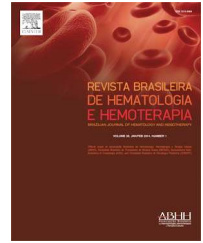




Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

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Scientific comment

‘Leaky gut’ in hematological malignancies[☆]



Carolina Costa-Lima, Erich Vinicius De Paula^{*}

Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil

ARTICLE INFO

Article history:

Available online 1 October 2014

In humans, the intestinal epithelium is a single layer of cells that constitutes one of the most important barriers between internal and external environments. The so-called ‘intestinal barrier’ (IB) is a dynamic structure composed of different types of cellular junctions that can be regulated by physiological and pathological stimuli, and act as a selective barrier to antigens and pathogens. Physiological mechanisms that regulate IB function are important for nutrient absorption and antigen permeation, with potential roles in the regulation of tolerance to non-self antigens.¹ However, pathological stimuli such as pathogens, cytokines and immune cells are also capable of affecting IB function as demonstrated in studies about tumor necrosis factor alpha (TNF- α)-mediated IB disruption.² Accordingly, a model known as ‘leaky gut syndrome’ has emerged based on the concept that TNF-mediated cycles of increased IB permeability may lead to translocation of macromolecules from the lumen into the lamina propria, and to amplification of mucosal immune activation. In the absence of appropriate regulatory signals, this vicious cycle may result in local or systemic immune-mediated diseases, such as Celiac disease, Crohn’s disease, food allergies, and even type-1 diabetes mellitus.³

Disrupted IB function has been described in patients with hematological malignancies, in whom it can occur as a consequence of cytotoxic therapy-induced epithelial damage or leukemic infiltration.^{4,5} The most straightforward consequences of IB disruption for these patients are increased antigen permeation, which could facilitate pathogen translocation, bacteremia, and nutrient malabsorption.⁶ Interestingly, an additional consequence of IB disruption in patients with hematological malignancies is a higher risk of acute graft-versus-host disease (aGVHD) in patients submitted to allogeneic hematopoietic stem cell transplantation (HSCT). In this context, translocation of luminal contents and activation of the underlying antigen presenting cells would enhance activation and proliferation of alloreactive donor cells. This could result in greater inflammatory cytokine production, sustained damage to endothelial and epithelial barriers, and donor T-cell infiltration. Together, these events have the potential of facilitating the development of aGVHD, as suggested by the observation of a higher risk of aGVHD in patients with increased IB permeability.⁷ Of note, it has been proposed that barrier-protecting agents could be beneficial for conditions associated with

DOI of original article: <http://dx.doi.org/10.1016/j.bjhh.2014.07.007>.

[☆] See paper by Leite et al. on pages 409–13.

^{*} Corresponding author at: Hematology and Hemotherapy Center, Universidade Estadual de Campinas (UNICAMP), Rua Carlos Chagas, 480, 13081-878 Campinas, SP, Brazil.

E-mail address: erich@unicamp.br (E.V. De Paula).

<http://dx.doi.org/10.1016/j.bjhh.2014.09.007>

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this pathogenic model, although no clinical data are yet available.³

In the current edition of the Revista Brasileira de Hematologia e Hemoterapia, Leite et al. report the measurement of IB permeability in patients with leukemia.⁸ Although no statistically significant results could be demonstrated, and the categorization of 'leukemias' used by the authors, which includes acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) as a single group, is of little biological significance, the report has the merit of reintroducing the subject of IB disruption to the agenda of malignant hematology. Using a classical measurement tool, based on the differential absorption of lactulose and mannitol, the authors demonstrate a clear trend toward increased IB permeability in patients with acute leukemia, before chemotherapy. Previous studies found similar results,^{5,9} indicating that IB disruption is indeed present in some of these patients, even before chemotherapy. Controversial results were obtained in patients before conditioning prior to HSCT, but IB disruption could always be detected after chemotherapy.^{7,9}

Considering the critical role of IB function in immune regulation, as well as recent insights into the cellular and molecular mechanisms that regulate barrier function in physiological and pathological conditions, there is much more than 'gut feeling' to support the relevance of the question addressed by Leite et al. to the field of malignant hematology.⁸

Conflicts of interest

The authors declare no conflicts of interest.

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