belongs to this group. Another group of TLRs, including TLR3, TLR7, TLR8 and TLR9, are expressed inside the cell and mainly in charge of recognize nucleic acids, such as single-stranded or double-stranded RNA, or CpG-rich DNA in specific cellular compartments. The relationship between polymorphisms in TLR1, TLR2, TLR4, TLR9 gene and patients' outcomes has been well studied in trauma cohort (Table 1). Three SNPs in TLR1 were studied in trauma patients. Among them, rs5743551 and rs4833095 were associated with increased risk of mortality in sepsis and gram-positive sepsis, respectively [11]. A SNP in TLR2, Arg753Thr, although has been reported to be associated with Gram-positive infections [12, 13], does not exist in Chinese population. While another tagging SNP (TLR2 19216T/C) has been shown to be associated with LPS induced cytokine production and an increased risk of sepsis and MODS after severe trauma [14]. Besides, two functional SNPs in TLR4 gene (−2242T/C and 11367G/C) were found to be related to sepsis morbidity [15–17].

Table 1 Effects of pattern-recognition receptors gene polymorphisms on the outcomes of trauma patients

Gene	Chrome location	Variation	Population	Study size	Fuctional effects	Associated clinical phenotype	References
TLR1	4p14	−7202A/G (rs5743551)	Whites	1498		Higher mortality with sepsis after traumatic injury	[11]
		742A/G (Asn248Ser) (rs4833095),	Whites	1498		Higher mortality in Gram positive sepsis	[11]
TLR2	4q32	−16934 T/A (rs4696480)	Mixed Ethnic	219		Higher risk of a gram-positive infection and SIRS	[71]
		R753Q (rs5743708)	Mixed Ethnic	68		Higher sepsis morbidity rate	[35]
		19216T/C (rs3804099)	Han Chinese	410	Cytokine production	Higher sepsis morbidity rate and MOD scores	[14]
TLR4	9q33.1	−2242T/C	Han Chinese	303	Cytokine produciton and promoter activity	Higher sepsis morbidity rate and MOD scores	[15]
		896 A/G	Whites	598		Decreased risk of complicated sepsis	[72]
			Mixed Ethnic	159		Increased risk for severe sepsis following burn trauma	[31]
			Mixed Ethnic	228		Increased risk for severe sepsis.	[40]
		11367G/C	Han Chinese	132	mRNA stability and TLR4 expression	Decreased sepsis morbidity rate and MOD scores	[16, 17]
TLR9	3p21.3	−1486T/C (rs187084)	Han Chinese	557	Cytokine production	Higher sepsis morbidity rate	[18]
		6577T/C (rs352162)	Han Chinese	557	Cytokine production	Higher sepsis morbidity rate and MOD scores	[18]

(continued)

Table 1 (continued)

Gene	Chrome location	Variation	Population	Study size	Fuctional effects	Associated clinical phenotype	References
MD-2	8q21.11	−1625C/G (rs11465996)	Han Chinese	105/726	MD-2 promoter activity,MD-2 expression	Higher sepsis morbidity rate and MOD scores	[19, 73]
CD14	5q31.1	−159C/T (rs2569190)	Han Chinese	105	CD14 promoter activity	Increased sepsis morbidity rate and MOD scores	[20]
			Han Chinese	106		Increased MOD scores	[74]
			Mixed Ethnic	228/149/233		Decreased risk for severe sepsis and mortality	[40, 48, 75]
		−1145G/A (rs2569191)	Han Chinese	105	CD14 promoter activity	Decreased sepsis morbidity rate and MOD scores	[20]
			Han Chinese	106		Increased MOD scores	[74]
LBP	20q11.23	Pro436Leu (rs2232618)	Han Chinese	454/1215	Higher median basal serum LBP levels	Higher susceptibility to sepsis and MOD	[23]
RAGE	6p21.3	−429T/C (rs1800625)	Han Chinese	728	Decreased production of TNFα and promoter activities	Decreased sepsis morbidity rate and MOD scores	[24]
NLRP3	1q44	−1017G/A (rs2027432)	Han Chinese	718	Increased production of IL-1βand transcription activity	Increased MOD scores	[25]
		5134A/G (rs12048215)	Han Chinese	718	Decreased production of IL-1β	Decreased sepsis morbidity rate	[25]
hGR/NR3C1	5q31	BclI C/G (rs41423247)	Han Chinese	95			[76]

We also found that TLR9 6577T/C (rs352162) were associated with sepsis morbidity and MOD scores [18].

