Research yields potential target for cancer, wound healing and fibrosis

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Research conducted by Allison Berrier, PhD, Assistant Professor of Oral and Craniofacial Biology at the LSU Health Sciences Center New Orleans School of Dentistry, and colleagues, provides insights that may help scientists design novel approaches to control wound healing and fight diseases such as cancer and fibrosis. The paper, β1 Integrin Cytoplasmic Domain Residues Selectively Modulate Fibronectin Matrix Assembly and Cell Spreading through Talin and Akt-1, will be published in the March 20, 2009 issue of the *Journal of Biological Chemistry*. The research team also included Drs. J. Angelo Green and Kenneth Yamada at the National Institute of Dental and Craniofacial Research, as well as Dr. Roumen Pankov at Sofia University in Sofia, Bulgaria.

The research concerns the regulation of integrins - proteins on the surface of cells that serve dual roles of anchoring cells within tissues and controlling cell behavior. Integrins anchor to extracellular proteins found outside the cell and this contact regulates important cellular activities that are critical for survival, proliferation and differentiation in both healthy tissues and tumors. Integrins are involved in the cellular response to injury and infection and are needed to repair damaged tissue.

Of the many integrins that exist, the beta-1 integrin is of great interest because it is involved in nearly every cell in the body. Its importance is demonstrated by the fact that mice, which are typically used as models for disease, cannot survive without the beta-1 integrin gene.

Beta-1 integrin is a cell surface protein that spans the membrane and has

a portion of the protein outside the cell and a portion of the protein inside the cell. The beta-1 integrin tail is the portion found inside the cell. The beta-1 integrin tail has two functions -- it connects integrins to the cellular infrastructure and to signaling pathways.

This study advances earlier research on the beta-1 integrin tail, that revealed the ability of this integrin tail to provide a scaffold for signaling proteins that control cell survival. The extracellular matrix is a complex mixture containing proteins such as fibronectin and collagen that provide structural support to cells and traction for cell movement. If cells are placed on top of extracellular matrix proteins the cells become activated by their integrins and trigger signaling for the cell to expand or spread over the matrix. Cell spreading is an intermediate step during cell migration on matrix proteins. Prior to the current study it was not clear whether the beta-1 integrin tail recruits the same or different proteins inside the cell to control two different integrin receptor functions outside the cell, namely, formation of fibronectin fibrils and cell spreading.

The researchers generated a panel of stable cell lines containing different mutations in cells of the beta-1 integrin tail. In the current study, the cell lines were used to determine the role of the beta-1 integrin tail in cell spreading and the production of fibronectin fibrils. Fibronectin is an anchorage protein present in connective tissues and it helps wound healing when it is deposited in damaged tissue. Cells can use their integrins to stretch fibronectin along their surface and this stretched or fibrillar fibronectin provides a docking site to bind additional fibronectin and other factors involved in inflammation and wound healing. An overabundance of fibrillar fibronectin around the cell is characteristic of fibrosis and excessive scarring. Therefore, understanding how cells regulate the ability of integrins to control the abundance of fibrillar fibronectin is of therapeutic interest.

These beta-1 tail mutations are thought to disrupt the ability of the beta-

tail to interact with their recruited proteins. The team found a defect in assembling fibronectin fibrils for the majority of the beta-1 integrin tail mutations. Further studies focused on studying two cell lines that were both unable to form fibrils. When adhesion to fibronectin was examined, one cell line spread whereas the other did not. They demonstrated that specific beta-1 tail mutations can affect cell signaling, cell spreading or formation of fibronectin fibrils. These studies revealed an ability of the cell to sort out different ways of controlling various integrin activities. For instance, the integrin beta-1 tail specifically recruited a protein called talin, found in this study to be important for integrins to form fibronectin fibrils, yet talin was dispensable for early cell spreading events. This ability to selectively adjust particular functions of the integrin may be a key to preventing the progression of diseases associated with abnormal integrin signaling or fibronectin fibril formation such as in cancer and fibrosis.

"Based upon these studies, the aim of my current research at the LSU Health Sciences Center New Orleans School of Dentistry focuses on those proteins that connect to integrin beta-tails in oral cancer because this knowledge will aid in developing therapeutics that selectively target aberrant integrin functions in oral cancer, " notes Dr. Berrier.

"Understanding the mechanisms by which the beta-1 integrin controls the many functions that it regulates is critical to designing drugs that are specific enough to block defective functions of the integrin while simultaneously maintaining normal activities of the integrin in healthy tissue," said Dr. Green.

Source: Louisiana State University Health Sciences Center