Study: Histone Deacetylase Inhibitors – A Potential Epidrug for Pancreatic Cancer by Céline Tiffon from Oasis Publishers

New York, NY, December 29, 2018 --(PR.com)-- Pancreatic cancer (scientifically known as Pancreatic ductal adenocarcinoma) is the most common subtype of human pancreatic cancer. Pancreatic tumors are generally hypoxic due to their avascular morphology.

Hypoxia is a condition in which the body or a part of the body is deprived of adequate oxygen supply at the tissue level. Hypoxia can contribute significantly to the aggressive behavior of cancerous cells, through hypoxia-induced expression of proangiogenic factors such as vascular endothelial growth factor (VEGF) and inflammatory cytokine interleukin-8.

N-myc downstream-regulated gene-1 (NDRG1) is a hypoxia-inducible and differentiation-related protein and candidate biomarker in pancreatic cancer. NDRG1 expression is lost in high-grade tumors. NDRG1 is a protein induced by cellular stress through HIF1-dependent and independent mechanisms, and by cellular differentiation.

For the first time, through this research study “Histone Deacetylase Inhibition Restores Expression of Hypoxia-Inducible Protein NDRG1 in Pancreatic Cancer,” Céline Tiffon confirms that the restoration of cellular differentiation is coupled to cell growth inhibition in-vitro by histone or non-histone protein acetylation, which increased NDRG1 expression, and restored responsiveness to hypoxia.

Cancer is a genetic disease characterized by inherited or sporadic mutations in tissue homeostasis, cell cycle control, and apoptosis genes. Cancer is also an epigenetic disease, because of the presence of genetic alterations in chromatin-remodelling enzymes or their aberrant activations that deregulates the epigenetic landscape. Céline Tiffon concludes that altered pancreatic cancer differentiation may result from epigenetic aberrations because cellular differentiation is also regulated by epigenetic mechanisms.

Recent studies have shown that epigenetics-based therapies (epidrugs) have great potential in the treatment of pancreatic cancer. The combination of the histone deacetylase (HDAC) inhibitor suberanilo hydroxamic acid (vorinostat) with chemotherapeutics and/or radiation have shown much positive results. In recent years, Trichostatin A (TSA), a hydroxamic acid, is another organic compound that is mainly used as a reference compound in HDAC inhibitor and cancer research.

In this research study, Céline Tiffon examines the effects of the differentiating histone deacetylase inhibitor Trichostatin A (TSA) in human pancreatic cancer cell lines, representing different tumor grades.

When conducting this study, TSA, a potent and reversible class I and II HDAC inhibitor, was applied to poorly differentiated PANC-1 cells. Both PANC-1 (poorly differentiated) and Capan-1 (moderately to well-differentiated) cells were treated with TSA. The morphological and gene expression changes were assessed in vitro, by microscopic analysis, colorimetric assays, cell counts, real-time polymerase chain reaction, and Western blotting. To compare with real-time PCR data, the mean cycle threshold values were analysed by one-way analysis of variance (ANOVA) followed by Dunnett multiple comparisons test.
using SPSS.

From this study, it was observed that the poorly differentiated PANC-1 cell line treated with TSA represents a good model of cellular differentiation. Céline Tiffon finds this particularly useful in the investigation of the relationship between the cell cycle, differentiation, and epigenetic mechanisms.

The study also confirms that NDRG1 upregulation by hypoxia was dependent on cellular differentiation through a series of experiments. The results of the study shows that in the absence of TSA, cells reverted to their original undifferentiated phenotype. Differentiated PANC-1 cells had higher NDRG1 protein levels, which were further increased by hypoxia along with induction of its phosphorylated form. In the absence of TSA, NDRG1 expression was substantially decreased, reverting back to control levels and losing its phosphorylated form. Hence, Céline Tiffon concludes that the upregulation of NDRG1 and its restored responsiveness to hypoxia appear to be related to the cellular differentiation state, whose restoration was mediated by TSA.

The study also finds that the transfection of PANC-1 cells with NDRG1 did not result in cellular differentiation. The study confirms TSA–induced histone acetylation in PANC-1 cells and differentiation by increased expression of pancreatic differentiation markers. Furthermore, NDRG1 expression was restored in TSA-differentiated pancreatic cancer cells, implying epigenetic regulatory mechanisms.

From this study, Céline Tiffon concludes that the use of the human ductal PANC-1 cell line, treated with TSA, represents a useful tool to study cellular differentiation through epigenetic mechanisms. Restoration of NDRG1 expression may represent a biomarker of malignant pancreatic tumors undergoing re-differentiation and redirecting toward a lower tumor grade. Hence, NDRG1 has been proposed as a tumor biomarker due to its high expression in malignant tissues. In pancreatic cancer, NDRG1 expression is related to the differentiation state of the tumor. Since hypoxia is a general feature of these tumors, NDRG1 has been hypothesized as a novel indicator of pancreatic malignancy.

Céline Tiffon observes that the poorly-differentiated phenotype and cell behavior associated with changes in hypoxia-regulated gene expression, were reversed by the differentiation of pancreatic cancer cells by the HDAC inhibitor TSA.

Hence, it can be concluded that histone deacetylase inhibitors offer a potential novel epidrug approach for pancreatic cancer, by reversing the undifferentiated phenotype and allowing patients overcome resistance, thereby responding better to conventional cytotoxic treatments.
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