Εισαγωγή στη Βιολογία του καρκινού

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Καθηγητής Ογκολογίας

Ιατρική Ιωαννίνων
δεν σπανίζει
### Lifetime Probability of Developing Cancer, by Site, Men, 2001-2003*

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 2</td>
</tr>
<tr>
<td>Prostate</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>1 in 12</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1 in 17</td>
</tr>
<tr>
<td>Urinary bladder‡</td>
<td>1 in 28</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 47</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 in 49</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 in 61</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 67</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>1 in 72</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 in 89</td>
</tr>
</tbody>
</table>

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

Figure 3: Aging Baby Boomers Predicted to Drive up Cancer Incidence. The majority of all cancer diagnoses are made in those aged 65 and older (blue line) (1, 4). In 2010, individuals in this age group made up 13 percent of the U.S. population (6). In 2030, when the baby boomers will be aged 65 or older, this segment will be nearly 20 percent of the population (6). This change will dramatically increase the total numbers of cancers diagnosed each year, with a 67 percent increase in cancer incidence anticipated for the segment of the population aged 65 or over (bars) (7).

Cancer: An Expensive Disease. Biomedical Research: A Wise Investment

Of all major causes of disease worldwide, cancer has the greatest economic burden from premature death and disability. The global economic toll is 20 percent higher than that from any other major disease, at $895 billion in 2008 (13). This figure does not include the direct costs of treating cancer. In the United States, the latest estimates from the NIH indicate that the overall economic costs of cancer in 2008 were $201.5 billion: $77.4 billion for direct medical costs and $124.0 billion for lost productivity due to premature death (1).

Given that cancer is the most costly disease to our nation, and it is poised to become the number one killer of Americans, it is urgent that we increase our investments in the scientific research needed to develop more effective interventions. This report highlights many of the remarkable recent advances that are the direct result of the dedicated work of thousands of researchers funded through the federal government and other sectors of the biomedical research enterprise. There is little doubt that the ability of these researchers to continue making lifesaving progress is in significant jeopardy given that NIH and NCI budgets are decreasing (see Funding Cancer Research and Biomedical Science Drives Progress, p. 69).
διαρκής καταστολή καρκινικής έναρξης και προαγωγής

Αλλαγές στο γενετικό υλικό (Genetic mutations) είναι συνήθη κυτταρικά γεγονότα: κάθε γονίδιο παθαίνει αλλαγές με συχνότητα 1/20.000 κύτταρα.

Δεδομένου ότι ο οργανισμός έχει τρισεκατομμύρια κύτταρα, κάθε στιγμή, εκατομμύρια κύτταρα προδιαγράφεται μοριακά (primed) να γίνουν καρκινικά.

τα πλείστα εξουδετερώνονται μέσω μηχανισμών κυτταρικής απόπτωσης, γήρανσης, ανοσοεπιτήρησης

πρωτοκήρυξη της αρρώστιας κατά τη διάρκεια του πολληφθείου των ιοονέμων και της κατάλυσης των μηχανισμών του ασθενούς για την καταπολέμηση της απότομης αγωγής.

επιταχύνοντας την απώλεια της πρόοδος και την ανάπτυξη της ακτινοβολίας, επειδή οι ιοονέμοι επιβιβάζονται και οι γονίδιοι επεκτείνονται με μεγάλη προσοχή.

προκειμένου να έχει την απόφαση να αποφύγει την κατάλυση της αγωγής και να ανοιχτοποιήσει την αρρώστια που έχει πετύχει μέσω της προπολιτικής απότομης αγωγής.

επειδή η αρρώστια είναι μια ιδιότητα της φύσης και της ζωής και δεν είναι τύπου καθαρής απότομης αγωγής.

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Leading Sites of New Cancer Cases and Deaths – 2015 Estimates

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>Prostate</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>220,800 (26%)</td>
<td>86,380 (28%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Prostate</td>
</tr>
<tr>
<td>115,610 (14%)</td>
<td>27,540 (9%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>69,090 (8%)</td>
<td>26,100 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Pancreas</td>
</tr>
<tr>
<td>56,320 (7%)</td>
<td>20,710 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>42,670 (5%)</td>
<td>17,030 (5%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>39,850 (5%)</td>
<td>32,000 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>38,270 (5%)</td>
<td>31,200 (4%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Pancreas</td>
</tr>
<tr>
<td>32,670 (4%)</td>
<td>24,120 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>30,900 (4%)</td>
<td>23,370 (3%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>25,510 (3%)</td>
<td>23,290 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>All sites</td>
</tr>
<tr>
<td>848,200 (100%)</td>
<td>810,170 (100%)</td>
</tr>
</tbody>
</table>

