ONCOLOGIA MOLECOLARE E CELLULARE

Michela Clerici

Cancro e oncologia

CANCRO: dal greco **καρκίνος** (karkinos), «granchio»

NEOPLASIA: dal greco **νέος** (nèos) «nuovo», e **πλάσις** (plásis), «formazione»

TUMORE: dal latino tumor, «rigonfiamento»

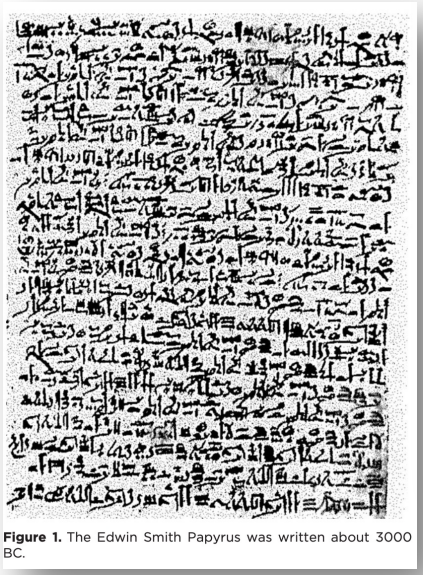


Figure 1. The Edwin Smith Papyrus was written about 3000 BC.

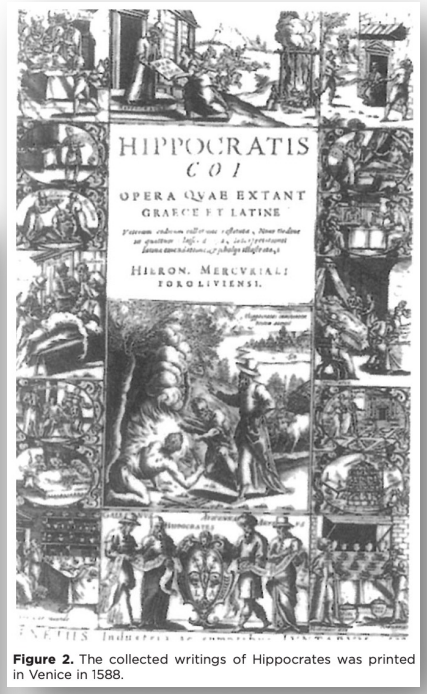


Figure 2. The collected writings of Hippocrates was printed in Venice in 1588.

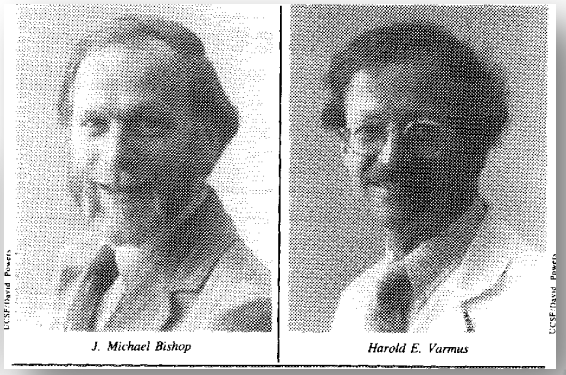
ONCOLOGIA: dal greco ὄ**γκος** (óncos), rigonfiamento e **λόγος** (lógos) «studio» è la branca della medicina che studia e tratta i tumori.

Hajdu, Cancer 2011. DOI: 10.1002/cncr.25553

Oncologia molecolare

- Carcinogeni sono spesso mutageni -> geni mutati promuovono proliferazione di cellule tumorali?
- Sviluppo del cancro è un processo lungo
- Singole cellule tumorali si comportano in maniera molto diversa dalla controparte in tessuti sani

