AB023. S023. Identification and targeting of a poor-prognosis subgroup of pancreatic cancer

Veronique Veenstra, Frederike Dijk, Eline Soer, Lan Zhao, Johannes Halfwerk, Gerrit Hooijer, Naomi Donner, Helene Damhofer, Marco Marzano, Anne Steins, Cynthia Waasdorp, Olivier Busch, Marc Besselink, Johanna Tol, Lieke Welling, L. Bengt van Rijssen, Hanneke Wilmink, Hanneke van Laarhoven, Jan Paul Medema, Louis Vermeulen, Sander van Hooff, Jan Koster, Joanne Verheij, Marc van de Vijver, Xin Wang, Maarten Bijlsma

Academic Medical Centre, Amsterdam, Netherlands

Abstract: Pancreatic ductal adenocarcinoma (PDAC) has the worst prognosis of all common cancers, but strongly divergent outcomes are apparent between patients. To reveal and address the intertumor heterogeneity that contributes to this, we have performed RNA-Seq gene expression analysis on a large number of resected PDAC samples (n=90). Unsupervised class discovery in this single-center PDAC-only dataset identified four subgroups with distinct clinical manifestations. Biological interpretation and network analysis comparisons to existing classification systems revealed a poor-prognosis subgroup characterized by mesenchymal features. Species-specific transcript analysis on matching patient-derived xenograft (PDX) models allowed assembly of an epithelium-tailored classifier for use on cell lines and primary cultures. Experimental validation in models for PDAC subtyped using the modified classifier confirmed mesenchymal features and a highly invasive growth pattern for the poor-prognosis subtype in contrast to more epithelial (non-mesenchymal) subtypes. To identify specific therapeutic vulnerabilities of this poor-prognosis subgroup, drug sensitivity screen data were queried. This revealed that cell lines and primary cultures of the mesenchymal subtype are particularly sensitive to the one of a kind drug elesclomol. We found that elesclomol perturbs mitochondrial functioning, and that this specifically affects mesenchymal PDAC cells. These effects were independent of reactive oxygen species levels, previously reported as the effector of treatment with elesclomol. Concluding, we have identified and functionally addressed the mechanisms responsible for poor-prognosis PDAC and propose that perturbation of mitochondrial function is a promising therapeutic strategy to improve outcome of those PDAC patients that are in most dire need of improved therapies.

doi: 10.21037/apc.2018.AB023

Cite this abstract as: Veenstra V, Dijk F, Soer E, Zhao L, Halfwerk J, Hooijer G, Donner N, Damhofer H, Marzano M, Steins A, Waasdorp C, Busch O, Besselink M, Tol J, Welling L, van Rijssen LB, Wilmink H, van Laarhoven H, Medema JP, Vermeulen L, van Hooff S, Koster J, Verheij J, van de Vijver M, Wang X, Bijlsma M. Identification and targeting of a poor-prognosis subgroup of pancreatic cancer. Ann Pancreat Cancer 2018;1:AB023. doi: 10.21037/apc.2018.AB023