

A Potential Window onto Early Pancreatic Cancer Development

Evidence of Cancer Stem Cell Growth after Exposure to Cadmium Chloride *in Vitro*

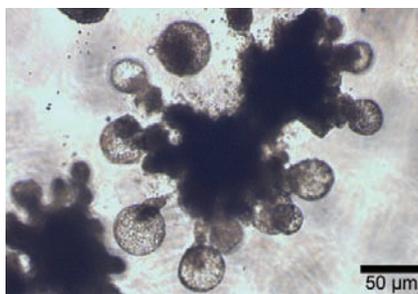
Cancer stem cells are a small subset of tumor cells that are postulated to underlie tumor initiation, growth, and metastasis. Research suggests that these cells may have begun as normal stem cells that underwent mutation or other changes that derail cellular programming and alter growth control pathways. Investigating a previously established link between cadmium exposure and pancreatic cancer, a new study finds that normal human pancreatic cells chronically exposed *in vitro* to a low level of cadmium chloride acquired cancer cell characteristics and generated what appeared to be cancer stem cells [*EHP* 120(9):1265–1271; Qu et al.].

Normal human pancreatic ductal epithelial cells were cultured with or without 1.0 μM of cadmium chloride for 29 weeks. The treated cells were sampled periodically and assessed for cancer cell characteristics, including increased secretion of matrix metalloproteinase-9 (MMP-9), increased invasiveness, increased anchorage-independent growth (i.e., ability to grow while floating freely in medium), and altered colony formation. Various subpopulations of pancreatic cancer stem cells have been shown to overexpress the genes *CD44*, *CXCR4*, *OCT4*, and *S100P*, which are involved

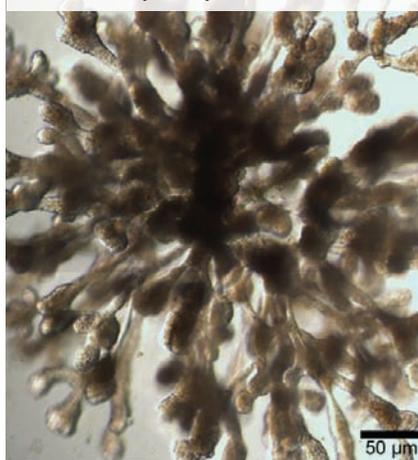
in various aspects of cancer growth and spread. Samples therefore were also analyzed for expression of these genes and their associated proteins. The results showed that, compared with control cells, those cells chronically exposed to cadmium (which the authors dubbed CCE cells) demonstrated characteristics typical of cancer cells.

Stem cells and cancer stem cells, when studied *in vitro*, often form free-floating spheres of cells for reasons not completely understood. The investigators isolated and further cultured spheres generated by control and CCE cells, then submitted them to the same analyses as earlier samples. Spheres derived from CCE cell cultures exhibited cancer cell characteristics and were more numerous and larger than control spheres. They also exhibited increased transcription and expression of *OCT4*, *CD44*, and *CXCR4*. In gel cultures CCE spheres grew aggressively and formed more intricate structures than control spheres; microscopically, these structures appeared malignant, with poorly differentiated cells of many shapes and sizes.

The study shows that *in vitro* exposure of normal human pancreatic cells to a nontoxic level of cadmium chloride can promote the development of cancer characteristics, thus strengthening the evidence for cadmium as a potential cause of pancreatic cancer in humans. Additionally, the study may help investigators define the very early stages of pancreatic cancer, a major advantage for a disease that typically is diagnosed only after it has metastasized.



Spheres derived from CCE cells (below) rapidly outpaced those derived from control cells (above).



Potential Mechanism for PM_{10} Effects on Birth Outcomes

In Utero Exposure Linked to Mitochondrial DNA Damage

A number of studies have associated exposure to particulate matter (PM) with adverse birth outcomes such as low birth weight. Much is still unknown, however, about the mechanisms that might induce these outcomes. Researchers now report an association between abnormal placental mitochondrial DNA (mtDNA) content—a marker indicative of mitochondrial dysfunction, which may be related to the development of some diseases—and fetal exposure to coarse PM (PM_{10}) during the last trimester of pregnancy [*EHP* 120(9):1346–1352; Janssen et al.]. Although similar to nuclear DNA in composition and function, mtDNA has fewer protective components and less-efficient repair mechanisms, rendering it particularly vulnerable to oxidative damage.

The 178 mothers in the study, who had given birth between 5 February 2010 and 3 April 2011, were part of a larger prospective initiative called ENVIRONAGE. The women were classified by age, ethnicity, smoking status, place of residence, and other demographics. Regional background levels of PM_{10} were calculated for each mother's home address using satellite-based data, and the distance from each home to a major road was geocoded. Mothers' residential PM_{10}

exposures were calculated for the following time periods: 0–7 days before delivery, each trimester of pregnancy (1–13 weeks, 14–28 weeks, and 29 weeks to delivery), and the last month of pregnancy.

Immediately after each delivery the research team collected the placenta and a sample of umbilical cord blood, which were assessed for mtDNA content. They then analyzed the relationship between mtDNA content and PM_{10} exposure as well as residential distance to major roads. They found that a 10- $\mu\text{g}/\text{m}^3$ increase in PM_{10} exposure was associated with a 10.1% reduction in placental mtDNA content in the last week of pregnancy, a 16.1% reduction in the last month of pregnancy, and a 17.4% reduction in the third trimester. Living closer to a major road—an indication of higher exposure to air pollution from traffic—was also associated with lower placental mtDNA content.

No statistically significant association was observed between cord blood mtDNA content and PM_{10} exposure during any defined time period. The researchers speculate this could reflect tissue-level differences in exposure or effects.

The study is limited by the researchers' inability to exclude the possibility of residual confounding or misclassification, but the findings suggest that prenatal PM_{10} exposure during the last trimester of pregnancy may cause mitochondrial dysfunction, indicating a possible window of susceptibility. Future research is needed to understand the potential health effects of decreased mtDNA content.

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