Review Article

Defects in innate and adaptive immunity in patients with sepsis and health care associated infection

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Abstract: Recent advances in sepsis therapy exclusively involve improvements in supportive care, while sepsis mortality rates remain disturbingly high at 30%. These persistently high sepsis mortality rates arise from the absence of sepsis specific therapies. However with improvements in supportive care, patients with septic shock commonly partially recover from the infection that precipitated their initial illness, yet they frequently succumb to subsequent health care associated infections. Remarkably today the pathophysiology of sepsis in humans, a common disease in western society, remains largely a conundrum. Conventionally sepsis was regarded as primarily a disorder of inflammation. More recently the importance of immune compromise in the pathophysiology of sepsis and health care associated infection has now become more widely accepted. Accordingly a review of the human evidence for this novel sepsis paradigm is timely. Septic patients appear to exhibit a complex and long-lasting immune deficiency state, involving lymphocytes of both the innate and adaptive immune responses that have been linked with mortality and the occurrence of health care associated infection. Such is the pervasive nature of immune compromise in sepsis that ultimately immune modulation will play a crucial role in sepsis therapies of the future.

Keywords: Sepsis; infection; immunity; lymphocytes; antigen presentation

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Introduction

Sepsis is a common disease in western society. With an annual incidence of 2–3 per 1,000 population, sepsis may account for as many deaths as acute myocardial infarction (1). Sepsis affects all age groups but is more prevalent at the extremes of age, and particularly with increasing age. With an increasing proportion of older age groups in the developed world, sepsis is becoming increasingly prevalent in western society. While the case fatality rate of sepsis in western society is decreasing, as the incidence of sepsis increases, the overall mortality is increasing (2). However, despite recent advances in supportive care, sepsis mortality rates remain disturbingly high at nearly 30% (3). With improved support of failing organ systems for patients with septic shock, patients with severe sepsis and septic shock endure a prolonged illness, often characterised by recurring health care associated infections (4,5). Thus while patients with septic shock commonly recover from the infection that precipitated their initial illness, they frequently succumb to subsequent health care associated infections. Why does this happen?

Sepsis pathophysiology

Surprisingly the pathophysiology of sepsis in humans remains a conundrum. Early sepsis research focused intensively on the concept that septic shock, and sepsis-related organ dysfunction, were induced by an exuberant pro-inflammatory response to systemic bacterial

products, notably the bacterial cell wall molecule lipopolysaccharide (LPS). Evidence supporting this idea accrued from experiments involving blockade of molecular mediators of inflammation that improved outcome in experimental animal and bench models of sepsis (6,7). The results of these experiments formed the rationale for human trials investigating cytokine antagonism in sepsis. Subsequently clinical trials have failed to show a consistent benefit from this therapeutic approach, with some even demonstrating worse outcome in patients (8,9).

These failures have given rise to increasing concerns regarding the broader applicability of various animal sepsis models to humans (10,11). The complex interplay between circulating bacteria and the innate immune response was further elucidated in studies examining human cytokine responses following exposure to live bacteria. Apparently the initial inflammatory response to pathogens may be beneficial, as it appears crucial in the priming of immune responses required to eventually clear infection (12). Furthermore an anti-inflammatory cytokine response to infection may not be beneficial, as for example the archetypic anti-inflammatory cytokine IL10, which is an important factor contributing to impairment of bacterial clearance in pulmonary sepsis (13).

New approaches

Gene arrays provide a useful platform to study genome-wide transcription patterns in lymphocytes of patients with sepsis. A systematic review of array-based transcription profiling in human sepsis, published in 2010, reviewed 12 microarray based studies including 784 patients, and performed between 1987 and 2010 (14). An immediate activation of both pathogen recognition receptors and associated signalling pathways is apparent from these studies. Yet there was no evidence supporting distinctive pro or anti-inflammatory phases of gene transcription in these studies of septic patients. It was also notable that in many of these genes array studies unequivocal evidence of immune suppression was observed, with non-survivors down-regulating genes linked to antigen presentation and those characterising T cell activation.

