■ VIRAL INFECTION

Therapeutic micromanagement

An antisense oligonucleotide that targets miR-122 reduces hepatitis C virus (HCV) replication in patients with chronic HCV type 1 infection (*N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1209026).

miR-122 contributes to the propagation of HCV by binding two sites in an untranslated region of the viral genome, protecting it from degradation. Harry Janssen *et al.* carried out a phase 2a clinical trial of miravirsen, a phosphorothioate antisense oligonucleotide that strongly binds and sequesters miR-122.

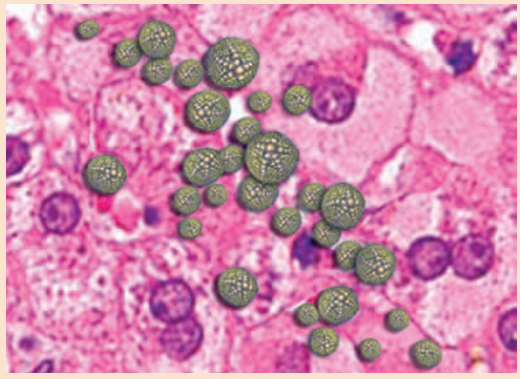
Thirty-six patients with chronic HCV type 1 infection were randomized to receive five weekly subcutaneous injections of miravirsen at doses ranging from 3 to 7 mg per kilogram of body weight over a month and were subsequently followed for 18 weeks.

The treatment resulted in a dose-dependent reduction in HCV RNA levels that lasted beyond administration of the oligonucleotide. Importantly, there were no serious adverse effects of miravirsen and no evidence of viral resistance, highlighting the strong therapeutic potential of this approach. —*JCL*

VIRAL INFECTION

Cloaked in a stolen envelope

Viruses are commonly classified as enveloped or non-enveloped, but a new study of hepatitis A suggests that this classic distinction may be overly simplistic (*Nature* 496, 367–371).



Chris Bjornberg / Science Source

Hepatitis A virus (HAV) is a non-enveloped RNA virus that causes enterically transmitted hepatitis. Now, Stanley Lemon and his colleagues show that a high percentage of HAV particles released from cultured liver cells are enveloped in a host-derived membrane. Circulating infectious virus of the same density as the enveloped form was also present in blood from HAV-infected humans and chimpanzees. Mechanistically, the authors found that the host endosomal-sorting complexes required for transport (ESCRT) proteins VPS4B and ALIX were needed for assembly of the enveloped HAV particles.

Notably, a neutralizing monoclonal antibody was unable to neutralize the enveloped form of HAV, suggesting that the virus might use this strategy to evade the host immune response. Passive transfer of antibodies can protect infected patients from disease after viral replication is well-established in the liver, and the authors found that antibodies targeted against the viral capsid could restrict replication of the enveloped virus in hepatocyte cultures even when the antibodies were applied several hours after infection. However, it is currently unclear how these effects are mediated, and this will need to be resolved in future studies. —*MS*

■ CANCER MICROENVIRONMENT

p53 acts in the hood

The tumor suppressor p53 restricts tumor initiation by triggering cell cycle arrest and apoptosis, and it can also limit tumor growth by inducing senescence, which results in the secretion of factors that reinforce growth arrest of the senescent cell. Now, this p53-mediated senescence function is shown to also limit tumorigenesis by directing stromal cells in the tumor microenvironment toward an antitumor phenotype (*Cell* **153**, 449–460).

Amaia Lujambio and her colleagues used a mouse liver cancer model in which injured hepatocytes induce hepatic stellate cells to proliferate and secrete factors. This triggered stromal changes leading to fibrosis and eventually cirrhosis, conditions that often precede liver cancer. During chronic damage, they found that stellate-specific deletion of p53 increased advanced liver injury and the malignancy of neighboring epithelial cells, which expressed p53, suggesting that the effect of this tumor suppressor in liver tumor initiation is not cell autonomous. The authors found that p53 induces senescence of hepatic stellate cells and the secretion of factors, such as interleukin-6 and interferon-γ, that promote a nontumorigenic phenotype in macrophages that limits proliferation of premalignant cells and eliminates senescent cells.

Although other stromal cells besides macrophages may be involved in this non–cell-autonomous tumor suppressive effect, the role of p53-induced senescence in promoting an antitumor microenvironment may allow investigation of new therapeutic avenues for liver cancer. —*CP*

■ CANCER THERAPY

A Notch further with SERCA

Mutationally activated NOTCH receptors are found in an increasing number of cancer types with an especially high prevalence in T cell acute lymphoblastic leukemia (T-ALL). A study now identifies small-molecule inhibitors of sarco/endoplasmatic reticulum calcium ATPase (SERCA) channels as Notch1-inhibiting agents (*Cancer Cell* **23**, 390–405).

Kimberley Stegmaier and her colleagues conducted two complementary gene expression–based high-throughput screens of libraries of small-molecule inhibitors and cDNAs in cell lines carrying activated Notch variants. They found that both approaches converged on SERCA activity, such that the most effective compounds inhibited SERCA channel activity and gene expression and the most potent cDNAs encoded SERCA channels.

The authors showed that SERCA inhibition interferes with early maturation of Notch1 in the endoplasmic reticulum, where the receptor is processed by proteases. Cleavage occurs within the heterodimerization domain adjacent to two domains of Notch1 that require Ca^{2+} for their proper folding. Therefore, the authors suggested that SERCA-mediated Ca^{2+} influx into the endoplasmic reticulum could support the correct folding and subsequent processing of Notch1. They also showed that mutations in the heterodimerization domain, which are the most frequent type of Notch mutations found in patients with T-ALL, conferred the highest sensitivity to SERCA inhibitors.

The discovery of SERCAs as druggable targets suggests an alternative to γ-secretase inhibitors, which are associated with severe side effects, for the treatment of T-ALL and may also have therapeutic utility in patients with other types of cancer who carry mutant Notch1 variants. —*BB*

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