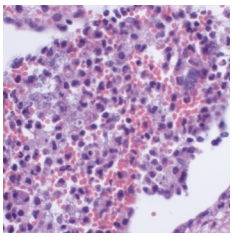
JCI The Journal of Clinical Investigation

In This Issue

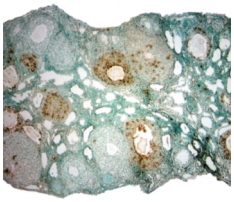
J Clin Invest. 2003;112(5):629-629. https://doi.org/10.1172/JCI119982.

In this issue

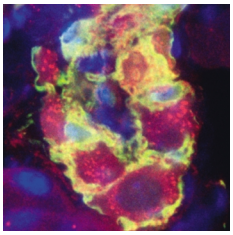
Meningitis beats up the blood-brain barrier. Meningitis occurs when pathogens in the blood cross the tightly sealed blood-brain barrier (BBB). Kelly Doran and colleagues have closely examined (pages 736–744) the initial response of the cells that comprise the BBB to the human meningeal pathogen, group B Streptococcus (GBS). Microarrays showed that GBS infection induced a highly specific and coordinate set of genes known to orchestrate neutrophil recruitment, activation, and enhanced survival. To identify specific bacterial triggers for BBB gene activation, the authors used precise allelic-exchange GBS mutants to identify the roles of a potent GBS exotoxin (stimulatory) and the surface polysaccharide capsule (inhibitory) in BBB activation. These results will help our understanding of how the BBB responds to infectious diseases and may point to a therapeutic target.Follicular development driven by angiogenesis. Follicles in the ovary require new blood vessel growth in order to develop. The newly formed ovarian blood vessels secure an increasing supply of gonadotropins, growth factors, oxygen, and steroid precursors to the growing follicle. Blockage of angiogenesis can inhibit follicle development partly by blocking hormonal feedback loops between the ovary and the pituitary gland. Ralf Zimmermann and colleagues showed the intraovarian role of VEGFR- 2 activity on follicular development by using a model in which the pituitary gland is absent, the prepuberally hypophysectomized mouse (pages 659–669). Hypophysectomy prevents […]



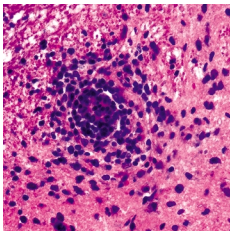
Meningitis beats up the blood-brain barrier. Meningitis occurs when pathogens in the blood cross the tightly sealed blood-brain barrier (BBB). Kelly Doran and colleagues have closely examined (pages 736–744) the initial response of the cells that comprise the BBB to the human meningeal pathogen, group B *Streptococcus* (GBS). Microarrays showed that GBS infection induced a highly specific and coordinate set of genes known to orchestrate neutrophil recruitment, activation, and enhanced survival. To identify specific bacterial triggers for BBB gene activation, the authors used precise allelic-exchange GBS mutants to identify the roles of a potent GBS exotoxin (stimulatory) and the surface polysaccharide capsule (inhibitory) in BBB activation. These results will help our understanding of how the BBB responds to infectious diseases and may point to a therapeutic target.



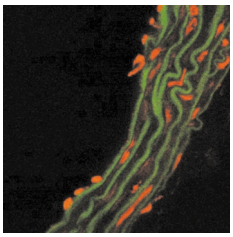
Follicular development driven by angiogenesis. Follicles in the ovary require new blood vessel growth in order to develop. The newly formed ovarian blood vessels secure an increasing supply of gonadotropins, growth factors, oxygen, and steroid precursors to the growing follicle. Blockage of angiogenesis can inhibit follicle development partly by blocking hormonal feedback loops between the ovary and the pituitary gland. Ralf Zimmermann and colleagues showed the intraovarian role of VEGFR- 2 activity on follicular development by using a model in which the pituitary gland is absent, the prepuberally hypophysectomized mouse (pages 659–669). Hypophysectomy prevents advanced follicle growth and maturation, but follicle development to the preovulatory stage could be stimulated with gonadotropins. The exogenous gonadotropins were unable to drive follicle development to the preovulatory stage in the presence of anti–VEGFR-2 antibodies. These results show that the intraovarian VEGF/VEGFR-2 pathway is critical for gonadotropin-dependent angiogenesis and follicular development.



Steady your nerves, steady your bowels. Formation of cranial parasympathetic and enteric neurons by neuronal precursors migrating from the neural crest requires glial cell line–derived neurotrophic factor (GDNF) signaling via GDNF family receptor α1 (GFRα1). Matti Airaksinen and colleagues examine the factors that could contribute to growth retardation in *GFRA2*$^{-/-}$ mice (pages 707–716). Neurturin (a GDNF family member) mRNA was localized in the gut circular muscle, and GFRα2 protein was expressed in enteric neurons and glia. In the *Gfra2*$^{-/-}$ mice, substance P–containing nerve fibers in the myenteric plexus were reduced, and motility was slower than in normal mice. Knockout mice had fewer intrapancreatic neurons, severely impaired cholinergic innervation of exocrine tissue, and little vagally-mediated stimulation of pancreatic secretion. Knockout mice had retarded growth that could be partially overcome with wet-mash feeding. These results suggest that the growth retardation of the *Gfra2*$^{-/-}$ mice is largely due to impaired salivary and pancreatic secretion and intestinal dysmotility.



Lymphotoxin comes out of the LIGHT. There is a long-standing conflict regarding the role of the lymphotoxin (LT) pathway in MS. By using different animal models, Jen Gommerman and colleagues demonstrate a clear role for LT in MS (pages 755–767). The authors used a fusion protein decoy, which blocks the LT pathway in vivo without evoking the developmental defects inherent in LT-deficient mice. Inhibition of the LT pathway prevented disease in two models of MS. Disease attenuation was due to inhibition of LT and not the related ligand LIGHT since LIGHT-mediated signals did not compensate when LTαβ-LTβR interactions were specifically targeted. These results suggest that the LT pathway and its ability to maintain lymphoid microenvironments are critical for sustaining late-phase T cell responses in MS.



Diabetic disruption of endothelial dysfunction. Tetrahydrobiopterin (BH4) is a suspected mediator of reduced endothelial NO synthase activity, which results in endothelial dysfunction characteristic of diabetes. The underlying regulatory mechanism, however, remains incompletely defined. Keith M. Channon and colleagues describe the generation of a novel transgenic mouse with endothelium-specific overexpression of guanosine triphosphate–cyclohydrolase I (GTPCH), the rate-limiting enzyme in BH4 synthesis (pages 725–735). The authors found that loss of endothelial BH4 in diabetes results from biopterin oxidation, rather than an alteration in biopterin synthesis. Comparison of healthy and diabetic mice revealed that overexpression of GTPCH increases endothelial BH4 synthesis and preserves NO-mediated endothelial function. The data indicate that endothelial BH4 is an important regulator of dysfunctional eNOS regulation in diabetes and represents a rational therapeutic target in the restoration of NO-mediated endothelial function in this and other vascular disease states.