MD-2, CD14 and LPS-binding protein (LBP) are the co-molecules involving in TLR4 sensing. A polymorphism in MD-2 promoter (MD2 −1625C/G) was reported to increase the promoter activity and expression level of MD2 in vitro. Patients carrying −1625G allele are more likely to develop sepsis and MODS after major trauma [19]. Although the results of CD14 researches are not consistent, our study found a synergistic effect of −159C/T and −1145G/A on the development of post traumatic complications [20]. The researches regarding LBP SNPs and sepsis also got conflicting results [21, 22]. However, we identified that people carrying LBP 436Leu had an increased risk of infection in Chinese population [23].

Besides of classical receptors involved in TLR4 pathways, several other PPRs have been also investigated. RAGE −429T/C polymorphism (rs1800625) was shown to be related to sepsis and MODS in severe trauma patients [24]. Compared with those carrying T allele, patients carrying C allele had a significantly lower sepsis morbidity rate and MOD scores. Rs2027432 in NLRP3, a member of NOD-like receptor family, was found to be significantly associated with higher risk of MODS. In addition, the NLRP3 5134A > G (rs12048215) polymorphism was found to be significantly associated with a lower sepsis morbidity rate. Moreover, the rs2027432 polymorphism was significantly associated with higher IL-1β levels [25].

2.2 Signal Transducing Adaptor Proteins

Interleukin-1 receptor-associated kinases (IRAKs) are a family of molecules, which play an important role in the regulation of natural immune system, as mediators of TLR/IL1R superfamily signaling. There are four IRAK genes found in the human genome (IRAK1, IRAK2, IRAK3 or IRAKM, and IRAK4). All of them have the similar domain structures, including a praline/serine/threonine-rich (PEST) kinase domain (KD) and an conserved N-terminal death domain (DD), which is important for dimerization and interaction with MyD88. Except for IRAK4, the other three mebers in IRAK famil all contain a C-terminal domain, which is required for TRAF6 binding and activation [26].

The relationship between IRAK1, IRAK3 and outcomes of major trauma patients were investigated (Table 2). One MODS-related polymorphism in IRAK1 gene was found out. IRAK1 encodes the interleukin-1 receptor-associated kinase 1, a serine/threonine kinases belongs to the Toll/IL-1 receptor (TIR) signaling family and a key regulator of NF-kappa B pathway. Sperry et al. [27] studied a cohort of 321 patients with a median ISS of 16 for the 1595T/C substitution (rs1059703) in exon 12 of IRAK1 which results in a non-synonymous mutation (p.L532S). They found patients carrying this polymorphism have an eightfold and 11-fold risk of MOF and death, respectively. Specially,this phenomenon is most prominent in males, whereas females carrying heterozygous are more likely to have a worse

Table 2 Effects of signal transduction gene polymorphisms on the outcomes of trauma patients

Gene	Chrome location	Variation	Population	Study size	Fuctional effects	Associated clinical phenotype	References
IRAK-1	Xq28	1595 T/C (rs1059703)	Mixed Ethnic	321		Greater risk of MOF and mortality	[27]
IRAK-3	12q14	15SNPs	African ancestry and European ancestry	474		Greater risk of ALI in African descent	[28]
REL	2p13-p12	rs842647 G/A	Chinese	753	Lower TNF-α production	Lower sepsis morbidity rate and MOD scores	[30]

outcome. Meyer et al. [28] genotyped 25 candidate genes for 474 critically ill trauma patients with acute lung injury (ALI) in a prospective cohort study using the IBC chip. IRAK3 was found to be associated with ALI in patients from African descent but not in European ancestry trauma subjects.

Nuclear factor-κB (NF-κB) family contains five members, p50, p52, p65 (RelA), RelB and c-Rel. The complexity of NF-κB can be activated by either canonical or non-canonical pathways and plays an essential role in inflammation [29]. More and more evidence indicates that polymorphisms in the NF-κB family genes may affect the magnitude of proinflammatory response. Our research investigated the relationship between Tag SNPs selected from NF-κB family genes, including NFKB1, NFKB2, RELA, RELB and REL, and outcomes in a Chinese trauma cohort [30]. One SNP, rs842647 in REL gene, was found to be associated with lower sepsis morbidity and MOD scores. Patients carrying rs842647 A allele had lower plasma TNF-α levels.

