Innate immunity, coagulation and surgery

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1. ABSTRACT

Inflammation is the host's defense mechanism to infection or trauma including surgical procedures. In the clinic, non-infectious inflammation plays an important part in cardiology (e.g. Percutaneous transluminal coronary angioplasty, PTCA), intensive care medicine (e.g. polytrauma), cardiac (e.g. extracorporeal circulation) and vascular surgery (e.g. reperfusion injury). An imbalance of the inflammatory response can cause an acute condition like sepsis or long-term Cardiovascular disease (CVD), both of which are leading killers in the Western world. Alterations in coagulation, innate immunity and endothelial function represent key aspects in the mechanism of inflammation and are the link between the pathogenesis of these two diseases. Studying inflammatory pathways or targeting specific mediators during inflammation may help to develop strategies to improve the clinical outcome of patients undergoing major surgery, where postoperative inflammation plays a crucial role.

2. GENERAL INTRODUCTION

Cardiovascular disease (CVD) is a growing health problem with high economic costs to run cardiac intensive care units (1), while sepsis and septic shock are the most frequent cause of death in non-cardiac intensive care units (2). These conditions have more in common than just leading statistics, cardiovascular disease and sepsis are both a result of inflammation (3-4), where coagulation (5-6), innate immunity as well as endothelial dysfunction are underlying factors in their pathogenesis (4,7) (Figure 1). Inflammation can be classified into acute and chronic responses. Chronic inflammation can cause coronary heart disease, while acute inflammation can result in e.g. bacterial infection leading to sepsis. Acute inflammation is also triggered and cascaded by surgery, burns and tissue injury. It is characterized by vasodilatation of blood vessels, edema due to exudation of plasma proteins, leukocyte infiltration and adherence to the endothelium and the release of chemotactic mediators. Local inflammation often results
3.2. Activation of TLRs by bacterial wall fragments

Inflammatory responses induced by cell wall components and nucleic acids of microorganisms are particularly initiated by the family of TLRs (11-12). Different TLRs are organized as receptor complexes, which sense most of the cell wall components spanning the diverse microbial world (9). TLR2 has been implicated in the signaling process of Gram-positive bacteria (e.g. *Staphylococcus aureus*) (13), while TLR4 is the main receptor for Gram-negative bacteria (e.g. *Escherichia coli*) (14). However, TLR2 detects also LPS and lipoproteins of certain Gram-negative bacteria such as *Helicobacter pylori* and *Francisella tularensis* (15-16). The wall of Gram-negative bacteria contains Lipopolysaccharide (LPS) or endotoxin, which is composed of the lipid A domain, an inner core and outer core oligosaccharide and, the O-antigenic polysaccharide domain (17-18). LPS is responsible for the initiation of Gram-negative shock, where pro-inflammatory mediators such as IL-1, IL-6, IL-8 and Tumor necrosis factor (TNF)-α are released by macrophages, monocytes and other cell types (19). In contrast, Gram-positive bacteria such as *Staphylococcus aureus* can cause multiple organ failure and septic shock without causing endotoxemia (20). The cell wall of Gram-positive bacteria contains lipoteichoic acid and peptidoglycan, which is a macroamphiphile (equivalent to LPS in Gram-negative bacteria) containing a substituted poly-(glycero-phosphate) backbone attached to a glycolipid (21). Peptidoglycan is a large polymer, which provides stress resistance and shape determining properties to bacterial cell walls. *In vivo*, lipoteichoic acid and peptidoglycan act in synergy to release cytokines such as TNF-α and Interferon (IFN)-γ and inducing Inducible nitric oxide synthase (iNOS) resulting in shock and multiple organ failure (22).

