Background

Malignant pleural mesothelioma (MPM) is an aggressive asbestosis-related malignancy with extremely poor prognosis, with a 5 year survival of approximately 5%. MPM remains difficult to treat - the current standard of chemotherapy care (a combination of cisplatin and pemetrexed) has been largely unchanged over the last decade and in most cases, is essentially palliative. Novel therapeutic targets are therefore urgently needed in this disease. Y-box binding protein-1 (YB-1) is a multifunctional oncoprotein associated with all of the hallmarks of cancer. Here, we evaluate YB-1 as a therapeutic target in this disease by investigating its role in driving malignant behaviour and chemoresistance of MPM cells.

Results

I. YB-1 is overexpressed in MPM and silencing inhibits MPM, but not non-malignant mesothelial proliferation.

(A) YB-1 protein was overexpressed in most MPM cell lines compared to the immortalised mesothelial cell line MøT-5A. (B) YB-1 knockdown via siRNA transfection did not affect MøT-5A proliferation, but did significantly inhibit MPM cell growth (45% cell lines) and (C) colony formation.

II. YB-1 knockdown induces apoptosis or G0/G1 cell cycle arrest, cisplatin sensitisation and impedes the migration of MPM cells.

Transfection of YB-1 siRNA induced (A) apoptosis or (B) an increase in G0/G1 population in MPM cells. (C) Cells undergoing apoptosis after YB-1 downregulation were sensitised to cisplatin, one of the most commonly prescribed drugs to patients suffering from MPM, while a slight increase in resistance was seen in cells undergoing cell cycle arrest. (D) YB-1 silencing significantly inhibited MPM cell migration.

III. YB-1 is important in MPM tumour formation in vivo.

MSTO cells stably expressing luciferase were transfected with 5 nM of either YB-1 or control (Co) siRNA and the next day intraperitoneally (IP) injected in vivo into SCID mice (n=5 per group). (A) Tumour growth was monitored in situ using the IVIS imaging system after luciferin substrate injection. (B) Detection of bioluminescence was also used to visualise tumour nodules when harvested. (C) Total tumour weight was significantly lower in mice injected with YB-1 vs Co siRNA transfected cells.

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Conclusions

YB-1 is a potential novel therapeutic target in MPM. It plays an important role in the growth and migration of MPM cells, can sensitize cells to cisplatin in vitro and is important in the growth of tumours in vivo. Our findings also indicate that this protein is involved in the acquired chemoresistance of MPM. Taken together, our data make a strong case to further investigate this oncogene’s potential as a therapeutic target in MPM.