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In This Issue

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Antibody-mediated blockade of viral replication

(See article on pages 1203–1213.)

Antiviral antibodies often protect the immunized host by binding the viral surface and preventing uptake by cells. However, a few protective antibodies are known that are not "neutralizing" in this sense, but act within the infected cell to block later stages in viral maturation. Earlier work from Greenberg's group identified 7D9, an anti-rotavirus IgA that falls in this latter category. The epitope for 7D9 occurs on the viral component VP6, an RNA polymerase required for replication of the rotavirus' RNA genome that is buried in the interior of the viral capsid and is inaccessible to antibodies once the viral particle is fully formed. Binding of the external virion protein VP7 causes VP6 to undergo a conformational change that prevents RNA elongation. In their present high-resolution analysis, Feng and coauthors now show that 7D9 binding induces a similar conformational and functional change in VP6. However, because the authors worked with cells that had incorporated the antibody at high levels through an artificial mechanism, it remains to be established how and where the protective antibody might interact when the IgA is internalized by a physiological route, such as that mediated by the polymeric IgA receptor. Interestingly, although rotaviruses are not enveloped in their mature state, they are known to enter the endoplasmic reticulum transiently, suggesting at least one point in viral biogenesis when the nascent viral particle might come in contact with an endocytosed IgA species such as 7D9.

Therapeutic transgene expression just in time

(See article on pages 1223–1229.)

The just-in-time delivery model beloved by business consultants finds its inspiration in physiological responses, whose efficiency and economy have been honed by evolution. Such an approach is not evident in most attempts at gene therapy, where the need to supply adequate doses of a therapeutic gene product usually takes precedence over subtle temporal or quantitative control of transgene expression. However, Miagkov et al. note that IL-10 and other anti-inflammatory molecules that have proved valuable in controlling rheumatoid arthritis (RA) can be harmful when supplied in excess: Normal joint physiology and host defense require a dynamic balance of pro- and anti-inflammatory gene expression. To control a relapsing and remitting inflammatory disease like RA, they propose to drive IL-10 secretion using an expression system that responds directly to the presence of pro-inflammatory cytokines. In the two-tier regulatory system they describe here, transgenic rat synovial fibroblasts rapidly induce IL-10 expression when animals are challenged with a bacterial component that would otherwise provoke a severe bout of RA. Transgene expression peaks 2 days after treatment — effectively blocking joint inflammation and swelling — but is nearly undetectable after 4. Hence, this regulatory system may allow for the homeostatic production of anti-inflammatory gene products. However, the authors note that the adenoviral delivery system used, being highly immunogenic, is not suitable for studies of their system's efficacy over the long term. For this reason, further study, even at the pre-clinical level, may require the use of a different vector.