2.3 Inflammatory Cytokines

In the course of sepsis, there is a comprehensive and systemic activation of immune responses. The markedly imbalanced cytokine response accompanying with sepsis forms a kind of 'cytokine storm', which converts normally beneficial responses of anti-inflammation into excessive, and finally causes damage to normal tissues. Various cytokines released from immune cells work as effectors and play an important role in the inflammatory response to infection. Thus, a number of polymorphisms in cytokine genes have been investigated using association studies (Table 3).

Table 3 Effects of cytokine gene polymorphisms on the outcomes of trauma patients

Gene	Chrome location	Variation	Population	Study size	Fuctional effects	Associated clinical phenotype	References
IL-1α	2q13	−889C/T (rs1800587)	Han Chinese	308	The lower serum levels of Il-1α	Higher sepsis morbidity rate	[77]
IL-1β	2q14	−1470G/C.	Han Chinese	308/238	Cytokine production	Lower sepsis morbidity rate	[77, 78]
		−511T/C (rs16944)	Han Chinese	308/238	Cytokine production	Higher sepsis morbidity rate	[77, 78]
			Caucasian	100			[79]
			Greek	183			[80]
		−31C/T (rs1143627)	Mixed Ethnic	159/228/149			[31, 40, 48]
			Han Chinese	308/238	Cytokine production	Higher sepsis morbidity rate	[77, 78]
		3953C/T (rs1143634)	Caucasian	100			[79]
			Unknown	97			[41]
IL-1RN	2q14.2	intron 2, VNTR	Greek	183			[80]
		rs315952	European	1002		Decreased risk of ARDS	[81]
IL-4	5q31	−589T/C (rs2243250)	Han Chinese	308	Higher plasma IL-4 and lower interferon-gamma production	Increased susceptibility of sepsis	[77, 82]
IL-6	7p21	−174G/C	Mixed Ethnic	68			[35]
			Mixed Ethnic	159/228/149			[31, 40, 48]
			African ancestry and European ancestry	474			[28]
			Caucasian	100			[79]
			Unknown	71			[83]
			Caucasian	57			[84]

(continued)

Table 3 (continued)

Gene	Chrome location	Variation	Population	Study size	Fuctional effects	Associated clinical phenotype	References
			Unknown	47			[85]
			Unknown	77		Increased mortality after acute severe TBI	[86]
		−572C/G (rs1800796)	Han Chinese	105/308	Reduced transcriptional activity of the IL-6 promoter, IL-6 production from leukocytes	Lower risk of sepsis	[42, 77]
			Unknown	47			[85]
		−597G/A (rs1800797)	Han Chinese	105			[42]
IL-8	4q13	−251A/T (rs4073)	Unknown	47			[85]
IL-10	1q31-32	−1082G/A (rs1800896)	Mixed Ethnic	68	Lower interleukin-10 production	Lower risk of sepsis	[35]
			Unknown	71	Lower interleukin-10 production		[83]
			Han Chinese	308	Lower lipopolysaccharide-induced IL-10 production	Higher sepsis morbidity rate and MOD score	[87]
			Caucasian	211	Lower interleukin-10 production	Higher severity of illness on admission, daily organ dysfunction scores and 60-day mortality	[88]
			Chinese	314		Higher morbidity rate of ARDS and 30-day mortality	[89]
			Unknown	119		Higher relative risk of MODS	[90]
		−819C/T (rs1800871)	Han Chinese	308	Lower serum levels of IL-10	Lower sepsis morbidity rate	[77]
			Mixed Ethnic	265	A trend for decreased levels of IL-10	A decreased risk for death	[91]
		−592C/A (rs1800872)	Unknown	119		Lower relative risk of MODS	[90]
			Mixed Ethnic	265		A decreased risk for death	[91]

(continued)

Table 3 (continued)

