

## Inhibition of chromatin assembly by major cigarette smoke component acrolein

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Acrolein is a  $\alpha,\beta$ -unsaturated aldehyde, which is abundant in cigarette smoke and coking fumes. It is a potential major carcinogen of smoking-related lung cancer, yet the underlying mechanisms are not fully understood. We find that acrolein forms adducts with histones and acrolein-modified histones are resistant to acetylation. Cellular fractionation analyses further reveal that exposure of cells to acrolein specifically inhibits acetylations of N-terminal tails of cytosolic histones H3 and H4, modifications that are important for nuclear import and chromatin assembly. Accordingly, the association of H3/H4 with histone chaperone ASF1B and translocator protein importin 4 is disrupted and the nuclear import of H3 is inhibited in cells following acrolein exposure. Moreover, ChIP (chromatin immunoprecipitation) assays exhibit that the levels of histone H3 are drastically decreased at the majority of genomic loci tested and H3 amount in chromatin fragments is depleted by acrolein exposure. These data indicate that acrolein exposure leads to compromise of the chromatin assembly. Interestingly, *in vitro* plasmid supercoiling assays reveal that treatment of either histones or ASF1B with acrolein has no effect on formation of plasmid supercoiling, while exposure of histones to acrolein prior to histone acetylation leads to the inhibition of RSF (Remodeling and Spacing Factor) chromatin assembly, which requires acetylated histones for efficient assembly. The results suggest that acrolein-protein adduct formation itself does not directly interfere with nucleosome assembly. We propose that acrolein compromises chromatin assembly via reacting with histone lysine residues at the sites critical for chromatin assembly and prevents these sites from physiological modifications.

### Biography

Chunyuan Jin has completed his PhD from Tokyo University and Postdoctoral studies with Dr. Gary Felsenfeld at NIH. He is an Assistant Professor of Environmental Medicine at NYU School of Medicine. He has published more than 25 papers in reputed journals such as *Nature Genetics* and *Genes & Development*.

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