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Extracellular YB-1 Stimulates Cell Migration and Confers Poor Prognosis in Pleural Mesothelioma



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Introduction



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Pleural mesothelioma (PM) is a rare but very aggressive malignancy arising from the linings of the chest cavity. One important driver of PM progression is the Y-box binding protein 1, which is frequently overexpressed in PM and is involved in regulating PM cell growth, migration and therapy resistance.

The Aim of this study was to characterize the roles and functions of extracellular YB-1 pleural mesothelioma.

Results I



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Analyses of publicly available RNAseq datasets (TCGA, Bueno et al.) and our immunohistochemistry data from two independent cohorts (N=68, N=63) revealed that YB-1 mRNA, but not protein levels are prognostic for shorter overall survival in PM tissue.

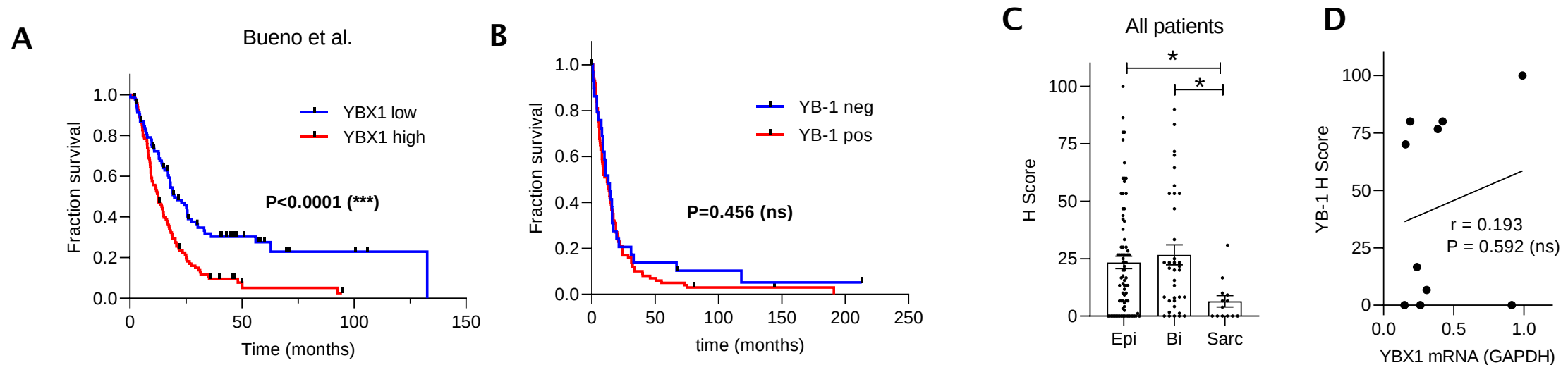


Figure 1: Kaplan-Meier curves of **(A)** 211 PM patients, according to their YBX1 mRNA expression, analysed from Bueno et al. and **(B)** 131 PM patients pooled from the Vienna and Sydney cohort, according to their YB-1 protein expression determined by immunohistochemistry. Log-rank (Mantel-Cox) test. **(C)** Distribution of H-Scores according to the 3 main histological subtypes (Epi: epithelioid, Bi: biphasic, Sarc: sarcomatoid). Each dot represents one patient. ANOVA with Tukey's multiple comparison test. **(D)** Pearson correlation between YBX1 mRNA levels normalized to GAPDH and YB-1 H-Scores of 10 PM tissue samples. *** $P < 0.001$; * $P < 0.05$; ns: not significant.

Results I



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YB-1 secretion could explain the lack of correlation between mRNA and protein data, and indeed we found an increase in active YB-1 secretion from PM cells after stresses such as cisplatin treatment or hypoxia.

