JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2003;111(12):1793-1793. https://doi.org/10.1172/JCI119976.

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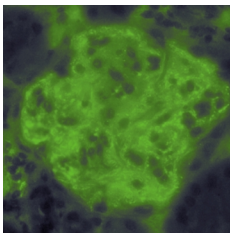
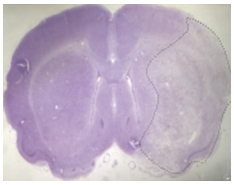
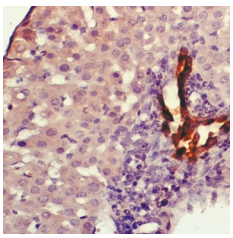
Targeting complement where it counts. Systemic inhibition of complement activation can compromise host defense mechanisms, and large doses of traditional inhibitors are required to attain inhibition in the serum. Stephen Tomlinson and colleagues demonstrate a more effective strategy (pages 1875–1885): targeting complement inhibitors to sites of complement activation and disease. The authors show the quantitative advantage of targeting complement inhibitors to sites of activation by the construction of fusion proteins containing complement receptor 2 binding domains. The strategy worked to target the kidney when tested in vivo in a mouse model of lupus nephritis associated with renal complement deposition. The magnitude of increased efficiency and the capacity to focus the inhibition offer substantial advantages in the design of both potential therapeutics and probes of complement mediated tissue injury.The multiple mechanisms of VEGF. Vascular endothelial growth factor (VEGF) is a proangiogenic molecule with therapeutic potential in ischemic disorders such as stroke. In order to determine how VEGF can promote neuroprotection and simultaneous neurogenesis during stroke, David Greenberg and colleagues examined outcome with and without intracerebroventricular administration of VEGF 24 hours after stroke was induced (pages 1843–1851). VEGF reduced infarct size, improved neurological performance, enhanced the delayed survival of newborn neurons in the dentate gyrus and subventricular zone, and stimulated angiogenesis in the striatal ischemic penumbra but not the dentate gyrus. In […]



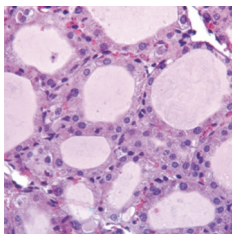
Targeting complement where it counts. Systemic inhibition of complement activation can compromise host defense mechanisms, and large doses of traditional inhibitors are required to attain inhibition in the serum. Stephen Tomlinson and colleagues demonstrate a more effective strategy (pages 1875–1885): targeting complement inhibitors to sites of complement activation and disease. The authors show the quantitative advantage of targeting complement inhibitors to sites of activation by the construction of fusion proteins containing complement receptor 2 binding domains. The strategy worked to target the kidney when tested in vivo in a mouse model of lupus nephritis associated with renal complement deposition. The magnitude of increased efficiency and the capacity to focus the inhibition offer substantial advantages in the design of both potential therapeutics and probes of complement mediated tissue injury.



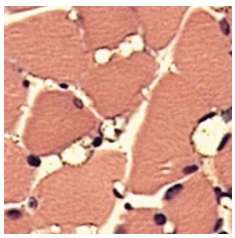
The multiple mechanisms of VEGF. Vascular endothelial growth factor (VEGF) is a proangiogenic molecule with therapeutic potential in ischemic disorders such as stroke. In order to determine how VEGF can promote neuroprotection and simultaneous neurogenesis during stroke, David Greenberg and colleagues examined outcome with and without intracerebroventricular administration of VEGF 24 hours after stroke was induced (pages 1843–1851). VEGF reduced infarct size, improved neurological performance, enhanced the delayed survival of newborn neurons in the dentate gyrus and subventricular zone, and stimulated angiogenesis in the striatal ischemic penumbra but not the dentate gyrus. In addition to an acute neuroprotective effect, VEGF also has a longer-latency effect on the survival of new neurons and on angiogenesis.



The difference a carbohydrate makes. Infection of neonatal mice with some reovirus strains produces a disease similar to infantile biliary atresia, but it is not known how the infection yielded biliary obstruction. Terence Dermody and colleagues examined reovirus strains differing only in the capacity to bind sialic acid as a coreceptor and showed that they differ strikingly in the capacity to target bile duct epithelial cells in newborn mice (pages 1823–1833). Sialic acid–binding reovirus strain T3SA+ (but not T3SA–) produced obstructive jaundice in mice, which is associated with bile duct inflammation similar to that observed in biliary atresia in humans. These observations suggest that the carbohydrate-binding specificity of a virus can dramatically alter disease in the host and that infection by sialic acid–binding reovirus strains is a possible contributor to the pathogenesis of neonatal biliary atresia.



Shedding receptor subunits in Graves disease. The etiology of Graves disease is multifactorial, with nongenetic factors playing an important role. Autoantibodies to the thyrotropin receptor (TSHR) usurp the function of thyrotropin in Graves disease, leading to thyroid hyperfunction and thyrotoxicosis. Sandra McLachlan and colleagues now show that the shedding of TSHR A subunits may induce or amplify the immune response to the TSHR and the production of receptor-activating antibodies (pages 1897–1904). Using a new adenovirus-mediated animal model of Graves disease, they show that hyperthyroidism occurs to a much greater extent when the adenovirus expresses the free A subunit as opposed to a genetically modified TSHR unable to cleave into subunits. These data provide new insight into the etiology of Graves disease.



Nerves sympathetic to angiogenesis. Sympathetic nerves regulate vascular tone and have long been suspected of providing trophic influences on the innervated tissues, but their angiogenic potential has not been considered. Neuropeptide Y (NPY), a sympathetic cotransmitter and vasoconstrictor, is a potent growth factor for vascular smooth muscle and endothelial cells at nonvasoconstrictive concentrations. Edward Lee and colleagues now show that NPY is proangiogenic in vivo (pages 1853–1862). Neuronally released NPY mediates angiogenesis via its Y2/Y5 receptors and NO- and VEGF-dependent pathways. The remarkable efficacy of NPY in restoring ischemic tissue vascularization and function suggests its therapeutic potential in ischemic cardiovascular diseases.