REVIEW

OPEN

Pathogenesis of infection in surgical patients

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Purpose of review
Despite the application of prophylactic antimicrobial therapy and advanced technologies, infection remains one of the most common causes of morbidity and mortality in surgical patients. Understanding the pathogenesis of surgical infection would offer new insights into the development of biomarkers to predict and stratify infection in patients, and to explore specific strategies to minimize this serious postoperative complication.

Recent findings
The acute nonspecific inflammatory response triggered by endogenous danger signals evoked by surgical insult is beneficial, while paradoxically associated with reduced resistance to infection. There is growing evidence indicating that primed inflammation by surgical insult exaggerates the dysregulation of the immune-inflammatory response to the invasion of pathogens postoperatively. Innate immune receptors, such as Toll-like receptors (TLRs), contribute to detecting both pathogen-associated molecular patterns and endogenous damage-associated molecular patterns, and to further amplifying inflammatory responses to infection. Current evidence shows the fascinating role of non-TLRs in the process of infection. Non-TLRs, such as membrane-associated triggering receptor expressed on myeloid cells family, cytosolic nucleotide-binding oligomerization domain-like receptors and nuclear receptor nuclear family 4 subgroup A receptors, are also crucial in triggering the immune responses and mounting an effective defense against surgical insults and the second hit of infection.

Summary
Understanding the pivotal role of non-TLRs in sensing exogenous and endogenous molecules, and the influence of primed systemic inflammation and depressed immune status on the defense against pathogen after surgical insult, would be helpful to fully explore the relevant sophisticated phenomena of surgical infection, and to elucidate the occurrence of heterogeneous constellations of clinical signs and symptoms among this special population.

Keywords
inflammation, non-Toll-like receptor, pathogenesis, surgical infection

INTRODUCTION

It is estimated that approximately 234.2 million major surgical operations are undertaken in the global healthcare annually [1]. The inpatient surgical complications, ranging from 3 to 17.4%, have substantial adverse influence on clinical processes and outcomes, dramatically prolong hospitalization and increase medical care cost [2–4]. The most frequent types of surgical complications include infection, postoperative bleeding, pulmonary embolism, deep vein thrombosis, stroke and cardiovascular events [5]. It was reported that around 11.9% of surgical patients experienced a postoperative infection episode, with an in-hospital mortality of 14.5%, which is hugely different to anesthesia-attributed mortality (34 per million) and total perioperative mortality (0.8%) [6–8]. Medical and surgical patients represent two different populations, and infection has a greater impact on the mortality in the surgical sets [9]. As the leading cause of morbidity and mortality in patients

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KEY POINTS

- Medical and surgical patients represent two different populations, and infection has a greater impact on the mortality in the surgical sets.
- DAMPs and alarmins can act synergistically with PAMPs to involve in immune-inflammatory response.
- The pivotal role of non-TLRs to sense PAMPs/DAMPs and to trigger immune response will provide a novel insight for the prevention and the treatment of surgical infections.

who underwent surgery, infections were shown to increase hospital costs by an average of $1398 per capita compared with those without in US hospitals [10]. The pathophysiology of surgical infection is a complex process, conducted by the primed and pretriggered host immune-inflammatory response to pathogen, predisposed by genetic factors and tailored by the location, the load and the virulence of the invading microbes in surgical patients [11–13]. Furthermore, increasing age, underlying illnesses such as diabetes mellitus, type of invasive procedure, prolonged duration of the surgical manipulation, ischemia and reperfusion, and transfusion might make the patients more susceptible to infection [14,15]. Despite numerous strategies oriented to defense against pathogens, surgical infection remains a challenging issue [16]. Better understanding of pathogenesis would be important for the improvement of infection outcomes following surgery.