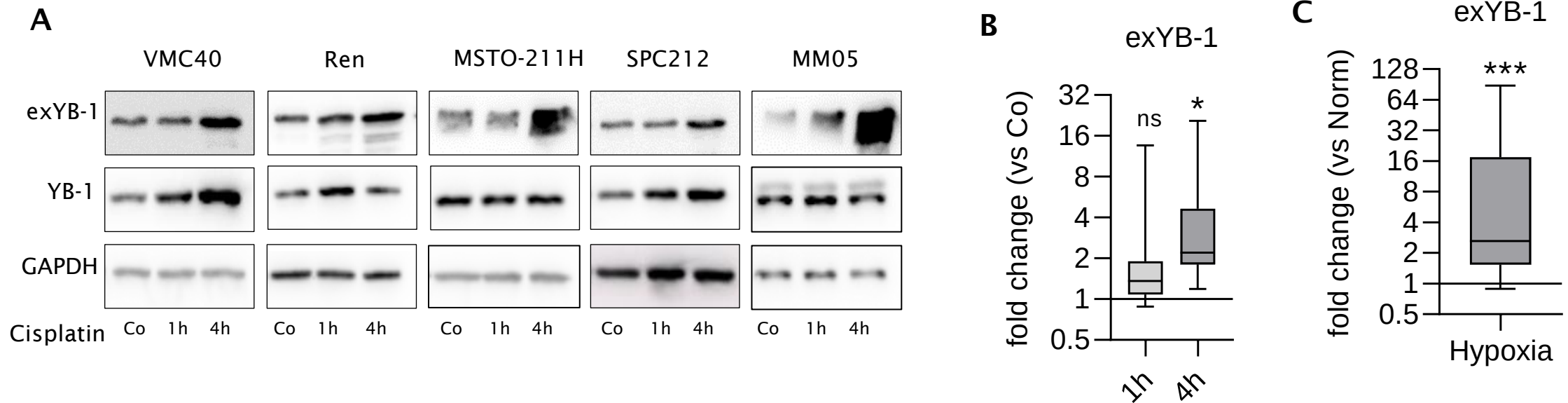


Figure 2: (A) Representative western blots showing secreted extracellular YB-1 (ex-YB1) and intracellular YB1 (YB-1) of PM cells after 1 h and 4 h exposure to 20 μ M cisplatin. GAPDH was used as reference. Pooled densitometric analyses of ex-YB-1 after (B) cisplatin treatment for 1 h or 4 h, normalized to untreated control (Co) and (C) after 24 h exposure to hypoxic or normoxic conditions. Kruskal-Wallis test and Dunns multiple comparison or Wilcoxon signed rank test. *** $P=0.0010$; * $P<0.05$; ns: not significant.

Results II



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Recombinant extracellular exYB-1 in turn stimulated scattering and cell migration not only in PM cells, but also in cancer-associated fibroblasts, normal mesothelial and endothelial cells.

