Occupational and Environmental Causes of Cancer

DICK CLAPP

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Outline

- Overview of “hallmarks”
- IARC categories and occupational/environmental carcinogens
- National Cancer Institute Occupational and Environmental Epidemiology studies
- Carcinogenic legacies and solutions going forward

Hanahan and Weinberg articles

- Article in Cell (2000) organized thirty years of scientific work into “hallmarks” scheme
  - Cited over 20,000 times since publication
- Extended “initiation-promotion-progression” stages with vastly more detailed explanation
- Article in 2011 updated hallmarks with insights from another decade of research
  - Cited over 13,000 times to date

Mechanistic Understanding in 2000

A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B

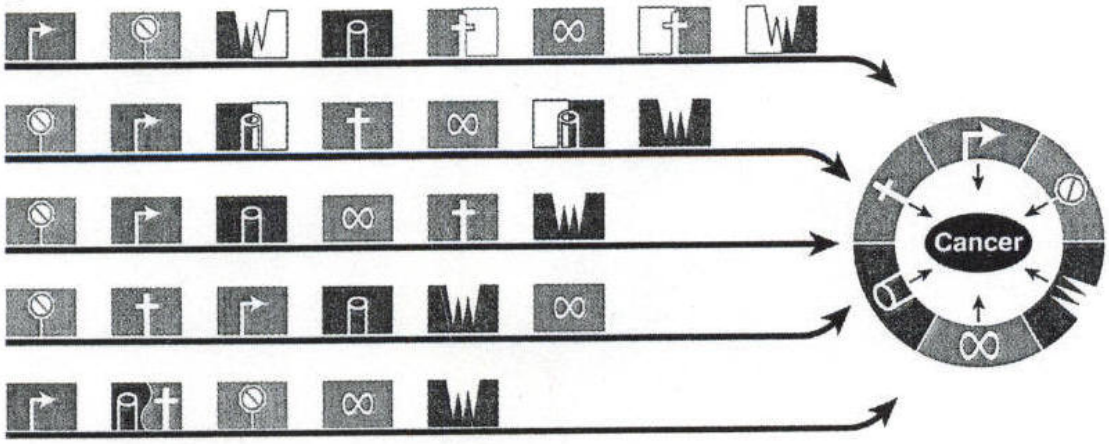
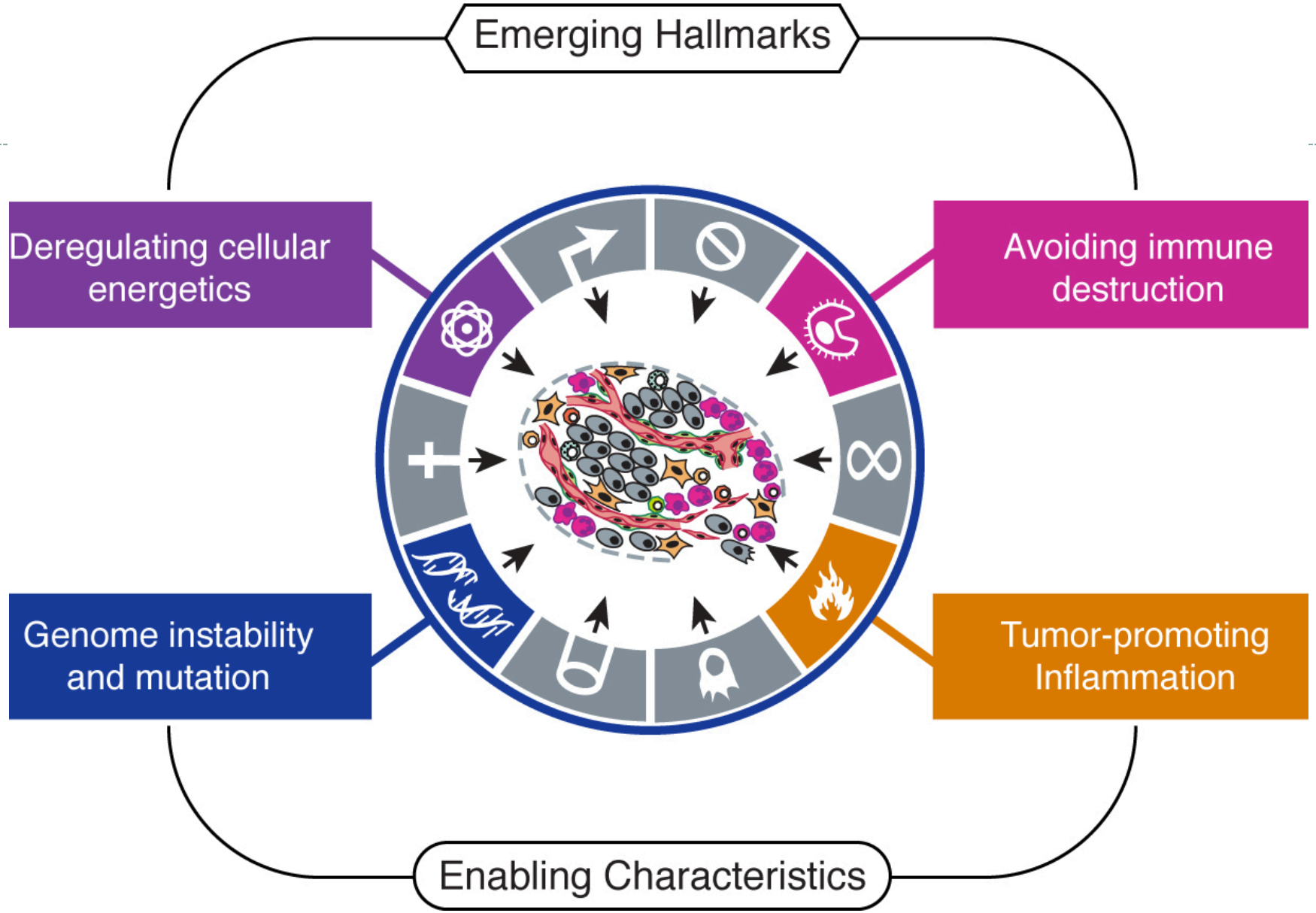


