

DECEMBER 11, 1998

Cellular Target of Leprosy, Deadly Viruses Found

A cell-surface protein involved in the genesis of muscular dystrophy is also the target that the leprosy bacterium uses to latch onto cells before invading them. And in an equally surprising twist, it appears that two hemorrhagic fever viruses gain entry to cells via the same molecular handle.

These discoveries could lead to new drugs to prevent nerve damage in leprosy patients and to thwart infection by the deadly viruses, according to two research teams that reported these findings in two articles in the December 11, 1998, issue of the journal *Science*. One team included scientists from the Howard Hughes Medical Institute (HHMI) at the University of Iowa and The Rockefeller University in New York. The second team included scientists from The Scripps Research Institute and the same HHMI group.

About 800,000 people worldwide suffer from leprosy, which is caused by the bacterium *Mycobacterium leprae*. Hemorrhagic fever viruses infect about 250,000 people and cause 5,000 deaths worldwide each year.

The molecular handle used by the bacterium and viruses is called dystroglycan (DG). It belongs to a common family of molecules called glycoproteins, which are often embedded in cell membranes.

DG is the cell-surface component of a group of associated proteins known as the dystrophin-glycoprotein complex. Originally identified by HHMI investigator Kevin Campbell and his colleagues, this complex nestles in the membrane of cells throughout the body, acting as a receptor for a protein called laminin. Laminin, in turn, links cells to the scaffolding, or matrix, that helps knit together the body's tissues.

When the complex is absent, cells do not interconnect properly with the matrix outside the cell. Duchenne muscular dystrophy, a fatal inherited disease, is caused by a genetic lack of dystrophin. The muscle cells of people with this disease waste away for lack of structural stability.

In a study published in the December 11, 1998, issue of the journal *Cell*, Campbell's group showed that DG is a central organizer for a fundamental tissue structure called the basement membrane. According to Campbell, this finding offers important insight into the construction of the basement membrane, which plays a key role in the formation of many of the body's tissues.

"In some cases, if cells don't contact basement membranes they die, and abnormalities in basement membranes accompany the formation of some tumors," says Campbell.

By studying embryonic mouse cells engineered to lack DG, Campbell and University of Iowa colleague Michael Henry found that the molecule is required for laminin to cluster on cell surfaces, which seems to be critical for basement membrane formation. Importantly, the researchers also found they could "rescue" DG-deficient mutant cells by using a harmless virus that adds back the gene that codes for the DG protein.

The interaction between DG and laminin also is critical to the process of infection. Experiments with the leprosy bacterium showed that it attached to DG only in the presence of a key fragment of laminin. This finding suggested that the bacterium relies on both laminin and DG to infect cells, and that the laminin molecule acts as a bridge between the bacterium and DG.

The researchers also found that a combined bacterium-laminin fragment would bind to both rat and human Schwann cells, which normally surround and protect nerve cells. When the bacterium was first exposed to isolated DG in solution and then to the cells, binding to the Schwann cells was blocked.

The discovery that DG is the bacterium's portal of entry may have clinical importance, said Campbell, because antibiotics can only treat the leprosy infection, not the severe nerve damage that accompanies infection by *M. leprae*.

"If we can dissect the region on DG that is involved in the bacterial binding, we could possibly develop a drug, to be used along with antibiotics, that would block its entry into the peripheral nerve," he said.

In a second set of experiments, Campbell and colleagues from The Scripps Research Institute found that members of a family of hemorrhagic viruses called arenaviruses, which include lymphocytic choriomeningitis virus (LCMV) and Lassa fever virus (LFV), also bind to DG on the surface of mouse cells.

The researchers found that mutated mouse cells that lacked DG could resist LCMV infection. However, when the researchers reintroduced the gene for DG into the DG-deficient cells, they once again became vulnerable to viral infection.

"At first we were surprised at the role of dystroglycan in bacterial and viral infection," says Campbell. "But if you think about it, it's a major glycoprotein sticking out of the cell. And many times bacteria and viruses take advantage of such molecules as a route to infection."

Anura Rambukkana at The Rockefeller University and Michael Oldstone at The Scripps Research Institute also participated in the DG studies.