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**Commentary**

In critically ill patients, disruption of intestinal epithelial cell function occurs due to exposure of the epithelium to toxic internal and external inflammatory stimuli, which are key factors that trigger sepsis and multi-organ dysfunction syndrome (MODS). A greater understanding of how trauma and gut failure lead to sepsis and progression to MODS is much needed. In this issue of the *JCI*, Armacki and colleagues identify mechanisms by which thirty-eight-negative kinase 1 (TNK1) promotes the progression from intestinal apoptosis and gut failure to bacterial translocation, sepsis, and MODS. Moreover, the results of this study suggest TNK1 as a potential therapeutic target to prevent sepsis and MODS.

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Intestinal hyperpermeability: a gateway to multi-organ failure?

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In critically ill patients, disruption of intestinal epithelial cell function occurs due to exposure of the epithelium to toxic internal and external inflammatory stimuli, which are key factors that trigger sepsis and multi-organ dysfunction syndrome (MODS). A greater understanding of how trauma and gut failure lead to sepsis and progression to MODS is much needed. In this issue of the JCI, Armacki and colleagues identify mechanisms by which thirty-eight-negative kinase 1 (TNK1) promotes the progression from intestinal apoptosis and gut failure to bacterial translocation, sepsis, and MODS. Moreover, the results of this study suggest TNK1 as a potential therapeutic target to prevent sepsis and MODS.

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Intestinal hyperpermeability and disease states

In health, the major function of the epithelial lining of the gastrointestinal tract is to act as a filter, allowing absorption of required nutrients, but barring bacteria, macromolecules, and toxic compounds, into the body (1, 2). Disruption of this epithelial barrier can lead to local gastrointestinal dysfunction and systemic abnormalities, such as bacterial translocation and sepsis (3). Disturbances in this barrier may also lead to enhanced uptake of a host of toxic substances, including inflammatory molecules, pathogenic bacteria, and antigens, from the intestinal lumen into the bloodstream, thereby promoting a state of chronic low-level inflammation (4). The resulting increase in intestinal permeability (hyperpermeability or leaky gut) allows further translocation of bacteria, antigens, and toxic substances through the mucosal layer of the gut, leading to activation of mucosal immune responses and, subsequently, abdominal pain and diarrhea (5). These inflammatory mediators signal epithelial, neuronal, and muscle cells, leading to intestinal dysfunction (6). It is well established that inflammatory conditions, such as inflammatory bowel disease (IBD), celiac sprue, and acute alcoholic gastroenteritis, are associated with increased gut permeability (7). For these conditions, acute symptoms usually coincide with acute inflammation, which leads to chronic abdominal pain, diarrhea, and bloating. Transient inflammation of the gut and intestinal hyperpermeability may cause a sensitization of the enteric nervous system that persists long after resolution of the inflammation (8–10). These local intestinal inflammatory mediators can also lead to increased intestinal permeability in a subset of patients with postinfectious, diarrhea-predominant irritable bowel syndrome (IBS) (11).