Figure 4. Parallel Pathways of Tumorigenesis

While we believe that virtually all cancers must acquire the same six hallmark capabilities (A), their means of doing so will vary significantly, both mechanistically (see text) and chronologically (B). Thus, the order in which these capabilities are acquired seems likely be quite variable across the spectrum of cancer types and subtypes. Moreover, in some tumors, a particular genetic lesion may confer several capabilities simultaneously, decreasing the number of distinct mutational steps required to complete tumorigenesis. Thus, loss of function of the p53 tumor suppressor can facilitate both angiogenesis and resistance to apoptosis (e.g., in the five-step pathway shown), as well as enabling the characteristic of genomic instability. In other tumors, a capability may only be acquired through the collaboration of two or more distinct genetic changes, thereby increasing the total number necessary for completion of tumor progression. Thus, in the eight-step pathway shown, invasion/metastasis and resistance to apoptosis are each acquired in two steps.

Source: Hanahan D and Weinberg R. The Hallmarks of Cancer. Cell 2000;100:57-70



Source: Hanahan and Weinberg, *Cell* 144:646-674, 2011

IARC Environmental/Occupational Carcinogens

- Those used in workplaces, released into the environment, or contained in consumer products
- International Agency for Research on Cancer (IARC) Classifications:
  - Group 1, Carcinogenic: 116
  - Group 2A, Probably: 73
  - Group 2B, Possibly: 287
  - Group 3, Not Classifiable: 506
  - Group 4, Probably not: 1

Total Reviewed: 982

~40% industrial carcinogens [exposures or circumstances]

Source: /ENG/Classifications/index.phpwww.monographs.iarc.fr

Table 17-3. Definite Human Carcinogens with Potential for Occupational or Environmental Exposure (IARC Group 1)*