| **Male**             | **Female**       |
| Lung & bronchus      | Lung & bronchus  |
| 71,660 (26%)         | 86,380 (28%)     |
| Prostate             | Prostate         |
| 40,290 (15%)         | 27,540 (9%)      |
| Colon & rectum       | Colon & rectum   |
| 23,600 (9%)          | 26,100 (8%)      |
| Pancreas             | Pancreas         |
| 19,850 (7%)          | 20,710 (7%)      |
| Liver & intrahepatic bile duct | Liver & intrahepatic bile duct |
| 14,180 (5%)          | 17,030 (5%)      |
| Leukemia             | Non-Hodgkin lymphoma |
| 10,240 (4%)          | 32,000 (4%)      |
| Esophagus            | Urinary bladder  |
| 12,600 (4%)          | 11,510 (4%)      |
| Uterine corpus       | Non-Hodgkin lymphoma |
| 10,170 (4%)          | 11,480 (4%)      |
| Kidney & renal pelvis| Liver & intrahepatic bile duct |
| 6,380 (2%)           | 3,420 (2%)       |

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

©2015, American Cancer Society, Inc., Surveillance Research

![Image](CA2015Figures2015.png)
Leading causes of death for all ages

Deaths per 100,000 population (log scale)

Year


All causes
Heart disease
Cancer
Stroke
Unintentional injuries
Chronic lower respiratory diseases

NOTE: Death rates are age adjusted.
SOURCES: CDC/NCHS, *Health, United States, 2008*, Figure 16. Data from the National Vital Statistics System.
τα βασικά του καρκίνου
καρκίνος

• έκρυθμος, μη ελεγχόμενος πολλαπλασιασμός κυττάρων τα οποία έχοντας υποστεί συσσωρευμένες γενωμικές & επιγενετικές βλάβες δημιουργούν ιστικές μάζες που λειτουργούν εκτός κανόνων ιστικής ομοιοστασίας και αποκτούν πλεονέκτημα ανάπτυξης επί των φυσιολογικών ιστών
therapies. For example, the deployment of apoptosis-inducing drugs may induce cancer cells to hyperactivate mitogenic signaling, enabling them to compensate for the initial attrition triggered by such treatments. Such considerations suggest that drug development and the design of treatment protocols will benefit from incorporating the concepts of functionally discrete hallmark capabilities and of the multiple biochemical pathways involved in supporting each of them. Thus, in particular, we can envisage that selective cotargeting of multiple core and emerging hallmark capabilities and enabling characteristics (Figure 6) in mechanism-guided combinations will result in more effective and durable therapies for human cancer.

CONCLUSION AND FUTURE VISION

We have sought here to revisit, refine, and extend the concept of cancer hallmarks, which has provided a useful conceptual framework for understanding the complex biology of cancer. The six acquired capabilities—the hallmarks of cancer—have stood the test of time as being integral components of most forms of cancer. Further refinement of these organizing principles will surely come in the foreseeable future, continuing the remarkable conceptual progress of the last decade.

Looking ahead, we envision significant advances during the coming decade in our understanding of invasion and metastasis. Similarly, the role of aerobic glycolysis in malignant growth will be elucidated, including a resolution of whether this metabolic reprogramming is a discrete capability separable from the core hallmark of chronically sustained proliferation. We remain perplexed as to whether immune surveillance is a barrier that virtually all tumors must circumvent, or only an idiosyncrasy of an especially immunogenic subset of them; this issue too will be resolved in one way or another.

Yet other areas are currently in rapid flux. In recent years, elaborate molecular mechanisms controlling transcription through chromatin modifications have been uncovered, and there are...
Cancer-associated malignancies (originated by the normal stem cells in the tissue) are also expressed by the CSCs. Recent research has interrelated the acquisition of CSC traits with both normal and cancer stem cells. This concordance suggests that the EMT program not only may enable cancer cells to physically disseminate from primary tumors but also can be a common constituent of many if not most tumors, albeit operationally through their ability to efficiently seed new tumors upon inoculation into recipient host mice.

Notably, the immune inflammatory cells present in tumors may also be important in creating and maintaining microenvironments that are created by the abundance of immune inflammatory cells (ICs) and can include both tumor-promoting as well as tumor-killing characteristics.

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Είδη καρκίνου

**Καρκινώματα**

- Πνεύμονα
- Μαστού
- Εντέρου
- Ουροδόχου
- Προστάτη

**Λευχαιμίες**

κυκλοφορούντα αιματοκύτταρα

**Λεμφώματα**

- Λεμφαδένες

**Σαρκώματα**

- λίπος
- οστά
- μύς
Απώλεια ελέγχου φυσιολογικής κυτταρικής ανάπτυξης

Φυσιολογικό κύτταρο

Μη επισκευαζόμενη γενετική βλάβη

Αποπτωση

Καρκινικός μετασχηματισμός

1η μετάλλαξη 2η μετάλλαξη 3η μετάλλαξη X μετάλλαξη

Ανάπτυξη εκτός ελέγχου
Φυσιολογική κυτταρική ανάπτυξη

Απομάκρυνση νεκρών κυττάρων

Επιδερμίδα

Πολλαπλασιασμός κυττάρων βασικής στοιβάδας με ασύμμετρη διαίρεση

Δερμίδα

Κυτταρική μετανάστευση
Καρκινική ανάπτυξη
Καρκινική ανάπτυξη
Καρκινική ανάπτυξη

1. Διήθηση παραρκειμένων ιστών
2. Είσοδος στην κυκλοφορία
3. Εποίκιση σε άλλους ιστούς
Κύτταρα καλοήθων όγκων αναπτύσσονται μόνο τοπικά.
• Δεν διηθούν
• Δεν μεταναστεύουν

