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In This Issue

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Combination therapy helps viruses destroy tumors Clinical trials of oncolytic virotherapy, a therapeutic strategy that uses viruses to infect and kill tumor cells while leaving normal cells unharmed, have yielded encouraging results. However, it is believed that it will be necessary to combine oncolytic virotherapy with standard therapies to maximize its clinical impact. Kottke and colleagues have now provided further support for this idea by showing that oncolytic virotherapy can be combined with inhibitors of VEGF165 — which are used widely in the clinic to treat several different cancers — to provide substantial regression and cure of tumors in immunocompetent mice (1551–1560). This combination approach worked when the VEGF165 inhibitor being used to treat mice harboring mouse melanoma cells expressing VEGF165 was transiently withdrawn prior to virus administration. This caused VEGF levels to rebound, permitting endothelial cells to support viral replication. The treatment regimen induced direct tumor cell lysis and triggered an attack on the tumor vasculature by the innate immune system. The latter aspect of the antitumor effect is of particular interest, since the ability of this combined therapeutic approach to target the tumor endothelium suggests that it could be used to treat many different types of cancer. Breathe easy with the enzyme LPCAT1 The leading cause of death in infants born prematurely is respiratory distress syndrome (RDS). It […]

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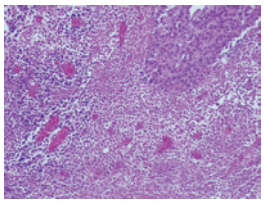

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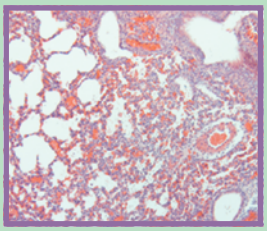
A good mimic promotes neuron survival

Brain-derived neurotrophic factor (BDNF) promotes neuronal survival, differentiation, and synaptic function, and altered BDNF expression and/or function has been implicated in several neurodegenerative conditions, including Alzheimer disease. Although several properties of BDNF preclude its therapeutic application, it has been suggested that molecules that stimulate the BDNF receptor tropomyosin-related kinase B (TrkB) might have therapeutic potential. Massa and colleagues developed a 2-step screening strategy to identify small molecules that bound TrkB, but not other Trk family members, and elicited downstream nanomolar neurotrophic activity (1774–1785). One of the identified compounds prevented neuronal degradation as efficiently as did BDNF in in vitro models of neurodegenerative conditions. Further, it stimulated TrkB in the hippocampus and striatum of mice after intranasal administration and improved motor learning after traumatic brain injury in rats. These data suggest that both this 2-step approach to drug discovery, in which in silico screening with a BDNF loop–domain pharmacophore was followed by low-throughput in vitro screening in mouse fetal hippocampal neurons, and the compounds it yielded could prove useful in developing new therapeutics for the treatment of neurodegenerative conditions.

Breathe easy with the enzyme LPCAT1



The leading cause of death in infants born prematurely is respiratory distress syndrome (RDS). It is caused by deficiency in pulmonary surfactant, a lipoprotein complex critical for optimal gas exchange. Lysophosphatidylcholine acyltransferase (LPCAT1) is a recently cloned mouse lung enzyme predicted, based on in vitro assays, to be involved in surfactant synthesis. To investigate the physiologic role of this enzyme, Bridges and colleagues generated mice bearing a hypomorphic *Lpcat1* allele (*Lpcat1*$^{GT/GT}$ mice) (1736–1748). Initial evidence of a role for LPCAT1 in surfactant synthesis in vivo was provided by the observation that a substantial number of neonatal *Lpcat1*$^{GT/GT}$ mice exhibited perinatal mortality from respiratory failure, characterized by hallmarks of respiratory distress. Further, levels of *Lpcat1* mRNA and LPCAT1 activity were reduced in neonatal *Lpcat1*$^{GT/GT}$ mice and directly correlated with both survival and lung tissue levels of saturated phosphatidylcholine (SatPC), the most critical and abundant phospholipid in pulmonary surfactant. As the decreased SatPC content in pulmonary surfactant from affected neonatal *Lpcat1*$^{GT/GT}$ mice was associated with a decreased ability of the surfactant to lower surface tension in vitro, the authors suggest that LPCAT1 activity must be maximal to achieve the SatPC levels necessary for the transition to air breathing.

Clinical trial drug exacerbates TB in mice

Type I IFNs are immune molecules that have a central role in antiviral host defense. They have been shown to be of clinical benefit in a number of viral infections and malignancies, and molecules such as poly-L-lysine and carboxymethylcellulose (Poly-ICLC) that potently induce long-lived type I IFN responses are in clinical trials. However, data generated by Antonelli and colleagues indicate that Poly-ICLC exacerbates pulmonary pathology and bacterial load in *Mycobacterium tuberculosis*–infected mice, leading them to suggest that such agents should be used with caution in individuals latently infected with *M. tuberculosis* (1674–1682). The marked increase in pulmonary bacterial load and widespread pulmonary necrosis observed in Poly-ICLC–treated *M. tuberculosis*–infected wild-type mice, which was absent in mice lacking the receptor for type I IFNs, was accompanied by a dramatic increase in the number of $CD11b^{+}F4/80^{+}Gr1^{int}$ myeloid cells in the lungs. These cells, which were recruited to the lungs by Poly-ICLC–induced CCL2 binding to CCR2 on their cell surface, preferentially supported bacterial growth, providing a mechanistic explanation as to why Poly-ICLC exacerbates pulmonary pathology and bacterial load in *M. tuberculosis*–infected mice.