Extracellular vesicle secretion promotes cisplatin chemoresistance in a context of late endocytic impairment

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In several recent works, defects in lysosomal function have been implicated in drug resistance. Indeed, lysosomes can sequestrate multiple chemotherapeutic agents reducing the accessibility of these drugs to their target sites. In contrast, it was also hypothesized that sequestration of drugs into lysosomes, in particular cisplatin, may also induce lysosomal damage and apoptosis. Therefore, it has been speculated that impairment of the lysosomal compartment, determining reduced cisplatin sequestration, protects cells from lysosome-dependent cell death and induces the chemoresistant phenotype. Resistance has also been associated with increased exocytosis of lysosomal content (through secretory lysosomes and/or extracellular vesicles) and with reduced size of the lysosomal compartment. On the basis of these previous observations, we decided to analyze the late endocytic pathway and extracellular vesicle secretion in cisplatin chemoresistance.

We have observed that cisplatin-resistant cell lines are characterized by impairment of late endocytic compartments compared to their chemosensitive counterparts. This dysfunction is accompanied by a reduction in the number of lysosomal proteins, in the number and size of lysosomes, and impairment of acidification, but also by an increase of CD9- and CD81-positive extracellular vesicle (EV) secretion. We demonstrated that dysfunctional endocytosis induces the increase of EV secretion which shuttle cisplatin outside of the cells and characterizes the chemoresistant phenotype.