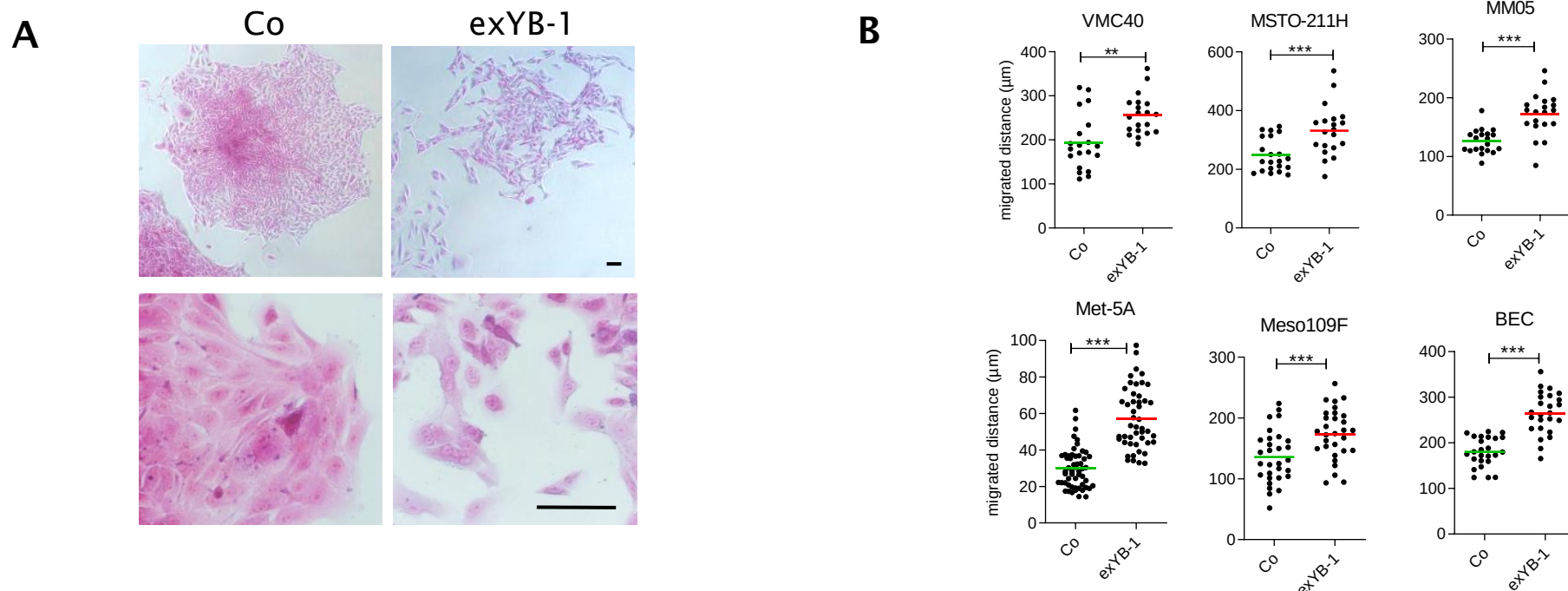


Figure 3: **(A)** Representative pictures of MM05 cells from the colony formation assays stained with crystal violet. Scale bar: 50 μ m. **(B)** Migrated distance of PM (top) and non-malignant (bottom) cell lines, determined by live-cell videomicroscopy over 72 h. Treatment with exYB-1 was 100 ng/ml. Each dot represents one cell. T-test, ** $P < 0.01$. *** $P < 0.001$.

Results II



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In support of this, phosphoproteome analysis revealed alterations in pathways associated with growth factor receptor-mediated signalling, microtubule reorganization and cell migration.