1989: Premio Nobel per la medicina



1975

DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA

Stehelin et al., Nature. 260: 170-3.
DOI: 10.1038/260170A0

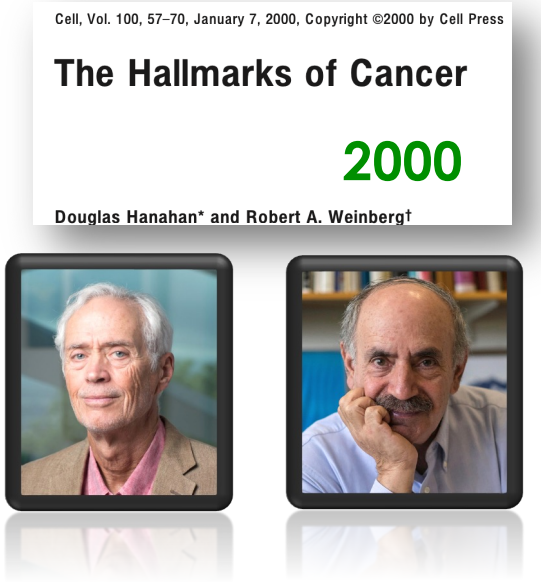
Descrizione primo proto-oncogene

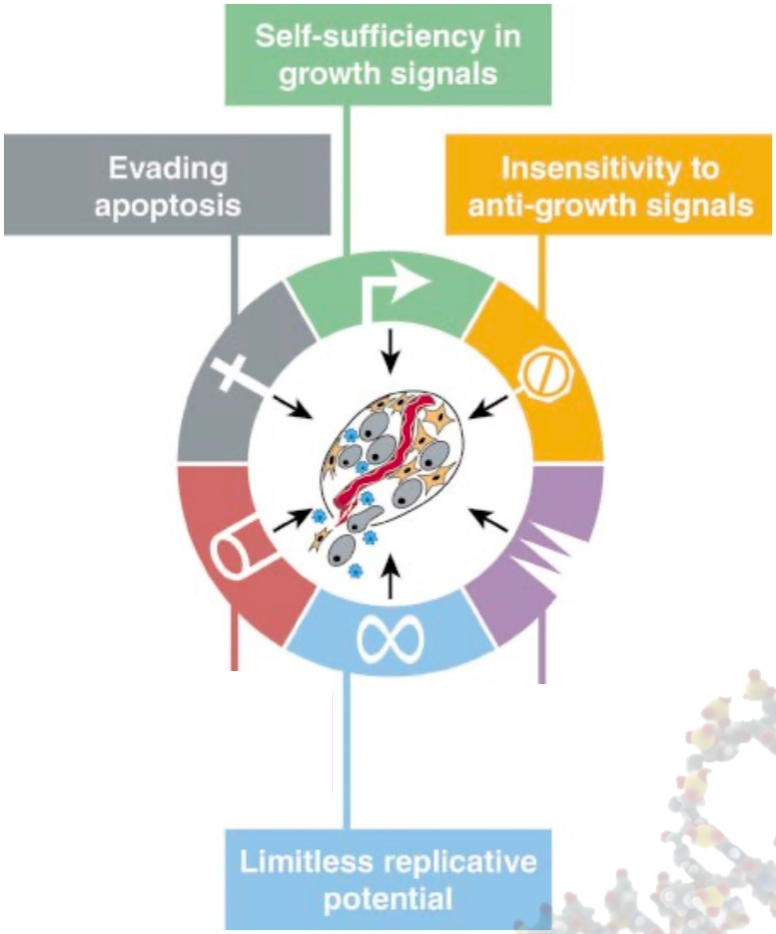
Cancer in XXI century

- multifacetd family of disease
- multistep process
- involves dinamic changes in the genome
- complex disease showing key common traits

The hallmarks of cancer

Cancer is a multistep process





A set of functional capabilities acquired by human cells as they make their way from normal to neoplastic growth states.

Capabilities that are crucial for their ability to form malignant tumors

Hanahan &Weinberg, 2000.

Cell heterogeneity in cancer

Ancillary cells (fibroblasts, endothelial cells,…) present in a tumor contribute to tumorigenesis and tumor cell proliferation

