P005 Cancer cell expulsion of anticancer drugs through shedding of microvesicles: association with drug resistance and tumour survival

Samireh Jorfi and Jameel M. Inal
London Metropolitan University, London, United Kingdom

Microvesicles (MVs) are small (0.1-≤1 μm in diameter) heterogeneous vesicles released from cells constitutively or upon activation, that mediate intercellular communication. Multi-drug resistance (MDR) has been defined as the ability of cancer cells to survive after treatment with various drugs. However, the mechanism(s) used by cancer cells to evade apoptosis induced by anticancer drugs remain unclear and was the subject of our investigation. Here we report a novel mechanism of cancer cell expulsion of anticancer drugs through the release of MVs, followed by the recruitment of lysosomes to the site of release to repair the resulting damage. In addition, we show for the first time that inhibition of MV release by pretreatment of PC3M cells with the calpain inhibitor, calpeptin, sensitizes cancer cells to drug-elicited apoptosis mediated by the addition of methotrexate (MTX) and docetoxel (DOC) using at least 10-fold lower concentrations, both *in vitro* and *in vivo*. Treatment of cancer patients with MET or DOC leads to significant side effects due to the use of higher doses. Here we show that these drugs when administered together with calpeptin can be given at doses 100 times lower and still induce effective killing of target cancer cells. Overall our studies shed light on the role of MV release in cancer cell expulsion of anticancer drugs and subsequent evasion and survival from apoptosis and suggest new combination therapies for existing cancer drugs.