5127
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Leptin Modulates Exosome Biogenesis in Breast Cancer Cells: an Additional Mechanism in Cell-to-Cell Communication

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Exosomes are small membrane vesicles secreted by both normal and malignant cells upon fusion of endosomal multivesicular bodies (MVBs) with the plasma membrane, which play an important role in cell-to-cell communication. Several reports have highlighted the involvement of exosomes in many aspects of breast cancer development and progression, thus mounting interest in the potential exploitation of these vesicles as cancer biomarkers, drug delivery systems, and for the development of novel therapies. It has been extensively demonstrated the involvement of the obesity hormone leptin in all steps of breast tumorigenesis, but up to now its role in modulating breast cancer exosome generation have not been investigated.

Here, we studied the effect of leptin on exosome biogenesis and secretion using as experimental model both estrogen receptor α (ERα)-positive MCF-7 and triple negative MDA-MB-231 breast cancer cells. First, we evaluated, by Transmission Electron Microscopy (TEM) MVB formation in cells treated with leptin. TEM analysis revealed that the number of MVBs in the cytoplasm of leptin-treated MCF-7 and MDA-MB-231 breast cancer cells was significantly increased compared to control untreated cells. Next, we characterized size distribution, particle number and protein cargo of exosomes, isolated by ultracentrifugation method, from conditioned media (CM) of cells treated or not with leptin. Nanoparticle Tracking Analysis revealed that the concentration of exosomes in the leptin treated MCF-7- and MDA-MB-231-CM was significantly higher compared to untreated samples. Furthermore, exosomes quantification by Acetylcholinesterase activity showed that the full leptin receptor antagonist, peptide LDFI, abrogated leptin-induced exosome secretion. Exosomes from leptin treated cells showed an increased expression of the leptin target gene Heat shock protein 90 (Hsp90) and its client protein HER2, along with activated leptin signaling effectors such as pJAK2, pSTAT3, and $pMAPK^{42/44}$ compared to exosomes from untreated cells. Mechanistically, our results demonstrated that, among protein involved in exosome biogenesis, leptin significantly increased protein expression of the well-known exosomal luminal marker Tumor susceptibility gene 101 (Tsg101), without affecting its mRNA levels. Co-immunoprecipitation studies revealed a specific interaction between the chaperone protein Hsp90 and Tsg101 in basal condition that was further increased after leptin exposure. Accordingly, leptin-induced Tsg101 protein levels were completely abrogated in the presence of specific Hsp90 inhibitor, 17-allylamino-17-demethoxygeldanamicin.

In conclusion, our results demonstrate for the first time that leptin was able to increase exosomes release in breast cancer cells, through an up-regulation of Tsg101 expression at posttranslational level. These findings, providing additional insights into the molecular mechanism governing exosome generation in breast cancer cells, might open new avenues for therapeutic intervention in breast carcinoma.