Keynote Lecture II
p53 Biological Network: Inflammation and Cancer

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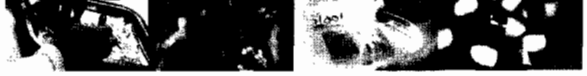
The outstanding scientific contributions of Curtis C Harris, MD, to the fields of molecular carcinogenesis and molecular epidemiology of human cancer, have placed him at the international forefront of cancer research. Dr Harris has received numerous honors throughout his distinguished career and according to *ISI Science Watch*, March 1998, is one of the 50 most cited biomedical scientists in the 1990's. Recent awards he has received include the Alton Ochsner Award relating Smoking and Health (American College of Physicians), Deichmann Award (International Union of Toxicology), Charles Heidelberger Award (International Society of Gastroenterological Carcinogenesis) and the Distinguished Service Medal, the highest honor of the US Public Health Service. Dr Harris has generated more than 400 journal publications, 100 book chapters, 10 books and 15 patents. He also serves as an Executive Editor for the journal, *Carcinogenesis*, and has held or currently holds elected offices in scholarly societies including the American Association of Cancer Research, the International Society of Differentiation, the Keystone Symposia on Molecular and Cellular Biology and the Aspen Cancer Conference. Dr Harris is the Chief of the Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD, and Clinical Professor, Division of Clinical Oncology, Georgetown University School of Medicine, Washington, DC.

Free radicals are ubiquitous in our body and are generated by normal physiological processes, including aerobic metabolism and inflammatory responses, to eliminate invading pathogenic microorganisms. Because free radicals can also inflict cellular damage, several defenses have evolved both to protect our cells from radicals—such as the p53 pathway and antioxidant scavengers and enzymes—and to repair DNA damage. Free radicals can cause an adaptive increase in certain of the protective base excision repair enzymes. Paradoxically, if the increase in enzymes is imbalanced, e.g., the DNA glycosylase is increased more than the apurinic endonuclease, frameshift mutations occur as a novel etiology of microsatellite instability. Understanding the relationship between chronic inflammation and cancer provides insights into the molecular mechanisms involved. In particular, we highlight the interaction between nitric oxide and p53 as a crucial pathway in inflammatory-mediated carcinogenesis.



While the postnatal environment can change rapidly between generations, the intrauterine environment remains relatively constant. The shape of the relationship between early life predictions and the mature environment indicates that different strategies may have to be adopted in different populations to address the ill-effects of a mismatch between developmental and later nutritional environment. In affluent populations, the focus might remain on promoting exercise and healthy diets in children, adolescents and adults. But in developing societies, significant health gains may result from strategies that improve the health of young girls and women of reproductive age, before and during pregnancy.

References and further reading

Gluckman PD and Hanson MA. Living with the past: evolution, development and patterns of disease. *Science* 305:1773-1776, 2004

Gluckman PD and Hanson MA. *The Fetal Matrix: Evolution, Development, and Disease.*, 1st edition. Cambridge University Press, Cambridge, 2005

Lillycrop KA, Phillips ES, Jackson AA, Hanson MA and Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *The Journal of Nutrition* 135:1382-6, 2005

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