Καρκινικά κύτταρα:
• Διηθούν περιβάλλοντες ιστούς
• Εισέρχονται στην κυκλοφορία
• Μεταναστεύουν
Κάθε καρκίνος έχει την δική του φυσική ιστορία (πορεία)

- Εγκέφαλος
- Λεμφαδένες
- Ηπαρ
- Μελάνωμα
Η διάγνωση απαιτεί βιοψία

Ιστοπαθολογία

Πρωτεωμικό προφίλ

Γενωμικό προφίλ
<table>
<thead>
<tr>
<th>Normal</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Normal Cells" /></td>
<td><img src="image2.png" alt="Cancer Cells" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Normal Cell" /></td>
<td><img src="image4.png" alt="Cancer Cell" /></td>
</tr>
<tr>
<td><img src="image5.png" alt="Normal Cells" /></td>
<td><img src="image6.png" alt="Cancer Cells" /></td>
</tr>
<tr>
<td><img src="image7.png" alt="Normal Cells" /></td>
<td><img src="image8.png" alt="Cancer Cells" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image9.png" alt="Normal Cells" /></td>
<td><img src="image10.png" alt="Cancer Cells" /></td>
</tr>
</tbody>
</table>

- **Normal Cells** show a **Large number of irregularly shaped dividing cells**.
- **Cancer Cells** exhibit **Large, variably shaped nuclei**.
- **Cancer Cells** also have **Small cytoplasmic volume relative to nuclei**.
- There is a **Variation in cell size and shape** in cancer cells.
- **Cancer Cells** lose **Loss of normal specialized cell features**.
- **Cancer Cells** show a **Disorganized arrangement of cells**.
- **Cancer Cells** have a **Poorly defined tumor boundary**.
Διαβάθμιση κακοήθειας καρκίνου & πρόγνωση

<table>
<thead>
<tr>
<th>Ποσοστό επιβίωσης</th>
<th>Χρόνια</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Στάδιο μελανώματος & πρόγνωση

![Graph showing clinical stage and prognosis](image)

Κλινικό στάδιο κατά την διάγνωση

100%

50%
2050 under this assumption. Even without any increase in the cancer incidence rate, the number of cases anticipated in 2050 (24 million) would be more than twice the number in 2002 (10.8 million). Most of this increase would occur in low- and middle-resource countries (3).

By comparison, the number of cancers that the International Agency for Research on Cancer projects by 2030 (26 million) is substantially higher than the estimate in Figure 2 (18.9 million) because the International Agency for Research on Cancer assumes a 1% annual increase in the incidence rate as well as the anticipated demographic changes in the population at risk (2).

Tobacco use and prevention of tobacco-related cancers

Tobacco use is the single largest preventable cause of cancer and premature death worldwide. An estimated 1.3 billion people in the world currently smoke tobacco; the vast majority of these smoke manufactured cigarettes (4). If current trends in smoking and population growth continue, the number of current smokers is expected to reach 2 billion worldwide by 2030 (5). As shown in Figure 3, smoking prevalence is highest among men in Eastern Europe, the former Soviet Union, China and Indonesia. Cigarette smoking among women has been decreasing in most high-resource countries but is stable or increasing in several countries in Southern, Central and Eastern Europe (4). With the decline of tobacco use in many industrialized countries, the geography of smoking has shifted from the developed to the developing world, especially for men. About 50% of men and 9% of women are current smokers in developing countries, compared with 35% of men and 22% of women in high-resource countries (4). Over 60% of all smokers in the world live in just 10 countries (in order): China, India, Indonesia, Russian Federation, USA, Japan, Brazil, Bangladesh, Germany and Turkey (6). The number of current smokers in China approximately equals the entire population of the USA. While most of these smokers are currently under age 40, the combination of continued smoking and aging will vastly increase the future adverse effects of tobacco use on cancer and other chronic diseases, unless effective campaigns can be mounted to promote cessation.