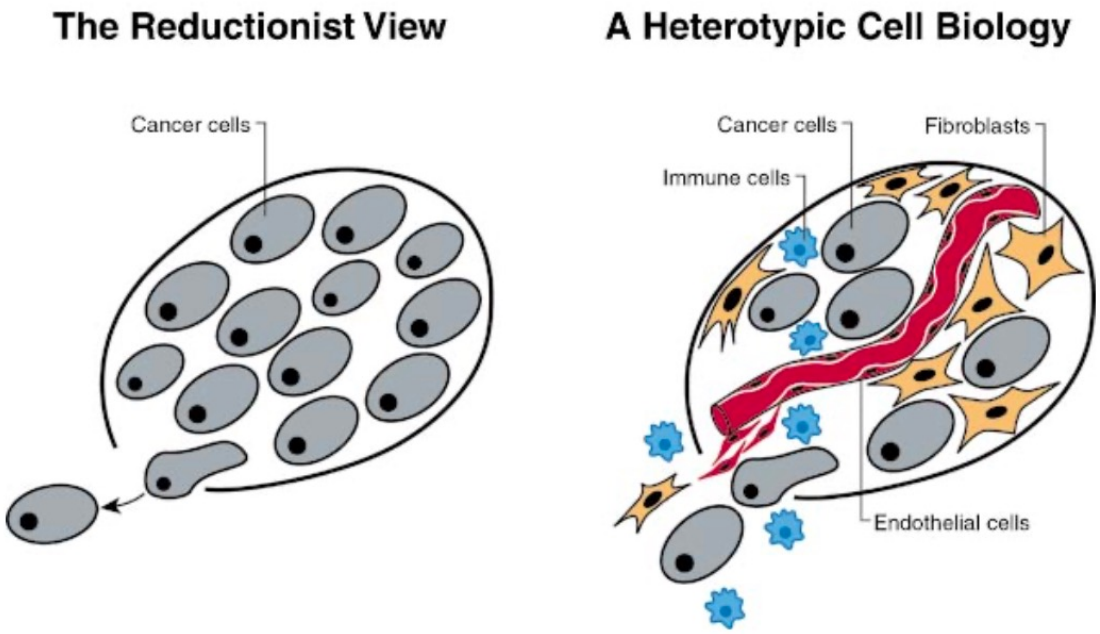


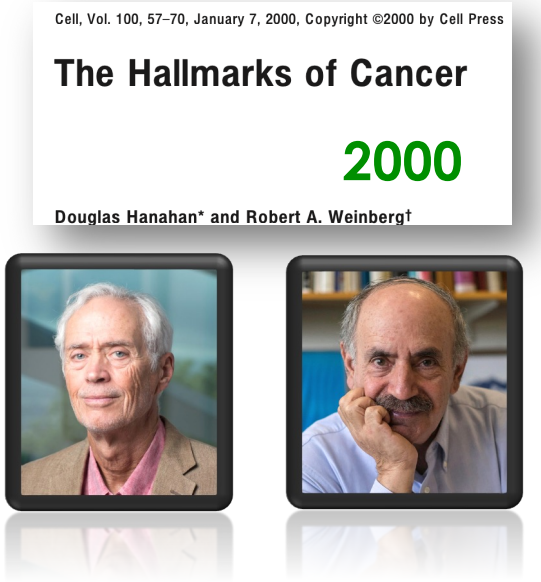
Figure 3. Tumors as Complex Tissues

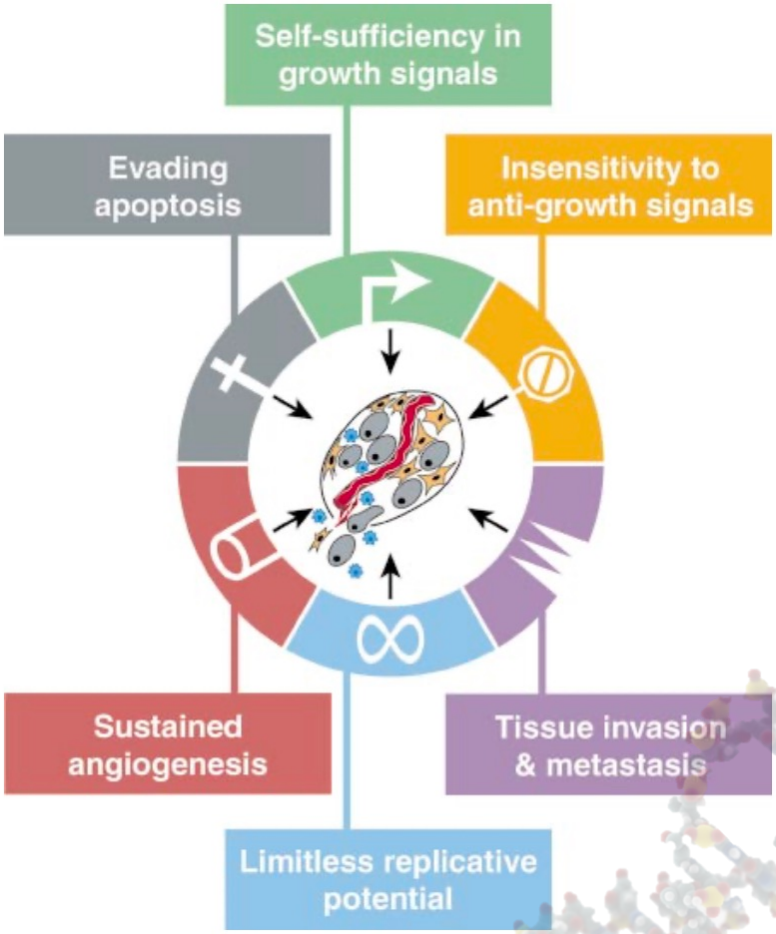
The field of cancer research has largely been guided by a reductionist focus on cancer cells and the genes within them (left panel)—a focus that has produced an extraordinary body of knowledge. Looking forward in time, we believe that important new inroads will come from regarding tumors as complex tissues in which mutant cancer cells have conscripted and subverted normal cell types to serve as active collaborators in their neoplastic agenda (right panel). The interactions between the genetically altered malignant cells and these supporting coconspirators will prove critical to understanding cancer pathogenesis and to the development of novel, effective therapies.

Hanahan &Weinberg, 2000.

