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Genetic and epigenetic factors in the regulation of the immune response

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Abstract

Purpose of review: This review will update readers on research examining the influence of genetic variation and epigenetics on the immune system and whether genetic variation influences the outcome of critically ill children.

Recent findings: While there have been few recent studies examining the role of genetic variation in the severity of disease or outcome in critically ill children, studies in critically ill adults have been informative. For example, genetic variations in the genes coding for various components of the immune response such as the TLR1, IL-1_{RA}, PCSK9, adonectin, Nrf2, elafin, sphingosine 1-phosphate receptor 3, and SVEP1 have been associated with various outcomes in critically ill adult populations. Many of the variants demonstrate functional consequences in the protein levels or activities. In critically ill children, there is an association with increased ICU length of stay in children with septic shock with one of the TLR1 variants.

Summary: The degree of influence of host genetic variation in the outcome in critically ill children remains a much understudied area of research. However, it remains important because it may not only help identify children at risk for worse outcomes but it may provide insight into mechanisms of critical illnesses and novel therapies.

Keywords

Genetics; polymorphisms; epigenetics; critical care

Introduction

The primary role of the immune system is to defend against invasive organisms. The innate immune system is responsible for immediate, nonspecific, responses and the adaptive for late, specific, responses and memory. The patterned responses of each of these arms of the immune system can vary between individuals in both magnitude and timing. At least part of

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Conflicts of Interest

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that inter-individual variation is likely dependent on both the individual's genome and epigenetic transcriptional regulation of the genome.

Genetic variants and the impact on the immune response

The link between genetics and immune dysfunction was first made when Burton identified agammaglobulinemia, the first primary immunodeficiency, approximately 65 years ago [1]. This identification was closely followed by the description of severe combined immunodeficiency (SCID) several years later. With technological advances in molecular biology and the sequencing of the human genome over 240 specific DNA mutations that cause primary immunodeficiency have now been identified [2–4]. Gene defects impact a spectrum of immune functions from limiting or preventing development of specific immune cells to mutations that affect immune cell functions, including some leading to increased susceptibility to specific organisms.

Mutations causing primary immunodeficiencies are rare and most critically ill children do not have a primary immunodeficiency. However, studies of adoptees indicate that an individual's genetic make-up influences the outcome from infection [5]. Adoptees with a biological parent who died due to infection before the age of 50 had a higher relative risk of death due to infection than the relative risk of death due to cardiovascular disease, cerebrovascular disease or cancer for adoptees with a biologic parent who died early of the indicated diseases. This observation combined with data from the Human Genome and the HAPMAP projects suggest that common genetic variants might contribute to an individual's susceptibility to infection, disease severity, and/or response to treatment.

The role of genetic variants in disease is generally explored using either candidate gene (genes for proteins known to be involved in the disease) or genome wide association studies (GWAS). For sepsis and acute respiratory distress syndrome (ARDS) most studies have used a candidate gene approach, as GWAS requires hundreds to thousands of patients. There is a lack of consensus between many of the early genetic association studies stemming from the initial lack of understanding of the differences in frequency of genetic variants and in linkage disequilibrium between races and ethnicities, the inadequate power in many studies, and the failure to correct for multiple comparisons. In addition, the characteristics of cohorts of both sepsis and ARDS patients often vary between studies as both diseases have multiple triggers and manifestations and heterogeneity in phenotypes confound genetic association studies. It is now clear that observed association of genetic variants with disease needs to be replicated in different cohorts and that the variant should either result in a change in level or function of the encoded protein, or be in linkage disequilibrium with a variant that affects level or function. In addition, the protein encoded by the gene with the variant should be examined for biological plausibility if it does not already have an established role in the pathologic process. Recently a number of common genetic variants associated with risk or outcome of sepsis or ARDS which meet the criteria described above have been reported in adult studies [6–10]. Variants identified in genes related to the immune system in which multiple studies have suggested a role in infection, sepsis or ARDS are described below focusing on those variants either implicated in children, or identified recently.

