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UK study provides insight into cancer progression

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The University of Kentucky has announced that Dr. Daret St. Clair, the James Graham Brown Endowed Chair and professor of toxicology, has published the first comprehensive study that provides insight into the relationship between two types of suppressors in cancerous tumors. The results will enhance the understanding of transcriptional mechanisms in carcinogenesis.

The study was supported by a National Cancer Institute research grant and was recently published in *Cancer Research*. St. Clair and her team generated transgenic mice expressing a luciferase reporter gene under the control of human MnSOD promoter-enhancer elements and investigated the changes of MnSOD transcription using the 7,12-dimethylbenz(a)anthracene (DMBA)/12-O-tetradecanoylphorbol-l3-acetate (TPA) multistage skin carcinogenesis model.

Manganese superoxide dismutase (MnSOD) plays a critical role in the survival of aerobic life, and its abnormal expression has been implicated in carcinogenesis and tumor resistance to therapy. Despite extensive studies in MnSOD regulation and its role in cancer, when and how the alteration of MnSOD expression occurs during the process of tumor development in vivo are unknown.

The results show that MnSOD expression was suppressed at a very early stage but increased at late stages of skin carcinogenesis. The suppression and subsequent restoration of MnSOD expression were mediated by two transcription factors, Sp1 and p53.

Exposure to DMBA and TPA activated p53 and decreased MnSOD expression via p53-mediated suppression of Sp1 binding to the MnSOD promoter in normal appearing skin and benign papillomas. In squamous cell carcinomas, Sp1 binding increased due to loss of functional p53. St. Clair's team used chromatin immunoprecipitation, electrophoretic mobility shift assay, and both knockdown and overexpression of Sp1 and p53 to verify their roles in the expression of MnSOD at each stage of cancer development.

The results identify MnSOD as a p53-regulated gene that switches between early and advanced stages of cancer. These findings also provide strong support for the development of a means to reactivate p53 for the prevention of tumor progression.

"This study reports a novel genetic model of skin cancer that reveals the importance of a linkage between an antioxidant enzyme, MnSOD, which plays an important role in survival, and the progression of cancer," said St. Clair, who also serves as associate director for basic research at the UK Markey Cancer Center. "In the future, developing a means to inhibit the enzyme MnSOD in advanced cancer may prevent resistance to cancer therapy."

Provided by University of Kentucky

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