Pathogen or host

The relative importance of the pathogenic attributes of infecting microorganisms in the pathophysiology of sepsis may have been overstated, particularly in comparison to the significance of the human immune response to infection. Evidence for this is provided by results of gene expression profiling, again using microarrays, in patients with staphylococcal infection (15). In this study the clinical characteristics of infection were associated with host gene transcription patterns, rather than any bacteriologic virulence factor. This hypothesis, that the human host response is of pivotal importance in the pathophysiology of sepsis in patients, and of equal or greater importance than the type of infection, is supported by other studies demonstrating similar gene expression patterns in patients with gram positive and gram negative infections (16,17). Lastly a recent study comparing cytokine gene expression in an enriched pool of monocytes and T lymphocytes reported a highly significant link between pattern of cytokine gene expression and clinical disease severity, regardless of the nature of the infectious pathogen (18).

Immunity

As an appreciation of the importance of immune compromise in the pathophysiology of human sepsis and health care associated infection is gaining more widespread acceptance, at this juncture it is worthwhile reviewing the evidence for specific aspects of immune deficiency in septic patients (19).

In human immunity monocytes are the principle lymphocytes of innate immunity, and act as antigen presenting cells (APC), to activate T lymphocytes of the adaptive immune system. It is crucially important to understand that regulation of T lymphocyte activation is mediated by monocyte surface human leukocyte antigen DR (HLA-Dr) expression, and by monocyte costimulatory ligands and cytokines. Activation of adaptive immune T lymphocytes is required to clear bacterial infection in humans.

Monocytes

Monocyte, macrophages and dendritic cells are classed as professional APCs, by nature of their ability to present antigens bound by surface HLA molecules, thereby activating T cells of the adaptive immune system. Co-stimulatory molecules that are present on the monocyte surface are essential co-factors for T cell activation. Human circulating monocyte populations may be broadly characterised on the basis of the expression of the antigens CD14 and CD16 (20,21). Although the $CD14^{+}/CD16^{+}$

monocyte subset are responsible for production of cytokines important in sepsis immune responses (22-24), monocytes contribute little to the overall levels of increased cytokines that are found in the blood of septic patients, despite their known function as cytokine secreting cells (25).

Monocytes of patients with sepsis express surface receptors that typify an overall activation state. These receptors include the immunoglobulin receptor CD64, in addition to CD163 (a scavenger receptor for the haemoglobin/haptoglobin complex) and CD206 (a mannose receptor) (26). Both surface expression of Toll receptors, and expression of Toll receptor genes TLR-2 and TLR-4, are increased on monocytes of patients with sepsis (27). Collectively these receptors characterise an appropriate activation state that is to be expected as a normal response in a patient with an infection (26,28).

Monocytes of patients with sepsis are however less responsive than those from healthy controls (29). LPS-induced monocyte tumor necrosis factor α (TNF-α) production is decreased in patients with sepsis, and has been used as an index of immune responsiveness in patients with sepsis, identifying patients likely to benefit from an immune adjuvant, such as granulocyte monocyte-colony stimulating factor (GM-CSF) (30). Furthermore, increased gene expression of inhibitory Toll receptor signalling molecules that have been reported in monocytes in patients with sepsis may predict subsequent mortality (31), and may be predictive of both subsequent staphylococcal bacterial co-infection and mortality in children with influenza (32).

Cytokine production by monocytes is inhibited by IL10, and archetypic anti-inflammatory cytokine that is over expressed in patients with sepsis. Thus *IL6*, *TNF*α and *IL12p40* gene expression in human monocytes are inhibited by IL10, and this effect is mediated in part by miRNA-187 (33).

Thus while some cell surface receptor expression suggest monocyte activation in sepsis, monocyte responsiveness in patients with sepsis appears to be very abnormal.

