Letter to the Editor

Surgical Site Infections in Gastroenterological Surgery

To the Editor:

In the insightful review article by Matsuda et al., "Surgical Site Infections in Gastroenterological Surgery" (J Nippon Med Sch 2023; 90: 2-10)[1], the authors have discussed risk factors and probable causes of surgical site infections (SSI), perioperative management for the prevention of SSI, systemic inflammatory response (sepsis) in SSI, and updated guidelines for the prevention of SSI[1]. While the authors highlighted significant aspects of SSI, we feel that the section on Systemic Inflammatory Responses in Surgical Site Infections, where the authors only mentioned the lipid mediator lysophosphatidylcholine (LPC) and the proinflammatory marker procalcitonin (PCT), is not comprehensive. It lacks coverage of the broad spectrum of inflammatory and anti-inflammatory surrogate markers involved in SSI. Therefore, we believe that the following topics be discussed to provide a complete understanding of the pathophysiology of SSI in gastroenterological surgery:

Systemic Inflammatory Response Syndrome (SIRS) in surgical patients is a severe condition marked by systemic inflammation and potential multi-organ dysfunction. A recent article has detailed SIRS in gastrointestinal surgery, summarizing studies of peer-reviewed articles published primarily after 2000, using PubMed and Google Scholar, to create an expert narrative review[2]. The search focused on systemic inflammation, immune responses to surgical trauma, clinical outcomes, and corticosteroid administration in adults undergoing surgery. Cellular injury is detected by pattern recognition receptors (PRRs) in innate immune cells such as monocytes, macrophages, dendritic cells, and neutrophils. PRRs recognize damage-associated molecular patterns (DAMPs) released from injured cells and pathogen-associated molecular patterns (PAMPs) from microbes, triggering inflammatory responses. Activation of PRRs leads to the release of pro-inflammatory cytokines, chemokines, and recruitment of immune cells. Concurrently, immune-suppressing processes balance the response, with IL-6 playing a dual role in inflammation and immune regulation. The M1/M2, and Th1/Th2 balance is crucial, as excessive M1 or Th1 suppression can increase infection risks. IL-10 and myeloid-derived suppressor cells further regulate and sometimes suppress immune responses post-surgery. In light of the snapshot on the pathophysiological aspects of sepsis[2], Matsuda et al.[1] should have emphasized these surrogate markers in SSI following gastroenterological surgery.

DAMPs play a critical role in exacerbating inflammation, injury, and fatality in both infectious and sterile disease conditions. However, their impacts in SSI were not discussed in the review article by Matsuda et al.[1]. Cold-inducible RNA-binding protein (CIRP) is a 172-amino acid nuclear protein belonging to the cold shock protein family. Under physiological conditions, intracellular CIRP acts as an RNA chaperone that promotes the translation of target mRNA. However, activation of cells by PAMPs or excessive stress conditions, such as hypoxia, shock, and sepsis, leads to the extracellular release of CIRP[3, 4]. Extracellular CIRP (eCIRP) binds to the toll-like receptor 4 (TLR4) and myeloid differentiation factor 2 (MD2) complex, functioning as a novel DAMP to enhance inflammatory responses, such as a cytokine storm[3, 4]. Recent studies have demonstrated that eCIRP significantly contributes to systemic inflammation, organ dysfunction, and mortality in conditions such as sepsis[3, 4]. CIRP has also been shown to have links in exacerbating inflammation and promoting tumorigenesis in colitis-associated cancer (CAC)[5]. These novel findings indicated that eCIRP could be a predictive biomarker of CAC risk and a new therapeutic target for cancer prevention in patients with inflammatory bowel disease[5]. Therefore, targeting eCIRP could represent an innovative therapeutic approach for those deadly

disorders. Considering the importance of the diagnostic biomarker of eCIRP in sepsis, the discussion about eCIRP's importance in SSI of gastroenterological surgery could add more value to this review on "Surgical Site Infections in Gastroenterological Surgery."

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https://doi.org/10.1272/jnms.JNMS.2024_91-614

Author Contribution: MA and PW developed the concept of eCIRP as a diagnostic biomarker for SSI after gastroenterological surgery. They both conceived the idea and prepared the draft.

Funding and Acknowledgment: This work was supported by National Institutes of Health (NIH) grants R01HL076179 (PW), R01GM129633 (PW), and R01GM129633 (MA).

Conflict of Interest: The authors declared that they have no competing interests.

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