Gene	Chrome location	Variation	Population	Study size	Fuctional effects	Associated clinical phenotype	References
					A trend for decreased levels of IL-10		
TNFα	6p21.3	−308G/A (rs1800629)	Mixed Ethnic	159		Increased risk for severe sepsis	[31]
			Mixed Ethnic	228		Lower risk for severe sepsis	[40]
			Mixed Ethnic	69		Increased risk of mortality	[32]
			Han Chinese	308	Cytokine production	Increased sepsis morbidity rate and MOD scores	[77]
			Han Chinese	306	Increased TNFαproduction	Increased sepsis morbidity	[92]
			Unknown	159	Higher TNF-alpha serum concentrations	Increased sepsis morbidity and mortality rate	[33]
			Unknown	152		Increased sepsis morbidity and mortality rate	[34]
TNFβ	6p21.3	252T/C (rs909253)	Unknown	70	Higher cytokine-producing capacity	Increased severe sepsis morbidity	[36]
IFN-γ	12q14	874A/T	Mixed Ethnic	68	Lower IFN-γproducing	Lower sepsis morbidity in African American	[35]
			Han Chinese	308	Lower IFN-γproducing		[77]
		CA repeat	Unknown	61		Increased sepsis morbidity	[93]
HMGB1	13q12	2179C/G (rs2249825)	Chinese	556	Higher HMGB1 production	Increased sepsis morbidity and MOD score	[94]

Tumor necrosis factor alpha (TNFα) is a typical pro-inflammatory cytokine which has been widely studied. The relationship between TNFα/−308 variation and sepsis has also been reported extensively. It was found that TNFα/−308 was association with sepsis severities and outcomes of patients repeatedly. Those A allele carriers have a tendency towards increasing TNFα plasma levels and a stronger inflammatory response [31–34]. However, conflicting results were reported in other studies [35, 36]. Interleukin (IL)-1 is another kind of important pro-inflammatory cytokine, including isoforms α and β. A polymorphism (46 bp VNTR) in the intron 6 of IL-1α gene was described as having no association with sepsis [37]. However, we found that genetic variations in the IL-1β gene had a close relationship with worse outcomes in major trauma patients [38, 39]. In addition, researches focused on polymorphisms in other cytokine genes, including IL-6, IL-10, TNFα/β, MIF and IFN-γ (Table 1). IL-6 −174G/C variation was studied in six cohorts of trauma patients, three cohorts of burns patients, and a cohort of traumatic brain injury (TBI) patients. Only two out of these articles described an increased risk of sepsis with presence of the −174C allele [40, 41]. However, only −572C/G, instead of −174G/C was identified in the promoter of IL-6 gene in Chinese Han population. Patients carrying the IL-6 −572 CC genotype had significantly more sepsis morbidity than with a CG or GG genotype [42]. Three SNPs (rs1800896, rs1800871 and rs1800872) in IL-10 promoter have also been widely studied in trauma cohorts. However, conflicting results were reported. A meta analysis from our lab [43] didn't find a strong association between those three SNPs and sepsis morbidity. Subgroup analysis by ethnicity indicated −592C/A was association with sepsis susceptibility in Caucasians, while −1082A/G in Asians, indicating there is a racial difference.

During the process of sepsis, cytokine genes tend to form crosstalk, interact with each other. Therefore, we further investigated the synergetic effects of 13 SNPs in 9 cytokines Among them, eight SNPs, including IL-1β/−31, IL-1β/−511, IL-1β/−1470, IL-4/−589, IL-6/−572, IL-8/−251, IL-10/−819, and TNFα/−308 were found to be susceptibility loci for sepsis morbidity and organ dysfunction in severe trauma patients. Additionally, patients carrying more than four risk alleles of these eight SNPs had more than 50 % risk to develop sepsis and multiple organ dysfunction [44].

2.4 Vascular Endothelial Cells Function

Endothelial cells, a truly pervasive organ in human body, are highly active and alterative during the progress of sepsis [45]. Pathogens may directly infect intact endothelial cells in some cases. Endothelial cells can also be activated by components of the bacterial wall (e.g. LPS), as well as various host-derived factors, including cytokines, chemokines, complement body, serine protease, protein fiber, platelets activation, leukocytes, hyperglycemia, oxidation and blood flow changes [46]. Activated endothelial cells may undergo structural changes and functional

changes, involving a great number of genes. Therefore, the relationship between gene variations and outcomes of trauma patients was studied.