LPS-induced host cell activation mediates the release of NF-κB, which regulates the expression of diverse genes including cytokines, chemokines and enzymes like Hemeoxygenase (HO)-1 and iNOS, as well as other biological responses (23-25). HO-1 is an enzyme system, catalyzing the rate-limiting conversion of heme to iron, carbon monoxide and biliverdin (converted to bilirubin), whereas iNOS produces Nitric oxide (NO). In stress situations, HO-1 is thought to be protective because of its ability to form the antioxidant agent bilirubin and the vasoactive gas carbon monoxide (26-27). In contrast, copious amounts of NO generated by iNOS have been associated with the pathophysiological features of septic shock, i.e. myocardial dysfunction and multiple organ failure (28-29). Besides extensive formation of NO, endotoxemia causes the generation of large quantities of oxygen free radicals such as hydrogen peroxide and superoxide anions (30). Simultaneously released superoxide anions and NO may yield the production of reactive NO species such as peroxynitrite, which is more potent in causing cell injury than its parent molecules (31). Interestingly, time- and concentration dependent NO can also enfold protective characteristics (32-33), whereas its ability to induce HO-1 might account to this protection (34). In rat lungs, iNOS derived NO induces HO-1 leading to lung protection during a subsequent LPS challenge (35).

3.3. TLRs and the Hypothalamic-pituitary-adrenal (HPA)-axis

The HPA-axis plays an important role in the pathogenesis and course of inflammatory diseases (36). In
### Table 1. List of known toll-like receptors (TLR) and examples of agonists

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<thead>
<tr>
<th>TLR</th>
<th>Agonist Species</th>
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<tr>
<td>TLR1</td>
<td>Triacyl lipopeptides (in association with TLR2) Bacteria and mycobacteria</td>
<td>HCV core, NS3 (in association with TLR2) HCV</td>
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<td></td>
<td>HCMV envelope gp B and gp H (in association with TLR2) HCMV</td>
<td>SAA (in association with TLR2) Host</td>
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<td>hBD-3 (in association with TLR2) Host</td>
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<td>TLR2</td>
<td>Triacyl lipopeptides (in association with TLR1) Bacteria and mycobacteria</td>
<td>Diacyl lipopeptides and LTA (in association with TLR6) Mycoplasma and Gram-positive bacteria</td>
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<tr>
<td></td>
<td>PG Gram-positive bacteria</td>
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<td></td>
<td>LPS Gram-negative bacteria</td>
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<td></td>
<td>ND Encephalitozoon cuniculi</td>
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<td></td>
<td>Yps3p Histoplasma capsulatum</td>
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<td>Hemagglutinin protein Measles virus</td>
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<td>Zymosan Saccharomyces cerevisiae</td>
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<td></td>
<td>Phospholipomannan Candidia albicans</td>
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<td>Mannan Candida albicans</td>
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<td></td>
<td>Glucuronoxylomannan Cryptococcus neoformans</td>
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<td>GPI-mutin Trypanosoma</td>
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<td>ND Encephalitozoon cuniculi</td>
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<td>ND German cockroach feces</td>
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<td>amyloid β Host</td>
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<td>TLR3</td>
<td>dsRNA Viruses</td>
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<td>TLR4</td>
<td>LPS Gram-negative bacteria</td>
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<td>ND Fusarium oxysporum</td>
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<td>Glucuronoxylomannan Cryptococcus neoformans</td>
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<td>Glycosaminoglycans Phospholipids</td>
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<td>Envelope proteins RSV, MMTV</td>
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<td>Flagellin Flagellated bacteria</td>
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<td>TLR5</td>
<td>Flagellin Flagellated bacteria</td>
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<td>TLR6</td>
<td>Diacyl lipopeptides and LTA (in association with TLR2) Mycoplasma and Gram-positive bacteria</td>
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<td>Zymosan Saccharomyces cerevisiae</td>
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<td>TLR7</td>
<td>ssRNA RNA viruses</td>
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<td>TLR8</td>
<td>ssRNA RNA viruses</td>
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<td>TLR9</td>
<td>CptG-DNA Bacteria and mycobacteria</td>
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<td>TLR10</td>
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<td>TLR13</td>
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HCV: hepatitis C virus; HCMV: human cytomegalovirus; SAA: serum amyloid A; hBD-3: human beta-defensin-3; LTA: lipoteichoic acid; PG: peptidoglycan; ND: not determined; HSV1: herpes simplex virus 1; LMW-HA: low molecular weight - hyaluronic acid; LPS: lipopolysaccharide; RSV: respiratory syncytial virus; MMTV: mouse mammary tumor virus (9, 119-134).

