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Elevated intestinal epithelial tight junction permeability leads to systemic graft-versus-host disease propagation

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On 1 February 2019, Sam C. Nalle from the Department of Pathology, The University of Chicago, Chicago, Illinois, USA, and colleagues published their analysis in *The Journal of Clinical Investigation*, on the impact of dysregulated intestinal permeability on the subsequent graft-versus-host disease (GvHD) propagation phase. Myosin light chain kinase (MLCK210), a serine/threonine-specific protein kinase that phosphorylates a specific myosin light chain, namely the regulatory light chain of myosin II, is also known as a key regulator of tight junction permeability. The study group hypothesized that MLCK210-dependent alterations in barrier function may drive GvHD propagation.

Methods

- Duodenal biopsies from patients with GvHD collected > 2 weeks post-transplant
- Donor female 129S6 and BALB/c mice
- Immunohistochemistry and immunofluorescence were performed
- Allogeneic bone marrow transplantation (allo-BMT)
- Cytokine measurements: ELISA – Ready-SET-Go! Kits
- MLCK210 transcript quantification
- Intestinal and vascular permeability assays
- Flow cytometry

Key findings

- MLCK210 activity and expression were elevated in human GvHD
- Intestinal epithelial MLCK210 upregulation and activity were increased after allo-BMT in mice
- Genetic MLCK210 inhibition in GvHD mouse model limited paracellular permeability and MLC phosphorylation in intestinal epithelia, but did not prevent increased microvascular permeability
- MLCK210-dependent processes contribute to systemic GvHD progression but has no effect on the initiation phase
- Cumulative GvHD severity and disease propagation are driven by MLCK210-dependent regulation of intestinal epithelial permeability
- MLCK210 deletion controls propagation of major antigen mismatch GvHD
- Intestinal epithelial MLCK210 is a key regulator of GvHD pathogenesis

- MLCK210 expression in the intestinal epithelium ameliorates the cytolytic function of CD8+ effector T cells within regional lymph nodes and this could be the major mechanism behind increased intestinal epithelial tight junction permeability and GvHD propagation

In conclusion, these findings demonstrate that MLCK210-mediated intestinal epithelial barrier dysfunction is a key driver to systemic GvHD propagation. These data also show that non-hematopoietic functions can be targeted, epithelial barrier integrity for instance, which may offer an alternative target for the treatment of GvHD.

Reference

1. Nalle S.C. *et al*. Graft-versus-host disease propagation depends on increased intestinal epithelial tight junction permeability. J Clin Invest.2019 Feb 1; 129(2): 902-914. DOI: 1172/JCI98554. [Epub 2019 Jan 22].