The hallmarks of cancer

Cancer is a multistep process





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The hallmarks of cancer

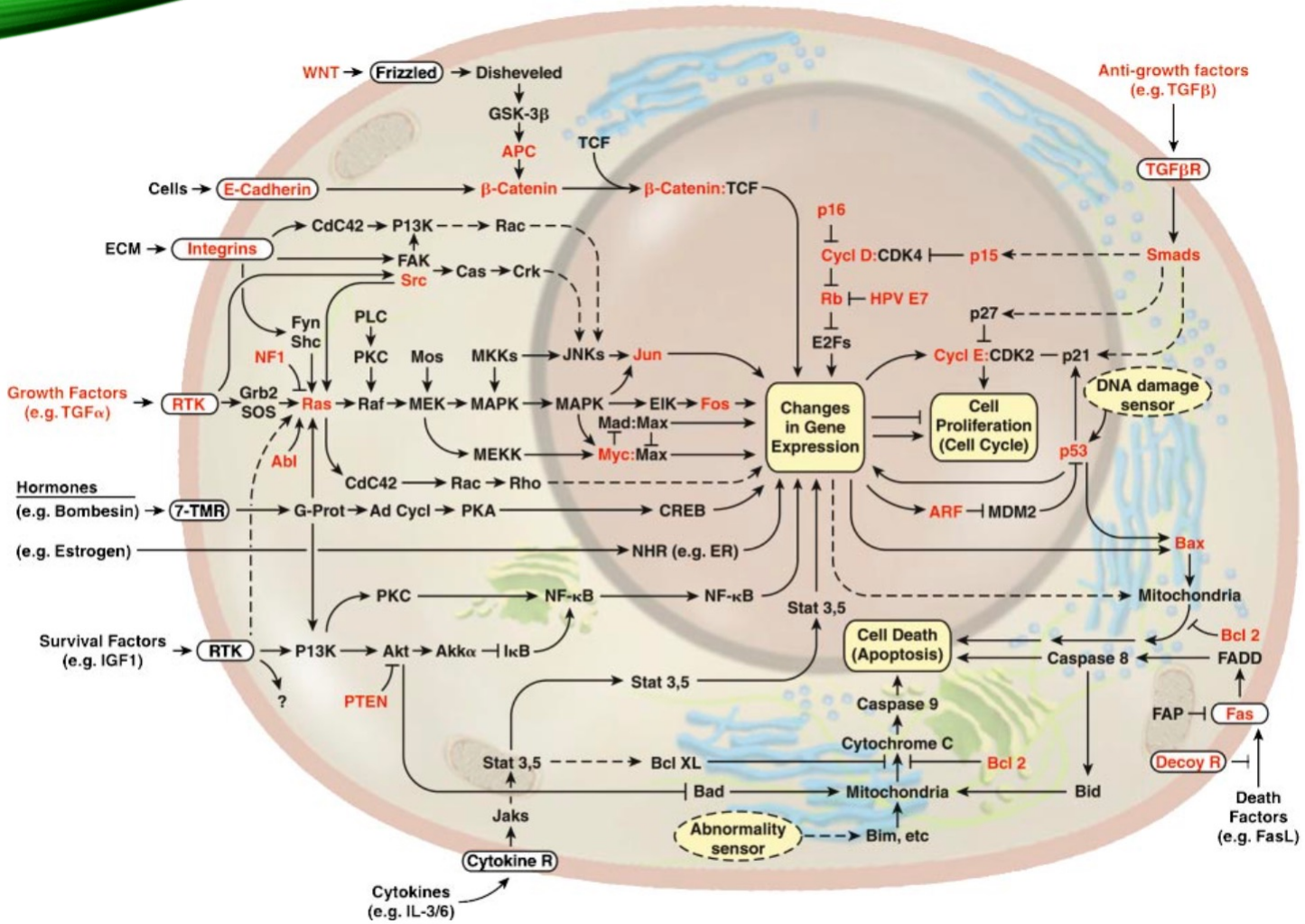


Figure 2. The Emergent Integrated Circuit of the Cell

Progress in dissecting signaling pathways has begun to lay out a circuitry that will likely mimic electronic integrated circuits in complexity and finesse, where transistors are replaced by proteins (e.g., kinases and phosphatases) and the electrons by phosphates and lipids, among others. In addition to the prototypical growth signaling circuit centered around Ras and coupled to a spectrum of extracellular cues, other component circuits transmit antigrowth and differentiation signals or mediate commands to live or die by apoptosis. As for the genetic reprogramming of this integrated circuit in cancer cells, some of the genes known to be functionally altered are highlighted in red.

Hanahan & Weinberg, 2000.

Hallmarks aquisition

There is no a precise order of hallmarks aquisition

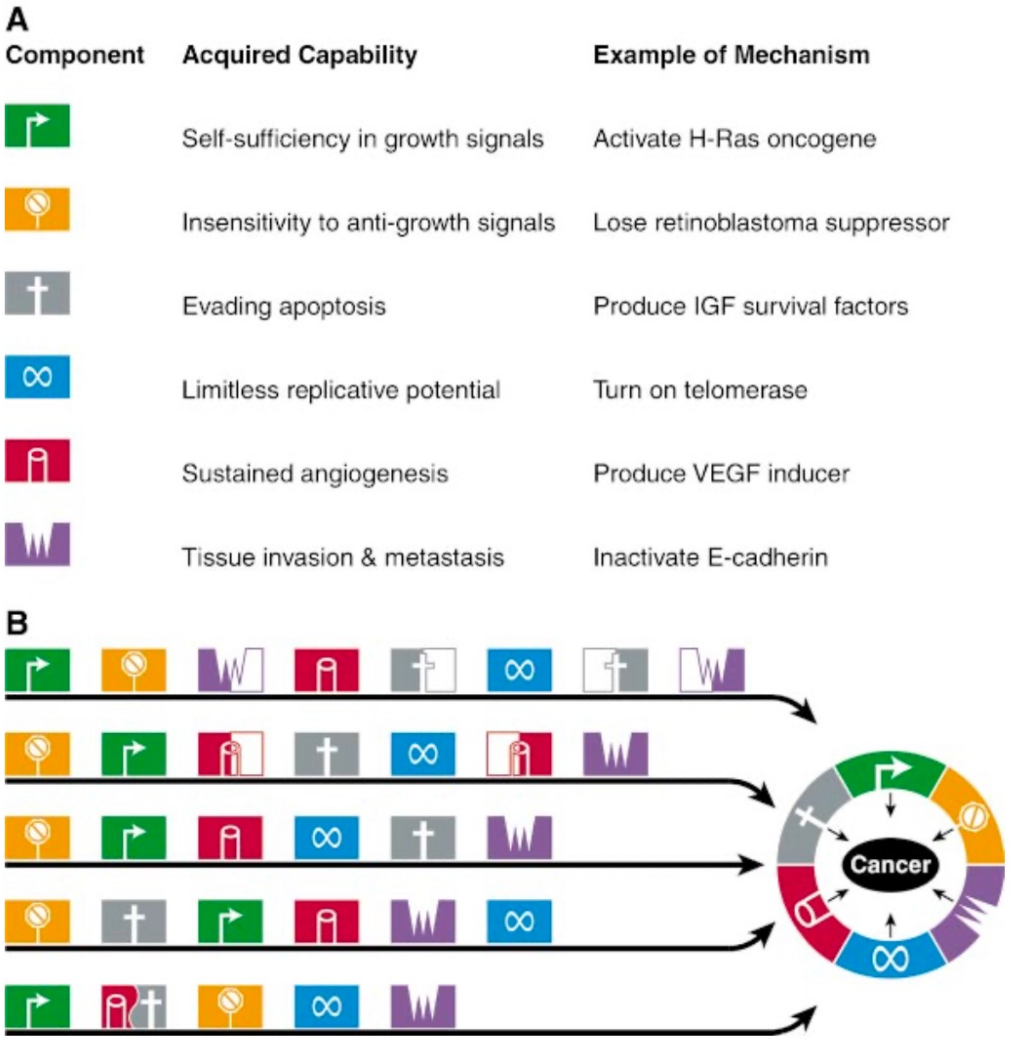
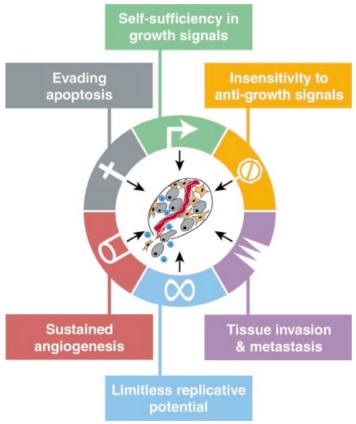