The International Agency for Research on Cancer designates at least 15 different types or subtypes of cancer as causally related to smoking (7). These include cancers of the lung and bronchus (all histological subtypes), larynx, oral cavity, pharynx, lip, nasopharynx, nasal cavity and paranasal sinuses, esophagus (squamous and adenocarcinoma), bladder, kidney (parenchyma and renal pelvis), pancreas, uterine cervix, stomach, liver and acute myeloid leukemia (7). Cancers attributed to cigarette smoking accounted for more than one-fifth of the estimated 1.42 million cancer deaths that occurred globally in the year 2000 (8). Lung cancer is the most common cancer caused by smoking, even though it accounts for less than half of all smoking-attributable deaths (9). Cigarette smoking accounts for 80% of lung cancer cases in men and 50% in women worldwide (5). Lung cancer has been the most common cancer in the world since 1985 (10).
Even without any increase in the cancer incidence rate, the number of cases anticipated in 2050 (24 million) would be more than twice the number in 2002 (10.8 million). Most of this increase would occur in low- and middle-resource countries. By comparison, the number of cancers that the International Agency for Research on Cancer projects by 2030 (26 million) is substantially higher than the estimate in Figure 2 (18.9 million) because the International Agency for Research on Cancer assumes a 1% annual increase in the incidence rate as well as the anticipated demographic changes in the population at risk.

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Fig. 2. Number and distribution of cancer cases by level of economic development and year assuming no change in the annual incidence rate.
Ιοί και βακτήρια

Χημικά

Ιοντίζουσα ακτινοβολία

κληρονομικότητα
Δίαιτα
Ορμόνες

αίτια, αίτια, αίτια, αίτια
κληρονομικήτητα

χημικά

ακτινοβολία

ιοί
A. Mutagenic agents

1. Ionizing radiation
   - UV radiation
   - HNO₂
   - α, β, γ
   - [CH₃⁺]
   - Free radicals
   - Desamination
   - Deletions or insertions due to faulty recombination

2. Thymine dimer
   - Formation of pyrimidine dimers
   - Base exchange C → U
   - Spontaneous loss of bases
   - Chemical modification of bases

3. Methyl nitrosamine
   - Reactive methyl group
   - Epoxide

4. Mutagenic derivative of benzo(a)pyrene
DNA μεταλλάξεις

DNA

CAAGCTAACCT

Normal gene

CAAGCGAACCT

Single base change

CAAGGGCCTAACCT

Additions

CAAGAACCCT

Deletions
Μερικοί εξωγενείς παράγοντες

Δεδομένα από το NCI
Heredity? Behaviors? Other Factors?

Colon Cancer
(Number of new cases per 100,000 people)

<table>
<thead>
<tr>
<th>Country</th>
<th>Japan</th>
<th>Japanese families in U.S.</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>5</td>
<td>7</td>
<td>50</td>
</tr>
</tbody>
</table>

Stomach Cancer
(Number of new cases per 100,000 people)

<table>
<thead>
<tr>
<th>Country</th>
<th>Japan</th>
<th>Japanese families in U.S.</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>100</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
Συνολική κατανάλωση κρέατος στις αναπτυσσόμενες και ανεπτυγμένες χώρες, με εκτιμώμενη μελλοντική κατανάλωση (σε εκατομμύρια τόνους)³
Tobacco Use and Cancer

Some Cancer-Causing Chemicals in Tobacco Smoke

- aminostilbene
- arsenic
- benz[a]anthracene
- benz[a]pyrene
- benzene
- benzo[b]fluoranthene
- benzo[c]phenanthrene
- benzo[f]fluoranthene
- cadmium
- chrysene
- dibenz[a c]anthracene
- dibenzo[a e]fluoranthene
- dibenz[a h]acridine
- dibenz[a j]acridine
- dibenzo[c g]carbazone
- N-dibutylNitrosamine
- 2,3-dimethylchrysene
- indeno[1,2,3-c d]pyrene
- S-methylchrysene
- S-methylfluoranthenene
- alpha-naphthylamine
- nickel compounds
- N-nitrosodimethylamine
- N-nitrosomethyl ethylamine
- N-nitrosodiethylamine
- N-nitrosonornicotine
- N-nitrosoanabasine
- N-nitrosoproperidine
- polonium-210
Low-Strength Radiation

Annual Sunshine (UV radiation)

Skin Cancer Incidence

High
Low

Least
Most

Detroit
Pittsburgh
Dallas
High-Strength Radiation

- **Leukemia Incidence**
- **X-ray Dose (atomic radiation)**

- **High**
- **Low**

- **Least**
- **Most**
### Some Carcinogens in the Workplace

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Occupation</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Mining, pesticide workers</td>
<td>Lung, skin, liver</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Construction workers</td>
<td>Lung, mesothelioma</td>
</tr>
<tr>
<td>Benzene</td>
<td>Petroleum, rubber, chemical workers</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Chromium</td>
<td>Metal workers, electroplaters</td>
<td>Lung</td>
</tr>
<tr>
<td>Leather dust</td>
<td>Shoe manufacturing</td>
<td>Nasal, bladder</td>
</tr>
<tr>
<td>Naphthylamine</td>
<td>Chemical, dye, rubber workers</td>
<td>Bladder</td>
</tr>
<tr>
<td>Radon</td>
<td>Underground mining</td>
<td>Lung</td>
</tr>
<tr>
<td>Soots, tars, oils</td>
<td>Coal, gas, petroleum workers</td>
<td>Lung, skin, liver</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Rubber workers, polyvinyl chloride manufacturing</td>
<td>Liver</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Furniture manufacturing</td>
<td>Nasal</td>
</tr>
</tbody>
</table>

