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Mutagenesis of p53 by reactive PAH and ROS

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 \mathbf{P} AHs (polycyclic aromatic hydrocarbons) are products combustion found in tobacco smoke and other lung cancer carcinogens, but they must be metabolically converted into DNA-reactive metabolites. P4501A1/P4501B1 plus epoxide hydrolase activate PAH to (\pm) anti-benzo[a]pyrene diol epoxide ((\pm)-anti-BPDE) which causes bulky DNA adducts. Alternatively, Aldo-Keto Reductases (AKRs) convert intermediate PAH trans-dihydrodiols to o-quinones, which cause DNA damage by generating reactive oxygen species (ROS). In lung cancer, the types or pattern of mutations in p53 are predominantly G to T transversions. The locations of these mutations form a distinct spectrum characterized by single point mutations in a number of hotspots located in the DNA binding domain. One route to the G to T transversions is via oxidative DNA damage. In a yeast model system for p53 mutagenesis, mutations observed with PAH o-quinones were predominately G to T transversions and those observed with (\pm)-anti-BPDE are predominately G to C transversions. The mutations observed with either PAH-treatment occurred randomly through the DNA-binding domain of p53. However, when the mutants were screened for dominance, the dominant mutations clustered at or near hotspots primarily at the protein—DNA interface, while the recessive mutations are scattered throughout the DNA binding domain, without resembling the spectra observed in cancer. We conclude that mutagenesis can drive the pattern of mutations, but that biological selection for dominant mutations drives the spectrum of mutations observed in p53 in lung cancer. Studies will be presented suggesting that AKRs protect from acute toxic effects of PAH at the expense of increasing the burden of oxidative stress on cells.

Biography

Dr. Jeffrey Field is professor of Pharmacology at the University of Pennsylvania School of Medicine. He earned a BA in biology from Columbia University and a PhD from the Albert Einstein College of Medicine with Dr. Jerard Hurwitz. During postdoctoral studies with Dr. Michael Wigler at the Cold Spring Harbor Laboratories, he isolated the first known Ras effector, the yeast adenylyl cyclase by developing the technology of epitope tagging. In his own lab at the University of Pennsylvania he established the central role of Pak kinases in Ras signaling and cell transformation. His current work centers on the role of the cytoskeleton in transformation and survival as well as mechanisms of smoking carcinogenesis.