

Gene Toxicity and Cancer



Yesterday

- In 1953, the double-helix structure of DNA was discovered by Watson and Crick. Mapping the human genome was decades away, and mutation was primarily viewed as an engine of evolutionary change and the possible cause of unusual diseases.
- As the field of genetics burgeoned in the 1960s, 1970s and 1980s, the workings of DNA, chromosomes and the constituent genes and proteins became a driving force in the biological sciences at large. Gradually genetics became central to biomedical research. As a testament to this rapid growth in the field, specific genes, called oncogenes, were associated with the occurrence of cancer, and tumor suppressor genes such as TP53 and RB were identified.
- By the early 1970s, the connection between mutations, the chemical and environmental agents that cause mutations, and a number of cancers emerged.

Today

- Research funded by NIH has characterized the genetic toxicity of various classes of oxidizing and environmental agents and established genetic toxicity as a major cause of cancer. This knowledge led to some of the most effective early screening techniques for cancer causing agents, and prevention of cancer through reduction of many genotoxic chemicals in the environment, such as butadiene, benzene, and urethane.
- This research also allowed physicians and researchers to understand the importance of gene toxicity in human health and disease and led to new treatments for cancer. NIH-funded research identified how cells protect themselves from cell death and harmful mutations after environmental exposure to genotoxic stress.
- For example, polluted air, tobacco smoke, and even barbecued food frequently expose humans to polycyclic aromatic hydrocarbons (PAHs) that form as a result of combustion. PAHs are metabolized in the liver into molecules that react with and damage the

genetic material, and lead to mutations, cell death, or other forms of toxicity.

- Extensive research on PAHs facilitated development and use of environmental protection policies and public education programs, and led to new forms of chemotherapy for cancer. Many therapeutic agents used in cancer treatment work by attacking cancer cells the same way that PAHs induce disease, by damaging the cancer cell's genetic material. Hence, the understanding of how PAHs create cancer cells aided the development of fundamental approaches in cancer chemotherapy.
- The Agricultural Health Study of licensed pesticide applicators from North Carolina and Iowa studies pesticide exposure, lifestyle data, and genetic data from a cheek swab sample. The study is a collaboration between the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), the U.S. Environmental Protection Agency (EPA), and the National Institute for Occupational Safety and Health (NIOSH) (<http://www.aghealth.org>).
- Major funding at NIH comes from NCI, NIEHS, and the National Institute of General Medical Sciences (NIGMS), with additional support from the Department of Health and Human Service's National Toxicology Program headquartered at NIEHS.
- Through the NIH National Toxicology Program (<http://ntp.niehs.nih.gov/>), genotoxicity tests are part of a standard array of studies of potentially hazardous chemicals. These tests are used widely in other governmental research and regulatory agencies and in the pharmaceutical and chemical industries to establish the risk and safety of chemicals and potential drug candidates.

Tomorrow

- Researchers are now poised to identify individual personal susceptibility and risk from exposure to PAHs and other forms of genotoxic stress based on heritable factors and co-exposures to other stressors.

- Researchers hope to harness strategic gene damage (targeted disruption) to enhance chemotherapy and discover even more precise targets (marks) for intervention.
- Researchers plan to use these discoveries to identify markers of genotoxic stress that place individuals at greater risk of developing cancer, so that individuals can avoid specific exposures or take additional remedial steps to prevent the onset of disease.

For additional information, visit the National Institute of Environmental Health Sciences (NIEHS) website:

<http://www.niehs.nih.gov/>