Common single nucleotide variants (SNVs) in the Toll-like receptor 1 gene (*TLR1*) have been implicated in differences in immune function in both adults and children. TLR1 forms a heterodimer with TLR2 and recognizes bacterial lipopeptides, lipoteichoic acid (from gram positive bacteria), and yeast [11]. The *TLR1* gene has two variants, one in the promoter region and one that results in an amino acid change, that account for 40% of the variability observed in ligand induced inflammatory cytokine production [12]. The G allele at rs5743551 in the promoter and the isoleucine (Ile) variant at amino acid position 602 (rs5743618) are associated with greater TLR2/1 ligand induced cytokine production. There is a high level of linkage disequilibrium between these variants suggesting that they are often inherited together and that the observed effect may be due to either a single variant or a combined effect. The Ile variant has a higher level of cell surface expression on peripheral monocytes [12, 13], which may explain at least part of the increased response in individuals with this variant. Interestingly, the G allele in the promoter is associated with gram positive sepsis and ARDS and with increased mortality and organ dysfunction in adult patients with sepsis in two independent cohorts [12] and with increased mortality in trauma patients [14]. Together these studies indicate that the presence of the G allele and/or the Ile variant may result in a hyperinflammatory response that contributes to worse outcomes.

TLR1 is also found on neutrophils and the impact of *TLR1* variants on neutrophil function may be involved in the observed association of these variants with outcomes. The Ile variant in TLR1 is involved in variability in neutrophil response and priming [15]. Priming using agonists for TLR2/1 in healthy individuals show marked differences in response with priming occurring in neutrophils from only half of the individuals tested. Neutrophils from individuals homozygous or heterozygous for Ile at amino acid 602 demonstrated TLR2/1 ligand induced priming whereas individuals without Ile showed little or no priming. Individuals with the Ile variant also express more TLR1 on the neutrophil cell surface [15]. Interestingly, in children with septic shock and positive bacterial cultures, the Ile variant is associated with increased ICU length of stay [15]. This is the first report indicating that a variant in *TLR1* may impact sepsis in children, though there is still work to be done to confirm whether multiple variants in TLR1 are associated with susceptibility to gram-positive infections and poor outcome in sepsis and whether such findings are also observed in other populations of critically ill children.

Genetic variants in the interleukin-1 receptor antagonist (IL-1ra) are also associated with variable outcomes in sepsis and ARDS. The IL-1ra gene, *IL1RN*, has multiple SNVs as well as a region of variable nucleotide repeats (VNTR). A multi-stage genetic association study in individuals of European descent using three different cohorts and examining ~2000 genes identified a variant in *IL1RN*, rs315952C, which is associated with decreased risk of ARDS and increased levels of serum IL-1ra [16]. This variant is also associated with increased LPS stimulated IL-1ra levels in healthy adults of European ancestry, but not in healthy adults of African ancestry, and with improved survival from septic shock in adults of European ancestry [17]. Genetic variants in *IL1RN* have been shown to be associated with the severity of meningococcal disease [18] and pneumonia [19] in children. However, these studies were performed before differences in genetic structure between races and ethnicities were reported and before the complexity of the genetic variation within the *IL1RN* gene was appreciated.

Recent work has begun to explore the role of genetic variants in less traditional components of the inflammatory response. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulatory molecule that inhibits clearance of endogenous lipid from the blood by decreasing hepatocyte LDL receptor density thereby decreasing LDL particle clearance; an important process for clearing lipid moieties from pathogens thereby decreasing the inflammatory response. Mouse models indicate that decreasing PCSK9 levels results in increased clearance of endotoxin, lower levels of proinflammatory cytokines and improved survival [20]. In humans loss of function variants of the *PCSK9* gene result in increased clearance, and gain of function variants result in decreased clearance of LDL cholesterol [21–30]. In adults enrolled in the Vasopressin and Septic Shock Trial (VASST) [31] the presence of at least one loss of function variant was associated with increased survival at 28 days even after adjusting for covariates [20]. These findings were replicated in a second independent cohort. Furthermore, patients with one loss of function allele had lower serum cytokine levels compared with those patients carrying the gain of function variant [20]. These studies have not yet been replicated in children with sepsis.