The interaction between inflammatory mediators and endothelial cells induces a net procoagulant phenotype, such as an increasing level of plasminogen-activator-inhibitor-1 (PAI-1). The insertion/deletion polymorphism in the promoter of PAI-1 gene(4G/5G) is investigated in a small severe trauma cohort by Menges et al. [47]. The PAI-1 4G allele was found to be associated with high plasma concentrations of PAI-1 and poor outcomes after severe trauma. Barber et al. [48] reported the similar results. Vascular endothelial growth factor A (VEGFA) encodes VEGF, a protein that is the most important member of the platelet-derived growth factor (PDGF)/vascular endothelial growth factor (VEGF) family. It acts on endothelial cells and has various effects, including inducing angiogenesis, vasculogenesis mediating increased vascular permeability and endothelial cell growth, inhibiting apoptosis and promoting cell migration. Meyer et al. [28] found that a set of SNPs in VEGFA gene (VEGFA block 1) was significantly associated with the morbidity of ALI in both African and European Ancestry trauma subjects. Angiopoietin-2, encoded by ANGPT2 gene, is expressed only in vascular remodeling. Two ANGPT2 polymorphisms, rs2442598 and rs1868554, were found to be strongly related to the plasma Angiopoietin-2 isoforms, as well as the morbidity of ALI in major trauma patients [49].

2.5 Acute-Phase Protein

Acute-phase proteins include two classes of proteins. One class is positive acute-phase protein whose plasma concentrations increase in response to inflammation. While the other class is negative acute-phase protein whose plasma concentrations decrease in response to inflammation. In response to injury, the liver produces a large number of acute-phase reactants. Their genetic variations have also been studied in trauma patients. Hildebrand et al. didn't find an association between SNPs in the calcitonin (CALCA) gene and systemic PCT levels or clinical outcomes of polytraumatized patients. Heat shock proteins (HSP) are released by cells when exposure to stressful conditions. High levels of heat shock proteins can be introduced by various kinds of environmental stress conditions, including trauma and inflammation. An association study in eighty major multiple trauma patients showed that HSPA1B AG and HSPA1L CT genotypes were significantly associated with increased plasma production levels of TNF-α and IL-6. HSPA1L CT genotype was also a significant risk factor of the development of liver failure [50]. However, Bowers et al. reported polymorphisms of HSP-70 (HSPA1B and HSPA1L loci) have no effect on infection morbidity or outcomes in critically ill patients after surgery [51]. The −144C/A loci in the promoter of HSP90beta gene was reported to be associated with higher expression of HSP90beta and low expression of TNF-alpha, as well as decreased MOD scores in a Chinese severe trauma cohort [52].

2.6 Other Genes

The mitochondrial genome (mtDNA) is the main source of oxygen-derived free radicals, also called as reactive oxygen species (ROS). ROS is an indispensable active substance for human beings. It can increase the activity of some enzymes, involve in the synthesis of some active substances such as prostaglandin. During inflammatory process, ROS can promote inflammatory cells phagocytosis and kill bacteria. However, the overabundance of ROS caused by oxidative stress reaction cause cell damage and result in patterns of secondary injury [53]. There are three association studies focusing on 4216T/C polymorphism of the NADH dehydrogenase 1 (ND1) gene conducted in burn and trauma cohort. However, conflicting results were reported. Canter et al. [54] showed that 4216T allele increased the in-hospital mortality after major injury. Trauma patients who carried 4216 T allele have 2.1 times more risk of death than C allele carriers. While Huebinger et al. [55] and Gomez et al. [56] both found that sepsis-related organ dysfunction and shock was significantly increased in burn and traumatic injury patients carrying 4216 C allele.

Micro RNA (miRNA) is a class of short single stranded endogenous non-coding RNA molecule (about 22 nucleotides) which participated in post-transcriptional regulation of gene expression function as RNA silencing [57]. It has been known that miRNAs can recognize their target mRNAs by seed sequence, 2–8 nucleotides at the 5′ end of the miRNA. Thus, a miRNA may have hundreds of mRNA targets. Meanwhile, a given target may be regulated by multiple miRNAs [58]. In recent years, growing evidence indicates that miRNA may play a major role in the pathogenesis of sepsis [58–60]. It has been reported that the miRNA expression profiles in both plasma and leukocytes are significantly different between sepsis patients and healthy controls [61]. There is also quite different between sepsis and nonsepsis systemic inflammatory response syndrome (SIRS) patients [62]. Recently, we conducted a systematic research of polymorphisms in pre-miRNA and their clinical relevance in major blunt trauma patients [63]. Nine SNPs were selected out from a total of 1048 human miRNAs and genotyped in three independent cohorts of severe trauma patients. Only one single SNP (miR-608 rs4919510) were identified to significantly increase the expression level of mature miR-608, as well as proinflammatory cytokines, such as TNF-α, IL-6 and IL-1β. Furthermore, patients carrying rs4919510 had a higher risk of developing sepsis and MODS in three independent study cohorts.

