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Chemotherapy induces secretion of exosomes loaded with heparanase that degrades extracellular matrix and impacts tumor and host cell behavior

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Abstract

The heparan sulfate-degrading enzyme heparanase promotes the progression of many cancers by driving tumor cell proliferation, metastasis and angiogenesis. Heparanase accomplishes this via multiple mechanisms including its recently described effect on enhancing biogenesis of tumor exosomes. Because we recently discovered that heparanase expression is upregulated in myeloma cells that survive chemotherapy, we were prompted to investigate the impact of anti-myeloma drugs on exosome biogenesis. When myeloma cells were exposed to the commonly utilized anti-myeloma drugs bortezomib, carfilzomib or melphalan, exosome secretion by the cells was dramatically enhanced. These chemotherapy-induced exosomes (chemoexosomes) have a proteome profile distinct from cells not exposed to drug including a dramatic elevation in the level of heparanase present as exosome cargo. The chemoexosome heparanase was not found inside the chemoexosome, but was present on the exosome surface where it was capable of degrading heparan sulfate embedded within an extracellular matrix. When exposed to myeloma cells, chemoexosomes transferred their heparanase cargo to those cells, enhancing their heparan sulfate degrading activity and leading to activation of ERK signaling and an increase in shedding of the syndecan-1 proteoglycan. Exposure of chemoexosomes to macrophages enhanced their secretion of TNF-α, an important myeloma growth factor. Moreover, chemoexosomes stimulated macrophage migration and this effect was blocked by H1023, a monoclonal antibody that inhibits heparanase enzymatic activity. These data suggest that anti-myeloma therapy ignites a burst of exosomes having a high level of heparanase that remodels extracellular matrix and alters tumor and host cell behaviors that likely contribute to chemoresistance and eventual patient relapse.

Summary

We find that anti-myeloma chemotherapy dramatically stimulates secretion of exosomes and alters exosome composition. Exosomes secreted during therapy contain high levels of heparanase on their surface that can degrade ECM and also can be transferred to both tumor and host cells, altering their behavior in ways that may enhance tumor survival and progression.