Innate immunity, coagulation and surgery

Rats with experimental allergic encephalomyelitis, an adrenalectomy leads to a chronic active disease and, glucocorticoid replacement promotes recovery from this disease (37). Similarly, an adrenalectomy produces severe inflammation in experimental models of acute pancreatitis. Hydrocortisone replacement decreases both the severity and mortality of this disease (38). Peripheral cytokines such as TNF-α, IL-1β and IL-6 modulate the activity of the HPA-axis (39) and are one of the end effectors of this axis. Cortisol and corticosterone, regulate innate and T-cell specific immune responses (40-41). Major inflammatory and infectious diseases are associated with excess glucocorticoid secretion. Several reports highlight the importance of an intact adrenal stress response to infection (36,42-43) and there is good evidence to suggest that impaired innate immunity mediated by TLRs is involved in the pathology of sepsis and cardiovascular disease (44-46). For both, TLR2 and TLR4 knock-out mice we have demonstrated a from Wild-type (WT) mice different morphology of adrenal glands. Basal corticosterone and ACTH plasma concentrations differed also from WT mice. Induction of systemic inflammation resulted in an impaired stress response in both, TLR2 and TLR4 knock-out mice reflected by reduced corticosterone and ACTH concentrations and altered release of pro-inflammatory cytokines (47-48). Recently, we have described the expression of TLR2 and TLR4 in human adrenals (49).

Critically ill patients with sepsis have increased levels of plasma cortisol with relatively normal...
concentrations of ACTH (42). Thus, the activation of the adrenal glands in response to inflammation is an important component of the host’s anti-inflammatory response. The immune system stimulates the secretion of Corticotropin-Releasing hormone (CRH) and ACTH, and can therefore affect the activity of the HPA-axis. Furthermore, the adrenal gland might be stimulated by inflammatory mediators directly (Figure 2). During chronic stress, high levels of inflammatory cytokines may be required to maintain increased glucocorticoid levels, allowing a shift away from androgen and estrogen synthesis towards increased cortisol production. This shift may be beneficial during sepsis or other severe illnesses; however, it could also contribute to tumor formation in endocrine glands and be a risk factor for patients with arteriosclerosis, diabetes, depression and autoimmune diseases. Relative adrenal insufficiency is a complication in a substantial number of patients with sepsis and is attributable to a high mortality rate. During septic shock or acute respiratory distress syndrome, replacement therapy with low-dose hydrocortisone showed improved survival (50-52). However, a recently published multicenter, randomized, double-blind, placebo-controlled trial suggests that hydrocortisone does not improve survival in patients with septic shock (53). Clinical trials are warranted to study the effects of genetic polymorphisms (e.g. TLRs) on the HPA-axis. This might help us to understand more about the cause of inconsistent effects of systemic inflammation on the HPA-axis in individual patients.

3.4. TLRs in surgery

Colorectal surgery is often accompanied by the unwanted effect of anastomotic leakage (see review (54)). This complication leads to post-operative infection increasing morbidity and mortality. On the molecular level, leakage of numerous bacterial species and fungi from a bowel or colon source results in the release of bacterial wall-fragments and the activation of TLRs, leading to local (e.g. peritonitis) or even systemic inflammation (e.g. sepsis) (55). Under experimental settings, the Cecal ligation and puncture (CLP) model consists of ligation of the cecum followed by a small puncture. Feces leaks out of the bowel through the perforation, thereby mimicking anastomotic leakage. In mice within the first 3 hours after CLP surgery, mRNA and protein expression of TLR2 and TLR4 are up-regulated in the liver, lung and spleen (56). In addition,
sham-operated animals (laparotomy only) show also a transient increase in TLR2 and TLR4 mRNA and protein expression, demonstrating that even the stress of anesthesia and sham surgery results in inflammation. Similarly, in the lungs of mice following a *Fumigatus conidia* challenge, an observed increase in TLR2 mRNA expression was still evident some 15 days after CLP surgery (57).

