Protein helps immune cells to divide and conquer

March 8 2009

Researchers at the University of California, San Diego School of Medicine have identified a key protein that is required for immune cells called B lymphocytes to divide and replicate themselves. The rapid generation of large numbers of these immune cells is critical to the body's antibody defense mechanism. However, when B cells grow unchecked, it can lead to immune cell cancers such as multiple myeloma or, when they grow to attack the wrong targets, to autoimmune disease. By discovering the role of the CD98hc protein, scientists may find new therapy targets for such diseases.

The study from the laboratory of Mark H. Ginsberg, MD., professor of medicine, will be published online March 8 in advance of print in *Nature Immunology*. It describes why CD98hc is essential in order for B lymphocytes to transition into antibody-secreting cells. It also describes how this relates to the protein's role in the signaling ability of integrins - a large family of adhesion molecules that transfer information between the inside and outside of a cell.

According to first author Joseph Cantor, PhD, UC San Diego School of Medicine, scientists have known for nearly 25 years that CD98hc, common to all vertebrates, probably played a role in their adaptive immune system, but it wasn't known how this protein functioned.

"This protein was used as a marker of activation because it was found in low levels on resting lymphocytes," said Cantor. "But when B or T lymphocytes were stimulated by antigens - for instance, to protect the

body against bacteria - levels of CD98hc went up 20 fold."

The scientists generated a mouse model lacking the CD98hc protein in B lymphocytes. When vaccinated, these mice were unable to mount a normal antibody response to the pathogen. Cantor says this was the first clue to the researchers of the protein's importance.

"In purifying B lymphocytes without the CD98hc protein, we discovered that the lymphocytes couldn't divide rapidly," Cantor said, adding that this proved the protein was essential to expanding the number of immune cells, a necessary step in the immune response. While deletion of the protein didn't impair early B cell activation, it did inhibit later activation of elements along the signaling pathway that push the cell forward to divide.

"Since B cells can't rapidly divide and replicate without CD98hc, perhaps by blocking this protein we could stop the unchecked growth of B lymphocyte cells that can result in cancer or block misdirected B cell attacks that can cause certain autoimmune diseases," said Ginsberg.

The CD98hc protein functions in cells by helping to transmit integrin signals, as well as transporting amino acids - the building blocks of proteins - into the cell. But the scientists didn't know which, if either, of these functions was related to the protein's role in the rapid division of immune cells. By replacing normal CD98hc in B cells with a version that lacked one or the other of these two functions, they discovered that the integrin-binding domain of this protein is required, but the amino acid transport function is dispensable for B cell proliferation.

"CD98hc interacts with certain integrin subunits to prompt signaling events that control cell migration, survival and proliferation. Our study shows that the rapid proliferation of B cells, necessary for the body to fight infection, is aided by the CD98hc protein's support of integrin

signaling," Cantor said.

Source: University of California - San Diego