PRIMED INFLAMMATION AND IMMUNE SUPPRESSION

Surgical procedures evoke the innate immune system, and a systemic inflammatory response syndrome is usually initiated within hours after the surgical injury. This acute nonspecific response is a sterile inflammatory response to tissue damage and blood loss, and is triggered by endogenous danger signals massively released from the damaged tissues [11,12,17]. It has been proven that most danger-associated molecular patterns (DAMPs) and alarmins can be mobilized from the injured tissues or cells into circulation by operative insult [18–20]. These DAMPs and alarmins include heat shock proteins, reactive oxygen species, high mobility group box 1, as well as mitochondrial DAMPs which are evolutionarily conserved patterns in pathogens. The DAMPs interact with various cell-surfaces and intracellular receptors in immune effector cells to activate these cells and then lead to overwhelming inflammatory processes, which include inducing neutrophils and macrophages to migrate across damaged endothelial cells into the injured sites to produce proinflammatory mediators [17,21,22].

The primed inflammation by surgical insults like trauma is initially beneficial as it helps to eradicate tissue debris. However, if not balanced by homeostatic anti-inflammatory mechanisms, it is detrimental to the integrity and repair of tissue in surgical patients, and might even elicit an overt depressed immune response due to extensive death of immune effector cells [12,23▪]. Usually, the increased nonspecific inflammatory response in the early phase of surgical hit is accompanied by suppression of surgical patients' ability to mount an effective defense against invading microbes. Previous clinical data indicate that the expression of major histocompatability complex class II antigens on monocytes is markedly decreased immediately after surgical insult [24]. The dysfunction or inability of monocytes increases the host's susceptibility to infection by the invading pathogens further stimulating immune cells via their pathogen-associated molecular patterns (PAMPs). Thus, a vicious cycle might be initiated postoperatively, with surgical hit resulting in inflammation and immunosuppression, which, in turn, leads to infection with further inflammation, tissue injury and organ failure (Fig. 1) [11,25].

Following surgery, when a second hit such as an invasion of pathogens occurs, a rapid cascade of the inflammatory mediators, such as C3a and C5a, ROS and cytokines have been monitored in animal model and patients [11,21,22,26,27]. In subgroups with surgical infection, like in elderly people and diabetic patients who already have a persistent low-grade activated inflammatory status at baseline [28,29], the proinflammatory response has been primed and triggered by already elevated baseline levels of cytokines. As a result of their reduced ability to produce anti-inflammatory mediators such as interleukin (IL)-10, immunosuppression can be aggravated and lead to fatal outcomes in these surgical patients [28,30]. Evidence for this hypothesis has been demonstrated in a large clinical study including more than 36 000 cases [31].

In addition, anesthetic management may influence defense mechanisms to surgical infections as well. There is growing evidence that high doses of opioids, like remifentanil, administered during surgery might induce immunosuppression through the activation of opioid receptors expressed on leucocytes, and also increase susceptibility to infection resulting from opioid withdrawal [32,33]. On the contrary, some interventions such as regional

