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Chronic exposure to particulate hexavalent chromium alters cdc20 protein localization, interactions and expression

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Hexavalent chromium [Cr(VI)] compounds are well established human lung carcinogens, but it is unknown how they cause lung cancer in humans. Recent data indicate that Cr(VI) induces chromosome instability in human lung cells, and genomic instability is considered a leading mechanism to explain chromate carcinogenesis. The spindle assembly checkpoint (SAC) is a critical regulator of the metaphase-to-anaphase transition and ensures genome stability by preventing chromosomal missaggregation events. Bypass of the SAC can lead to genomic instability, manifested as aneuploidy, which eventually leads to tumor formation and cancer. Recent studies in our laboratory demonstrated that chronic exposure to zinc chromate induces SAC bypass in a concentration- and time-dependent manner in human lung fibroblasts. To further study these events, we focused on the cell division cycle 20 (Cdc20) protein, a downstream effector protein in the SAC. Cdc20 has not been studied after Cr(VI) exposure, but other studies show that experimentally induced alterations of Cdc20 localization to kinetochores or of Cdc20 protein expression leads to aneuploidy. Here, we investigated the effects of zinc chromate, a particulate Cr(VI) compound, on Cdc20 localization, protein expression and interactions. Our data show Cdc20 is a target for particulate Cr(VI). Chronic zinc chromate exposure altered Cdc20 kinetochore localization and reduced the interaction of phosphorylated Cdc20 with Mad2, which may underlay zinc chromate-induced SAC bypass.

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DNA structure-induced genetic instability in mammals

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Naturally occurring repetitive DNA sequences can adopt alternatively structured DNA (i.e., non-B DNA), and often map near chromosomal breakpoint "hotspots", implicating non-B DNA in translocation-related cancer etiology. We have found that two types of non-B DNA structures, H-DNA and Z-DNA, are intrinsically mutagenic in mammals. For example, an endogenous H-DNA-forming sequence from the human *c-MYC* promoter and a model Z-DNA-forming CpG repeat induced mutations in mammalian cells, largely in the form of deletions resulting from DNA double-strand breaks. Characterization of the mutants revealed microhomologies at the breakpoints, consistent with a microhomology-mediated end-joining repair of the double-strand breaks. We have constructed transgenic mutation-reporter mice containing these human H-DNA-forming and Z-DNA-forming sequences, to determine their effects on genomic instability in a chromosomal context in animals. We found that both H-DNA- and Z-DNA-forming sequences stimulated genetic instability in mice, suggesting that these non-B DNA-forming sequences represent endogenous sources of genetic instability. These results demonstrate that naturally occurring DNA sequences are mutagenic in mammalian cells and may contribute to disease etiology and evolution. Our current studies are designed to determine the roles of mammalian helicases, polymerases, and DNA repair enzymes in an effort to elucidate the mechanism(s) involved in non-B DNA-induced genetic instability.

Biography

Karen M. Vasquez's research efforts are focused within an overall theme of genome instability, DNA damage, and mechanisms of repair. She has worked in these fields for more than 20 years, and has published more than 75 peer-reviewed papers in these areas. She serves on the editorial boards for *Molecular Carcinogenesis, Mutation Research, DNA Repair, Environmental and Molecular Mutagenesis,New Journal of Science, andtheJournal of Biological Chemistry*. She is a member of the Board of Scientific Counselors for the NIEHS, and has served on numerous review committees for NIH and other funding organizations both nationally and internationally.