CD157 is a promising marker for the design of tailored therapies in patients with malignant pleural mesothelioma

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Malignant pleural mesothelioma (MPM) is a lethal tumor difficult to treat. Cisplatin (CDDP)-based chemotherapy is the standard first-line treatment but its efficacy is often limited due to intrinsic or acquired resistance. We demonstrated that the CD157 glycoprotein is expressed in 85% of MPM patients where its high expression correlated with poor prognosis. *In vitro*, high CD157 expression was associated with a more aggressive phenotype, activation of the PI3K/mTOR pathway and reduced CDDP sensitivity.

In this study we exploited the potential utility of CD157 as a marker for the design of new strategies combining PI3K/mTOR and autophagy inhibition with chemotherapy, in order to improve the prognosis in MPM patients with high CD157 expression.

MPM cell line models engineered to overexpress (MSTO-211H cells) or knockdown (CG98 cells) CD157 were used in conventional *in vitro* assays to investigate *i)* the ability of NVP-BEZ235, a dual PI3K/mTOR inhibitor, to improve CDDP-sensitivity in CD157-positive MPM, and *ii)* the potential implication of autophagy in the CD157-associated chemoresistance.

We showed that i) NVP-BEZ235 inhibits mTORC1, mTORC2, and PI3K/PDK1 signalling pathways and reduces cell growth, especially in CD157-positive MPM and ii) CDDP blocked CD157-negative cells in S-phase, eliciting a strong pro-apoptotic effect, whereas, dose-dependently blocked CD157-positive MPM in G2-phase thus limiting the cytotoxic effect of chemotherapy. Noteworthy, when combined with CDDP, NVP-BEZ235 proved able to abrogate the CDDP-mediated cell cycle arrest in G2/M phase, thus restoring apoptosis with a stronger synergistic effect in CD157-positive cells compared to the CD157-negative cells.

Furthermore, we demonstrated that CD157-positive MPM cells show higher basal autophagy compared to CD157-negative MPM. Pharmacologic blockade of autophagy with Chloroquine (CQ) dampened cell proliferation and, used in combination with CDDP, CQ had a stronger anti-tumor effect in CD157-positive MPM cells compared to CD157-negative cells.

Overall, the reduced sensitivity to CDDP in CD157-positive MPM relies on deregulation of the PI3K/mTOR pathway, and at least partly, on increased protective autophagy. These results highlight the potential clinical utility of CD157 as a marker to select a subgroup of patients, who might benefit from chemotherapy combined with NVP-BEZ235 and inhibitors of autophagy.