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MCL1 inhibition reduces the aggressive phenotype of MDA-MB-231 cells

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Abstract: MDA-MB-231 cell line is a Triple Negative Breast Cancer (TNBC) which is among the most aggressive subtype of breast cancer characterized by high metastatic potential, drug resistance and, generally, poor clinical outcomes (1). Previously we reported that inhibition of MCL1, an antiapoptotic member of BCL2 family, by A-1210477 reduces invasion and migration in this cell model. In addition, we observed a possible reversion in Epithelial Mesenchymal Transition (EMT) features evidenced by the reduction of Vimentin and increase of E-cadherin protein, related to DNMT1 downregulation. Here, we confirm this aspect reporting N-cadherin, Mucin1 and Cytokeratin-19 evaluation, suggesting EMT/MET reversion as well as E-cadherin gene re-expression. An important role in the initiation and progression of cancer is sustained by cancer stem cells (CSCs) a subpopulation which contribute to tumor heterogeneity displaying drugs resistance (2). MDA-MB-231 cells are also characterized by features associated with CSCs therefore, we evaluated if MCL1 inhibition was able to reduce stemness potency in this cell line, we analyzed the expression of the main surface stemness markers following A-1210477 treatment such as $CD44^{+}/CD24^{-/low}$ population. Cytofluorimetric analysis showed that A-1210477 treatment enriched $CD24^{+}$ subpopulation, lowering that of $CD44^{+}$. In addition, we observed a significant decrease in $CD49f^{+}$ and $CD326^{+}$ cells as well as some stemness marker genes SOX2, Nanog, and OCT3/4. Moreover, reduced expression levels of CD133 protein are also reported. Finally, we observed an interesting enrichment in subpopulation $CD117^{+}$ (c-Kit), a putative marker of luminal progenitor cells in the human breast and known as good therapeutic target in TNBC (3).
Our data seem to confirm that MCL1 inhibition produces drastic effects not only in EMT/MET reversion but also on stemness features in this cell line, suggesting MCL1 protein as a possible new molecular target in TNBC drug resistance management.

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