Leukemia cells rely on vesicles from neighboring stromal cells to resist common cancer treatments

Leukemia is a cancer of white blood cells that occurs in both children and adults. Strides have been made in curing most types of leukemia. However, acute myeloid leukemia (AML) continues to resist the same treatment strategies. AML cells arise inside the bone marrow amidst other cell types whose function in a healthy person is to support the production of essential blood cells. However, in the presence of AML, these neighboring stromal cells appear to be reprogrammed to increase their adhesive properties, retain leukemia cells in the bone marrow and minimize exposure to circulating chemotherapy. AML stromal cells provide a protective sanctuary and promote leukemia cell survival, but the mechanism by which this influence is exerted remains unclear. We recently showed that reprogrammed stromal cells in AML patients protect leukemia cells remotely, without the need for direct cell contact, through the release of vesicles called exosomes.

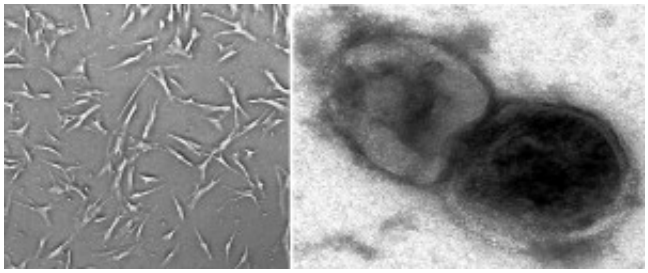

Fig. 1. Light micrograph of bone marrow stromal cells isolated from an AML patient (left) and an electron micrograph of exosomes released in culture by stromal cells (right).

Specifically, in our experiments, we grew stromal cells from the bone marrow samples of healthy individuals (N-BMSCs) and from patients with AML (AML-BMSCs). We then collected the exosomes released from the two stromal cell populations and studied them comparatively in content and in function. We first examined micro-RNA (miRNA), which are small RNA molecules, some of which can regulate cancer cells by lowering gene activity. Micro-RNA-155 and miRNA-375 are clinically validated risk factors in AML, and we found that exosomes released from AML-BMSCs, but not N-BMSCs, are filled with miRNA-155 and miRNA-375. We also examined signaling proteins and found that TGF-?, a protein linked to a decreased chance of cure in AML, was present in high amounts in AML-BMSC exosomes, but undetectable in N-BMSC exosomes. Thus, for the first time, we show the release of risk factors that increase the chance of a poor outcome in AML occurring via exosomes from non-cancerous, reprogrammed stromal cells.

To further study the potential role of stromal exosomes in drug resistance we mixed AML cells with exosomes from either AML-BMSC or N-BMSC. We then exposed those AML cells to a common

chemotherapy drug that broadly kills cancer cells (cytarabine), or to a drug that more specifically targets a survival pathway in AML cells (AC220). Both drugs are currently used to treat AML patients. To our surprise, we found that exosomes from both stromal cell populations protected AML cells from the broad effects of cytarabine. However, only exosomes from AML-BMSCs protected the cells against the more targeted treatment with AC220. This is the first report of stromal-mediated resistance to chemotherapy occurring via exosomes in AML, with AML-BMSC exosomes providing notable gains in resistance to therapy that is targeted more specifically at the leukemia cell.

We will next turn our attention to why AML-BMSC exosomes promote gains in protection against targeted therapy relative to N-BMSC exosomes, but not against general chemotherapy? We hypothesize that the coincident miRNA and cytokine enrichment observed in AML-BMSC exosomes may provide an explanation. This strategy will enable us to discover novel treatments that target the stromal cells that enable AML drug resistance, leading to a higher cure rate for all patients with AML.

Publication

Alterations in acute myeloid leukaemia bone marrow stromal cell exosome content coincide with gains in tyrosine kinase inhibitor resistance.
Viola S, Traer E, Huan J, Hornick NI, Tyner JW, Agarwal A, Loriaux M, Johnstone B, Kurre P.
Br J Haematol. 2015 Jun 11