Bacterial translocation is another undesired effect with an occurrence of about 15% in patients undergoing elective surgery (58-59). Enteric organisms translocate from gut across the intact intestinal mucosa to normally sterile conditions like the mesenteric lymph nodes and other internal organs. In addition, this route of passage also allows the transfer of endotoxins (60). Increasingly, reports have inferred a role for bacterial translocation in the morbidity of post-operative sepsis (61). As wall fragments of Gram-positive and Gram-negative bacteria activate TLRs, anastomotic leakage, bacterial translocation and endotoxin release could have implications on their activation and expression. However, the impact of systemic inflammation on TLR expression on leukocytes remains unclear. Up-regulation, no change and down-regulation has been demonstrated and seems to be influenced by time, the cause of systemic inflammation (SIRS, sepsis, septic shock), the type of TLR and leukocyte (62-66). After Coronary artery bypass grafting (CABG) with the use of Cardiopulmonary bypass (CPB), monocytes of patients demonstrate a down-regulation of TLR2 and TLR4 expression, although on day 2 post-surgery, monocytic expression of TLR2 and TLR4 is increased (67). In contrast, Peripheral blood mononuclear cell (PBMC)s of patients who underwent gastrointestinal surgery demonstrated a decrease in the expression of TLR2 and TLR4 initially after surgery. TLR4 expressions returned to preoperative levels within one week after surgery, whilst TLR2 expression took some two weeks to return to preoperative levels (68). The expression status of TLR2 or TLR4 might also have functional consequences. In a study, despite the expression of TLR4 being significantly higher in patients suffering with Systemic inflammatory response syndrome (SIRS) than with normal healthy volunteers, ex vivo production of TNF-α by LPS was reduced in blood from patients with SIRS, indicating LPS hypo responsiveness (69). In another study involving patients with sepsis, severe sepsis and septic shock, no changes in TLR2 or TLR4 expression on PBMCs has been observed. However ex vivo stimulation demonstrated a decreased responsiveness of PBMCs to several stimuli (65).

TLR polymorphisms may influence the outcome of surgical procedures. For example renal transplant recipients with TLR4 polymorphism present a lower risk of post-transplant atherosclerotic events and acute allograft rejection, but experience severe infectious episodes more frequently (70). It is a well known fact that whereas some patients succumb to sepsis after surgery, others will recover unevenly, although having received identical treatment for the same condition. In addition it is unclear why some patients recover from sepsis, whereas others succumb to multi-organ failure and finally death. In these clinical scenarios, it is likely that there are individual differences in the biological responses to SIRS or sepsis. Such differences may include molecules/receptors (e.g. TLRs, CD14, macrophage migration inhibitory factor), various cytokines, CD11b, DNA polymorphisms for genes of the coagulation system, eicosanoids, glucocorticoid secretion, free radicals generation and antioxidant status. The influence of TLR polymorphism on the perioperative phase of patients is still poorly understood. To date there are very few studies with large patient populations to gain further insights into this field. Furthermore, different types of single nucleotide polymorphism for some TLRs are described, which also needs consideration in future clinical trials (71).

4. COAGULATION SYSTEM

4.1. Hemostasis and surgery

The initiation of hemostasis occurs when the integrity of the vasculature is compromised. This process involves the interaction between blood vessel walls, platelets and the activation of a complex cascade of cellular components and soluble factors such coagulation and fibrinolytic factors. Rupture of a blood vessel results in exposure of the sub-endothelium and the initial phase of vasoconstriction to minimize blood loss at the site of injury. Circulating platelets adhere to collagen expressed on endothelial cells via interactions largely mediated with the plasma protein von Willebrand’s factor (72). Platelets become activated through the binding of thrombin and they release several mediators such as ADP and thromboxane A2, which promote platelet interactions and aggregation (73). As a result a platelet plug is formed, providing a temporary measure to stop blood loss. Platelets also release a number of phospholipids and lipoproteins, which activate the coagulation cascade, which is sub-divided in to the intrinsic, extrinsic and common pathway. The extrinsic pathway is activated through Tissue factor (TF) expressed by LPS production of TNF-α by LPS was reduced in blood from patients with SIRS, indicating LPS hypo responsiveness (69). In another study involving patients with sepsis, severe sepsis and septic shock, no changes in TLR2 or TLR4 expression on PBMCs has been observed. However ex vivo stimulation demonstrated a decreased responsiveness of PBMCs to several stimuli (65).

During cardiac surgery and CPB, perioperative and postoperative bleeding are a major challenge for surgeons undertaking these procedures. In particular postoperative bleeding has a major influence on morbidity and mortality (76). Therefore patients undergoing such surgery are at considerable risk. Increased postoperative bleeding after CPB has been attributed to impairment of hemostatic system by for e.g. platelet dysfunction (77),
hyperfibrinolysis (78), hemodilution (79) and excessive activation of both the intrinsic and extrinsic pathway by blood contact with extracorporeal surfaces (80-81). Therefore, it is imperative that during such procedures, hemostasis screening and careful monitoring of blood components and coagulation factors are carried out (82-83).