Adiponectin, one of the most abundant gene products in adipose tissue is an adipokine secreted by adipocytes which exhibits an anti-inflammatory activity [32–36]. Adiponectin inhibits NF-kappa-B signaling [37, 38], decreases TNF- α expression [39], and increases the anti-inflammatory cytokines IL-10 and IL-1ra [40]. One variant in the 3' untranslated region (UTR) of adiponectin gene, *ADIPOQ*, results in increased levels of adiponectin [41, 42] and is associated with increased mortality in ARDS [43] supporting the previously described association between the higher levels of adiponectin and mortality in adults with ARDS [43].

Variants in several other genes related to the immune system have been reported to be associated with risk or outcome in sepsis or ARDS, including variants in Nrf2, a transcription factor involved in regulating antioxidant response. Several reports indicate that variants in Nrf2 are associated with ARDS though the functional impact of the implicated variants is unknown [44–46]. Variants in elafin (peptidase inhibitor 3), a proteinase inhibitor thought to protect against deleterious effects of proteinases during inflammation, and sphingosine 1-phosphate receptor 3, a protein implicated in lung inflammation, have been reported to be associated with ARDS [47]. Lastly, a SNV that changes an amino acid in the protein SVEP1, a cell surface protein involved in cell adhesion, is associated with increased mortality and organ dysfunction in individuals of European ancestry with septic shock [48]. Whether variants in elafin, sphingosine 1-phosphate and SVEP1 are involved in risk of ARDS or mortality in septic shock in children remains unknown.

Epigenetic mechanisms as regulators of the inflammatory response

The complexity of the inflammatory response begins with the control of expression of inflammatory genes. Genome-wide expression patterns of peripheral blood mononuclear cells in critically ill children demonstrate both activation and suppression of inflammatory genes with a pattern that differs in patients with different outcomes [49–53]. Epigenetic changes are key regulators impacting the expression of inflammatory genes [54–56] and may have long-term implications following the severe inflammatory responses that occur in

critically ill children [57]. By definition “an epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence” [58]. The three main epigenetic mechanisms, DNA methylation, histone post-translational modifications and non-coding RNA (microRNA) silencing of gene expression, are involved in regulating the inflammatory response. This section of the review will focus on key aspects of epigenetic mechanisms as they relate to the inflammatory response. Unfortunately, studies examining epigenetic processes in critically ill children are woefully lacking.

DNA Methylation

DNA methylation is the addition of a methyl group at position 5 of the pyrimidine ring of cytosine in areas of DNA enriched with CpG repeats (also known as CpG islands). Methylation in promoter or enhancer regions of DNA typically results in transcriptional silencing. Methylation of both the TNF- α [59] and Interleukin-6 (IL-6) promoters [60] are associated with decreased production of inflammatory diseases. DNA methylation also plays a key role in activating dendritic cells' ability to promote a Th2 response [61]. In addition, DNA methylation is a key component in establishing endotoxin tolerance in monocytes [62]. Changes in DNA methylation patterns may be driven by pathogens themselves resulting in alterations of the inflammatory response [63]. Currently there is little data regarding DNA methylation and its impact on severe acute inflammatory disorders, but age related changes in the inflammatory response in children might result from changes in DNA methylation patterns [64].

