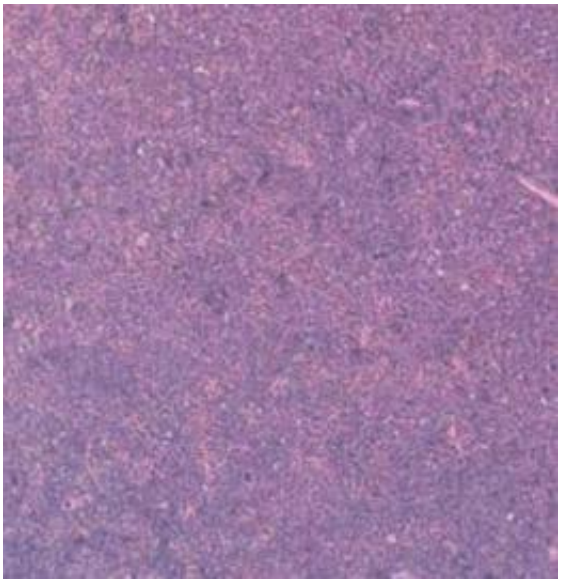
Chemosensitivity of cancer cells depends on their protein dependency

October 26 2009



The spleen of mice overexpressing the oncogene c-myc and the anti-apoptotic protein MCL-1 is crowded with leukemia cells. Credit: Brunelle, J.K., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200904049.

Two different anti-apoptotic proteins support cancer cell survival via an identical mechanism, yet differ in their sensitivity to chemotherapeutic drugs, report Brunelle et al. The study will be published online October 26, 2009 and in the November 2, 2009 print issue of the *Journal of Cell Biology* (JCB).

Cancer cells often become dependent on one or more anti-apoptotic

proteins to avoid death while continuing to proliferate. BCL-2, for example, is overexpressed in many cancers and mops up pro-apoptotic proteins to prevent them from permeabilizing mitochondria and initiating cell death. Other tumors are reliant on a related protein called MCL-1, but less is known about this member of the BCL-2 family. Brunelle et al. created leukemic mice overexpressing MCL-1 and compared them to similar mice that produced excess BCL-2.

The leukemias suffered by these two types of mice were identical, yet a technique called BH3 profiling was able to distinguish between cells derived from the different animals by demonstrating a dependency on one or other of the two anti-apoptotic proteins. Immunoprecipitation experiments revealed that MCL-1 and BCL-2 both work by sequestering the same two pro-apoptotic targets.

Surprisingly then, leukemia cells reliant on MCL-1 were much more sensitive to a range of chemotherapeutic drugs than their BCL-2-dependent counterparts were. Brunelle et al. found that the different cytotoxic drugs all caused a rapid decrease in MCL-1 protein levels via proteosome-mediated degradation, allowing cell death to proceed quickly. BCL-2 protein is more stable however, so additional time and more drug is needed to kill BCL-2-dependent cancer cells.

Thus, the block in apoptosis selected during oncogenesis is not necessarily complete, and can have a major influence on the cancer's chemosensitivity. Senior author Anthony Letai now plans to use BH3 profiling on human tumors, to determine which anti-apoptotic protein a patient's cancer is dependent on and to correlate this with the tumor's response to chemotherapy.

More information: Brunelle, J.K., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200904049

Source: Rockefeller University (news : web)