Figure 4. Parallel Pathways of Tumorigenesis

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.

Hanahan & Weinberg, 2000.

How the hallmarks are generated?



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

2000

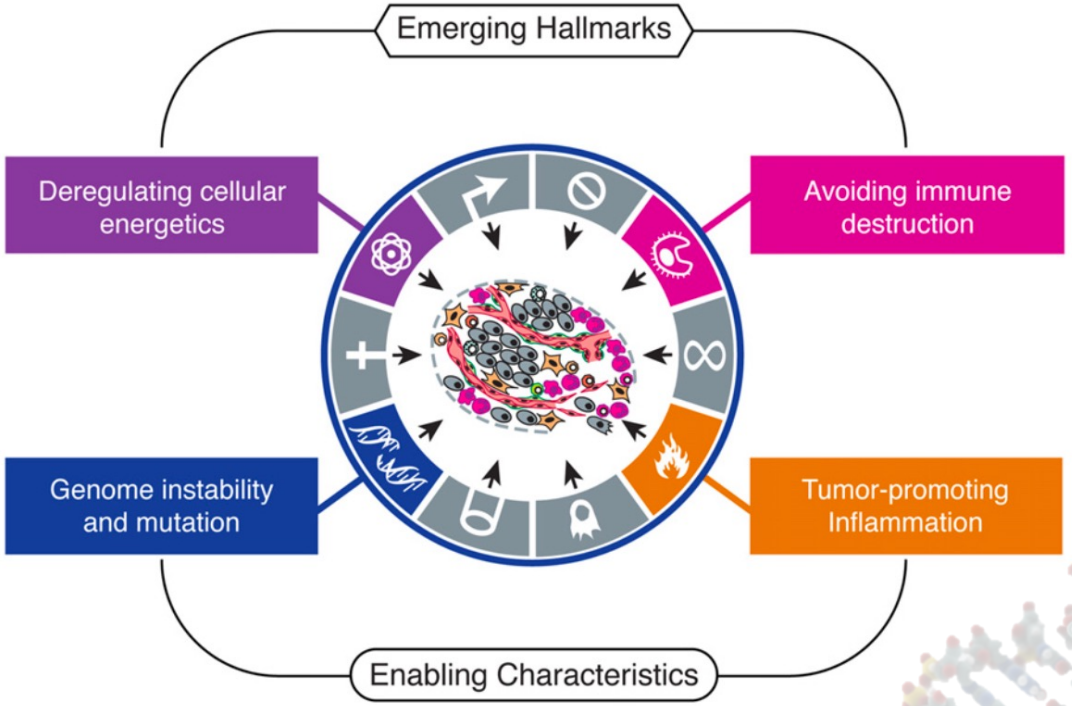
Douglas Hanahan* and Robert A. Weinberg†