Σε μοριακό επίπεδο
circuit can be segmented into distinct subcircuits, each of which is specialized to support a discrete cell-biological property in normal cells and is reprogrammed in order to implement a hallmark capability in cancer cells (Figure 2). Only a subset of hallmark capabilities are addressed in this figure, either because their underlying control circuits remain poorly understood or because they overlap extensively with those portrayed here.

An additional dimension of complexity involves considerable interconnections and thus crosstalk between the individual subcircuits. For example, certain oncogenic events can affect multiple capabilities, as illustrated by the diverse effects that prominent oncogenes, such as mutant \( \text{RAS} \) and upregulated \( \text{MYC} \), have on multiple hallmark capabilities (e.g., proliferative signaling, energy metabolism, angiogenesis, invasion, and survival). We anticipate that future renditions of this integrated circuit will encompass subcircuits and associated hallmark capabilities that are still not addressed here.

**ENABLING CHARACTERISTICS AND EMERGING HALLMARKS**

We have defined the hallmarks of cancer as acquired functional capabilities that allow cancer cells to survive, proliferate, and disseminate; these functions are acquired in different tumor types via distinct mechanisms and at various times during the course of multistep tumorigenesis. Their acquisition is made possible by two enabling characteristics. Most prominent is the development of genomic instability in cancer cells, which generates random mutations including chromosomal rearrangements; among these are the rare genetic changes that can orchestrate hallmark capabilities. A second enabling characteristic involves the inflammatory state of premalignant and frankly malignant lesions that is driven by cells of the immune system, some of which serve to promote tumor progression through various means.
Extracellular Signals
HER family, PDGFR, IGF-IR, TGF-α

Nuclear Transcription
C-jun, Fos, c-myc, Elk-1, CREB, SRF
• Ο καρκίνος γενετικής κλωνικής νόσος

— “particular, incorrect combination of chromosomes” would generate a malignant cell endowed with the ability of unlimited growth which would pass the defect on to its progeny.

• Boveri, T. In *Zur Frage der Entstehung Maligner Tumoren* 1-64 (Gustav Fisher, Jena, 1914)
TRANSMISSION OF A MALIGNANT NEW GROWTH BY MEANS OF A CELL-FREE FILTRATE

PEYTON ROUS, M.D.

NEW YORK

A tumor of the chicken, histologically a spindle-celled sarcoma, has been propagated in this laboratory since October, 1902, and in the past few months has developed extreme malignancy. From a bit inoculated into the breast muscle of a susceptible fowl there develops rapidly a large, firm growth; metastasis takes place to the viscera; and within four or five weeks the host dies. The behavior of the new growth has been throughout of that of a true neoplasm, for which reason the fact of its transmission by means of a cell-free filtrate assumes exceptional importance.

EXPERIMENTS

For the first experiments on the point we used as a preliminary filter-paper and the ground tumor suspended in Ringer’s solution. It was supposed that the slight paper barrier, which allows the passage of a few red blood-cells and lymphocytes, would suffice to hold back the tumor and render the filtrate innocuous. Such has been the experience of other workers with mouse and dog tumors. But in the present instance characteristically growths followed the inoculation of small amounts of the watery filtrate, and followed also the inoculation of the fluid supernatant after centrifugalization of a tumor emulsion.

These results led to more critical experiments, which will be here detailed. Tumors of especially rapid growth and young, well-grown, barred Plymouth Rock fowls were used throughout.

EXPERIMENT 1.—Tumor material from the breast of Chicken 92 (tumor generation 6 A) was ground with sterile sand, suspended in a considerable bulk of Ringer’s solution, and shaken for twenty minutes in a machine. The sand and tumor fragments were separated out by centrifugation in large tubes for five minutes at 2,000 revolutions per minute. Of the supernatant fluid a little was pipetted off, and this centrifugated anew for fifteen minutes at over 3,000 revolutions per minute. From the upper layers sufficient fluid for inoculation was now carefully withdrawn. The pure-bred fowls were inoculated in one breast with 0.2 c.c. of the fluid, in the other with a small bit of tumor tissue. All developed sarcomas at the site of this latter inoculation, and in seven to eight weeks growth slowly appeared at the point where the fluid had been injected.

