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Clues to cancer pathogenesis found in cell-conditioned media

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Primary effusion lymphoma (PEL) is a rare B-cell neoplasm distinguished by its tendency to spread along the thin serous membranes that line body cavities without infiltrating or destroying nearby tissue. By growing PEL cells in culture and analyzing the secretome (proteins secreted into cell-conditioned media), investigators have identified proteins that may explain PEL pathogenesis, its peculiar cell adhesion, and migration patterns. They also recognized related oncogenic pathways, thereby providing rationales for more individualized treatment. The results are published in *The American Journal of Pathology*.

A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, a condition, or disease, and can help develop personalized therapeutic approaches for patients. Analysis of secretomes is a new strategy for discovering biomarkers involved in cancer pathogenesis based on the reasoning that these fluids will be enriched in proteins secreted by cancer cells, shed from cancer cell surfaces, or released from the interior of cells (through vesiculation, cell lysis, apoptosis, or necrosis). The content of the secretome may reflect the functional state of the cells at a specific time point.

In this study, investigators from the Istituto Nazionale dei Tumori of Milan and the Centro di Riferimento Oncologico of Aviano, Italy, analyzed secretomes from four established PEL cell lines (CRO-AP2, CRO-AP3, CRO-AP5, and CRO-AP6; established in the laboratories directed by Antonino Carbone, MD) as well as from four PEL clinical samples and three primary solid lymphomas. PEL tumor cells are characterized by Kaposi's sarcoma-associated herpesvirus (KSHV) infection, and the primary solid lymphomas were also KSHV-positive.

Protein content was measured using two complementary mass spectrometry platforms. The experiments allowed cells to grow for 16 to 18 hours and were performed under serum-free conditions to increase the ability to detect secreted proteins. Of 266 identified proteins, 139 (52%) were secreted and 127 were considered to have an intracellular origin or were secreted in an unconventional fashion. "Most of the proteins we recognized in the secretome of PEL are new with respect to previous studies utilizing conventional proteomic analysis and gene expression profiling," said Annunziata Gloghini, PhD, of the Department of Pathology of the Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy.

"Importantly, 27 proteins were shared by secretomes from all PEL cell lines," added Dr. Gloghini. The researchers found that the PEL secretomes were enriched with proteins specifically involved in inflammation and the immune response (eg, HMGB1, GRAA, and PCBP2) and cell growth (eg, LEG1, STMN1, and S10A6). Other proteins play roles in mRNA processing (eg, ANM1 and PCBP2) or cell structure, adhesion, migration, and organization (eg, EZRI, MOES). Some proteins have enzymatic activity (eg, CATA and GSTK1).

Comparison of secretomes from PEL with those from other tumor cell lines identified 20 proteins specific to the PEL cell lines. This suggests that secretome profiling provides a source of tumor biomarkers and may ultimately improve patient management.

The investigators also investigated the association between the proteins found in the PEL secretome and biological function. Using pathway/network enrichment analysis, they found that the pathways most activated in PEL cell lines were involved with regulation of autophagy (an intracellular catabolic mechanism) through LRRK2-mediated signaling pathways and with apoptosis and survival through granzyme A signal. "The extracellular functions of granzyme A might be involved in the particular tropism of PEL and its cell growth," says Italia Bongarzone, PhD, of the Department of Experimental Oncology and Molecular Medicine of the Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy. "Further studies are needed to confirm and validate the importance of these pathways/processes and their roles in lymphoma tumorigenesis and progression."

More information: "Primary Effusion Lymphoma: Secretome analysis reveals novel candidate biomarkers with potential pathogenetic significance," by Annunziata Gloghini, Chiara C. Volpi, Dario Caccia, Ambra V. Gualeni, Anna M. Cilia, Antonino Carbone, and Italia Bongarzone (dx.doi.org/10.1016/j.ajpath.2013.11.028), The *American Journal of Pathology*, Volume 184, Issue 3 (March 2014)

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