3 The Effect of Precision Medicine on Trauma Therapy

As the concept of precision medicine, it is encouraged to use accurate clinical information and evidence to appropriately manage a patient at an individual level or at a community level. Thus, clarifying the relationship between genetic background

and trauma can not only provide early warning diagnostic methods for traumatic complications, but also directly affect the clinical treatment of trauma patients.

An excessive immune inflammatory response and the imbalance of pro-inflammatory and anti-inflammatory factors are believed to be, at least partly, the underlying pathogenesis of complications after trauma. A group of cytokines, such as TNFα, TNFβ, IL-1α, IL-1β, IL-4, IL-6, IL-8, IL-10 and IFN-γ, were involved. The plasma levels of several cytokines have been reported to be associated with the course of disease and clinical outcome in trauma patients [64] and were thought to have potential therapeutic role in trauma patients. Injection of recombinant TNFα into human or animal can induce various symptoms of sepsis, suggesting that TNFα is a key factor in the pathogenesis of sepsis. Therefore, researches attempted to reduce the inflammatory response of sepsis patients using TNFα inhibitors [65]. Although the method has a certain effect on animal model, results from large-scale clinical trial showed that anti-cytokine therapy can not reduce, but even increase the mortality rate of sepsis patients [66]. However, the anti-TNFα therapy has been considered as an effective treatment in patients with arthritis [67] and inflammatory bowel disease [68]. The major challenges for anti-cytokine therapy maybe just how to choose the appropriate subjects.

Recent studies found that the individual TNFα expression levels induced by LPS stimulation among different healthy people may vary as much as 10 times. It is mainly determined by the genotype of two polymorphisms (−308 and −376) in the promoter region of TNFα gene. We can selected out the patients with potential high expression levels of TNFα on admission to hospital by just a simple genotyping. Thus, the anti-TNFα treatment may achieve success in clinical.

The traditional surgical procedures, including access, exposure, bleeding, resection, reconstruction, and drainage etc. Surgeons should strictly abide by the principles to achieve a perfect operation. However, in clinical practice, it is common that patient died due to the neglect of physiological state although underwent a successful surgery. It is well recognized now that multiple trauma patients have more possibility to die from their intra-operative metabolic failure rather than a failure operation. For example, patients with major injuries and shock will not survive if had a complex operation such as pancreaticoduodenectomy or formal hepatic resection. The surgeons should undergo a shift in their mind and aim at save patients first rather than complete a perfect operation. Therefore, Rotondo et al. [69] proposed the damage control operation (DCO) in 1993. Taking patients with massive hemorrhage as an example, coagulation dysfunction is the main cause of poor prognosis. Therefore, the surgeon should end the surgery as soon as possible, and transfer the patient to a critical care facility to restore his coagulation dysfunction. The deterministic surgery should be performed only when the patient achieve a stable physiological state. Pape et al. [70] conducted a multi-center clinical study in 2007. They observed 165 cases of major blunt trauma patients, and compared the morbidity rate of acute lung injury (ALI) between patients with an external fixator first, conversion to an intramedullary nail later and initial definitive stabilization of the femur shaft with an intramedullary nail. The results showed that in stable patients, primary femoral nailing could significantly decrease the

ventilation time. However, in borderline patients, those who underwent definitive stabilization at the first time had a higher incidence of lung dysfunctions. Based on that, the authors suggested that it is crucial to take the patient's preoperative condition into account when deciding on what type of initial fixation to perform. Thus, it is essential to find an early and accurate way to determine the response of trauma patients to certain treatment.

Researches on the relationship between gene polymorphisms and post traumatic response have made a great breakthrough in the recent years. It is possible to use genetic polymorphisms to evaluate the patients' response and predict the morbidity of complications. Selection an appropriate treatment or operation according to the patient's genetic background may completely change the current treatment of trauma patients, and bring the clinical treatment of trauma into the era of personalized medicine.

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