EXPERIMENT 2.—Tumor from Chicken 20 (tumor generation 6 A) was ground, suspended, and shaken as above. But after one centrifugation the fluid was passed through a Berkefeld filter No. 2 (course). Before filtration, it was pinkish-yellow, cloudy; afterwards, faintly yellow, limpid. Nine fowls were inoculated with 0.2 c.c. of the filtrate in each breast, twenty-two more received filtrate in one breast, a bit of tumor in the other. Of the nine, one slowly developed a sarcoma in each breast, and later microscopic growths were found in its lungs. Of the twenty-two receiving both filtrate and tumor, five developed sarcomas where the filtrate had been injected, and these five showed especially large growths from the tumor bit.

The Berkefeld filter employed was later found slightly porous to Bacillus prodigiosus.

EXPERIMENT 3.—The filtrate was similarly prepared except that a small Berkefeld filter (No. 5 medium) impermeable to Bacillus prodigiosus, was used. As before, the filtration was done at room temperature. Fowl 124 (generation 7 A) furnished the material. Twenty chickens were inoculated in each breast with the filtrate, but none have developed tumors.

EXPERIMENT 4.—In this experiment the material was never allowed to cool. About 15 gm. of tumor from Chicken 140 (generation 7 B) was ground in a warm mortar with warm sand, mixed with 200 c.c. of heated Ringer’s solution, shaken for thirty minutes within a thermostat room, centrifugated, and the fluid passed through a filter similar to that used in Experiment 3. Both before and after the experiment, this filter was found to hold back Bacillus prodigiosus. The filtration of the fluid was done at 28.5 C., and its injection immediately followed. In four of ten fowls inoculated with the filtrate only (0.2 to 0.5 c.c. in each breast) there has developed a sarcoma in one breast, and though the growths required several weeks for their appearance their enlargement is now fairly rapid. Pieces removed at operation have shown the characteristic tumor structure.

CHARACTER OF THE TUMOR

As has been pointed out, the special significance of these results lies in the growth’s identity as a tumor. The original sarcoma was found as a unique instance in a flock of healthy fowls; and, though susceptible normal chickens and others with the tumor have since been kept together in close quarters for long periods, no instance suggesting a natural infectivity of the growth has occurred. When inoculated, it is at first a local disease, very tenacious on the good health of the host. At this time intercurrent illness of the fowl will check the nodule’s growth or even cause it transiently to disappear. For long the sarcoma could be transferred only to fowls of the same pure-bred variety in which it arose, and this only in an occasional individual; but like many tumors, it has gained on repeated transplantation a heightened malignancy, and the power to grow in other varieties of the same animal. Yet in these it does not do well; and it has not been successfully transplanted to other species.

Histologically, the growth has always consisted of one type of cells, namely, spindle-cells in bundles, with a slight, supporting, connective tissue framework. The picture does not in the least suggest a granuloma; and cultures from the growth remain sterile as regards bacteria. At the edge of the invading mass there is often practically no cellular reaction, but lymphocytes in small number may be present, as is common with tumors in general. Metastasis takes place early, through the bloodstream, and the secondary nodules have the same character as the primary. Several instances of the sarcoma’s direct extension into vessels have been encountered. The secondary growths are distributed especially to the lungs, heart and liver, and in the last organ they sometimes become unbounded. The host becomes emaciated, cold and droisy, and shortly dies.

Transplantation experiments with the tumors resulting from the filtrate are at present under way. The tumor of Experiment 2, which arose in the fowl that received filtrate alone, has already been successfully transplanted.

Sixty-Sixth Street and Avenue A.

Length of Treatment of Syphilis.—The first two years’ treatment is the most important period for the patient and on its thoroughness depends largely his future well-being. Treatment should be actively pursued for at least five years; that is, the treatment should be persistent for three years, less strenuous during the next two. The patient should be under observation the next several years. In fact, it is best for the patient to undergo treatment for three or four weeks each year during his lifetime. —A. G. Nelder, in Yale Medical Journal.
«καρκινικά» γονίδια

- Αρκετά έχουν ταυτοποιηθεί.

- Μεταλλαγές των υπεύθυνων γονιδίων οδηγούν σχηματισμό πρωτεϊνών που
  - Υπερλειτουργούν
  - δυσλειτουργούν
  - υπολειτουργούν.
«καρκινικά» γονίδια

tαξινομούνται σε 3 κατηγορίες:

- Ογκογονίδια
- Ογκοκατασταλτικά γονίδια
- Επιδιορθωτικά του DNA
[πρωτο]-ογκογονίδια λειτουργούν ελεγχόμενα ως:

- αυξητικοί παράγοντες
- Υποδοχείς αυξητικών παραγόντων
- Ενδοκυττάριες πρωτεϊνές μεταγωγής σήματος
- Αντι-αποπτωτικές πρωτεϊνές
- Πυρηνικές μεταγραφικές πρωτεϊνές
οδηγεί σε:

- Υπερπαραγωγή-υπερδραστηριότητα
- Αυξημένο κυτταρικό πολλαπλασιασμό
- Απώλεια αποπτωτικής λειτουργίας
Ογκοκατασταλτικά γονίδια
A final point to consider is that Bell inequalities are independent of quantum physics. Their violation falsifies the existence of a common list of instructions, and a falsification is a fact that will remain true regardless of the nature of the physics, whether quantum physics or an as-yet-unveiled form of physics. With their study, demonstrate a method for generating guaranteed, private randomness.