Monocyte-T cell interactions

The interaction between the monocyte co-stimulatory protein CD40 and CD40 ligand (CD40L) on $CD4^+$ T lymphocytes is an important step in T lymphocyte activation. This interaction also enhances surface expression by monocytes of other co-stimulatory molecules, namely CD80 and CD86. Expression of surface CD40 on monocytes in patients with sepsis is decreased (34). Surface expression of CD80 is markedly lower on monocytes from septic patients (35), and fails to increase in response to CD40/CD40L ligation. Gene expression of yet another co-stimulatory molecule CD86 is also down-regulated in patients with sepsis (36). Collectively these studies demonstrate that, despite evidence for monocyte activation in sepsis, downstream monocyte signalling is nonetheless impaired in septic patients.

Programmed cell death-1 (PD-1) and programmed death-1ligand (PD-L1)

The programmed cell death receptor PD-1 and its ligand PD-L1 are important in regulating the interaction between monocytes and T cells. The PD-L1 ligand is expressed on APCs in response to stimulation, and also expressed on T and B lymphocytes upon activation. Formation of a PD-1 receptor/PD-L1 ligand complex transmits inhibitory signals, involved in reducing proliferation of T lymphocytes. In patients with sepsis, $CD4^+$ and $CD8^+$ T lymphocyte expression of PD-1 is increased, as is monocyte PD-L1, facilitating this immune inhibitory signalling pathway (37). Blockade of this receptor-ligand interaction reduces apoptosis in T cells, increases TNFα and IL6 production, and decreases production of IL10 by monocytes. Greater expression of monocyte PD-1 itself is reported in association with health care associated infection and mortality in patients with severe sepsis (38,39). Modulation of the PD-1/PD-L1 pathway in patients with sepsis is currently being evaluated as a potential sepsis immune therapy.

Monocytes, HLA-Dr and sepsis

The expression by monocytes of the MHC class II antigen presenting molecule HLA-Dr, which is crucial for T lymphocyte activation and expansion, is markedly downregulated in humans with severe sepsis, and remains so for at least 28 days after the onset of sepsis (40). After major trauma, this decrease in HLA-DR expression is related to the occurrence of subsequent sepsis and health care associated infection (41,42). However, this decrease in HLA-Dr expression does not consistently predict clinical outcome in trauma patients (43). By contrast, the decrement in monocyte HLA-Dr expression is reliably predictive of mortality and the occurrence of health care associated infection in patients with severe sepsis (44-46). Therefore, quantification of monocyte HLA-Dr expression has been advocated both as a sepsis biomarker, and as a tool to identify profoundly immune suppressed sepsis patients, who are at risk for health care associated infection, and for

inclusion in clinical trials of immune adjuvant therapies, such as GM-CSF (46,47).

Stimulation by the cytokine interferon gamma (IFNγ) restores monocyte HLA-DR expression, and attenuates the reduction in LPS induced TNFα production. On this basis, IFNγ has also been proposed as an immune adjuvant for patients with sepsis (48).

Monocytes and the IL12 family cytokines

The IL12 family of cytokines regulate the interaction of innate and adaptive immune responses: IL12, IL23 and IL27 are members of this cytokine family that are produced by APCs (49). These cytokines regulate $CD4^+$ T cell differentiation into specific phenotypes. IL12 promotes $CD4^+$ T cell differentiation to a Th1 phenotype with production of IFNγ, which is of pivotal importance in clearing intracellular bacterial infection in humans. IL12 production by monocytes has been extensively studied in humans: IL12 is composed of two subunits, p35 and p40 (p40 is also a component of IL23). In postoperative surgical patients, production of IL12p40 subunit by monocytes is reduced (50). Pre-term neonates produce less IL12p40 than mature infants, with the decrement in production being more marked in neonates who develop sepsis (51). In trauma patients, inducible monocyte IL12 production is decreased in patients who develop health care associated infection and sepsis (52). The importance of IL12 in immunity is also reflected by a case of recurrent paediatric sepsis linked to an underlying deficiency in IL12 production, where *in vitro* studies of circulating lymphocytes noted near complete absence of IFNγ production (53).

