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Long-term exposure to cigarette smoke extract induces hypomethylation in the RUNX3, H19, and IGF2 loci in cultured urothelial cells

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Cigarette smoking is the single most important epidemiological risk factor for bladder cancer but it is not known whether systemic exposure of bladder epithelial (urothelial) cells to soluble contents of the cigarette smoke is directly causative to bladder cancer. The cigarette smoke extract (CSE) causes DNA damages as well as hypermethylation of tumor suppressor gene promoters and is a transforming agent of airway epithelial cells following long-term treatment. We undertook this study to investigate if long-term CSE treatment of urothelial cells results in tumor suppressor hypermethylation and tumorigenic transformation. The RUNX3 tumor suppressor gene promoter was hypomethylated with significant increases of the completely unmethylated haplotype after long-term CSE treatment of an immortalized urothelial cell line UROtsa, whereas RUNX3 promoter hypermethylation was reported for bladder cancers of smokers. Long-term CSE-induced hypomethylation was also observed for the H19-IGF2 locus. Transcription of the DNA methyltransferases DNMT1 and DNMT3B was greatly reduced by the long-term CSE treatment, potentially serving as the mechanism for the hypomethylation phenotype. Several hypermethylated loci in airway epithelial cells following long-term CSE treatment were unaffected by the long-term CSE treatment of the urothelial cells, which were also unable to grow in soft-agar, i.e., remain untransformed. In conclusion, urothelial cells directly exposed to CSE, simulating systemic exposure to the soluble contents of cigarette smoke, have a hypomethylated phenotype in genes that show hypermethylation in bladder cancers. Efforts directed at developing epigenetic tests for early detection and diagnosis of bladder cancer should take this phenomenon under careful consideration.

Biography

Karl X. Chai received his Ph.D. in Biochemistry and Molecular Biology in 1992 from the Medical University of South Carolina (MUSC, Charleston) and continued on to postdoctoral studies in molecular genetics of hypertension in MUSC. He is now an Associate Professor of Biomedical Sciences in the University of Central Florida, College of Medicine, with active research in membrane receptor cell signaling and epithelial cancers. Dr. Chai has published more than 40 papers and book chapters and is serving as an Academic Editor for PLoS ONE.

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