Figure 1 | Covering all the bases in metastatic assessment. Ding et al. performed genome-wide analysis on three tumour samples: a patient’s primary breast tumour; her metastatic brain tumour, which formed despite therapy; and a xenograft tumour in a mouse, originating from the patient’s breast tumour. They find that the primary tumour differs from the metastatic and xenograft tumours mainly in the prevalence of genomic mutations.
to the carcinogenic process is \textit{“metallazimo”}. 

![Graph showing mutant allele frequency (%) across different samples.]

The graph illustrates the mutant allele frequency (%) across different samples, with error bars indicating the standard deviation. The x-axis represents the genes analyzed, and the y-axis shows the mutant allele frequency percentage. Different colors represent different sample types: Xenograft, Tumour, Metastasis, Normal, and Error. The x-axis includes gene symbols such as FLNC, SNED1, PTFR1, PARVA, CCDC385A, ZNF799, SLC44A1, CHST7, NCAPD1, CBPAP, PPPDE1, CHST7, NUBP1, NRK, KIAA0467, AOCY3, PDCD1, PIK3C3, MUC17, YWHAJ, ENSG0000022487, EFHC2, DYN1C1, PRPS2, MAP3K8, PAF1C1, KCN2, PRTM4, PTK2B, TADA2L, NALCN, DDX11, CSMD1, DDHD1, DHR30, TERF2IP, XRO1, OR4Q3, DDX11, DDX20, TXNDC6, DDX11, DDX11, D8S111, ENSG0000012418, CHGB, MYCBP2, TGFBI, TP53, and others.

The graph shows the frequency of mutant alleles across different samples, with bars indicating the average frequency and error bars representing the standard deviation. The data were obtained from the alignment of sequence reads using the cnvHMM algorithm (K.C., X.S., E.R.M., L.D. and R.K.W., unpublished) to detect copy number variations.

Elevated copy number alterations in metastasis and xenograft show that 111 (average span 342.5 Mb, 383.1 Mb and 562.5 Mb were deleted, in primary tumour, but only 101 and 97 regions in the metastasis.

Table 1 lists the genomic positions. Read depth correction was not applied to the number data from all three tumours with those from peripheral

Unpublished) was applied to the aligned sequence reads to detect

The cnvHMM algorithm (K.C., X.S., E.R.M., L.D. and R.K.W., unpublished) was applied to the aligned sequence reads to detect.

A missense mutation (F299V) in JNK, was found to be present in all three tumours, but at 8- and 7% in primary tumour overlap with broader copy number segments in metastasis (Fig. 2 and Table 1).

We also identified three missense mutations associated with tumour progression. Here we describe the genomic analyses of four DNA samples from an African ancestry.

The disease also often result in a rapidly fatal clinical course. The disease also often result in a rapidly fatal clinical course.

therapy options and frequently poor response to standard chemo-

therapy often result in a rapidly fatal clinical course. 

The consequent absence of approved targeted therapy often result in a rapidly fatal clinical course.

Randomly sampled peripheral blood from her peripheral blood, primary tumour, brain metastasis and an early passage xenograft (harvested 101 days after initial engrafting from her peripheral blood, primary tumour, brain metastasis and an early passage xenograft (harvested 101 days after initial engrafting).

Informed consent for full genome sequencing was obtained and DNA samples were prepared in-mouse (HIM) xenograft tumour line was generated from a sample of her primary tumour biopsied before treatment.

These authors contributed equally to this work.

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Case presentation and previous characterization of samples
Τα ογκοκατασταλτικά γονίδια (TSG)

- Προλαβαίνουν
  - γονιδιωματική αστάθεια
- Επιτηρούν την καλή λειτουργία:
  - Κυτταρικού κύκλου
  - Σημείων ελέγχου
  - Μεταγωγής σήμανσης
Ογκοκατασταλτικά: «κληρονομική υπόθεση»

- Υπεύθυνα για την κληρονομούμενη προδιάθεση για εκδήλωση καρκίνου
Ογκοκατασταλτικά: "κληρονομική υπόθεση"

