Chemotherapy Promotes Release of Exosomes Which Upregulate Cholesterol Synthesis and Chemoresistance in AML Blasts

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Extracellular vesicles (EVs) are emerging as a key mediator of intercellular communication as well as a major mechanism of functional reprogramming of cells in disease [1-2]. All cells produce EVs, which freely circulate and are found in all body fluids. EVs are heterogenous, consisting of subsets of vesicles with different sizes, distinct origins, and various functions (Figure 1). They mediate a broad variety of biological events ranging from cellular activation, inflammation, blood coagulation, angiogenesis, cellular transport, and others. Among these vesicles, a subset of small EVs (30-150 nm in diameter) originating from multivesicular bodies (MVBs) in parent

Figure 1: Different types and origins of extracellular vesicles released from cancer cells.

In the recently published article entitled “Increased small extracellular vesicle secretion after chemotherapy via upregulation of cholesterol metabolism in acute myeloid leukemia” [8], we reported that exosomes play a critical role in AML progression by establishing and driving a vicious cycle of chemoresistance in leukemic blasts. The mechanisms involved in exosome-mediated chemoresistance of AML blasts to CT are largely unknown, but our data suggest that it may be related to the excessive sEV release by AML blasts. At the same time, we and others have observed that AML blasts exposed to CT contain high cholesterol levels [9-10]. Lipids, including cholesterol, have been linked to sEV packaging and secretion [11]. Further, CT or ionizing radiation as well as other stress responses, additionally promoting cancer progression. This accommodating cross-talk between cancer cells and sEV secretion works against efficacy of chemotherapy and establishes a vicious cycle of chemoresistance. Furthermore, blast-derived sEVs in plasma of AML patients treated with CT-induced chemoresistance by up-regulating HMGCR activity, cholesterol production and proliferation in cultured naïve AML cells and also upregulated a massive release of HMGCR (+) sEVs into extracellular space. The autocrine mechanism initiated and mediated by blast-derived sEVs sets up a cycle of events that is mechanistically driven by the upregulation of cholesterol metabolism and the release of HMGCR (+) sEVs. This sEV-driven mechanism not only allows AML cells to avoid death, presumably by packaging drugs into vesicles, but it promotes expansion of cholesterol-enriched chemoresistant AML cells which, in turn, promote further release of HMGCR (+) sEVs. This accommodating cross-talk between cancer cells and sEV secretion works against efficacy of chemotherapy and establishes a vicious cycle of chemoresistance. Further, since the blast-derived sEVs in plasma of AML patients have been shown to carry immunosuppressive molecules such as TGFβ-1, FasL, PD-L1 [6], their elevated levels in plasma contribute to inhibition of anti-leukemia immune responses, additionally promoting cancer progression. Our experiments showed that blast-derived HMGCR+ sEVs are the central and key element in this vicious cycle of chemoresistance in AML.
Chemoresistance induced by sEV is not limited to sEVs produced by tumor cells. While cancer cell-derived sEVs deliver molecules derived from parental cancer cells, sEVs released from non-malignant cells in the context of CT might also play a significant role in cancer promotion and chemoresistance. We found that sEVs isolated from post-CT AML plasma which contained no detectable leukemia blasts had high levels of HMGCR and other immunosuppressive molecules. Ex vivo studies with non-malignant peripheral blood mononuclear cells (PBMC) showed that CT treatments similarly enhanced sEV secretion and that the released sEVs carried elevated levels of enzymatically active HMGCR which was blocked by statins. This finding implies that HMGCR (+) sEVs in the peripheral circulation might impede cholesterol level reducing efficacy of statins. In such case, blocking of the sEV release and/or the sEV uptake by recipient cells or removal of circulating sEVs represent potentially promising strategies for enhancing therapeutic efficacy of statins and lowering chemoresistance in patients with cancer treated with CT.

In the in vitro experiments, treatment with Simvastatin, the HMGCR inhibitor, blocked CT-induced enhancement of sEV release from AML cells. This suggests that the use of statins in combination with SOC CT could reduce cholesterol levels in cells and in sEVs thus reducing the overall sEV burden and potentially improving the efficacy of chemotherapy. Indeed, various studies, including Phase I and II clinical trials, have reported on the beneficial effects of statins in cancer treatments [14]. In relapsed AML cases, treatments with Pravastatin in conjunction with Idarubicin and Cytarabine significantly improved complete remission rates [15]. While these studies have not been focused on the role sEVs might play in the treatment efficacy, it seems reasonable to suggest that the beneficial effects of statins in cancer patients could be enhanced by lowering the harmful burden of HMGCR+ sEV in the blood stream, thereby sensitizing cancer cells to chemotherapy. Alternatively, sEVs might uptake circulating statins, carry statins to cancer cells and by lowering cellular cholesterol levels increase tumor cell sensitivity to chemotherapy. This study suggests that the use of these well-tolerated, widely used cholesterol level-reducing drugs could be a potential solution for blocking detrimental effects of tumor-derived HMGCR +sEVs in hematological and other malignancies.

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**References**