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013

2011

Hallmarks of cancer (acquired capabilities) and enabling characteristics



Hanahan & Weinberg, 2011

Hallmarks of Cancer: The Next Generation

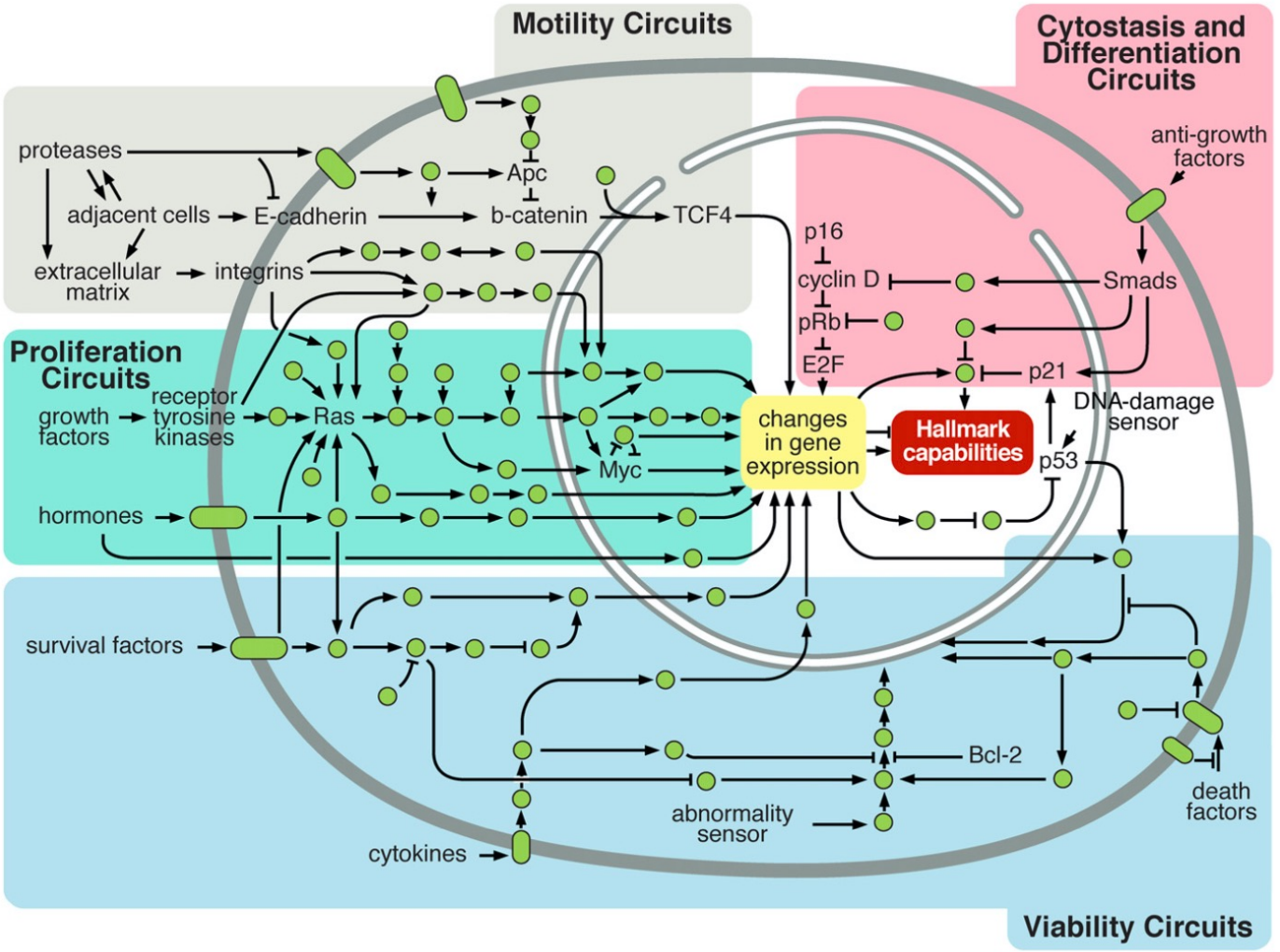


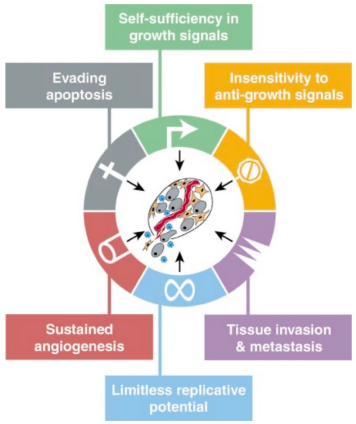
Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment, as outlined in Figure 5.

Hanahan & Weinberg, 2011

The hallmarks of cancer

Cancer is a multistep process



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Hallmarks of Cancer: The Next Generation

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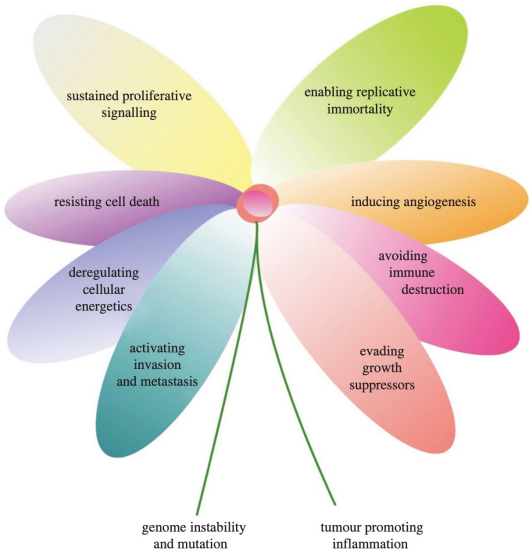
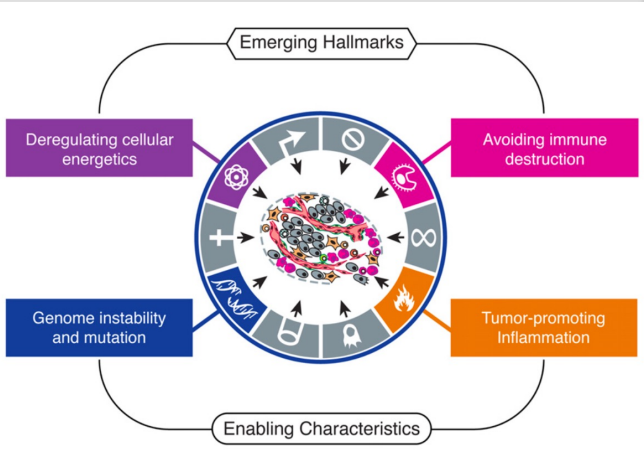
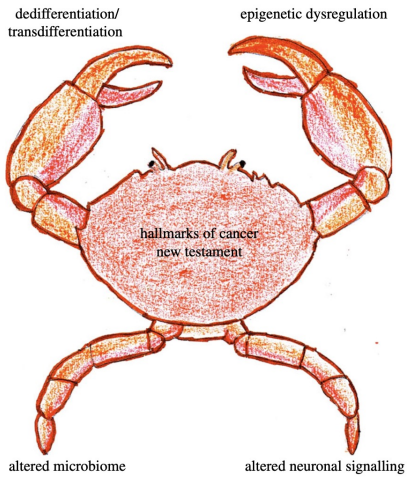