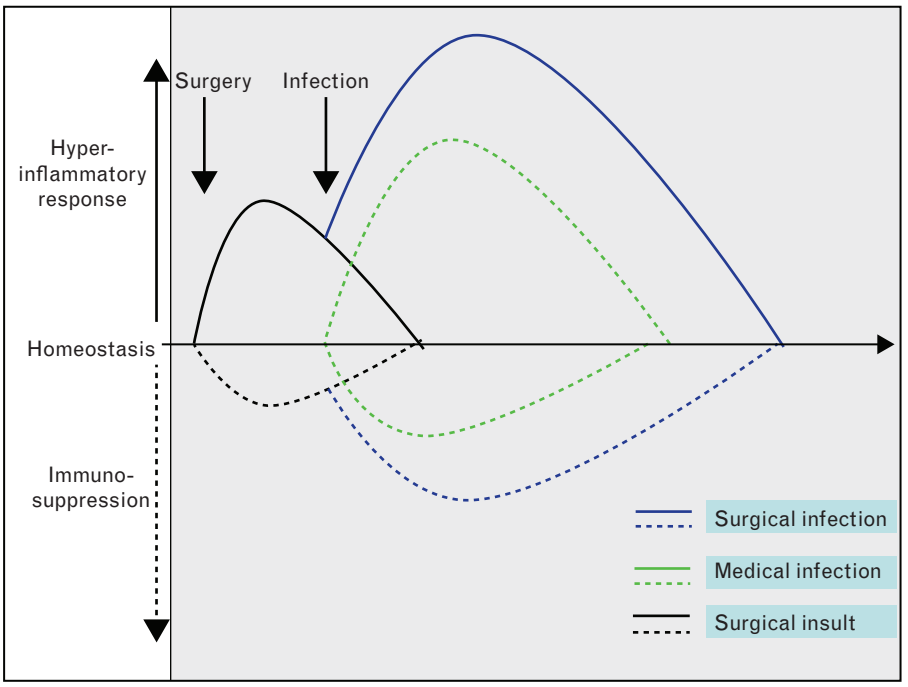

FIGURE 1. Immune-inflammatory response model in patients with surgical infection, medical infection and surgical insult. The Y axis represents the level of immune-inflammatory response. The ebb represents a dynamic change of the immune-inflammatory status. Tissue damage, as well as a stress humoral and neural response, evoked by operative insult can mobilize danger-associated molecular patterns (DAMPs) and alarmins which subsequently spillover into the circulation, activate immune cells and then lead to overwhelming inflammatory processes [18–22]. Accompany with the increased nonspecific inflammatory response, the surgical patients' ability to mount an effective defense against invading pathogens is suppressed which increases the susceptibility to infection [11,12]. In surgical patients, DAMPs and alarmins can act synergistically with pathogen-associated molecular patterns (PAMPs) to further stimulate immune cells, and further lead to deteriorative proinflammatory response and immunosuppression with an increased risk of multiorgan dysfunction and death [11,17,23▪,24–26].

nerve blocks have shown benefits in reducing the primed inflammatory response [34].

INFLAMMATION, INFECTION AND INNATE IMMUNE RECEPTORS

As innate immunity has long been known to detect foreign nonself materials, innate immune receptors sensing endogenous DAMPs have been studied recently, most of which were found to be shared with exogenous PAMPs [35,36]. Toll-like receptors (TLRs), the major family of pattern recognition receptors (PRRs), are responsible for identifying both microbial PAMPs and endogenous DAMPs released from cells under stress such as trauma and damaged cells to trigger the intracellular signaling cascade [37]. The primed TLRs signaling is amenable to recruit the immune cells to the sites of infection and inflammation, to mediate the motivation of the adaptive immune response, to kill the invading pathogens, to halt their proliferation and spread and to repair damaged tissue [37,38]. Ten TLRs members have been identified in humans, so far. These type I transmembrane proteins are characterized by three domains: the extracellular domain, which contains leucine-rich repeats that mediate the recognition of ligands; a transmembrane region; and a cytoplasmic Toll-IL-1 receptor (TIR) domain that activates downstream signaling pathways [39]. Individual TLR can recognize distinct molecular patterns and be stimulated by their respective inducers. Both PAMP and DAMP engage in the induction of TLRs conformational changes including homodimer or heterodimer of TLRs. The resulting TLRs dimers then recruit a specific set of adaptor molecules, such as TIR domain-containing adaptor protein (TIRAP) and myeloid differentiation primary response gene 88 (MyD88), activate the downstream pathway and result in the upregulation or downregulation of inflammation-related gene expression [38–41]. Elevated production of inflammatory cytokines, chemokines and antimicrobial peptides would enhance the bacterial eradication and damaged tissue repairing [37]. For example, the