Effect of intestinal hyperpermeability on sepsis and MODS

Disruption of intestinal epithelial cell function in critically ill patients occurs as the result of exposure of the epithelium to toxic internal and external inflammatory stimuli, which trigger sepsis and multi-organ dysfunction syndrome (MODS). As intestinal permeability increases and proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, are released into the systemic circulation, fluid is extravasated from the gut, and extravascular edema occurs (12). Moreover, proinflammatory cytokines induce changes in tight junction proteins in the gut, leading to hyperpermeability (13–15). In addition to the loss of the intestinal barrier function, the microbiome is altered and characterized by an increase in the number of virulent and invasive bacteria, thereby resulting in dysbiosis and a dysregulated immune response that increases systemic inflammation. All of this culminates in enhanced apoptosis, particularly in intestinal and pulmonary epithelial cells. In healthy individuals, the intestine contains a large microbiome populated with commensal bacteria. During sepsis and MODS, this population shifts to include more virulent and pathogenic bacteria, altering the complex crosstalk between the immune system, microbiome, and intestinal epithelium (16). Effectively, the gastrointestinal tract serves to hasten MODS, and altered levels of citrulline and intestinal fatty acid-binding proteins are markedly elevated in critically ill patients. This pathology is further propagated by bacterial translocation from the gut and systemic absorption of endotoxins (17, 18). Systemic endotoxins are largely responsible for propagating the inflammatory cascade, and injection of LPS into mice stimulates sepsis and leads to altered epithelial barrier function. Proinflammatory cytokines, including IL-1, IL-6, and TNF-α, are subsequently released, leading to endothelial injury and cardiac depression. Figure 1 summarizes the importance of the intestinal barrier and different mechanisms involved in the development of sepsis and MODS. The gut is a major driver of uncontrolled inflammation, proinflammatory cytokine release, and end-organ damage and failure. Intestinal hyperpermeability serves as a bioprotective gateway in the host, via feedback mechanisms, that prevents a deleterious cascade, namely the vicious circle, which exacerbates sepsis and MODS. Important-
In this issue, Armacki and colleagues (22) propose that thirty-eight-negative kinase 1 (TNK1), a member of the ACK family of kinases that was first isolated from CD34+Lin−CD38− stem/progenitor cells (23), may be an important mediator of apoptosis and subsequent organ failure. TNK1 transcripts are found in fetal tissues, including the gastrointestinal tract, but only in a few adult tissues, including the small intestine, colon, prostate, ovaries, and testis. There is also some evidence that TNK1 may play a role in differentiation of the gastrointestinal tract, particularly the small and large intestine (24).

Armacki et al. studied the effect of TNK1 on intestinal integrity and its potential role in MODS using a Tnk1-knockin mouse model that harbors a tetracycline-inducible active form of TNK1 at the X-chromosomal Hprt locus. In this model, TNK1 multifactorial and are not well elucidated. In critically ill patients, intestinal injury and the resulting intestinal hyperpermeability leads to transmural bacterial translocation from the gut to the systemic circulation, and the uptake of systemic inflammatory mediators and cytokines are contributing factors (20). Sepsis is now clearly recognized as a cause of organ failure that results directly from a dysregulated host response to inflammation and infection (21). Even with early recognition of sepsis, patients often go on to develop MODS, which is characterized by inflammatory and systemic damage to critical organs. Moreover, the transition from sepsis to MODS occurs despite early initiation of antimicrobial therapy, volume resuscitation, and circulatory support with vasopressors. MODS also has serious consequences and extremely high mortality and morbidity despite aggressive interventions.

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expression induced crypt-specific apoptosis, leading to bacterial transloca-
tion, septic shock, and early death. In vivo, TNK1 led to STAT3 phosphorylation, nuclear
translocation of p65, and subsequent release of IL-6 and TNF-α. Perhaps even
more interestingly, gut-specific deletion of Tnkl protected intestinal mucosa from
experimental colitis induced by 4% dextran sodium sulphate (DSS) and prevent-
ed cytokine release in the gut. Moreover, TNK1 was also deregulated in the gut of
murine and porcine trauma models and in patients with IBD. Together, these find-
ings by Armacki et al. are provocative and sug-
gest that TNK1 might be a missing link in the progression from intestinal apoptosis
and gut failure to bacterial translocation, sepsis, and MODS. Despite these prelim-
inary findings, caution needs to be taken in extrapolating these results to humans.
Future clinical studies that target TNK1 in the intensive care unit (ICU) setting
of sepsis and subsequent monitoring are required to determine if this approach is
able to prevent multiple organ damage in critically ill patients.

Conclusions and potential strategies to manage MODS and sepsis
A greater understanding of how trauma and gut failure lead to sepsis and pro-
gression of MODS is much needed. The study by Armacki et al. supports a role
for TNK1 in the progression from intestinal apoptosis and gut failure to bacterial translocation, sepsis, and MODS and adds another possible mechanism for progression.
A number of approaches have been described to prevent sepsis and MODS in critically ill patients, none of which have led to successful therapies. Armacki et al. provide a hypothesis for a potential role for TNK1 as a therapeutic target to pre-
vent sepsis and MODS. Novel therapeutic approaches, such as targeting TNK1, are
needed to prevent and/or reverse the del-
eterious effects of critical illness in the gut and its consequences. These findings by
the authors will need further validation in clinical trials that target TNK1 in the ICU
setting of sepsis to prevent multiple organ damage in critically ill patients.

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