2021



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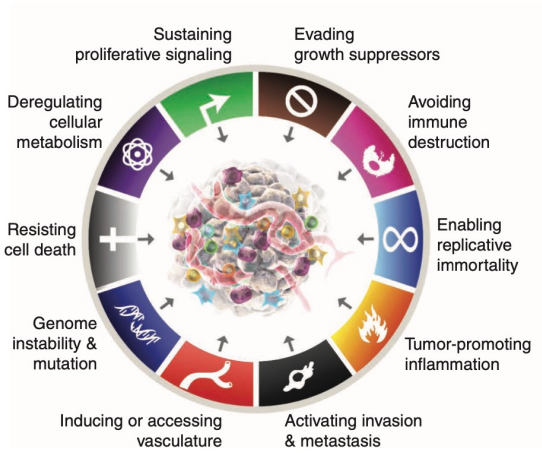
Hallmarks of cancer—the new testament

Sasi S. Senga and Richard P. Grose
Centre for Tumour Biology, Barts Cancer Institute, Queen Mary University of London, London EC1M 6BQ, UK
RPG, 0000-0002-4738-0173

The hallmarks of cancer

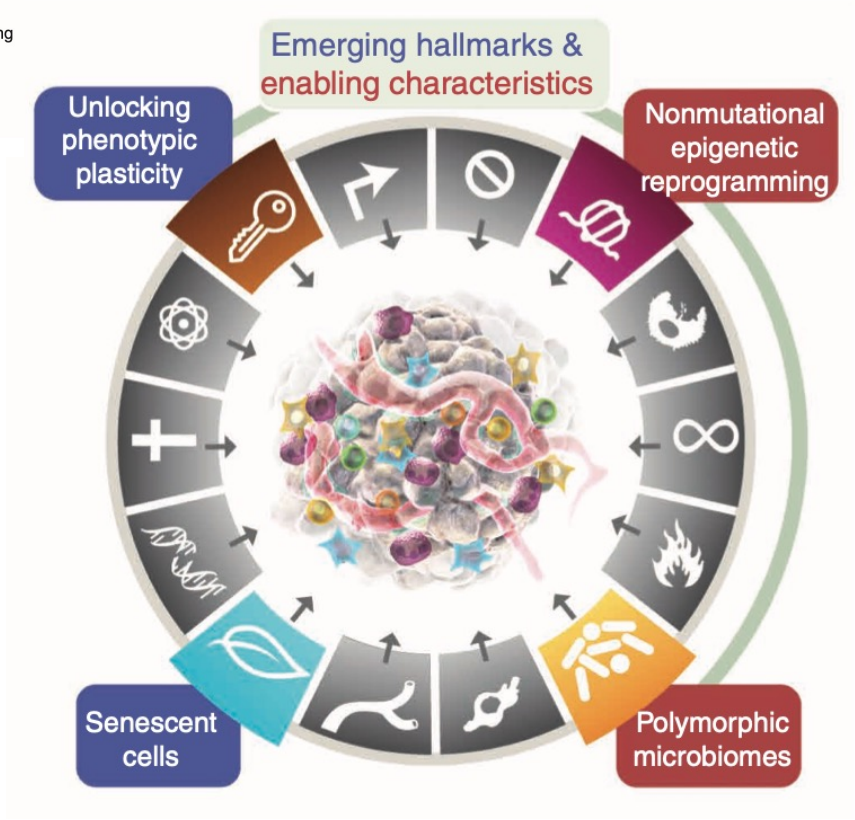


REVIEW

Hallmarks of Cancer: New Dimensions

Douglas Hanahan

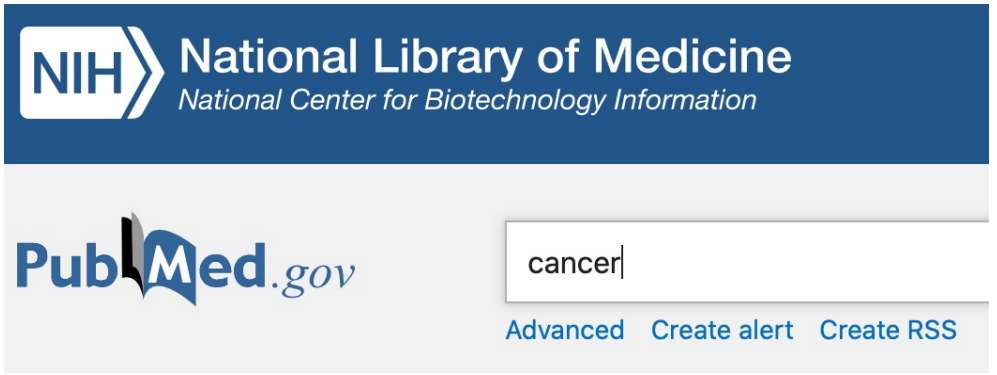
JANUARY 2022 CANCER DISCOVERY

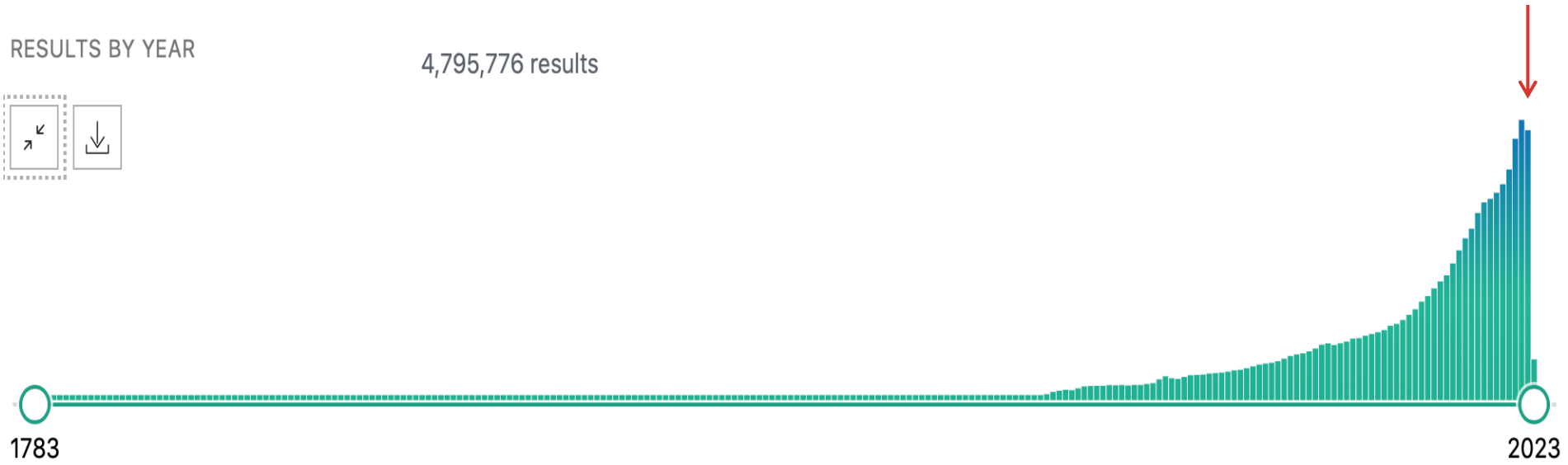


Hanahan, 2021

Cancer literature

- 273.274 pubblicazioni nel 2022

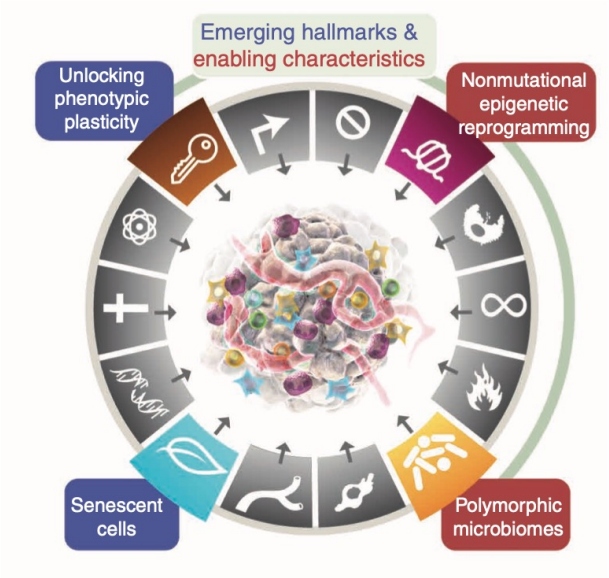




Obiettivi

- Approfondire i meccanismi genetico-molecolari alla base della tumorigenesi, i principi base dell'oncologia molecolare e della progressione tumorale, tramite anche la ricostruzione di percorsi sperimentali.
- Tumorigenesi come un percorso a tappe, con particolare attenzione al ruolo dell'instabilità genetica nella progressione tumorale.
- Fornire gli strumenti necessari alla comprensione ed alla valutazione critica della letteratura scientifica inerente l’oncologia molecolare.

