



Drug resistance in pancreatic cancer: New player caught in act



Gabriele Capurso^a, Claudio Sette^{b,c,*}

^a PancreatoBiliary Endoscopy and EUS Division, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute IRCCS, Milan, Italy

^b Institute of Human Anatomy and Cell Biology, Università Cattolica del Sacro Cuore, Rome, Italy

^c IRCCS Fondazione Santa Lucia, Rome, Italy

Most human cancers display high levels of heterogeneity, a feature that often impacts negatively on the response to treatments. Indeed, while radio and/or chemotherapy initially cause remission of the tumor mass, residual neoplastic cells that are capable to withstand treatments can often give rise to tumor relapse, which typically presents with more aggressive and sometimes lethal phenotypes. In this regard, pancreatic ductal adenocarcinoma (PDAC) represents a remarkable example. PDAC is a devastating disease with a poor clinical outcome, which is mainly due to late diagnosis, resistance to chemotherapy and radiation and lack of specific targeted therapies [1,2]. As a consequence, most patients are diagnosed at an advanced stage and display an expected 5-year survival rate of ~5% [1,2]. Based on these features, PDAC is envisioned to represent the second cause of cancer-related death by 2020 [1,2]. These facts highlight the urgent need for identification of novel therapeutic targets and/or early biomarkers of the disease that may help significantly improve clinical management of the disease and life expectancy of patients.

The poor sensitivity of PDAC cells to chemotherapy is related to many factors, including reduced bioavailability of the drugs in tumor cells, abnormalities in drugs metabolism and rapid acquisition of the capacity to activate alternative compensatory pathways [3]. Furthermore, the tumor microenvironment, including the surrounding stromal compartment and immune cells, contributes to the low response of PDAC cells to treatments and represents an additional problem in the design of novel therapies for this disease. The current standard adjuvant treatment in the advanced PDAC setting is still represented by gemcitabine used as single agent [4]. New therapeutic strategies are now available and include treatments with intensified regimens, such as the multidrug FOLFIRINOX or the combination of gemcitabine with nab-paclitaxel, alone or with further addition of cisplatin and capecitabine [5]. However, although these new regimens have led to some small improvements in survival, life expectancy of advanced PDAC patients remains very poor [2].

In the present issue of *Ebiomedicine*, Patzak and colleagues examined the role of Cytosolic 5'-nucleotidase 1A (NT5C1A), a recently described gemcitabine-inactivating enzyme that dephosphorylate gemcitabine monophosphate (dFdCMP), in the response of PDAC cells to

chemotherapy [6]. The study shows that NT5C1A is strongly expressed in the majority of tumor cells from resected PDAC patients, but not by the surrounding stromal cells. NT5C1A rapidly metabolizes gemcitabine to inactive derivatives in PDAC cells, thus preventing its genotoxic action. Moreover, although NT5C1A expression levels were not shown to predict survival, by using both PDAC cell lines and mouse models, the authors clearly demonstrated that NT5C1A expression is positively associated with gemcitabine resistance. In line with its gemcitabine-specific mechanism of action, NT5C1A expression does not affect the cytotoxicity of other drugs, such as Nab-Paclitaxel [7], which acts through a different molecular pathway and synergizes with gemcitabine [5,7].

The lack of association between NT5C1A expression in resected samples and clinical outcome observed by the authors might be due to the fact that not all patients of their cohort underwent homogeneous post-operative adjuvant treatment with gemcitabine. Furthermore, as no details are provided regarding other variables affecting prognosis of resected patients, such as their TNM stage, resection margins, age and comorbidities [6], the lack of association with overall survival might not be unexpected. Future studies should focus on the association with recurrence-free survival or disease-specific survival in homogeneous cohorts of resected patients who underwent adjuvant treatment with gemcitabine and examine all other clinically relevant covariates. Given the gemcitabine-specific mechanism of action of NT5C1A, such studies may contribute to address patients exhibiting high levels of this enzyme toward other regimens comprising different genotoxic agents, such as FOLFIRINOX or more innovative targeted therapies, thus helping to better “personalize” the therapeutic choice for PDAC patients.

An intriguing aspect of this study is represented by the possible positive effect of the expression of NT5C1A in the stromal compartment, which apparently lead to improved sensitivity toward gemcitabine in the *in vitro* experiments [6]. While the expression of stromal NT5C1A in the human resected samples did not correlate with overall survival, it will be interesting to evaluate whether there is a ratio between the epithelial and the stromal expression of the enzyme that might be measured and associated with sensitivity to the drug. Another interesting observation made by the authors is the repression of NT5C1A expression in PDAC cell lines, even when they were established *ex vivo* from NT5C1A-expressing tumors [6]. While this observation can contribute to explain the discrepancy between gemcitabine sensitivity of PDAC cells *in vitro* and resistance of tumors to the drug *in vivo*, it may also

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* Corresponding author at: Institute of Human Anatomy and Cell Biology, Università Cattolica del Sacro Cuore, Rome, Italy.

E-mail address: claudio.sette@unicatt.it (C. Sette).

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more generally suggest that PDAC cells rapidly acquire a different transcriptome signature *in vitro*. This feature would be in line with the documented plasticity of PDAC cells [8], further stressing the need to compare *in vitro* and *in vivo* mechanisms when studying PDAC biology and to investigate molecular features of PDAC longitudinally during treatments.

In summary, this study sheds light on a novel key player, and on its mechanism of action, involved in the resistance of PDAC cells to gemcitabine, the current standard of care for this disease [4]. Being an enzyme, NT5C1A is conceivably “druggable”. Thus, this study offers a window of opportunity to counteract the deleterious resistance to chemotherapy that makes of PDAC one of the most untreatable human cancers to date.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74:2913–21.
- [2] Ducreux M, Seufferlein T, Van Laethem JL, Laurent-Puig P, Smolenschi C, Malka D, et al. Systemic treatment of pancreatic cancer revisited. *Semin Oncol* 2018 [pii: S0093-7754(18)30266-5].
- [3] Ghaneh P, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer. *Gut* 2007;56:1134–52.
- [4] Javed MA, Beyer G, Le N, Vinci A, Wong H, Palmer D, et al. Impact of intensified chemotherapy in metastatic pancreatic ductal adenocarcinoma (PDAC) in clinical routine in Europe. *Pancreatology* 2019;19:97–104.
- [5] Reni M, Zanoni S, Peretti U, Chiaravalli M, Barone D, Pircher C, et al. Nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in metastatic pancreatic adenocarcinoma (PACT-19): a randomised phase 2 trial. *Lancet Gastroenterol Hepatol* 2018;3:691–7.
- [6] Patzak M.S., Kari, V., Patil, S., Hamdan, F.H., Goetze, R.G., Brunner, M., et al. Cytosolic 5'-nucleotidase 1A is overexpressed in pancreatic cancer and mediates gemcitabine resistance by reducing intracellular gemcitabine metabolites. *EBioMedicine*. [This issue].
- [7] Passacantilli I, Panzeri V, Terracciano F, Delle Fave G, Sette C, Capurso G. Co-treatment with gemcitabine and nab-paclitaxel exerts additive effects on pancreatic cancer cell death. *Oncol Rep* 2018;39:1984–90.
- [8] Hermann PC, Sainz Jr B. Pancreatic cancer stem cells: a state or an entity? *Semin Cancer Biol* 2018;53:223–31.