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New methodology for phenotyping P450 polymorphisms and susceptibility to environmental toxicants using humanized budding yeast

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Human susceptibility to xenobiotics, such as pharmaceutical drugs and genotoxicants, is highly variable. Much variability is conferred by polymorphisms in P450 genes and in housekeeping genes involved in basic DNA repair and metabolism. Since humans express multiple P450 genes, it is often difficult to discern which variant P450 gene confers xenobiotic susceptibility. In addition, epidemiological studies are often limited due to small patient populations. As a model xenobiotic, the potent liver carcinogen aflatoxin B1 (AFB1) was used, which is metabolically activated by CYP1A2 and CYP3A4. Since budding yeast do not express P450 genes that can metabolically activate AFB1, it was possible to phenotype CYP1A2 variants and 2) profile the yeast genome for resistance to AFB1. AFB1 activation based on DNA adducts, Rad51 polymorphisms, cell survival, and genome instability was characterized. Considering that 31% of (*Saccharomyces cerevisiae*) budding yeast genes are very similar to human genes, it was hypothesized that genes that confer AFB1 resistance in budding yeast will also confer resistance in humans. CYP1A2 was introduced into the diploid yeast collection containing ~5000 single gene deletions. Using state-of-the-art next generation DNA sequencing, ~500 genes were identified that confer AFB1 resistance, including genes that function in DNA repair, checkpoint response and adaptation, DNA damage tolerance, and oxidative stress. Future studies will be focused on identifying whether down-regulation of these human orthologs also confer AFB1 sensitivity. The author and his co-workers are now profiling resistance to additional P450-activated xenobiotics and phenotyping CYP1A1 polymorphisms.

Biography

Michael Fasullo completed his PhD from the Department of Biochemistry at Stanford University School of Medicine and did a Postdoctoral fellowship at Columbia University. He has been a faculty member at Loyola University of Chicago and The Albany Medical College, and is currently located at the College of Nanoscale College and Engineering, State University of New York. He has published more than 25 papers in reputed journals and has served as a reviewer for Genetics, Nucleic Acids Research, Cell Cycle, and for several National Institutes of Health grant review panels.

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