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BIOLOGIC ANTICANCER ACTIVITY OF DESIGNED ANKYRIN REPEAT PROTEINS (DARPINS) TARGETED AGAINST DNMT1 AND CONJUGATED TO DOCETAXEL LEADS TO ERADICATION OF CHEMORESISTANT MUTATED SQUAMOUS CELL EPSOPHAGEAL CANCER STEM CELLS

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Introduction Current anticancer therapies succeed at eradicating bulky disease but miss a tumour reservoir consisting of stem/progenitor cells (SCs) that lead to disease recurrence and metastasis. Tumour stem cells are characterised by upregulation of hTERT which is the limiting factor for telomerase activity. DNA methylation leads to hTERT gene expression.
Methods We obtain specimens of surgically resected oesophageal Ca from distant lymph node metastatic sites from patients chemoresistant to vinca alkaloids like vinorelbine-tartrate, and isolate the mutated tumour stem cells. We treat them with DARPins targeting DNMT1 conjugated to docetaxel.
Results Post-treatment, we observed downregulation of DNMT1 blocking methylation of hTERT promoter inhibiting its transcription and subsequent telomerase activity. Stem cell markers p63, CD44, CD117, CD90, CD133, BCRP1, b-catenin and methylation marker SCNN1B were downregulated. After DNA demethylation, there was upregulation of thymosin b10, p16/Rb, RASSF2, p53 and PTEN lipid/protein phosphatase. Subsequently, there was inhibition of chemoresistant factors, such as choline-kinase, PI3K-AKT/PKB-mTOR, Ras/Raf/Erk/TGFa/EGFR, COX-2, PGE2, PDGF, VEGF, cyclin D1, HIF-1a, survivin and aurora – A/STK15/BTAK. There was enhancement in adheren junction formation. Docetaxel polymerised microtubules blocking cell cycle at G2/M while it phosphorylated antiapoptotic bcl-2 upregulating tumour suppressor gene beclin1 which induced autophagy. Activation of procaspase 10 and procaspase 8 formed DISC which induced type I, II and III PCD and aponecrosis of mutated tumour stem cells.
Conclusion Combination of molecularly targeted therapies such as DARPins and conventional cytostatic agents such as docetaxel could provide a potent strategy to eradicate metastatic mutated ESCC stem cells resistant to conventional chemotherapy with vinca alkaloids such as vinorelbine.
Competing interests None.
Keywords cancer stem cells, squamous cell oesophageal Ca, designed ankyrin repeat proteins, DARP, chemoresistance, apoptosis, aponecrosis, autophagy, type II-III PCD.