Exposures	Examples of Occurrence	Tumor Sites or Types for Which There Is Sufficient Evidence in Humans	Other Sites or Types with Limited Evidence in Humans
Aflatoxins (naturally occurring mixtures of)	Grains, peanuts (farmworkers)	Liver	
4-Aminobiphenyl	Dye and rubber industry	Bladder	
Arsenic and arsenic compounds	Insecticides, nonferrous metal smelting, mining and milling of ores containing arsenic	Lung, skin, urinary bladder.	Kidney, liver, prostate
Asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthrophyllite)	Mining and milling, insulation, shipyard workers, sheet metal workers, asbestos cement industry	Lung, mesothelioma, larynx, ovary	Colorectum, pharynx, stomach
Benzene	Chemical industry	ANLL	ALL, CLL, MM, NHL
Benzidine	Rubber and dye industries	Bladder	
Benzidine-based dyes	Coloring paper, textiles, and leather		
Benzo[a]pyrene			
Beryllium and beryllium compounds	Beryllium extraction and processing, aircraft and aerospace industries, electronics and nuclear industries	Lung	
1,3-butadiene	Chemical and rubber industries	Hematolymphatic organs	
Bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME)	Chemical industry	Lung	
Cadmium and cadmium compounds	Metalworking industry, batteries, soldering, coatings	Lung	Prostate, kidney
Chromium (VI) compounds	Chromate production plants, dyes and pigments, plating and engraving, chromium ferro-alloy production, stainless steel welding	Lung	Nasal cavity and paranasal sinuses
Coal tar pitches	Coal distillation	Skin, scrotum, lung, bladder	
Coal tars	Coal distillation	Skin, lung	
Dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin)	Herbicide production and application	All sites combined, lung	
Dyes metabolized to benzidine			
Erionite	Environmental (Turkey)	Mesothelioma	
Ethylene oxide	Sterilant in health care settings; chemical component		Lymphoid tumors (NHL, MM, CLL), breast
Formaldehyde	Production, pathologists, medical laboratory technicians, plastics, textile industry	Nasopharyngeal, leukemia	Sinonasal

National Cancer Institute Occupational and Environmental Epidemiology Studies

- Agricultural Health Study (with NIEHS, NIOSH, EPA)
  - Enrolled a cohort of ~57,000 farmers and pesticide applicators and 32,000 spouses in mid-1990s in Iowa and North Carolina; followed-up in approximately five-year intervals
  - Dozens of publications have reported results for cancer and individual pesticides; prostate cancer in farmers and multiple findings for individual pesticides (including EDCs like atrazine, glyphosate, et al.) and other cancers and Parkinson's Disease
  - On-going research will examine children and offspring as well as specific gene-environment interactions and genetic pathways such as mutations in the apoptosis pathway in chronic lymphocytic leukemia

NCI OEEB studies, cont.

- Diesel Exhaust in Miners Study (with NIOSH)
  - Assembled a retrospective cohort of 12,315 workers in eight underground mines and followed through 2012; used state-of-the-art exposure assessment methods
  - Case-control study of respirable elemental carbon and lung cancer relied on by IARC in categorizing diesel exhaust as Group I carcinogen
  - Survived challenges by industry-affiliated scientists

NCI OEEB studies, cont.

- New England Bladder Cancer Study (with State Health Departments in Maine, New Hampshire, Vermont)
  - Case-control study of over 2,600 subjects in geographic area with high bladder cancer mortality and high arsenic in soil and groundwater.
  - Examined associations with arsenic, disinfection byproducts, nitrates using detailed interviews and biological samples
    - Multiple publications found excess risk from arsenic in soil, interaction with smoking and risk from other exposures in both males and females

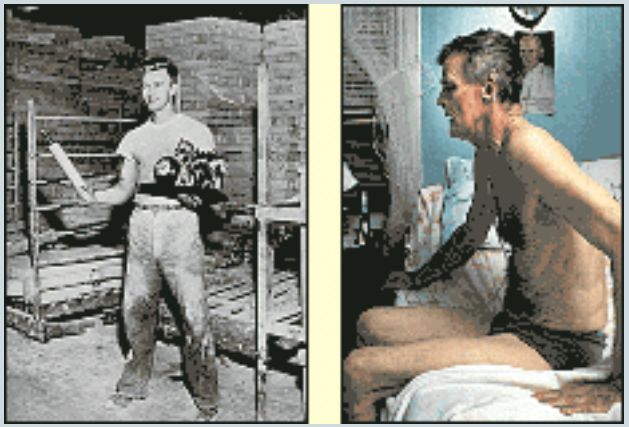
NCI OEEB Studies, cont.