In addition to the risk of excessive bleeding, cardiac surgery and CPB are also associated with major inflammatory responses (67,84-85). Contact activation of the extracorporeal circulation to non-endothelial surfaces and ischemia/reperfusion injury to the heart and lungs triggers inflammation (86-87). Activation of coagulation ties in closely with the activation of the inflammation. Tissue factor is up-regulated by the onset of inflammation leading to hypercoagulability, and increased expression of plasminogen activator inhibitor, which inhibits fibrinolysis. The results are an increase in the tendency of thrombosis (88) and several studies have suggested that this may be an important mechanism in organ injury in conditions like SIRS, sepsis and cardiac surgery (89-93). Therefore, as well as identifying mediators of coagulation, it is also important to identify mediators in inflammation to combat complications in surgery. TF is an ideal candidate as it is a key player in coagulation and a major player in inflammation. In a state of hypercoagulability, TF activates clotting signals which include coagulant mediators, fibrin and its fragments, all of which are pro-inflammatory and contribute to inflammation (for review see (94)).

TF activates clotting factor VII which initiates a cascade of clotting mediators starting with the conversion of X to Xa. The clotting signal is complete with the final conversion of soluble fibrinogen to fibrin and the formation of a clot. The pro-inflammatory signals of these clotting mediators are elicited through the interactions of the protease-activated receptor (95) and such effects include the activation of cytokines, adhesion molecules and growth factors (95-97). Aside to its role in hemostasis, fibrinogen and its fragments mediate a number of pro-inflammatory and its fragments, all of which are pro-inflammatory and contribute to inflammation (for review see (94)).

A recent study determined that in cardiac surgery, surgical trauma contributes with a higher degree to the inflammatory response than CPB (108). This is consistent with another study where a number of pro-inflammatory cytokines were profiled during various stages of different cardiac-thoracic procedures. 6 h after CABG, IL-6 levels were maximal in patients who underwent extra-corporeal circulation as well as those who did not (off-pump surgery). IL-6 was also elevated in patients receiving thoracic surgery; however, levels were lower than both cardiac surgery groups. Lipoprotein binding protein was elevated in all three groups from 6 h to 3 days after surgery, although off-pump patient levels were significantly higher than in the other two groups. Procalcitonin was also elevated in all groups, with the extracorporeal circulation patients having the highest levels (109). It was concluded that the impact of extracorporeal circulation on the inflammatory response after cardiac surgery may not be so important as surgical trauma and reperfusion injury. To further elucidate the molecular mechanisms of systemic inflammation in on- and off-pump CABG, the gene expression patterns in leukocytes and plasma proteins was determined. In addition to the usual pro-inflammatory cytokines (IL-6, IL-10 and TNF-α) released, proteomic analysis revealed that IFN-γ, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1 and macrophage inflammatory protein-1β also extend the list of mediators released on CPB. Systemic analysis of transcriptional genes in circulating leukocytes revealed that up-regulation of adhesion molecules L-selectin and ICAM-2, signaling cytokine and fibrinogen levels. Preoperatively, IL-6 was elevated in AAA patients versus age-matched controls. During aortic clamping, IL-6, IL-10 and Monocyte chemoattractant protein (MCP)-1 significantly increased, while fibrinogen decreased. After aortic declamping, IL-6, IL-10 and MCP-1 increased further compared with levels during aortic clamping, fibrinogen had a further decrease. After one week, postoperative levels of IL-6, IL-10 and MCP-1 had all decreased (but were still elevated compared with baseline values), while sII-2R and fibrinogen showed an increase in comparison with baseline (104).

In orthopedic surgery using a LPS-stimulated whole blood assay, one study has revealed that 6 days after surgery, there is suppression in leukocyte capacity to express the cytokines TNF-α and IL-10. In blood taken preoperatively and postoperatively (day 1) and exposed to LPS, no changes were observed in TNF-α and IL-10 levels. However on day 6, a significant reduction in the expression of both TNF-α and IL-10 was observed when compared to preoperative levels, concluding that during this time, patients are susceptible to septic complications (105). A similar method was used to determine cytokine levels in newborns before, 5 and 10 days after cardiac surgery. Ex vivo production of the pro-inflammatory cytokines TNF-α, IL-6 and IL-10 was reduced 5 days after surgery. A clear association between the preoperative ex vivo production of IL-6 and postoperative respiratory morbidity was also revealed (106). In adult patients undergoing cardiac surgery, suppression of TNF-α after CPB has also been observed (107).

