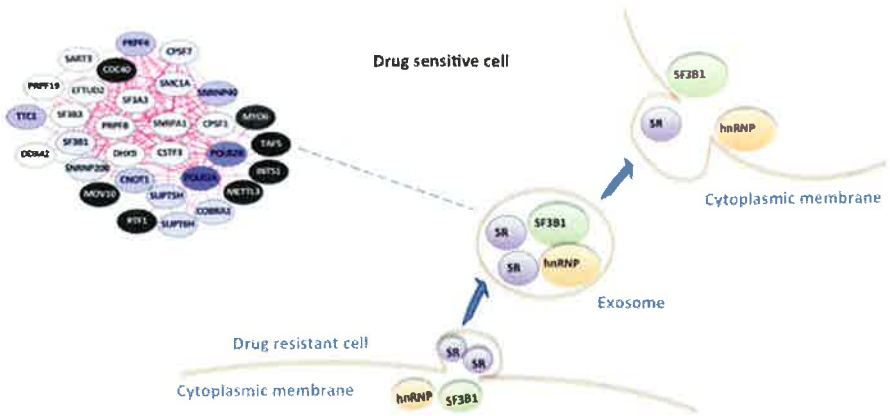
Leukemia cells teach other cells not to self-destruct

By Bree Yanagisawa

In acute myeloid leukemia, or AML, relapses are a major concern. About 65 percent of adult patients with AML go into remission through chemotherapy, but more than half of those patients relapse.

Residual AML cells are thought to cause these relapses. These cells persist in the patient despite chemotherapy and may expand and re-create the cancer. The cells survive chemotherapy using various mechanisms, including avoiding the usual cell-death pathways. In a recent paper published in the journal **Molecular and Cellular Proteomics**, Connie Jimenez at the VUmc Cancer Center Amsterdam and her colleagues Anna Wojtuszkiewicz and Jacqueline Cloos dissect the interplay between these residual AML cells and their surrounding environment.



Acute myeloid leukemia cells use exosomes to transfer resistance to neighboring cells.

When things go wrong inside a cell, apoptotic mechanisms are in place to serve as a self-destruct signal. Cancer cells are capable of avoiding these typical processes, making them harder to kill. In the study, the researchers found that resistance to self-destruction may be passed from AML cells to surrounding cells via secreted exosomes.

The extent to which cancer cells can ignore self-destruct signals fluctuates over the course of the disease. Counter to what one might expect, patients who carry AML cells that are highly resistant to apoptosis at diagnosis can have AML cells with decreased levels of such resistance after chemotherapy. This suggests that the cell death pathways are governed by complex mechanisms.

The researchers collected samples from patients with AML at the beginning of disease and after remission. When they examined the apoptotic profiles of residual AML cells and surrounding normal lymphocytes within the bone marrow, the researchers were surprised to find that the two different cell types shared similar levels of proteins typically involved in apoptosis. In addition, when cultured together, AML cells that were especially resistant to apoptosis were capable of making low-resistance cells more likely to ignore self-destruct signals. These findings suggest the apoptotic profiles of cells are being influenced by external factors.

The authors profiled secreted proteins from AML cells with high and low levels of resistance to apoptosis. Unexpectedly, the most prominent types of proteins identified weren't apoptotic proteins. Many of the identified secreted proteins were those usually involved in gene regulation, hinting at a potential mechanism by which AML cells can influence their surroundings. Furthermore, these secreted proteins are housed in vesicles that originate from the AML cells. Jimenez says that these findings suggest that "by secreting vesicles, leukemic cells may affect the global expression profiles of the recipient cells."

In the future, the authors intend to look into the ways in which these secreted proteins affect surrounding cells.

"Unraveling the mechanisms of communication between leukemic cells, including stem cells, and their microenvironment is crucial to the efficacy of cancer treatment," says Jimenez. "Our work suggests that it is a mutual interaction in which not only the cells of the bone marrow niche can promote survival of leukemic cells but leukemic cells themselves are shedding vesicles, which can influence their neighboring cells."

Bree Yanagisawa (byanagisawa@asbmb.org) is a science writing intern at ASBMB Today and a Ph.D. candidate in pathobiology at the Johns Hopkins School of Medicine.