Protective role of the lymphatics from sepsis

Young-Kwon Hong

In this issue of Blood, Jang et al elegantly demonstrate a previously unidentified role of lymphatics in protecting our body from the gut flora–induced sepsis using a novel mouse model. This study has a significant impact on our current understanding of not only the function of the lymphatics, but also the pathology of sepsis and related intestinal inflammatory diseases.

The lymphatic system has long been thought to function as a secondary fluid drainage system for the blood circulation and has received considerably less scientific and medical attention than the blood vascular system. Many biological and medical textbooks only describe the lymphatics as a network of passive channels that drain and transport tissue fluids, immune cells, and intestinal nutrients with an opportunistic role in tumor metastasis. However, a series of landmark discoveries in recent lymphatic research have significantly changed these old-fashioned views of the lymphatics. For example, dermal lymphatic vessels in the skin have been recently found to control salt-sensitive interstitial fluid volume and blood pressure. In addition, recent studies have shown that lymphatic vessels are essential for reverse cholesterol transport. In this issue of Blood, another discovery in the neglected field of lymphatic research is reported by Jang et al. They initially intended to determine the effect of systemic lymphatic ablation on tissue fluid homeostasis using a novel mouse model that selectively expresses the diphtheria toxin receptor in lymphatic endothelial cells. Unexpectedly, however, the mice died within a few days on administration of diphtheria toxin, before the appearance of signs of systemic fluid accumulation. Detailed follow-up studies have causally associated the lethality with typical symptoms of sepsis, including increased serum endotoxin levels and decreased lymphocyte and platelet numbers as well as enlarged Peyer patches that are densely packed with immune cells. The authors then found that, although the majority of lymphatic vessels appeared to be uncompromised, lacteals (specialized lymphatic capillaries that absorb dietary lipids in the small intestine and lymph node lymphatics) immediately disappeared within several hours of toxin administration. Interestingly, this acute ablation of lacteals was found to cause disintegration of adjacent blood capillaries and subsequently lead to dissolution of the entire architecture of the villi, triggering severe acute intestinal inflammation and sepsis (see figure).

This study provides us several lines of important information. Among them, the protective role of the intestinal tissue integrity will be newly added to the expanding list of lymphatic functions. This point is particularly exciting considering that more experimental data point dysfunctional lymphatics as a key contributing factor to the pathogenesis of Crohn disease, a type of inflammatory bowel disease that is often associated with compromised intestinal villi.

In addition, the animal model used in the current study could potentially be developed as a new tool to study sepsis. Sepsis is causally defined as a systemic infection by bacteria, viruses, fungi, and/or parasites mainly in blood and is clinically manifested as systemic inflammatory response syndrome in the presence of infection, including low blood pressure; cognitive impairment; metabolic acidosis; elevated heart rate;
respiratory dysfunction; capillary leakiness; decreased lymphocyte counts; hypothermia or hyperthermia; and, eventually, multiple organ dysfunction.6 This overwhelming, dysregulated systemic immune response claims millions of lives worldwide each year. Numerous surgical and nonsurgical animal models have been developed to date, including cecal ligation and puncture and lipopolysaccharide-based toxemia models. Because sepsis can occur for multiple reasons and can be aggravated by various risk factors, not a single animal model is perfect enough to recapitulate most of the clinical symptoms of sepsis. Notably, although decades and billions of dollars have been spent on these animal models, some recent studies alarm us about the uncomfortable possibility that these rodent models rather poorly mimic human inflammatory disease and thus may have seriously misled our fights against this deadly disease. This is especially true when judged by huge differences in the genomic profiles between mouse models and patients with sepsis.7,8 This possibility haunts the troubling fact that none of nearly 150 drug candidates for sepsis tested during past decades has landed to the clinics.

Yes, mice are not humans, and yes, they are “experimental” models. Despite the substantial gap between 2 species, the current animal models have helped us tremendously to understand the disease. Moreover, considering the complex and heterogenic nature of sepsis, it would be better to have multiple animal models that could recapitulate different aspects of sepsis. In this context, the study by Jang et al provides us another useful model against this very challenging disease. This is especially true when judged by huge differences in the genomic profiles between mouse models and patients with sepsis.7,8 This possibility haunts the troubling fact that none of nearly 150 drug candidates for sepsis tested during past decades has landed to the clinics.

In this issue of Blood, Nixon and colleagues report on the impact of HIV infection on hematopoiesis. Hematopoietic stem cells (HSCs)/progenitor cells were subjected to HIV infection in vitro and in vivo using a humanized mouse model. They conclude that direct infection of intermediate progenitor cells by HIV adversely affects their hematopoietic potential, resulting in the observed cytophenias in HIV patients.1

Patients with long-term HIV infection often exhibit multiple hematopoietic syndromes that encompass anemia, granulocytopenia, and thrombocytopenia, suggesting a central deficiency in hematopoiesis.2 A number of previous studies attempted to delineate the mechanism by which these conditions ensue.3 However, clear understanding of the impairment mechanism(s) remained an intractable problem because of the paucity of studies using a suitable experimental animal model that closely recapitulates human hematopoiesis during an ongoing HIV infection in vivo.

Three main possibilities exist for the observed hematological abnormalities.2,3 The first being the direct productive HIV infection of the early HSCs themselves with resultant deleterious effects. Although many previous studies were unable to detect HIV infection of CD34+ HSCs, more recent evidence pointed to infection in at least a subset of individuals.2,6 However, its impact other than in viral latency is unclear. Effects of HIV on intermediate progenitors were not fully evaluated until the present study. Second, even without direct productive infection, it is possible that HIV proteins such as the envelope protein and/or abnormal levels of cytokine milieu in the bone marrow (BM) of infected individuals may have indirect effects on hematopoietic progenitors, with many previous studies attesting to this. Alternatively, prolonged antiretroviral therapy in conjunction with other frequently used drugs in these patients may compromise the BM microenvironment, with resultant adverse effects on differentiating hematopoietic cells of various lineages. Accumulated evidence thus far suggests that a combination of these factors may play a role and contribute to overall hematopoietic deficiency. However, teasing out the individual contribution of each of these factors in vivo has proven to be difficult.

The studies of Nixon et al1 exploited a humanized mouse model to extend the results seen with direct in vitro exposure/infection of CD34+ HSCs and their later intermediate progenitor cells. The
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