Paneth cells in gut GVHD: a Panglossian perspective

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In this issue of Blood, Levine et al present an intriguing analysis highlighting the potential clinical impact of Paneth cell loss in gastrointestinal (GI) acute graft-versus-host disease (GVHD).1

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.3 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 prognosticator.3,4 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.5 Importantly, on multivariable analysis GVHD clinical severity (GI stage II-IV), GI histology (pathologic grade 4) and elevated serum REG3α levels at disease onset independently predicted 4-week clinical response and 1-year NRM. Independently, another group reported Paneth cells as a preclinical GI GVHD target, showing widespread Paneth cell loss within the inflamed small intestine after MHC-mismatched murine HSCT.6

The current report bolsters the association of Paneth cell loss and clinical GI GVHD. In a retrospective analysis of duodenal biopsies from 116 GI (predominantly lower intestinal) GVHD patients and 26 no-GVHD controls, the authors documented a correlation between loss of Paneth cells and clinical GI GVHD severity (diarrhea) (P = .008), independent of the histologic grade of duodenal GVHD.1 However, after adjusting for histologic grade of lower intestinal GVHD, Paneth cell loss was only borderline associated with clinical GI GVHD severity (P = .057). More 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 (53% 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 Lieberkühn) 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.6 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.6,7 Supplementation of 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.8 ISCs are a GI GVHD target, and ISC loss contributes to the epithelial pathology of GVHD.9 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 nonspecific corticosteroids, remain positive.

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REFERENCES


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PRCP actions on the endothelium in vitro and in vivo.

Promotion of endothelial cell proliferation

Induction of sprouting angiogenesis and vessel maturation

Stimulation of endothelial cell migration

Modulation of neointimal formation

Enhancing endothelial cell survival

PRCP regulates angiogenesis in vivo

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In this issue of Blood, Adams et al provide evidence for an important novel function of prolylcarboxypeptidase (PRCP), or angiotensinase C, in endothelial cell physiology and angiogenesis.1

Angiogenesis, the process by which new blood vessels are generated during development, has a critical role in solid tumor progression and hematological malignancies.2 Understanding how druggable proteins regulate this complex process is crucial for the development of new pharmacological leads for anticancer therapy.

The PRCP gene encodes for a serine protease that generates plasma kallikrein from prekallikrein and degrades angiotensin II and α-melanocyte-stimulating hormone (α-MSH) by proteolysis of their C-terminal Pro-X bonds.3,4 PRCP also was recognized to inactivate α-MSH1-13’s ability to stimulate the melanocortin 4 receptor to induce anorexia by proteolysing its C-terminal Pro-X bond.5 In vivo loss of function of PRCP in gene trap (PRCP-Δ/Δ) mice confirms that a major role of this protein is in metabolism because these mice have significantly reduced body weight.6 In fact, PRCP-Δ/Δ mice have better glucose tolerance and less insulin resistance than their wild-type controls.6

These observations were used to control food intake, with encouraging results: a selective PRCP inhibitor termed UM8190 induces murine anorexia.7 It is of further interest that the peptide product angiotensin-(1-7) of PRCP protease action also promotes adipogenesis.8 This latter observation suggests an autocrine function of PRCP action in fat metabolism.

A role for PRCP in vascular development has been suspected, because its transcripts are up-regulated during an active growth phase of the chick extra-embryonic vasculature,9 it is overexpressed in the endothelium,9 and the protein is present at surface of endothelial cells.3 A series of experiments that investigated the role of PRCP in blood pressure and coagulation control showed that, even in the presence of metabolic health, PRCP-Δ/Δ mice are hypertensive and prothrombotic.10 These animals have vascular inflammation with reduced Kruppel-like factors 2 and 4, uncoupled nitric oxide, and reduced
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