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Short Communication

Histone Deacetylase Inhibition Restores Expression of Hypoxia-inducible Protein NDRG1 in Pancreatic Cancer

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Abstract

Pancreatic ductal adenocarcinoma, the most common subtype of human pancreatic cancer, affects both men and women and is highly aggressive, with a five-year survival rate of only about 5%. N-myc downstream-regulated gene-1 (NDRG1) is a hypoxia-inducible and differentiation-related protein and candidate biomarker in pancreatic cancer. As NDRG1 expression is lost in high-grade tumors, the effects of the differentiating histone deacetylase inhibitor trichostatin A (TSA) were examined in human pancreatic cancer cell lines representing different tumor grades. Panc-1 (poorly differentiated) and Capan-1 (moderately- to well-differentiated) cells were treated with TSA. Effects were assessed *in vitro* by microscopic analysis, colorimetric assays, cell counts, real-time polymerase chain reaction, and western blotting. Treatment of Panc-1 cells over four days with 0.5 µM TSA restored cellular differentiation, inhibited proliferation, and enhanced $p21^{Cip1}$ protein expression. TSA upregulated NDRG1 mRNA and protein levels under normoxia from day one and by six-fold by day four ($p<0.01$ at all time points). After 24 h under hypoxia, NDRG1 expression was further increased in differentiated cells ($p<0.01$). Favorable changes were identified in the expression of other hypoxia-regulated genes. HDAC inhibitors offer a potential novel epi-drug approach for pancreatic cancer by reversing the undifferentiated phenotype and allowing patients to overcome resistance and better respond to conventional cytotoxic treatments. Restoration of NDRG1 expression may represent a biomarker of malignant pancreatic tumors undergoing re-differentiation and redirecting toward a lower tumor grade. The use of the human ductal Panc-1 cell line treated with TSA represents a useful tool to study cellular differentiation through epigenetic mechanisms.

Biography

Céline Tiffon has completed her PhD in Tumor Biology from the University of Bern in 2007 and postdoctoral studies from the United Kingdom and France. She currently works as a scientific officer at the French National Cancer Institute.

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