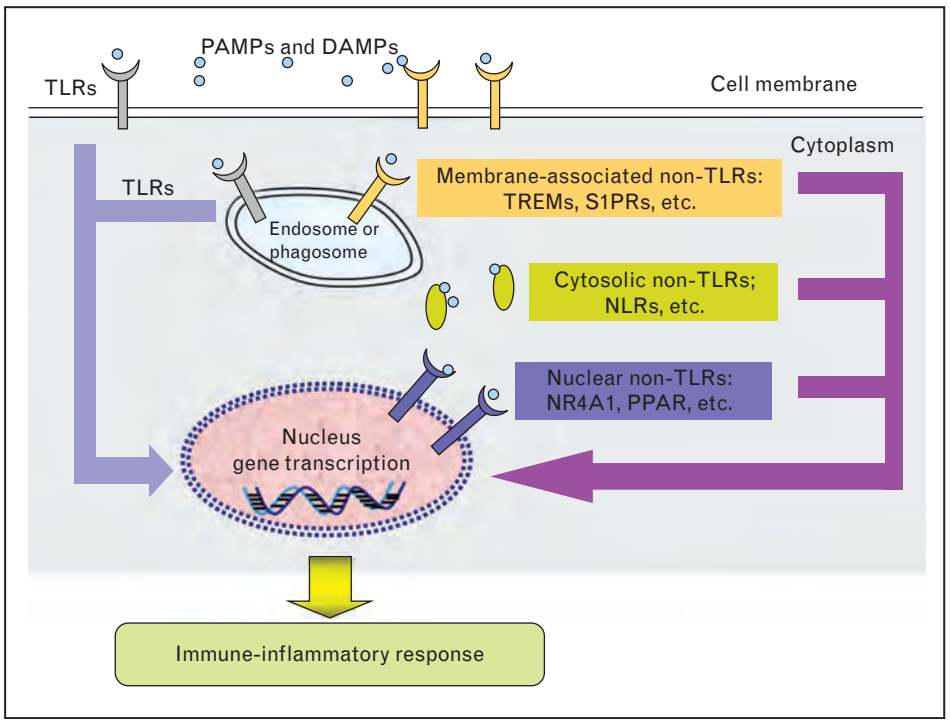

FIGURE 2. Both Toll-like receptors (TLRs) and non-TLRs can sense PAMPs from invading pathogens and/or DAMPs released from stressed or damaged cells, trigger various intracellular signaling pathways to upregulate/downregulate the transcription of specific genes, and further modulate immune-inflammatory response. DAMPs, danger-associated molecular patterns; PAMPs, pathogen-associated molecular patterns.

extracellular domain of TLR2 detects peptidoglycan from Gram-positive bacteria and forms heterodimer with either TLR1 or TLR6, and the extracellular domain of the TLR4 assisted by myeloid differentiation factor 2 detects lipopolysaccharides from Gram-negative bacteria and forms TLR4 homodimer [42,43]. Both TLR2-TLR1 or TLR2-TLR6 heterodimer and TLR4 homodimer can further recruit the TIRAP and MyD88 adaptor to transmit signals in the nuclear factor-kappa B (NF-κB) -dependent manner. Recently, it was discovered that TLR2 within the endosome might activate type I interferon (IFN) gene in IFN regulatory factor (IRF)3/IRF7-dependent manner, and TLR4 within phagosome could result in the production of type I IFN through the activation of TNF receptor-associated factor 3-TANK-binding kinase 1-IRF3 pathway [37,44].

Although the interaction of TLRs with PAMPs or DAMPs plays the central role in the initiation of immune responses against invading pathogens, recent accumulating evidence also sheds light on the importance of non-Toll-like receptors (non-TLRs) to sense infection and damaged tissue and to trigger immune response. In addition to TLRs, non-TLRs, such as triggering receptors expressed on myeloid cells (TREMs) and nucleotide-binding oligomerization domain-like receptors (NLRs), involve in recognition of DAMPs and PAMPs, and act solely or cooperatively with TLRs to modulate the immune response after surgical hit or infection [40,45]. This hypothesis is strongly supported in the clinical investigation that patients devoid of functional TLR signaling show limited and transient susceptibility to infection during childhood and have increasingly rare incidence of infection with age [46]. Here, we will review the sensing and signaling pathway by non-TLRs to delineate the course of infection and inflammation (Fig. 2).

According to the anchored location of receptors, innate immune receptors are classified as membrane-associated receptors such as the TREM family, cytosolic receptors like NLRs and nuclear receptors like nuclear family 4 subgroup A (NR4A) receptors.

