New Family of Adhesion Proteins Discovered

Some of the proteins that help white blood cells find where to go in the body have unusual—and highly similar—structures

TO FIGHT DISEASE EFFECTIVELY, the white blood cells of the immune system have to circulate around the body in the bloodstream, while remaining ready to move into any site where they might be needed. The cells reach their destinations with the aid of adhesion proteins that allow them to stick to cells only in appropriate target tissues.

In two papers in this issue of *Science*, researchers report that they have cloned and sequenced the genes for two of the proteins that participate in these interactions. They find that the proteins have similar, but unusual structures that mark them as belonging to a novel family of adhesion proteins. They are joined in the new family by a third protein, with an as yet unknown function.

Not only is the research helping to explain how white blood cells find their way around the body, but it is also producing a better understanding of inflammation. It may, for example, provide new therapeutic strategies for preventing the damage that may be done by the white cells that participate in acute inflammatory reactions.

The two proteins described in this issue mediate different kinds of white cell interactions. One protein, the gene for which was cloned by Mark Siegelman, Matthijs van der Rijn, and Irving Weissman of Stanford University School of Medicine, is the "lymph node homing receptor" (see p. 1165).

The homing receptor directs the cells that carry it, which include blood lymphocytes of both the B and T type, into the peripheral lymph nodes. It does this by binding to sites on the lining of blood vessels called high endothelial venules that serve as the port of entry to lymph nodes.

Lawrence Lasky of Genentech, Inc., in South San Francisco, Steven Rosen of the University of California, San Francisco, and their colleagues have also cloned the lymph node homing receptor gene. Their report is in press in *Cell*.

Michael Bevilacqua, Siegfried Stengelin, Michael Gimbrone, and Brian Seed of Harvard Medical School cloned the gene for the second adhesion protein, which is known as ELAM-1 for "endothelial leukocyte adhesion molecule 1" (see p. 1160). This protein is not located on white cells, but appears on the lining of blood vessels that have been stimulated by inflammatory lymphokines, such as interleukin-1 and tumor necrosis factor. ELAM-1 attracts the white cells called neutrophils to inflamed sites where the cells help to clean up the area by ingesting bacteria and other detritus.

The third member of the new family is the protein GMP-140, which is so called because it is a *g*ranule *m*embrane *p*rotein with a molecular weight of 140,000. Rodger McEver and his colleagues at the University of Oklahoma in Oklahoma City have cloned and sequenced the gene for this protein. (The paper is in press in *Cell*.) The function of GMP-140 is unknown, but it, too, may be an adhesion protein and perhaps also involved in inflammation.

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All three proteins have a mosaic structure, made up of a tandem array of sequences apparently adopted from sequences occurring in three other types of proteins with diverse functions. "It seems that nature has decided to embody a number of different protein functional domains in a single-chain molecule for the purposes of lymphocyte homing," Siegelman says.

Each protein is embedded in the membrane of the cells that carry it so that a short segment on the carboxyl end projects to the cell interior while most of the protein sequence is on the outside. The outermost portion of each protein consists of a sequence of about 120 amino acids with a structure typical of those of the animal lectins. "This family is quite different from the other families of cell-cell adhesion molecules," Bevilacqua says, "and the first prominent difference is the lectin domain."

Lectins are proteins that bind carbohydrates. The presence of such a domain on the outermost—and presumably business—end of the adhesion molecules suggests that they recognize and bind to carbohydrates, rather than proteins, when finding their partners. Earlier evidence had indicated that the homing receptor binds to carbohydrate.

After the lectin domain comes a sequence containing about 35 amino acids that is similar to the sequence of epidermal growth factor. And then closest to the membrane is a repeated sequence containing about 60 amino acids that resembles a sequence found in certain proteins that regulate the complement system. (The proteins of the complement system work with various immune cells to rid the body of foreign pathogens.)

The role of these two inner domains is unknown. They may contribute to the binding specificity of the adhesion proteins, but may also have additional functions. The complement regulatory domain, for example, may help to control complement activity at inflamed or injured sites.

Moreover, adhesion molecules such as the lymph node homing receptor may be involved in the cell-cell interactions needed for early immune system development as well as in the eventual migrations of lymphocytes into lymph nodes. Proteins known to influence cell fates during the development of the fruit fly and of the roundworm *Caenorhabditis elegans* have epidermal growth factor domains that are very similar to the one in the homing receptor.

Understanding the function of the adhesion molecules may have clinical implications. The presence of the lymph node homing receptor can influence metastasis sites for mouse lymphoma cells, according to the Stanford workers.

ELAM-1, because it helps draw neutrophils into inflamed sites, is a possible target for drugs to combat potentially harmful inflammatory conditions. Although the white cells are part of the body's defenses against foreign invaders, they can harm normal tissues. "They will destroy everything in their vicinity if you tickle them the wrong way," Seed points out.

Activated neutrophils may contribute to the lung damage sometimes experienced by people who have been given high oxygen concentrations while on a respirator and to the heart muscle damage that may occur when a blocked coronary artery is suddenly reopened, as may happen in heart attack patients who are given clot-dissolving drugs. GMP-140 is likely to be present on blood vessel walls at clot and injury sites and may also play a role in these conditions.

Further work on the adhesion molecules will include efforts to determine whether blocking ELAM-1 and GMP-140 is helpful in reducing the untoward efforts of neutrophil activation. ■ JEAN L. MARX