Finding Out How a Viral Hitchhiker Snags a Ride

To enter a cell, a virus must find the "receptor" that invites it in. A new—and unusual—one has just been found

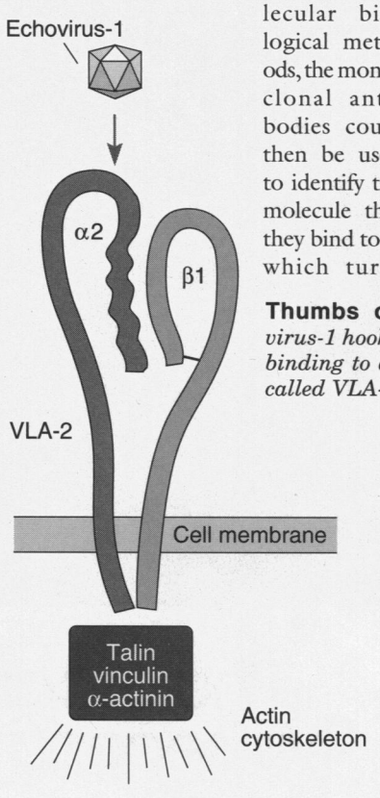
VIRUSES AREN'T LIKE DRIVERS GLIDING DOWN a superhighway, in charge of their own fate; they're biological hitchhikers, extending their thumbs and grabbing a free ride in one of the multitude of cells roaming through their host. And just as a hitchhiker's thumb isn't enough to guarantee him a ride, the virus must depend on the "willingness" of a viral receptor—a normal molecule on the cell surface—to hook it on board and give it a lift deep into the cells' interior. Which explains the race to identify these receptors: Lock the car door, roll up the windows, and viral diseases will be no more—so goes the theory. Yet, to date, only a handful of virus receptors have been identified. So the feat noted in this issue of *Science* (page 1718) by Jeffrey M. Bergelson and his colleagues in Robert Finberg's group at the Dana-Farber Cancer Institute in Boston, who have identified the molecules that act as receptors for the human echovirus type 1, deserves special mention.

Their discovery is intriguing for at least two reasons. It could ultimately help to prevent or treat echovirus infections, which cause two-thirds of the 30,000 to 50,000 cases of viral meningitis in adolescents and children requiring hospitalization in the United States each year. And for basic researchers, the discovery has created special excitement because the receptor Bergelson and his colleagues identified belongs to a class of molecules—the integrins—that have never before been identified as viral receptors.

There are some 30 types of echoviruses, and all are members of a family known as picornaviruses, which includes the rhinoviruses that cause the common cold and poliovirus. Until the announcement from the Finberg lab, all the receptors discovered for picornaviruses had been members of the very large and important class of cellular proteins known as the immunoglobulin gene superfamily (IGG-SF), which includes antibodies and a variety of cell-surface molecules.

In 1989, after the first data on picornavirus receptors were published, researchers began looking at how the IGG-SF proteins fit with the virus particle, or virion. "There's a cleft on the virion surface to which a piece of the IGG-SF fits," says Vincent Racaniello, a microbiologist at Columbia University who identified the poliovirus receptor. Says the codiscoverer of the rhinovirus receptor, Jeffrey Greve of Molecular Therapeutics Inc., a division of Miles Laboratories, in West Haven, Connecticut: "From these earlier results, we might have predicted that all picornaviruses bind to members of the IGG-SF." But Greve adds: "Now all bets are off."

The work that upset assumptions relied on techniques that are now becoming standard in the field of virology. The Dana-Farber team isolated monoclonal antibodies that specifically prevent echovirus-1 binding to a line of human cells in culture. Because they block the viral binding, it is assumed that they are binding to the same receptors that the virus itself binds to. By immunological and molecular biological methods, the monoclonal antibodies could then be used to identify the molecule that they bind to—which turns out to be the integrin known as VLA-2. The 20 or so integrins normally function in cell-to-cell interactions and in contacts between cells and the complex network known as the extracellular matrix. By mediating such contacts, the integrins play a role in cell migration, inflammation, blood clotting, and immune responses.



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Thumbs out. *Echovirus-1 hooks a ride by binding to an integrin called VLA-2.*

Although it's exciting from the point of view of basic research, identifying the molecule that this specific echovirus binds to is only one step toward understanding echoviral diseases. After the virus binds to its receptor, it must enter the cell and reproduce, and Bergelson is now beginning to use what is known about the receptor to tease out those additional steps in the infection process. Bergelson says he intends to genetically alter VLA-2 in cell lines to characterize more precisely the site where echovirus-1 binds and "to understand the role that the receptor plays in events that happen after binding."

Understanding that process could ultimately save lives. "In the 30 years that the Centers for Disease Control (CDC) have been collecting data on echoviruses, there have been fatal cases associated with almost every type," says Mark Pallansch of the CDC. In the 1950s, however, when the echoviruses were first identified, their potentially fatal effects weren't known. Indeed, their name comes from the acronym for "enteric cytopathic human orphan"—and orphan meant they hadn't been linked to any known diseases. Now, however, it is known that echoviruses cause some fraction of the 100 to 200 deaths of young infants each year from viral meningitis. And in the past 2 years, echovirus-11 has popped up as the culprit for most cases of viral meningitis nationwide. (Oddly, most of the echovirus-11 cases struck in the Midwest during 1990 and then, for unknown reasons, moved to the Northeast in 1991; all that is known is that these viruses are more common in the north than in the south.)

Meanwhile, the type Bergelson and his colleagues studied, echovirus-1, isn't a common disease-causing strain. Yet, according to virologist Joyce Fingeroth of the Dana-Farber Cancer Institute, who identified CR2 as the receptor for Epstein-Barr virus, finding the receptor for echovirus-1 could be the first step toward finding the receptor for the other, more pathogenic, strains. It's possible, she says, that other echoviruses may also bind to integrins. "If that's true," she adds, "specific therapies or vaccines may be developed that interfere with virus binding but do not affect binding of the other [molecules that bind to integrins]." Clinical strategies like that aren't going to be available tomorrow, but the current work on viral receptors offers an initial hope that some, at least, of the more menacing cellular hitchhikers can eventually be turned away before they hitch their pain-causing ride. ■ **ROBIN EISNER**

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