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Unraveling the potential role of autophagy in CD157-associated chemoresistance in malignant pleural mesothelioma.

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Introduction. Resistance of cancer cells to cytotoxic agents is a major challenge in malignant pleural mesothelioma (MPM) patient management. Recently, we demonstrated that the CD157 glycoprotein is expressed by ~80% of MPM surgical specimens and its expression levels correlate with poor prognosis. *In vitro,* high CD157 expression has been associated with enhanced cell growth, migration, invasion and activation of the PI3K/Akt/mTOR pathway leading to resistance to platinum-based chemotherapy. The inhibition of mTOR with Everolimus or of both PI3K and mTOR with BEZ-235 proved to be able to revert chemoresistance in CD157-positive cells. As increasing evidence indicates that autophagy has a key role in platinum-based chemotherapy resistance, in this study we investigated the potential implication of autophagy in CD157-mediated chemotherapy resistance in MPM.
Materials and methods. CG98 (CD157-positive) and MSTO-211H (CD157-negative) MPM cell lines (both native and engineered for CD157 expression), were used as models, to study apoptosis and autophagy. Using Western blot and immunofluorescence, we analysed the expression of caspase-3 and PARP, as hallmarks of apoptosis, and of LC3II, a protein associated with autophagosomes. Cell proliferation in the presence or absence of Chloroquine (CQ) and Bafilomycin autophagy inhibitors was assessed by PrestoBlue Cell Viability assay.
Results and discussion. Treatment with cisplatin (CDDP) induced a more robust caspase-3 activation and PARP cleavage in CD157-negative than in CD157-positive cells, suggesting that CD157-associated resistance is at least partly related to an impaired apoptotic response. Moreover, treatment with CQ or Bafilomycin induced greater accumulation of LC3II and had a stronger growth inhibitory effect in CD157-positive than in CD157-negative cells, indicating that autophagy could act as a prosurvival mechanism contributing to CD157-associated drug resistance. Preliminary results showed that CDDP treatment, alone or in combination with autophagy inhibitors, promotes high levels of autophagy in CD157-positive cells, corroborating the notion that CDDP is able to elicit the autophagic flux in platinum-resistant cells.
Conclusion. These results support the rationale to hypothesize the implication of autophagy in CD157-associated resistance and highlight the potential clinical utility of CD157 as a marker for selecting patients with particularly aggressive MPM who might benefit from a combined therapy.