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TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE

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Albumin Gains Immune Boosting Credibility

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Albumin has long been used as a clinical intervention for renal protection in our patients with decompensated cirrhosis.[1] Numerous studies have demonstrated the clinical utility of albumin in hepatorenal syndrome and spontaneous bacterial peritonitis.[2] The benefits of albumin infusion have historically been attributed to its physiologic function as a volume expander, mitigating oncotic pressure losses from the intravascular space and thereby preserving blood flow to the kidney.[3] Earlier this year, a compelling study from collaborators in England and Spain as part of the DASIMAR (Dimethylarginines and Ischemia Modified Albumin as Prognostic Biomarkers in Patients With Acute-on-Chronic Liver Failure) study established a key immunologic function for albumin in the setting of acutely decompensated cirrhosis.[4] Using serum samples from across a spectrum of patients with cirrhosis and non-cirrhotic liver disease, researchers utilized simple *in vitro* experiments to measure the effect of cirrhotic or control serum on phagocyte function. Prostaglandin E_2 (PGE_2) is a cyclooxygenase-derived lipid mediator of inflammation with pleiotropic immunomodulatory function. PGE_2 regulates immune cell trafficking to tissue compartments, blunts antimicrobial T-helper 1 responses, and suppresses the bactericidal activity of phagocytes by inhibiting FcγR-mediated phagocytosis and oxidative burst-mediated bacterial killing.[5,6]

O'Brien and colleagues elegantly demonstrate markedly elevated circulating PGE_2 in decompensated cirrhotics. Elevated PGE_2 was shown to drive *in vitro* (human monocytes) and *in vivo* (mouse models) immunosuppression and susceptibility to bacterial infection. Administration of albumin led to relief of immunosuppression, seen as a recovery of phagocyte function and ability to clear a bacterial challenge. Albumin, it turns out, functions as a sink for circulating PGE_2. Infusion of albumin attenuated PGE_2-mediated immunosuppression in their model systems. Beyond its immunomodulatory function, PGE_2 acts on four receptors in the kidney and has a direct role in the regulation of renal perfusion.[7] So in addition to the known benefit of intravascular volume expansion, albumin infusions are boosting the effective immune response of the cirrhotic patient as well as regulating the physiologic concentrations of PGE_2 seen by the kidney and thereby directly altering blood flow beyond its oncotic effect. Molecular adsorbent recirculating system therapy with albumin dialysis theoretically has an even greater capacity to alter the body's load of PGE_2, although this effect has yet to be assessed.

What does this mean for our patients and practice? Albumin has an established role in the treatment of hepatorenal syndrome and spontaneous bacterial peritonitis. Our cirrhotic patients succumb to infections more than any other manifestation of their illness. O'Brien's group taught us we have always had one of the most important tools to modulate immunity in our cirrhotics ever since it was first used in the 1940s.[8] The "bad humours" albumin infusions were thought to counter are being revealed. The DASIMAR team has reminded us that rescuing immune function in these patients should be at the forefront of clinical thought and scientific investigation.

PAS DE TROIS: macrophages, microbiota, and enteric neurons collaborate in motility

The fields of neurophysiology and immunology have been slowly creeping toward each other, gingerly establishing synapses of their own, recognizing the intimate entanglements of their respective cells of interest are more profound and purposeful than ever imagined. It is well known that the enteric nervous system (ENS) and brain communicate directly in the regulation of digestion. Gastroenterologists know well that motility dysfunction in the former drives significant consternation in the latter, leading patients to our clinics in droves with chronic constipation, irritable bowel disease-diarrhea subtype, bloating, and the like. Dysbiosis should come to mind when these patients seek us out for help. Indeed several of the tools we use to combat motility problems act in part by purposefully modifying the microbiota.[9] The FODMAP diet cuts off the supply lines for bacterial fermentation in the bowel and changes the pool of gut-active metabolites elaborated by commensals.[10,11] Antibiotics either directly debulk the microbial populations in the gut or provide selective pressure to its inhabitants. Agents such as rifaximin can improve symptoms in some IBS patients and diarrhea in our bacterial overgrowth population, whereas other antimicrobials are busy generating new referrals by

altering motility in patients taking antibiotics for non-gastrointestinal indications. As such, the connection between motility and microbiota has been suspected for generations.

Recently, authors of a remarkable piece of work published in *Cell* have elucidated one mechanism linking neurophysiological control of motility to gut microbiota.[12] They found a key player in this regulation was the tissue-resident macrophage of the intestinal muscularis. Using immunofluorescent staining techniques and careful cell sorting, Muller and colleagues demonstrate the close approximation of muscularis macrophages (MMs) and enteric neurons. They further showed MMs are recruited to the ENS plexus by neuronal production of soluble colony stimulating factor-1 (CSF-1). In turn, ENS cell signaling activity is augmented by bone morphogenic protein-2 (BMP-2) elaborated from the MM population. These investigators demonstrate the interaction between nerve cells and immune cells, along with the presence of gut microbiota, maintains normal peristalsis. Using a physiology technique that elicits the peristaltic reflex in *ex vivo* rings of colonic tissue subjected to incremental distending forces, the authors translate the molecular signals into muscle contractions before our eyes. Perturb the system by eliminating MMs, turning off CSF-1, inhibiting BMP-2, or removing commensals and peristaltic contractions are derailed.

This physiologic mechanism linking microbiota and motility is at once ground-breaking and reassuring. Like many great pieces of science, this work elucidates the molecular mechanism underlying an aspect of functional disease we always knew to be true but could never quite fully explain. Muller and colleagues illustrate the three way dance of the immune system, enteric nerves, and gut microbiota in the regulation of peristalsis and open new molecular pathways for exploration as potential therapeutics for our patients struggling with motility disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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