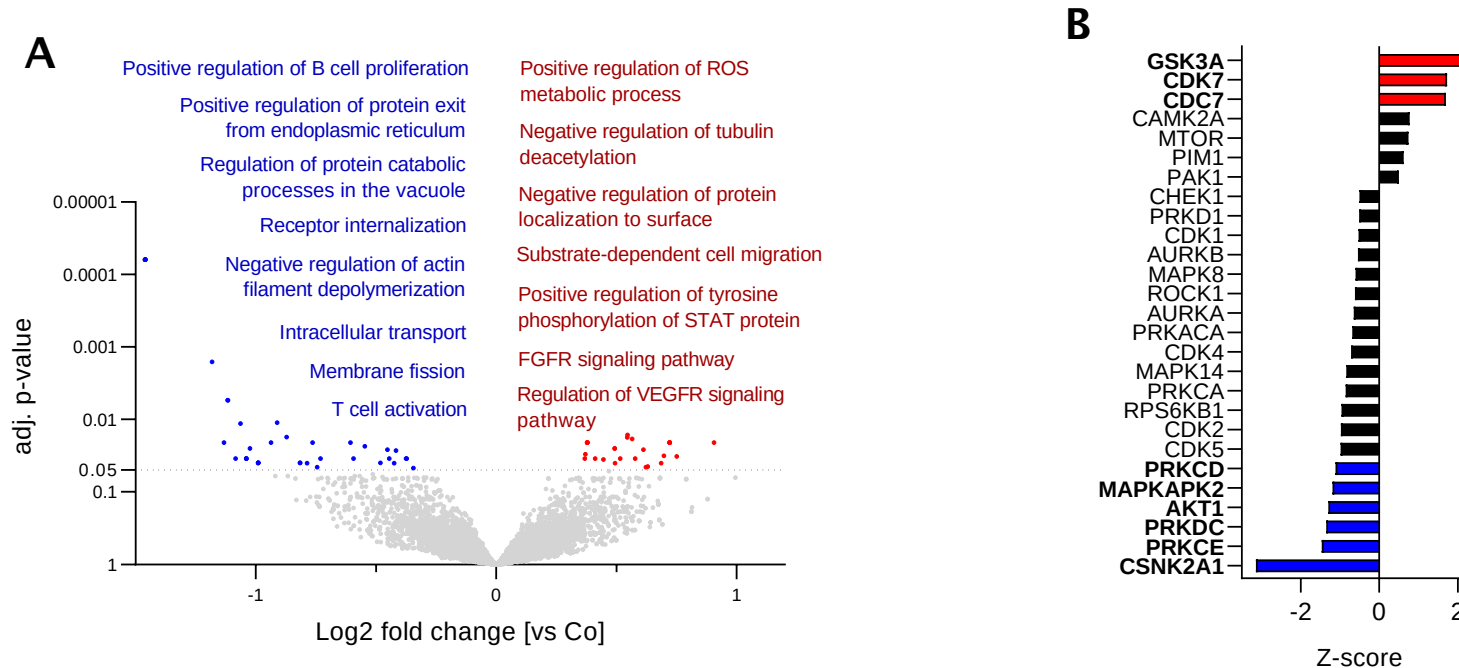


Figure 4: Phosphoproteomics analysis was conducted after 1 h treatment with 100 ng/ml exYB-1. **(A)** Gene set variation analysis (GSVA) to quantify the enrichment of Gene Ontology Biological Process (GO:BP) terms in treated versus untreated (Co) MSTO-211H cells. **(B)** Kinase-substrate enrichment analysis (KSEA) of the phosphoproteomics data. The cut-off values for significantly altered kinase (red, blue) were adj.P<0.05 and Z-score >0.5.

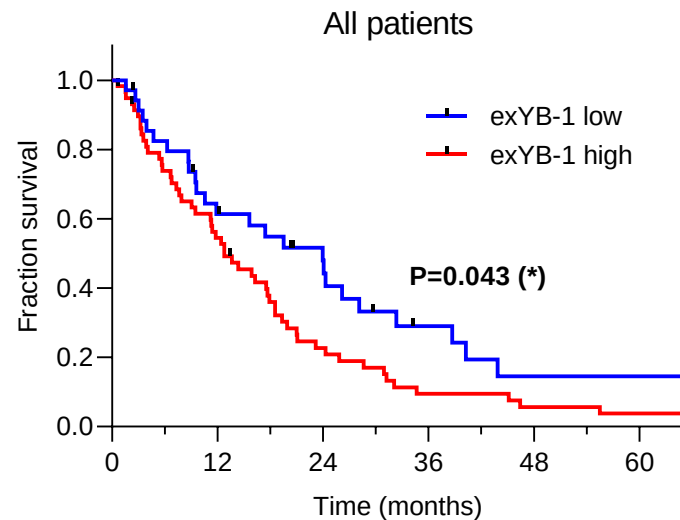
Results III



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Finally, we analysed the presence of exYB-1 in serum samples (N=94) and while no significant correlation with histological subtype or disease stage was found, multivariate analysis confirmed serum levels of YB-1 as an independent predictor for overall survival in PM.

A



B

Variables			Univariable			Multivariable
	n = 94	OS (95% CI)	p-value	HR	95% CI	p-value
Age			0.393	–	–	–
< 65	41 (44%)	17.9 (16.7-19.1)				
> 65	53 (56%)	11.9 (7.5-16.2)				
Sex			0.547	–	–	–
Male	77 (82%)	13.6 (7.9-19.3)				
Female	17 (18%)	17.7 (14.1-21.2)				
Histology			0.065	–	–	–
Epithelioid	71 (76%)	17.9 (14.6-21.2)				
Non-epithelioid	23 (24%)	8.7 (2.0-15.4)				
YB-1 levels			0.043 (*)	1.8	1.1-3.0	0.020 (*)
High	59 (63%)	24.0 (13.4-34.6)				
Low	35 (37%)	12.8 (8.2-17.3)				
Stage			0.003 (**)	1.1	0.5-2.5	0.765
Early	37 (39%)	21.0 (15.4-26.7)				
Late	57 (61%)	9.5 (6.3-12.7)				
Treatment			<0.001 (***)	1.8	1.0-3.5	0.067
MMT including MCR	44 (47%)	19.3 (15.5-23.2)				
CHT +/- RTH	43 (46%)	9.5 (7.1-11.8)				
BSC	7 (7%)	3.6 (2.4-4.8)				

Figure 5: (A) Kaplan-Meier curve of all patients stratified according to high and low exYB-1 expression. Log-rank (Mantel-Cox) test, * P<0.05. **(B)** Univariable and multivariable survival analyses of PM patients (N=96). Abbreviations: OS, overall survival; CI, confidence interval; HR, hazard ratio; MMT, multimodality treatment; MCR, macroscopic complete resection; CHT, chemotherapy; RTH, radiotherapy; BSC, best supportive care.

Conclusion



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Our study identified YB-1 mRNA but not protein as a prognostic tissue marker for PM patients. We further demonstrated that PM cells actively secrete YB-1 and that exYB-1 induces aggressive behaviour in multiple cell types. Importantly, we also showed that, rather than intracellular YB-1 in the tumor cells, extracellular YB-1 in serum holds prognostic information. Circulating YB-1 may therefore represent a clinically accessible biomarker, reflecting adverse prognosis in PM patients