Paneth cells in gut GVHD: a Panglossian perspective

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Comment on Levine et al, page 1505

Acute GVHD remains a major toxicity of allogeneic hematopoietic stem cell transplantation (HSCT) that is associated with significant nonrelapse mortality (NRM) and is clinically staged according to the severity of target organ involvement (skin, GI tract, liver). Visceral (GI, liver) involvement is a determinant of greater clinical GVHD severity and thus a worse prognosis. Importantly, acute GVHD outcomes are heterogeneous. Clinical factors for worse NRM and survival in acute GVHD include HLA-mismatch, older recipient age, unrelated donors, and GVHD clinical severity (grade 3–4), with the day 28 response to therapy an important additional prognostic factor. To improve outcomes, the transplant community needs better diagnostic, prognostic, and therapeutic tools for high-risk GVHD patients earlier in their disease course.

The Paneth cell backstory is interesting. The same group undertook an unbiased proteomic screen to identify regenerating islet-derived 3-α (REG3α), a C-type lectin secreted by small intestinal Paneth cells, as a novel diagnostic and prognostic marker in acute lower GI GVHD. Importantly, Paneth cell counts at diagnosis correlated with response to GVHD therapy at week 4 (P < .001), even after adjusting for clinical GVHD severity, with a mean of 11.5, 6.4, and 4.9 Paneth cells/high power field (hpf) in patients with complete, partial, and no response, respectively (vs 18.5 cells/hpf in no-GVHD controls). Based on receiver operating curve cutoffs, a mean of <4 Paneth cells/hpf identified GVHD patients at high risk of 6-month NRM (55% vs 23%; P < .0001). In multivariable analysis, Paneth cell count <4/hpf (hazard ratio 2.5, P = .02) and colonic histologic grade 3-4 GVHD (hazard ratio 4.2, P < .001) independently predicted for NRM. Paneth cell counts appear highly reproducible, with a specific location (base of the crypts of Lieberkuhn) and morphology (lysozyme positive). Is it therefore time for upper GI biopsies in all GI GVHD? Not yet. The obvious caveats apply, such as the need for: longer term follow-up beyond 6-month NRM; independent datasets to confirm findings (and ROC cutoffs); and ultimately, prospective assessment of the risks, benefits, and costs. Even if predictive, Paneth cell count assessment may be more suitable for GVHD clinical trial design (eg, high-risk cohort studies) rather than individual patient decision-making (note that almost one-half of the high-risk Paneth group did not experience NRM).

Additional questions arise. How do the Paneth cell data fit with REG3α? Counterintuitively, because loss of Paneth cells with a fall in luminal REG3α secretion should result in lower serum REG3α levels. However, as the authors speculate, at GVHD onset, with luminal REG3α still present, presumably its leak back into the circulation is at a level commensurate with the severity of generalized GI epithelial disruption. If so, Paneth cell counts and REG3α levels are likely correlated, and we need to determine whether REG3α levels and Paneth cell counts remain independent predictors of acute GVHD outcomes.

Are there therapeutic implications? Paneth cells secrete a large number of antimicrobial polypeptides, including α-defensins that are critical regulators of the enteric microbiota, promoting survival of physiologic commensal bacteria (eg, *Firmicutes* and *Bacteroidetes* sp.) and inhibiting pathogenic gram-positive and -negative bacteria (eg, *Escherichia coli*). Indeed, in the murine GI GVHD model, Paneth cell loss was associated with loss of microbiota diversity and outgrowth of pathogenic *E. coli*. Whereas prophylactic enteric antibiosis offered benefit in some models, in others its negative impact on commensal microbiota outweighed the benefit of pathogen suppression, with the concern that antibiotic-associated microbiota chaos may have feedback effects that actually worsen GVHD. Supplementary enteric commensals and/or Paneth cell polypeptides may offer an alternative “physiologic” strategy for microbiota diversity preservation and GVHD control.

Also, Paneth cells are generated from intestinal stem cells (ISCs), reside adjacent to the ISC niche, and have a critical role in ISC maintenance. ISC loss contributes to the epithelial pathology of GVHD. Paneth cell loss, derived from but also contributing to further ISC loss, could worsen GVHD. If so, this would highlight preclinical GVHD.
control strategies centered on ISC protection, for instance via the Wnt agonist R-spondin 1 or interleukin-22, whose deficiency contributes to ISC loss and murine GI GVHD.9,10

The Paneth cell promises much, and I, who for want of better therapy still treat acute GVHD with nontarget corticosteroids, remain positive.

Conflict-of-interest disclosure: J.K. has received research funding from Millennium Pharmaceuticals, Otsuka Pharmaceuticals, and Prometheus Laboratories; is on the advisory Boards of Millennium Pharmaceuticals and Spectrum Pharmaceuticals; is a consultant for Eleven Biotherapeutics and Takeda Pharmaceuticals; and has received honoraria from OptumHealth Education.

REFERENCES


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