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Arsenic-induced acquisition of cancer stem cell-like characteristics during malignant transformation of human pancreatic epithelial ductal cells

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Emerging data indicates cancer stem cells (CSCs) may be critical to the carcinogenic process. Arsenic is linked with human pancreatic diseases potentially including cancer. Our prior work showed chronic cadmium exposure of a human pancreatic ductal epithelial (HPDE) cell line caused oncogenic transformation and formation of CSC-like cells. Thus, we studied if inorganic arsenic exposure could induce a similar tumor cell phenotype in HPDE cells and derivative non-adherent spheroids, which are enriched in stem cells (SCs or CSCs). HPDE cells were chronically exposed to sodium arsenite (2.5 μM) for up to 30 weeks and cancer cell characteristics were assessed including matrix metalloproteinase-9 (MMP-9) secretion, invasion, colony formation and expression of cancer relevant genes by RT-PCR or immunoblotting. Non-adherent spheroid formation was used to assess CSC-like production and tumor cell phenotype was assessed in such spheres. Chronic arsenic exposed (CAE) cells (30 weeks) showed morphological changes (loss of contact inhibition, atypical foci of cell mounding), increased MMP-9 secretion and colony formation, and marked over-expression of pancreatic cancer markers (*S100P*, *PSCA*), oncogenes (*C-myc, C-jun*), and the cell proliferation marker *Cyclin D1*, all typical for pancreatic cancer cells. CAE cells also became tolerant to arsenic (LC50 74.8±1.9 μM) compared to control (18.1±2.1 μM) which is common in chronic treatment. Compared to control, CAE cells produced 300% more non-adherent spheres, which contain an abundance of SCs or CSCs. CAE-derived spheres were more invasive, secreted more MMP-9, and over-expressed markers for pancreatic CSCs (*CXCR4, CD133, CD44*) and *S100P*. Single spheres from CAE cells rapidly produced aggressive, highly branched, poorly differentiated glandular-like structures in Matrigel. Thus, chronic arsenic causes acquisition of multiple tumor cell characteristics in HPDE cells. These data support the plausibility of arsenic as a human pancreatic carcinogen.

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AChE inhibition: One dominant factor for swimming behavior changes of *Daphnia magna* under DDVP exposure

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The key enzyme that hydrolyzes the neurotransmitter acetylcholine in cholinergic synapses of both vertebrates and invertebrates, acetylcholinesterase (AChE) is strongly inhibited by organophosphates. AChE inhibition may induce the decrease of swimming ability. According to previous research, swimming behavior of different aquatic organisms could be affected by different chemicals, and there is a shortage of research on direct correlation analysis between swimming behavior and biochemical indicators. Therefore, swimming behavior and whole-body AChE activity of *Daphnia magna* under dichlorvos (DDVP) exposure were identified in order to clarify the relationship between behavioral responses and AChE inhibition in this study. In the beginning, AChE activity was similar in all treatments with the control. During all exposures, the tendency of AChE activity inhibition was the same as the behavioral responses of *D. magna*. The AChE activity of individuals without movement would decrease to about zero in several minutes. The correlation analysis between swimming behavior of *D. magna* and AChE activity showed that the stepwise behavioral response was mainly decided by AChE activity. All of these results suggested that the toxicity characteristics of DDVP as an inhibitor of AChE on the swimming behavior of organisms were the same, and the AChE activity inhibition could induce loss of the nerve conduction ability, causing hyperactivity, loss of coordination, convulsions, paralysis and other kinds of behavioral changes, which was illustrated by the stepwise behavioral responses under different environmental stresses.

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