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HISTONE DEACETYLASE INHIBITION RESTORES EXPRESSION OF HYPOXIA-INDUCIBLE PROTEIN NDRG1 IN PANCREATIC CANCER

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Pancreatic ductal adenocarcinoma 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 p21Cip1 protein expression. Trichostatin A upregulates 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 24hrs 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 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. Furthermore, lifestyle and environmental factors especially nutrition and chemical exposure, induce effects on human health from gestation and beyond via epigenetic modifications.

BIOGRAPHY

Céline Tiffon obtained her PhD in Tumor Biology from the University of Bern, Switzerland and working on the subject of liver and pancreatic cancers. She carried out Postdoctoral Research at the Cancer Science Division of the University of Southampton, United Kingdom. Her research interests focused on the molecular mechanisms triggered by two licensed HDAC inhibitors in cutaneous T-cell lymphoma with a particular emphasis on cytokine expression. She continued with Postdoctoral Research at the University of Burgundy, France and working on the topic of endocrine disruptors. Currently, she is working as a Scientific Officer at the National Cancer Institute, France.

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