OMICS Group Conferences
Accelerating Scientific Discovery
2nd International Summit on Toxicology
October 7-9, 2013 Hampton Inn Tropicana, Las Vegas, USA

Chromosome instability induced by hexavalent chromium is a result of impaired DNA repair and mitotic disruption

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Abstract

Hexavalent chromium (Cr(VI)) is a human lung carcinogen with potential worldwide exposure. One leading hypothesis for the carcinogenicity of hexavalent chromium (Cr(VI)) suggests that Cr(VI) causes a DNA double strand break (DSB) repair deficiency leading to mitotic disruption, chromosome instability and ultimately neoplastic transformation. To determine if cells could induce these phenotypes and induce cells that survive with them as permanent phenotypic changes, we exposed human lung cells to lead chromate for three sequential 24 h periods, each separated by about a month. After each treatment, cells were seeded at colony forming density, cloned, expanded and retreated. Each generation of clones was tested for chromosome instability, DNA repair capacity and ability to grow in soft agar. We found that after the first treatment, lead chromate-treated cells exhibited a normal chromosome complement with a few clones showing a repair deficient phenotype. The second exposure revealed more than half of the clones acquired an abnormal karyotype with both numerical and structural alterations and more with deficient DNA DSB repair. The third treatment resulted in more abnormal clones, previously abnormal clones acquiring additional abnormalities, and most clones were repair deficient. Further investigation revealed that some clones exhibited centrosome amplification, abnormal mitotic figures, and aberrant Mad1 kinetochore localization, suggesting these clones have underlying permanent defects in mitotic regulation. Additionally, several were unable to form Rad51 foci in response to radiation, suggesting a defect in the homologous recombination repair pathway. Finally, clones from the third generation were able to form colonies in soft agar suggesting neoplastic transformation. This work was supported by NIEHS grant ES016893 (J.P.W.) and the Maine Center for Toxicology and Environmental Health.

Biography

Sandra Wise completed her Ph.D. in Biochemistry and Molecular Biology in 2013 from the University of Maine. She is the director of the cytogenetics and genomic instability program in the Wise Laboratory of Environmental and Genetic Toxicology at the University of Southern Maine. She has authored or co-authored more than 56 papers in reputed journals and book chapters.