Exploring a new function for cytidine deaminase in pancreatic cancer metabolism

Audrey Frances¹, Marion Gayral¹, Estelle Saland², Delphine Pagan¹, Lucille Stuani², Hubert Lulka¹, Alix Vignolle-Vidoni¹, Naima Hanoun¹, Anthony Lemarié³, Frédéric Lopez⁴, Sophie Vasseur⁶, Jean-Sébastien Hoffmann⁷, Marlène Dufresné¹, Jérôme Torrisani¹, Louis Buscail¹, Jean-Emmanuel Sarry² and Pierre Cordelier¹

Affiliations: Centre de Recherche en Cancérologie de Toulouse (INSERM U1037) team 10¹, 11¹, 18², 27 and proteomic platform⁴. Service de Gastro entérologie et de Nutrition, CHU Toulouse⁵. Centre de Recherche en Cancérologie de Marseille, Team « Cellular stress »⁶.

Cytidine deaminase (CDA) is a cytoplasmic enzyme, which known function is to convert cytidines and deoxycytidines into uridines and deoxyuridines and therefore to maintain the pyrimidine pool equilibrium via the pyrimidine salvage pathway. Notably, we found that CDA is over-expressed in pancreatic adenocarcinoma (PDAC) and is involved in resistance to treatment as CDA degrades chemotherapies like gemcitabine. We identified that CDA is also an independent factor of poor prognosis, which emphasis its importance in pancreatic carcinogenesis. Functional studies recently highlighted that CDA may have a new and unknown function as a regulator of cancer cell metabolism. Indeed, silencing CDA in experimental models of PDAC using shRNA affects the cells in such a way they drastically die from apoptosis, while preventing tumor growth in vivo. We found that this phenotype is mitochondria-related as transcriptomic, proteomic and metabolomic studies performed in cells invalidated for CDA pinpointed this organelle. CDA-depleted cancer cells suffer from replicative stress, but also from metabolic, energetic and oxidative stresses. Pancreatic cancer cells invalidated for CDA shift to glycolysis for energy production, show redox imbalance with increased rates of lactate and NAD+, down-regulation of key Krebs cycle enzymes expression and massive decrease in mitochondrial respiratory capacity and coupling. These alterations in DNA and energy metabolism are driving molecular traits as they occur very rapidly following CDA invalidation and precede apoptosis. Finally, our results suggest that this unforeseen role of CDA is independent of its known catalytic activity. Taken together, this study demonstrates for the first time that CDA is essential to PDAC carcinogenesis with a new function in cellular metabolism. Thus, CDA targeting may afford new opportunities for the management of PDAC, a disease with no cure.