Cancer Research

Experimental and Molecular Therapeutics

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Abstract

While Docetaxel offers an improvement in overall survival of patients with HRPc, unfortunately relapse is almost inevitable. Reasons for failure of docetaxel to increase survival beyond a median of 2.5 months have yet to be completely elucidated. Extracellular proteins and RNAs secreted in small vesicles known as exosomes may hold relevance as predictive biomarkers of docetaxel response. This study aimed to (i) characterize in vitro models of docetaxel resistance from three prostate cancer cell lines: DU145, PC3 and 22Rv1 compared to their aged-parent populations; (ii) isolate exosomes from medium conditioned by these cell line models and investigate their effects on motility, invasion, proliferation and docetaxel resistance of secondary cells; and to (iii) perform a proof-of-principle translational investigation of the clinical relevance of exosomes isolated from prostate cancer serum. We successfully generated docetaxel-resistant prostate cancer cell lines that were found to be substantially more resistant to docetaxel than age-matched sensitive cells (109 ± 7.4 fold for DU145RD; 71 ± 8.4 fold for 22Rv1RD; 19 ± 2.3 for PC2RD). In addition, all resistant variants displayed cross resistance to the anthracycline Doxorubicin (4.3 ± 1.0 for DU145RD; 8.3 ± 1.2 for 22Rv1RD; 4.2 ± 1.2). Docetaxel-resistance was associated with alterations in motility, migration, invasion, proliferation, anchorage independent growth and response to TRAIL-induced cell death. Furthermore, MDR-1/P-gp expression associated with docetaxel-resistance (detected in two of the

resistant three cell lines) was also detectable in corresponding exosomes secreted from those cells. Application of exosomes derived from DU145 and its docetaxel resistant variant, DU145RD, did not infer any significant affects on the motility of DU145 cells or the invasion of DU145 or 22RV1 cells. Interestingly, however, in the presence of DU145RD exosomes, a significant increase in docetaxel resistance was observed in both DU145 cells (~22%; $p < 0.01$) and 22RV1 cells (~15%; $p < 0.001$); effects that were independent of proliferation influences. In order to explore the clinical relevance of exosomes in prostate cancer, we performed a pilot study using serum from docetaxel-treatment naive prostate cancer patients and healthy age-matched controls. We observed a significant increase of invasion (~20%; $p < 0.05$) and proliferation (~10%; $p < 0.05$) of cells in the presence of prostate cancer exosomes. Our in vitro observations and preliminary clinical studies indicate that exosomes play an important role in prostate cancer and may offer potential as vehicles containing predictive biomarkers and new therapeutic targets. Acknowledgements: Science Foundation Ireland's SRC award to MTCL (08/SRC/B1410).

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