Agent orange chemical, dioxin, attacks the mitochondria to cause cancer

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Researchers with the University of Pennsylvania School of Veterinary Medicine have demonstrated the process by which the cancer-causing chemical dioxin attacks the cellular machinery, disrupts normal cellular function and ultimately promotes tumor progression.

The team identified for the first time that mitochondria, the cellular sub-units that convert oxygen and nutrients into cellular fuel, are the target of tetrachlorodibenzodioxin, or TCDD. The study showed that TCDD induces mitochondria-to-nucleus stress signaling, which in turn induces the expression of cell nucleus genes associated with tumor promotion and metastasis.

The mechanism the research team has described is directly relevant to understanding incidences of breast and other cancers in human populations exposed to these chemicals. With a better understanding of this underlying cellular mechanism, researchers hope to improve their understanding of tumor growth and promotion.

"Now that we have identified this signaling mechanism we can look at ways to disrupt this complex chain of events," said Narayah Avadhani, chair of the Department of Animal Biology at Penn's School of Veterinary Medicine and the study's lead investigator. "Our ultimate goal is to block the propagation of this mitochondrial stress signaling and inhibit the expression of the proteins that combine to assist cancer growth."

A well-characterized mechanism of TCDD action occurs through activation of arylhydrocarbon receptors, AhR, by directly binding to the protein subunits. Activated AhR mediates the transcriptional activation of many genes including those involved in fatty acid metabolism, cell cycle regulation and immune response.

The present study, however, shows that TCDD starts the chain of events that promote tumor progression in vivo by directly targeting mitochondrial transcription and induction of mitochondrial stress signaling. A unique feature of this TCDD-induced signaling is that it does not involve the action of AhR but occurs through increased calcium levels in cells and activation of calcium responsive factors. A net result of signaling cascade is slowing down of cellular apoptosis, increased cell proliferation and tumor cell metastasis. Taken together, this study describes a novel mechanism of TCDD-induced tumor progression and emergence of metastatic cancer cells.

TCDD is the most toxic compound in the dioxin family. Formed as a by-product during waste incineration, paper, chemical and pesticide manufacturing, it was the toxic ingredient in Agent Orange and closed the Love Canal in Niagara Falls. The public health impact of dioxin, according to the Environmental Protection Agency, compares to that of the pesticide DDT.

The study appears online and in the Dec. 17 issue of the *Proceedings of the National Academy of Sciences* and was performed by Avadhani, Gopa Biswas, Satish Srinivasan and Hindupur Anandatheerthavarada of the Penn School of Veterinary Medicine.

Source: University of Pennsylvania