IL27 appears to inhibit bactericidal potency of polymorphs in humans (54). Elevated IL27 has been observed in patients with sepsis, and indeed has been advocated as a biomarker in paediatric sepsis (55,56). However it is not clear whether IL27 is a marker of any infection, or whether it is linked with the occurrence of severe sepsis (18).

IL23, produced by monocytes, promotes $CD4^+$ T lymphocyte differentiation to an activated Th17 phenotype, which is crucially important in the clearance of extracellular bacterial and fungal infections. Thus inherited defects in IL17 and its receptor are associated with chronic mucocutaneous candidiasis (57). Decreased *IL23* gene expression has been linked with the occurrence of sepsis in patients with infection, and with health care associated respiratory infection after thoracic surgery (56,58).

Dendritic cells

Dendritic cells (DCs) differentiate into professional APCs from monocytes (59). Phenotypically, circulating DCs are commonly divided into $CD11c^+$ myeloid dendritic cells (mDCs) and $CD123^+$ plasmacytoid dendritic cells (pDC) based on surface expression of these antigens (60). Both mDCs and pDCs have been shown to be decreased in patients with septic shock. Furthermore, persistent depletion of mDCs was associated with both mortality and with developing health care associated infection in existing ICU patients (61,62).

Ancillary features linking monocyte activation and sepsis

Other factors such as polymorphisms in TNF promoter regions have been shown to influence susceptibility to pathogens such as *meningococcus*, through effects on monocyte TNFα production (63). Further, regulation of TNFα production by monocytes, at the post-transcriptional level by miRNA-125b, has been recently reported in the setting of neonatal sepsis (64). In addition molecules such as CTLA-4 (cytotoxic T lymphocyte antigen-4) and BTLA (B- and T-lymphocyte attenuator) have been shown to impair innate and adaptive immune cell responses in sepsis (65).

Thus mechanisms of lymphocyte activation by monocytes appear to be crucially deranged in patients with sepsis.

T lymphocytes

T lymphocytes play a pivotal role as facilitators and effectors of the adaptive immune response to infection. An effective functioning pool of T lymphocytes is essential to control and then eradicate infection. $CD4^+$ T lymphocytes expand and are activated in response to antigen presentation by monocytes, in combination with the interaction of costimulatory ligands with their cognate receptors.

The gamma chain cytokines (IL2, IL7 and IL15) are important regulators of T lymphocyte homeostasis and expansion. Inherited defects in receptors for these cytokines account for many cases of severe combined immune deficiency (66). Septic patients and patients with health care associated infection after thoracotomy exhibit inappropriate down regulation of these gamma chain family cytokines IL2 and IL7 (67).

CD4 Th1

T lymphocytes have a capacity to differentiate into distinct phenotypes. The Th1 T lymphocyte phenotype

characteristically secretes IFNγ and is essential to the clearance of intracellular bacterial infection. Interestingly in trauma patients, the $CD4^+$ T cell phenotype is skewed toward a Th2 phenotype, in contrast to the typical Th1 responses that should be seen in the setting of bacterial infection.

CD4 Th17 lymphocytes

$CD4^+$ T cells expressing IL17 (Th17 phenotype) are important in host defences at mucosal surfaces, but represent less that 1% of the total population of $CD4^+$ cells in sepsis patients (28). There are few human studies of the role of IL17 expressing $CD4^+$ cells in sepsis (68). In patients with severe thermal injury, blood levels of IL17 were increased in paediatric patients. Furthermore, IL17 levels in whole blood were detected in greater concentrations in adults than in children (69,70). However, when $CD4^+$ cells were studied in thermally injured adults, there was a marked decrease in the number of $CD4^+$ cells expressing IL17, with this finding mirrored by a reduction in inducible $CD4^+$ IL17 production (71). Furthermore, thermally injured adult patients exhibited a marked decrease in expression of RORt (the signature $CD4^+$Th17 transcription factor) in response to T cell receptor stimulation and following challenge with *Candida albicans*. Thus although the role of $CD4^+$Th17 T lymphocytes in sepsis is presently unclear, there appears to be an association between down regulation of $CD4^+$TH17 pathways and sepsis in humans.

