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**Cellular Responses to Environmental DNA Damage**

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**Deadline for Applications: September 16, 1991**

# COVER LEGEND



Epidemiological studies reveal that diet is an important factor in human cancer development. About a half century ago, a Swedish scientist, Dr. E. M. P. Widmark, found malignant tumors in the mammary glands of mice with their dorsal skin painted with extracts of roasted horse muscle [*Nature (Lond.)*, 143: 984, 1939]. Fifty years later, Dr. Takashi Sugimura, pictured top right (National Cancer Center, Tokyo), who was not aware of Dr. Widmark's milestone work, was at home on a day when his wife was broiling dried fish. Smoke moved from the kitchen to his room. Suddenly an inspiration occurred to him that the smoke and the charred part of the fish might contain carcinogens. Because he was working on the mutagenicity/carcinogenicity of food additives using Ames's *Salmonella* system at that time, he asked his colleagues to work on this subject, but few showed interest. Dr. Minako Nagao, top left (National Cancer Center), however, explored this idea and actually observed mutagenicity in broiled fish and meat heated under ordinary cooking conditions. The first reports were given at a joint meeting of the AACR and Canadian Cancer Conference held in Toronto and at the Cold Spring Harbor Symposium entitled "Origins of Human Cancer," both in 1976 (*Origins of Human Cancer*, Book C, p. 1561, 1977). Nagao reported in an original paper that broiled meat was mutagenic to *Salmonella typhimurium* TA98 with metabolic activation (*Cancer Lett.*, 2: 221, 1977). She also found the mutagenicity of smoke (*Cancer Lett.*, 2: 335, 1977).

These findings triggered subsequent studies of a series of new environmental mutagens/carcinogens, the heterocyclic amines, which are produced by pyrolysis of amino acids and proteins and by heating

meat. Studies of the isolation of mutagenic principles, their organic structure determination, synthesis of compounds, their metabolism, their carcinogenicity in long-term tests using rodents, and risk analyses have been carried out systematically and successfully by various collaborators with Dr. Sugimura, who remains the leading researcher in the field. Here follows a brief introduction to collaborators and synopses of their research.

Takuo Kosuge, top center (University of Shizuoka), an organic chemist, investigated charred substances used in folk medicine and helped to isolate and synthesize mutagenic principles contained in various amino acid pyrolysates, Trp-P-1, Trp-P-2, Glu-P-1, and Glu-P-2 (*Proc. Jpn. Acad.*, 53: 58, 1977; *Proc. Jpn. Acad.*, 54B: 248, 1978). During a visit to Dr. Sugimura's laboratory in 1977, Dr. John Weisburger was apprised of these pioneering findings and suggested that these mutagens might be the then unknown genotoxic carcinogens for organs such as the colon or breast [E. Farber *et al.* (eds.). *Pathophysiology of Carcinogenesis in Digestive Organs*. Tokyo: University of Tokyo Press, pp. 1-20, 1977]. Dr. Neil Spingarn from Weisburger's laboratory spent time in Tokyo to develop isolation procedures with the Tokyo group. This led to the discovery of IQ, MeIQ, and MeIQx, in collaboration with Drs. Hiroshi Kasai and Susumu Nishimura (National Cancer Center) (*Chem. Lett.*, 1980: 1391, 1980; 1981: 485, 1981). In long-term studies on mice and rats, Drs. Hiroko Ohgaki, bottom center, and Shozo Takayama, bottom left (National Cancer Center), demonstrated the carcinogenicity of many heterocyclic amines [*Science (Washington DC)*, 213: 346, 1981; 233: 312, 1986; *Proceedings of the 21st International Symposium, Princess Takamatsu Cancer Research Fund*, 1991], including that of PhIP, recently discovered by Dr. James Felton's group (Livermore National Laboratory) [*Carcinogenesis (Lond.)*, 7: 1081, 1986]. Dr. Margaretha Jägerstad, bottom right (University of Lund), demonstrated that IQ and MeIQx are produced by heating creatinine, sugars, and amino acids and provided the evidence that the essential 2-amino-3-methylimidazo part of these mutagenic and heterocyclic amines stemmed from creatinine. This finding explained why these compounds form only during heating and cooking of food containing creatinine, such as commonly eaten meats or fishes (*Mutat. Res.*, 126: 239, 1984). The carcinogenicity of IQ in nonhuman primates was demonstrated by Dr. Richard H. Adamson's group (National Cancer Institute, Bethesda) (*Jpn. J. Cancer Res.*, 81: 10, 1990). Heterocyclic amines are a new class of environmental carcinogens to which humans are being continuously exposed.

Sidney Weinhouse