Histone Modifications

Chromatin consists of DNA wound around an octamer of histone proteins (H2A, H2B, H3, H4) forming nucleosomes that are linked together by regions of DNA containing H1 histone protein. Epigenetic modifications of chromatin are critical in regulation of transcriptional expression in part by creating different conformations of chromatin. Heterochromatin is tightly packed chromatin that limits access to promoter regions (the “gene off” state). Euchromatin is more loosely packed chromatin allowing for access to promoter regions (the “gene on” state). Each histone protein can be modified by acetylation, methylation, phosphorylation, ubiquitination or sumoylation of amino acid tails. These modifications impact the conformation of the histone and its interactions with other proteins. Chromatin remodeling complexes are involved in establishment and maintenance of nucleosome complexes and in histone modifications which regulate expression [55]. Chromatin remodeling complexes consist of enzymes, DNA binding proteins and adaptor proteins. The components of the complexes act as readers (i.e. identification of methylated CpG islands), writers (i.e. Histone acetyl transferases) or erasers (Histone deacetylases) of the epigenetic code [55]. Thus chromatin-remodeling complexes are key in regulating whether DNA is in a heterochromatic or euchromatic state.

The role of epigenetics in the regulation of inflammatory response includes evidence that chromatin modifications are involved in reducing production of TNF- α [57], IL-1 β [65], and IL-12 [66]. Histone modifications are also important in the development [54] and polarization of macrophages [67]. The most compelling evidence of the importance of epigenetic histone modifications for critical illness is that epigenetics is involved in

establishing the immunosuppressed phase of inflammation through effects on cellular energetics. The NAD⁺ sensing deacetylase, sirutin 1, is instrumental in immune and metabolic reprogramming and is responsible for the shift from a glucose dependent pro-inflammatory state to a fatty acid oxidative anti-inflammatory state in experimental models [68]. Future studies will be required to determine whether such changes are also seen in critically ill children.

microRNA

MicroRNAs are small 18–22 nucleotide strands of non-coding RNA. Primary microRNA is transcribed by RNA polymerase II as a much longer transcript that undergoes a series of processing steps to generate the mature microRNA. The mature microRNA is part of the RNA-induced silencing complex and binds complementary regions in the 3' or 5' UTR of mRNA encoding for specific proteins. The degree of binding between the microRNA-mRNA results in either transcriptional repression or degradation of the mRNA [69] decreasing the level of the protein.

The importance of microRNAs in regulating the inflammatory response has been established in both models of inflammation as well as in critically ill patients. One of the first studies investigating LPS stimulated microRNA production revealed increases in miR-146a/b, miR-132 and miR-155 [70]. Later studies demonstrated that miR-146 down regulates IRAK-1 and TRAF-6 [70], proteins involved in intracellular response to IL-1 β . miR-146 also down regulates IL-1 β stimulated production of both IL-8 and RANTES in lung alveolar epithelial cells [71]. Other work indicates that miR-146 is involved in the development of endotoxin tolerance [72]. Another microRNA, miR-155, is induced by TLR 2, 3, 4 and 9 ligands as well as TNF- α and regulates the innate inflammatory response through effects on macrophage differentiation [73] and inflammatory hematopoiesis [74].

These early investigations linking microRNAs to regulation of the immune response have led to studies examining microRNAs as biomarkers for diseases [69]. Several groups have attempted to use circulating microRNA profiles to define the severity of SIRS and sepsis as well as to distinguish SIRS from sepsis with mixed results [69]. Unfortunately, due to the variability in organisms, the changing patterns of microRNA production and the heterogeneity of patients with sepsis none of these studies are ready for clinical implementation. An increased understanding of the physiologic role of microRNAs together with the results from ongoing clinical trials [75] may result in identification of microRNAs that will be useful as biomarkers or therapeutic targets in acute inflammatory states.

Conclusion

In summary, growing evidence continues to support the role of genetic variation in the susceptibility to or outcome of sepsis and ARDS and the role of epigenetics in controlling gene expression in critically ill children. Though the number of genetic variants and epigenetic processes with strong evidence of impact on variability of disease in sepsis and ARDS is not large it will continue to increase. Carefully designed and analyzed genetic and epigenetic studies are needed to provide further insight into the mechanisms of critical illnesses.

- Genetic variation in genes involved in the immune response are associated with various outcomes in critically ill adults and children with sepsis, trauma, or specific organ failure
- Many of these variations are shown to impact the levels or functional activities of the gene product
- Epigenetics plays a role in the immune response but there is little data on how it influences critically ill adults and children

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