Lymphocyte subpopulations

Additional T lymphocyte subpopulations, including $CD4^+CD25^+Foxp3^+$ T regulatory cells (T reg), gamma delta (γδ) T cells and NK-T cells, are increasingly recognised as of importance in immune responses in injury and sepsis (72,73). This importance may be attributed to the capacity of these rare niche lymphocytes that are not dependent upon APCs for activation, to interact with both innate and adaptive arms of the immune system.

In general absolute lymphocyte numbers are reduced in sepsis. Activated $CD4^+$ Th1 and $CD4^+$ Th17 cells appear to be reduced, as are the population of circulating γδ T cells, in patients with sepsis, while the population of inhibitory $CD4^+$T reg cells is increased or unchanged (28,74,75).

Interestingly persistent T cell lymphopenia in sepsis, resulting in changes in proportions of $CD4^+$ T cell subsets, has been recently observed in an elderly patient cohort. In this study a reduction in immunocompetent $CD4^+CD28^+$ T cells (rather than inhibitory and regulatory T cells) was linked to poor prognosis (76). Lymphopenia is also observed in patients with infection who are not septic: one study demonstrated decreased active and naïve $CD4^+$ and $CD8^+$ lymphocytes in patients with acute respiratory infection from *Legionella* species. Complete recovery of lymphocyte counts was observed following resolution of the acute infection (77). Thus while lymphopenia appears to be a feature of all infections, persistent lymphopenia as seen in sepsis is linked with adverse outcomes.

T cell function

T lymphocytes in patients with sepsis express both the lymphocyte activation marker CD69 and Ki67 as a marker of proliferation (78). Apoptotic markers were also more prominent in $CD4^+$ but not $CD8^+$ cells of patients with sepsis. Hence, the population of $CD4^+$ cells of patients with sepsis includes the full gamut of proliferating T cells, activated T cells and T cells undergoing apoptosis.

A study measuring cellular ATP content in $CD4^+$ T cells from sepsis patients showed a decrease in $CD4^+$ T cell ATP levels in non-survivors, thus linking mortality in sepsis with a failure of T lymphocyte activation (79). In patients with severe sepsis, T cell receptor diversity is markedly reduced and this reduction in T cell receptor diversity correlates with the occurrence of health care associated infection (80). This study again linked a failure of T cell activation and expansion with mortality in human sepsis.

Further evidence of a link between T lymphocyte dysfunction and sepsis was gleaned from a study of patients who developed sepsis after trauma. T lymphocytes in patients who subsequently developed sepsis, sampled at the time of splenectomy prior to the onset of infection, exhibited a decrease in inducible IFNγ (81). This study is interesting as it supports the hypothesis that an attenuated immune response is present before the onset of sepsis, and thus may be causal rather than coincidental in nature.

Thus sepsis in patients has consistently been associated with persistent lymphopenia and failure of T lymphocyte activation, which in turn have been linked with health care associated infection and excess mortality in patients.

Neutrophils

Neutrophil function has also been shown to be impaired in sepsis. Activation of TLR2 by LPS can induce neutrophil apoptosis (82). Low neutrophil counts are associated with poorer outcomes in sepsis, and detection of phenotypically immature granulocytes has been proposed as a biomarker of severity (83,84). Despite expressing increased activation

markers, neutrophil trafficking is nonetheless impaired in sepsis. This may be due to lower levels of expression of the adhesion molecule CXCR2 which is important for neutrophil chemotaxis. For example, lower levels of CXCR2 expression were observed in neutrophils of patients who died of sepsis. IL33, a recently identified member of the IL1 cytokine family, has been shown to prevent this TLR mediated reduction in CXCR2 dependent chemotaxis (85).

Conclusions

In conclusion, septic patients, and patients who develop health care associated infection, appear to exhibit a profound complex and long lasting immune deficiency state, involving lymphocytes of both the innate and adaptive immune responses. In time immune modulation must play a crucial role in sepsis therapies of the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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