5. SURGERY AND CYTOKINES

Surgical procedures alter the expression patterns of cytokines, which relate to postoperative inflammatory responses and/or deterioration of the immune system, leading to increased risk of infection. Open Abdominal aortic aneurysm (AAA) surgery induces a profound inflammatory and coagulative response through influencing Innate immunity, coagulation and surgery
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mediators IL-1, IL-8, IL-18 receptors and TLR 4, 5 and 6 also occur after contact with CPB (110). Therefore gene array and multiplex analysis are ideal techniques to profile key players as well as unidentified mediators in the inflammatory responses during various kinds of surgery. This way forward may uncover new potential targets for improving clinical outcome after such procedures.

6. GENETIC POLYMORPHISM AND INFLAMMATION

During surgery, induction of anesthesia and the trauma of surgical procedures induce a localized inflammatory response that stimulates the innate immunity initiating defense mechanisms and wound healing. This is important for patient outcome and recovery, however as discussed there are certain complications that can arise perioperatively and/or postoperatively. Abdominal surgery often results in SIRS and intra-abdominal sepsis (TLR activation) (111-112). Cardiac surgery runs the risk of bleeding (76), thrombosis (93) and inflammatory responses (109). In all cases, continued efforts to reduce such complications are on-going. However whereas in the past clinicians have focused on identifying the mechanisms and pathology of such complications, perhaps a different approach could be to identify and profile genetic variations of crucial genes in innate immunity and coagulation pathways. Genetics may explain the wide variation observed in individual responses to e.g. infection or why individuals have different outcomes after surgery. In recent years, the genetic risk for infections has become increasingly recognized, yet still underestimated. For example a Single nucleotide polymorphism (SNP) of TLR1 (TLR1-7202A/G) is associated with worse organ dysfunction, increased gram positive infections and death in sepsis (113). Patients with a TLR4 gene mutation have a higher incidence of Gram-negative infections (44). Specifically patients with TLR4 Asp299Gly allele have higher incidences of Gram-negative infections (114) and this polymorphism is also attributed to the severity of SIRS (115). We have shown that TLR2 (47) and TLR4 (48) knock-out mice have an impaired adrenal stress response to bacterial wall fragments. During surgery, the HPA-axis is activated during the acute phase response (116). Therefore it would be interesting to investigate the outcome and risk of bacterial infection of patients with TLR polymorphism after for e.g. cardiac or colorectal surgery.

Asp299Gly TLR4 polymorphism has been linked to a reduced risk for acute coronary events and atherosclerosis (45,117). In both studies individuals with this polymorphism had also lower levels of fibrinogen, adhesion molecules and in the latter study reduced levels of pro-inflammatory cytokines and acute phase reactants. Again, how would these individuals fair after cardiac surgery, where such mediators are involved in the pathomechanisms of the inflammatory response (110)? Genetic polymorphisms of TLRs, coagulation factors and cytokines could have a major impact on clinical outcome after surgery. The concept of a patient with a subcutaneous silicon chip carrying a genetic profile has been presented as a theoretical case for the year 2010 (118). Such technology could identify multiple allelic variants resulting in individualized targeted therapy and improving clinical outcome in general and after surgical procedures.

7. PERSPECTIVE

Although current knowledge suggests that numerous factors can influence an individual response to inflammation, little is known about how much each player contributes to a patient’s clinical outcome. At present, basic research and large clinical trials (according to www.clinicaltrials.gov, currently 375 trials are underway focusing on sepsis) are needed to separate these factors into positive and negative effectors as well as elucidating their overall importance during inflammation. With such knowledge it would be feasible to screen high risk patients undergoing major surgery, with the aim to optimize their therapy and improve clinical outcome.

8. ACKNOWLEDGEMENTS

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Key Words: Toll-like receptors, Innate Immunity, Coagulation, Fibrin Fragments, Inflammation, Surgery, Review

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