Screening for matrix effect in leukemia subtypes could sharpen chemotherapy targeting

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Location, location, location goes the old real estate proverb but cancer also responds to its neighborhood, particularly in the physical surroundings of bone marrow cells where human myeloid leukemias arise and where, according to two Harvard bioengineers, stiffness in the surrounding extracellular matrix (ECM) can predict how cancer subtypes react to chemotherapy. Correcting for the matrix effect could give oncologists a new tool for matching drugs to patients, the researchers say.

In work to be presented at the ASCB/IFCB meeting in Philadelphia, Jae-Won Shin and David Mooney of Harvard University's Wyss Institute for Biologically Inspired Engineering in Cambridge, MA, describe building a three-dimensional (3D) hydrogel system with tunable stiffness to see how relative stiffness of the surrounding ECM affected the resistance of human myeloid leukemias to chemotherapeutic drugs. They found, for example, that chronic myeloid leukemias (CML) grown in their viscous 3D gel system were more resistant to a widely used cancer drug, Imatinib (Gleevec), than those cultured in a rigid matrix. Using this and other data from their variable ECM system, the researchers screened libraries of small molecule drugs, identifying a subset of drugs they say will be more likely to be effective against CML, regardless of the surrounding matrix. By correcting for the matrix effect, Shin and Mooney believe their novel approach to drug screening could more precisely tailor chemotherapy to a patient's individual blood cancer type.

Though leukemia is relatively rare, it is the sixth leading cause of cancer death in the U.S. and is notoriously resistant to therapy. Patients usually undergo multiple courses of chemotherapy in hopes of eliminating all of the cancer cells. Part of the difficulty in targeting drugs is that proliferating cancer cells of all types are known to shape and be shaped by their physical neighbors. In myeloid leukemias, which start in blood precursor cells in the bone marrow, the cancer's growth radically alters the composition of its ECM including fluids, molecules, and fibers. Uncontrolled deposition of collagen in the ECM, for examples, is a telltale sign of certain leukemias. While myeloid leukemia subtypes are defined by distinct genetic mutations and the activation of known signaling pathways, the Harvard bioengineers looked to see if changes in matrix stiffness played a part in cancer cell proliferation and if myeloid leukemia subtypes could be sorted out by their responses.

Cancer cells are not two-dimensional and the recent development of 3D culturing systems has changed our views of how many types of cancer progress in three-dimensional human tissues. Shin and Mooney's 3D hydrogel system allowed them to vary the stiffness of the matrix and uncover different growth patterns, which they used to profile different leukemia subtypes. They also looked at a cellular signaling pathway, Protein Kinase B (AKT), known to be involved in mechanotransduction and thus sensitive to stiffness in different leukemia subtypes. They discovered that CML cells in the 3D hydrogel were resistant to an AKT inhibitor while AML cells grown in the same conditions were responsive to the drug, supporting their idea that a tunable matrix system could be a way to sort out subtypes by drug resistance.

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