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Is PAI-1 good or bad? Knockdown of PAI-1 in PANC-1 human pancreatic adenocarcinoma and in vitro invasiveness

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It is generally accepted that overexpression of plasminogen activator inhibitor 1 (PAI-1) correlates with worse prognosis and more invasive phenotype of many cancers, including pancreatic adenocarcinoma (PAC). We down-regulated PAI-1 expression in PANC-1 cells via shRNA knockdown (KD). The down-regulated variant (PD-PANC) exhibited neural morphological traits compared to cuboidal morphology of WT PANC-1s or vector-transfected cells. RT-PCR demonstrated that KD of PAI-1 leads to decreased expression of mesenchymal markers transcripts concurrently with increased expression of epithelial and neural transcripts, suggesting partial mesenchymal-to-epithelial transition. Importantly, PD-PANC1s expressed markedly more E-cadherin in a larger proportion of cells, whereas TUBB3 was expressed predominantly in cells with neural morphology. Despite this apparent more epithelial phenotype, PD-PANC-1s exhibited more invasive behavior in vitro. Although, the invading cells expressed more PAI-1 and less E-cadherin transcripts than non-invaders, it could not explain the observed increase in invasiveness. Using fluorescent supra-vital staining in a mixed vector/PD-PANC-1 population, we demonstrated that cells that down-regulated PAI-1 created environment promoting invasion of the few cells expressing high PAI-1 level. We previously reported that PD-PANCs exhibit higher uPA activity and continuously convert plasminogen to plasmin, which have been shown to activate matrix metalloproteinases. Indeed, inclusion of plasminogen enhanced invasion of PD-PANC-1s. In conclusion, our results suggest that fine balancing of different activities rather than extensive ablation of the "offending" PAI-1 protein maybe a better strategy in maintaining a less aggressive PAC phenotype.

Biography

Yoram Oron has completed his PhD from Hebrew University, Jerusalem and Post-doctoral studies from University of Virginia School of Medicine. He has taught Physiology and Pharmacology at Tel Aviv University (TAU), was a Department Chair, and TAU Director of International Academic Relations. His career included Visiting Associate Professorship at Cornell Medical School and numerous periods as Visiting Scientist at NIDDK, NIH. He has published more than 110 papers in reputed journals and has served as an Editorial Board Member of several journals. He is currently a TAU Professor Emeritus.

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