Michael Fasullo et al., J Clin Toxicol 2015 2015, 5:3
http://dx.doi.org/10.4172/2161-0495.S1.015

OMICS International
conferenceseries.com
4th Global Summit on
Toxicology
August 24-26, 2015 Philadelphia, USA

Determining genetic susceptibility to food carcinogens using *Saccharomyces cerevisiae* (Budding Yeast)

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The human response to environmental carcinogens that require bioactivation is highly variable. Environment, lifestyle, and genetics are factors that influence bioactivation. Genetic factors include polymorphic P450 and DNA repair genes; however, epidemiological studies may lack significance due to inadequate patient numbers. We used budding yeast as a model organism to determine genetic susceptibility to food-associated carcinogens, including benzopyrene (BaP), aflatoxins (AFB1) and heterocyclic aromatic amines (HAAs). Budding yeast does not contain P450s that activate these compounds, so we introduced expression vectors that contain specific human P450 and NAT2 genes. In yeast, either CYP1A2 or CYP1A1 activates AFB1, while both CYP1A2 and NAT2 are required for activation of IQ. To measure genotoxic effects, we measured recombination and mutation frequencies, Rad51 foci, growth inhibition and DNA adducts, as in a previous publication concerning CYP1A2 polymorphisms. Here, we analyzed two CYP1A1 polymorphisms, T461N and I462V, correlated with breast and lung cancer. Although some studies have suggested that these polymorphisms confer reduced activity, both CYP1A1 polymorphisms are highly efficient at activating the AFB1and benzo[a]pyrene dihydrodiol (BaP-DHD). To determine resistance genes, we used a high throughput approach for screening the yeast deletion library expressing specific P450 genes. Screens for aflatoxin resistance identified checkpoint and RNA metabolism genes that are mutated in cancers. We are now performing screens to identify genes involved in resistance to 2-amino-3-methylimidazo [4,5-f] quinoline (IQ). Preliminary data identified both recombinational repair and DNA damage tolerance genes. Further high throughput analysis will be performed using other food carcinogens, including 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP) and 2-amino-3,8-dimethylimidazo [4,5-f] quinoxaline (MeIQx).

Biography

Michael Fasullo earned his PhD at Stanford University School of Medicine, Department of Biochemistry, and completed his Postdoctoral studies at Columbia University in the field of DNA repair and recombination. He has published over 25 papers in the field of DNA damage response, radiation repair and environmental toxicology. His current interest centers on high throughput screening for resistance to P450-activated carcinogens. He is currently an Associate Professor at the State University of New York Polytechnic Institute, Albany, NY.

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