- Other studies include Shanghai Women's Health Study, Los Angeles AARP cohort and many others
  - Research incorporates molecular epidemiology and advanced genetic methods, biomarkers, diet and "lifestyle" factors
- On-going studies of diesel exhaust, formaldehyde, benzene, TCE, acrylonitrile, carbon black, pesticides
- New exposure focus will include carbon nanotubes
- Combines epidemiology, quantitative exposure assessment, biological and genetic methods to understand mechanisms of carcinogenesis

Additional insights still to come

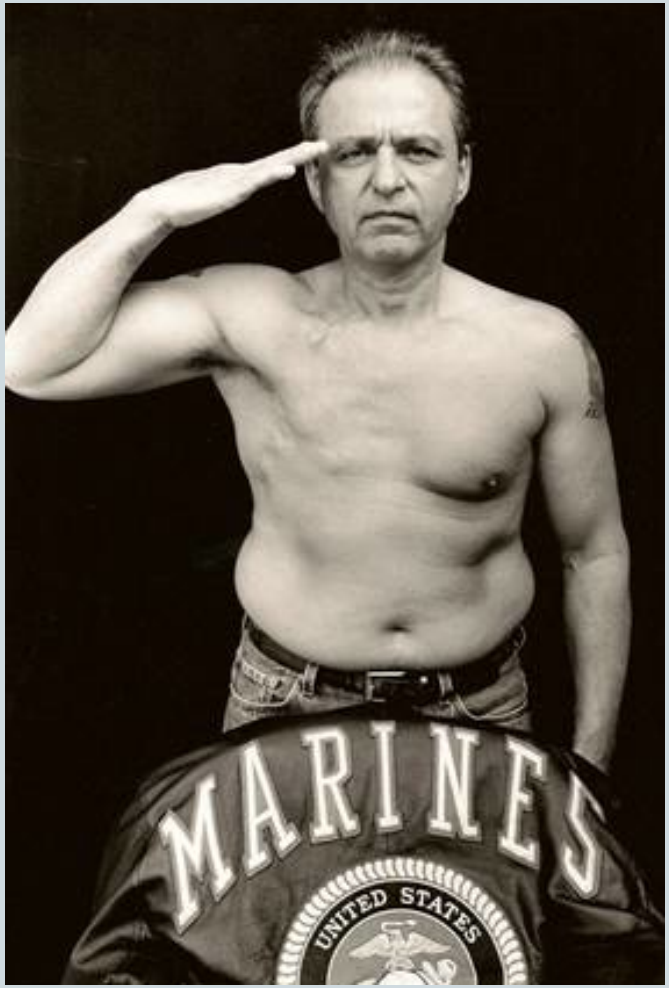
- Role of electromagnetic fields, shift work, gene-environment interactions
- Further research on endocrine-disrupting chemicals and windows of vulnerability
- Ecosocial approaches and multi-level analyses

Asbestos legacy continues



- Remains leading cause of lung cancer world-wide
  - Never fully “banned” in the US.
  - Exposure occurring across lifecycle: mining, processing, disposal
- Produces both occupational & environmental cancers
  - “take home” exposures and Third Wave exposures still occurring
- Interacts with tobacco smoke

Camp Lejeune Cancer Studies



- TCE, Perc, benzene in drinking water in 1950s through 1985 at Marine training base
- Hundreds of thousands of veterans and dependents exposed to contaminated drinking water (low ppb to 1,600 ppb of TCE)
- Male breast cancer results just reported
- ATSDR studies on-going

Solutions going forward

"A precautionary prevention-oriented approach should replace current reactionary approaches to environmental contaminants in which human harm must be proven before action is taken to reduce or eliminate exposure"