Membrane-associated receptors: triggering receptors expressed on myeloid cells

TREMs are cell surface innate immune receptors which belong to the immunoglobulin superfamily. Two members of the TREM protein family, TREM-1 and TREM-2, were most studied. TREMs consist of a single extracellular immunoglobulin-like domain of the V-type, a transmembrane region with a charged lysine residue, and a short cytoplasmic tail. As the

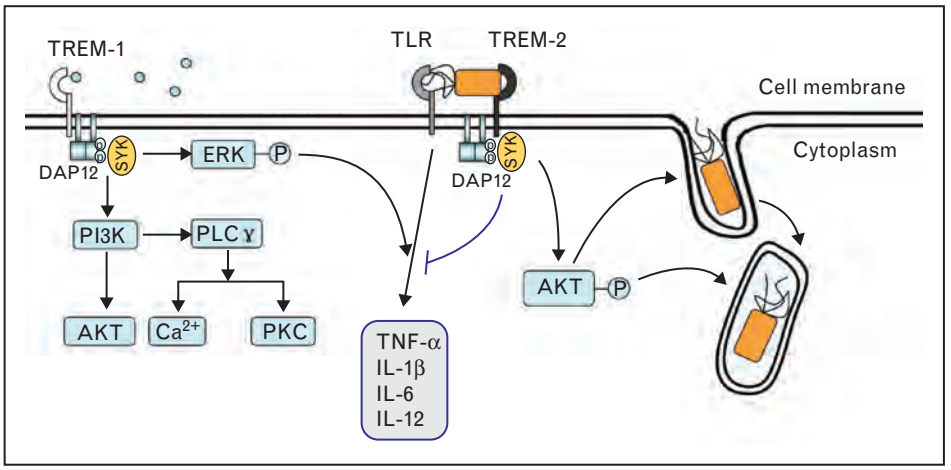

FIGURE 3. The TREMs signaling pathway during the course of immune-inflammatory response. TREMs associated with the DNAX activation protein-12 (DAP-12) chain subunit can activate phosphatidylinositol 3-kinase (PI3K), the phosphorylation of phospholipase (PL) Cγ and extracellular signal-related kinase (ERK)1/2 [47–49]. TREM-1 can act as an amplifier of the systemic inflammatory response syndrome associated with infection [52–54]. TREM-2 can act as a negative regulator inhibiting TLR-mediated inflammatory response, and enhance the host's ability to eradicate damaged cells and invading pathogens [59–61]. TREMs, triggering receptor expressed on myeloid cells.

intracytoplasmic domain lacks any signaling capacity, TREMs associate with a transmembrane adaptor protein, DNAX activation protein-12, to activate intracellular pathways, which include activation of phosphatidylinositol 3-kinase, the phosphorylation of phospholipase Cγ and extracellular signal-related kinase1/2, and an increase in intracellular calcium. Finally, these pathways modulate cellular activation and effector function (Fig. 3) [47–49].

TREM-1 is an amplifier of inflammatory response to infectious stimuli by synergy with TLR signaling [50]. The ligand for TREM-1 remains unknown. A very recent study found that complex between neutrophil peptidoglycan recognition protein 1 and bacterially derived peptidoglycan constitutes a potent ligand capable of binding TREM-1 and inducing known TREM-1 functions [51], indicating that TREM-1 might detect endogenous DAMPs and/or exogenous PAMPs in the case of surgical hit or infection. The role of TREM-1 in bacterial infection *in vivo* was evidenced mainly by using agents interfering with TREM-1 signaling. Treating infection models with small peptides or fusion proteins containing the extracellular domain of TREM-1 can fine-tune the inflammatory response and improve survival while preserving the capacity for bacterial clearance [50,52,53]. This protective effect was further confirmed in TREM-1 knockout mice challenged with different pathogens [54]. These studies not only demonstrate that TREM-1 plays a critical role in host immune response, but also suggest that therapeutic targeting of TREM-1 after surgical hit or tissue damage holds considerable promise by dampening excessive inflammation while maintaining effective microbial control. In addition, the soluble triggering receptor expressed on myeloid cells (sTREM-1) was identified as an early marker of infection in the surgical intensive care unit, indicating that sTREM-1 might be a useful tool to diagnose infection in surgical patients [55].

In contrast to TREM-1, TREM-2 was initially identified as a negative regulator inhibiting TLR-mediated inflammatory response [56,57]. TREM-2 can bind anionic carbohydrate molecules from both microorganisms and human cells [58]. Thus, TREM-2 is a key receptor for phagocytosis, which engulfs not only microbes but also apoptotic cells and cell debris [59–61]. This characteristic is especially pivotal in surgical infection to eradicate damaged cells and invading pathogens but keep the inflammatory response balanced.