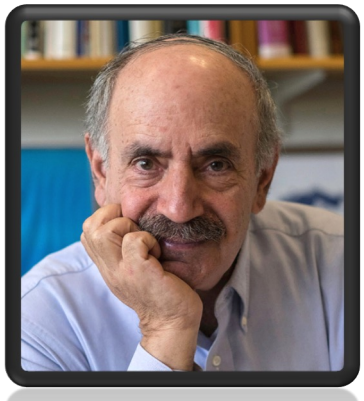
Programma



- Principi generali di oncologia
- Oncogeni e oncosoppressori
- Meccanismi di soppressione tumorale
- Senescenza ed apoptosi
- Instabilità genetica e cancro
- Telomeri e telomerasi
- Cellule staminali e cancro
- Genomica del Cancro
- Verso la terapia personalizzata: letalità e citotossicità sintetica nella cura del cancro

Materiale didattico

- Articoli di ricerca originali e reviews
- Testo consigliato: Robert A. Weinberg, La biologia del cancro, Zanichelli
- Presentazioni delle lezioni



Ricevimento

Su appuntamento oppure al termine delle lezioni.

Michela Clerici – stanza 5051 – U3, piano 5

E-mail: michela.clerici@unimib.it

Esame

Prova orale: discutere e applicare le conoscenze, gli approcci e le metodologie appresi durante il corso per affrontare lo studio di specifici aspetti nel campo dell'oncologia molecolare.

Appelli d'esame

- 27 Aprile 2023
- 9 Maggio 2023
- 13 Giugno 2023
- 11 Luglio 2023
- 14 Settembre 2023
- 10 Ottobre 2023
- 7 Novembre 2023
- 12 Dicembre 2023
- Gennaio: da definire
- Febbraio: da definire