- p53
  - πολλοί καρκίνοι, Li-Fraumeni
- BRCA1, BRCA2, CHEK2
  - μαστού - ωσθηκών
- retinoblastoma - rb
  - ρετινοβλάστωμα
- p16
  - μελάνωμα
<table>
<thead>
<tr>
<th>Event</th>
<th>Sporadic Tumor</th>
<th>Hereditary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception</td>
<td>Two normal alleles (all cells)</td>
<td>Heterozygosity for mutant allele (all cells)</td>
</tr>
<tr>
<td>1st spontaneous</td>
<td>Heterozygosity for mutant allele (one cell)</td>
<td>Loss of heterozygosity (one cell)</td>
</tr>
<tr>
<td>mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd spontaneous</td>
<td>Loss of heterozygosity (one cell)</td>
<td></td>
</tr>
<tr>
<td>mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitosis</td>
<td></td>
<td>Tumor Growth</td>
</tr>
</tbody>
</table>
2010: ο καρκίνος είναι γενετική & επιγενετική νόσος
oncomirs
# RNA

## Box 1 | Prominent members of the RNA family

<table>
<thead>
<tr>
<th>Classic RNAs mediating protein synthesis</th>
<th>Non-coding regulatory RNAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mRNAs (messenger RNAs)</strong></td>
<td><strong>siRNAs (small interfering RNAs)</strong> Small RNAs (20–25 nucleotides in length) formed through cleavage of long double-stranded RNA molecules. siRNAs are particularly important for taming the activity of transposons and combating viral infection, but they can also regulate protein-coding genes. Synthetic siRNAs can also be artificially expressed for experimental purposes.</td>
</tr>
<tr>
<td><strong>rRNAs (ribosomal RNAs)</strong> RNA constituents of the ribonucleoprotein particles known as ribosomes, which mediate the decoding of mRNAs to the amino-acid sequences of proteins.</td>
<td><strong>piRNAs (Piwi-associated RNAs)</strong> Small RNAs (25–30 nucleotides in length) that are generated from long single-stranded precursors. They function in association with the Piwi subfamily of Argonaute proteins, and are essential for the development of germ cells.</td>
</tr>
<tr>
<td><strong>tRNAs (transfer RNAs)</strong> Adapter molecules carrying individual amino acids to the site of protein synthesis that recognize specific codons in mRNA.</td>
<td><strong>miRNAs (microRNAs)</strong> Small RNAs (20–25 nucleotides in length) that are encoded by specific genes and function in repressing mRNA translation or in mRNA degradation in plants and animals. They are processed from long, single-stranded RNA sequences that fold into hairpin structures.</td>
</tr>
</tbody>
</table>

---

H.G. & W.F.
miRNA: miRNA* ds complex

 pri-miRNA (primary microRNA transcript)

 pre-miRNA (precursor microRNA)

 Dicer

 pri-miRNA

 Microprocessor

 Drosha-DGCR8

 RanGTP

 Exportin-5

 TF

 pol II/III

 DNA

 nucleus

 cytoplasm

 miRNA*

 TRBP

 PACT

 m7G

 Helicase

 miRISC assembly

 Ago2

 ORF

 3' UTR

 m7G

 AB
Ετεροχρωματίνη
Μεθυλιωμένο DNA

Ευχρωματίνη
Μη μεθυλιωμένο DNA

αποακετυλιωμένα άκρα ιστονών

ιστόνες

Μεθυλιωμένα ζεύγη CpG

ακετυλιωμένα άκρα ιστονών

RNA Πολυμεράση ΙΙ

ιστόνες

Metagrapofikoii paragontes

νουκλέοσωμα

mRNA

MBP
Epigenetics in cancer

- Global hypomethylation
- Gene promoter-associated (CpG island-specific) hypermethylation
μικρο-περιβάλλον του ξενιστή
Original image from Ide et al (1939) showing an extensive vascular network in transplanted rabbit epithelioma
All in the Stroma: Cancer’s Cosa Nostra

After focusing for decades on what happens within tumor cells to make them go wrong, biologists are turning to the tumor environment and finding a network of coconspirators.
αγγειογένεση
Support system. Promoting new blood vessel growth is one of many ways that tumor cells can make the microenvironment more hospitable to cancer.
Μικρός όγκος (1–2mm)

Μεγάλος, αγγειοβριθής με μεταστατικό δυναμικό όγκος

Αγγειογόνος διακόπτης
Φυσιολογικά αγγεία

Αγγεία που διηθούν ένα κακοήθη ογκο

Παράγοντες διαφοροποίησης

OXI αυξητικοί παράγοντες

Ισχυρές συνδέσεις

Περικύτταρα

Αυξητικοί παράγοντες (VEGF)

Ιντεγκρίνες

Διαφυγή

Λιγότερα περικύτταρα
σύμφωνη μεταστατική ικανότητα
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Detection rate (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>20-40</td>
<td>(10)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>20-50</td>
<td>(113 – 116)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>40-60</td>
<td>(117 – 119)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>35-60</td>
<td>(120, 121)</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>30-40</td>
<td>(60, 122)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>20-35</td>
<td>(112, 123, 124)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>20-30</td>
<td>(123, 125, 126)</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>20-30</td>
<td>(127 – 131)</td>
</tr>
</tbody>
</table>
Νόσος καρκινικών βλαστικών κυττάρων;