Cytosolic receptors: nucleotide-binding oligomerization domain-like receptors

Recent studies revealed the emerging roles of NLRs, one of major family of cytosolic PRRs to detect the intracellular pathogens or danger signals in inflammation [62]. NLRs are characterized by three structural domains: a leucine-rich repeat domain at the C-terminus, being the ligand-sensor for recognizing intracellular PAMP and DAMP; the NACHT domain (nucleotide-binding domain or NAIP, CIITA, HET-E and TP1) responsible for NODs oligomerizing and preparing for signal transduction; and the effector domain at N-terminus [63]. The effector domains of

human NLRs are structurally variable, which result in the activation of multiple signaling pathways and biological functions [64]. Oligomerization of NODs can activate the inflammatory kinase receptor-interacting protein2, or induce the ubiquitination of NF-κB-essential modulator, which is a key component of the NF-κB signaling complex, further strongly regulating the activity of NF-κB [62,65]. An interesting overlap between the signaling pathways triggered by NLRs and TLRs has been revealed, which suggests cooperation between these pathways and NLRs joining TLRs as crucial innate sensors of pathogens in the process of infection [45,66▪]. Currently, emerging progress has been made in the characterization of a relative novel subfamily of NLRs, such as NACHT-LRR-PYD-containing proteins (NALPs), in inflammation and infection immunity [67]. NALP1 and NALP3 evolve in the sensing of endogenous danger signals independent of the microbial trigger. This is illustrated by the discovery that several stimuli, such as sterile crystals made up of uric acid, asbestos or aluminum hydroxide, can trigger the NALP3 inflammasome, activate caspase-1 and cleave pro-IL-1β to the maturation of IL-1β [68,69]. Recently, it was discovered that activation of NALP3 in intestinal epithelial cells limits pathogen colonization and dampens the ensuing intestinal inflammation during the early course of infection, and the polymorphisms of NALP3 have been demonstrated to functionally link with the susceptibility to inflammatory disease [70▪]. The investigation of the physiological function of those cytosolic NLRs in inflammation and immunity will shed more light on the pathogenesis of infection in surgical patients.

Nuclear receptors: nuclear receptor nuclear family 4 subgroup A receptors

NR4A1, the member of orphan NR4A subfamily, is a transcription factor which maintains pivotal roles in metabolism, proliferation, apoptosis and inflammation [71]. NR4A1 contains a variable N-terminal region, a conserved DNA binding domain, a hinge region, a ligand binding domain and a C-terminal region [72]. The NR4A1 regulates cytokine production and mediates the growth factor signaling pathway. The expression of NR4A1 in inflamed human synovial tissue, psoriatic skin, atherosclerotic lesions, lung and colorectal cancer cells is aberrant [73]. Recently, it has been demonstrated that NR4A1 participates in hepatitis C virus (HCV) infection via regulating the expression of cellular receptors and apolipoprotein E, to determine HCV replication and facilitate HCV entry and spread [74]. Emerging data and concepts strongly suggest intrinsic links between NR4A1 and inflammatory disease through integrating complex cytokine signals including protein kinases, wingless type and mitogen-activated protein kinase pathways [75]. However, the exact interaction between NR4A1 and infection is poorly understood and needs to be investigated in the future.

CONCLUSION

Infection is one of the most common causes for morbidity and mortality in surgical patients with prolonged hospital length of stay and increased medical care costs, reduced functional independence and impaired long-term outcome. The fundamental mechanisms for the susceptibility to surgical infections remain still to be elucidated. No doubt, a better understanding of the pivotal role of non-TLRs will provide a novel insight for the prevention and the treatment of surgical infections. Surgical infections seem to be different from those in medical populations, with characteristics including the primed systemic inflammatory response by surgical insult, immediate postoperative immune suppression, various invasive interventions and anesthetic techniques, and in addition exposure to specific hetero-pathogens, transfusion and reperfusion. Taking these factors together, the course of surgical infections is much more complex than nonsurgical infections. The strategies to prevent and defend against pathogen invasion and to prevent organ injury should target at reducing inflammation, however, without aggravating immunodepression.

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Conflicts of interest

There are no conflicts of interest.

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