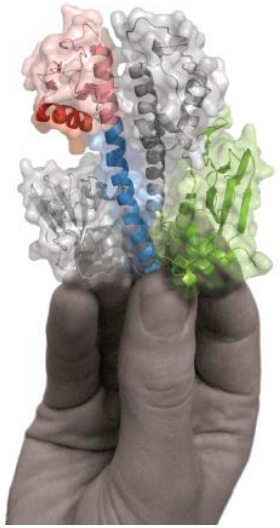
SAPIENZA
UNIVERSITÀ DI ROMA

Comunicazione Scientifica Biomedica

la Scienza a portata di mano



Comunicazione delle Scienze Biomediche

Prof.ssa Cristina Cerboni

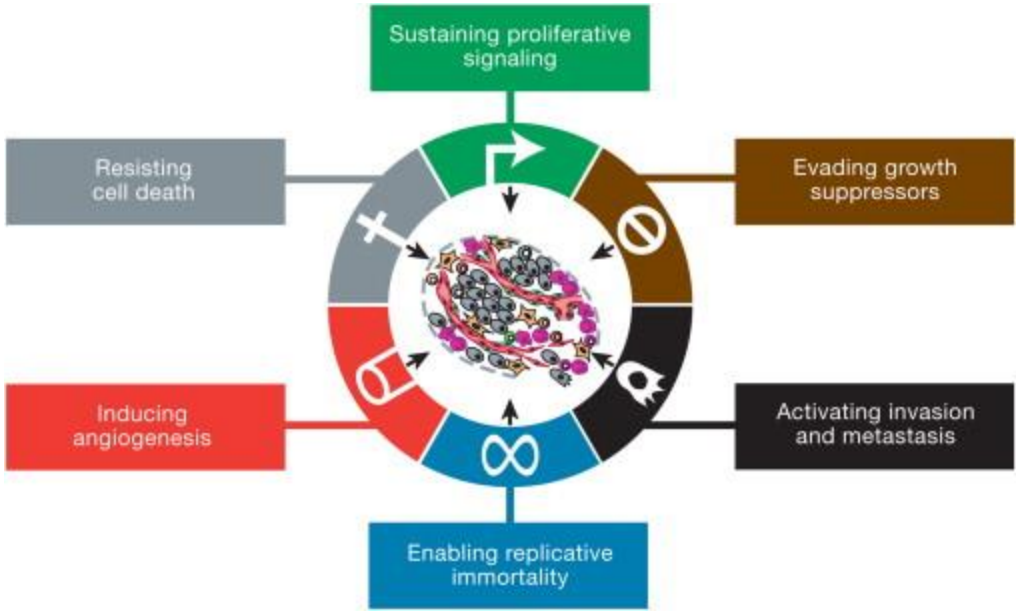
Immunità e tumori

Anno Accademico 2024-2025

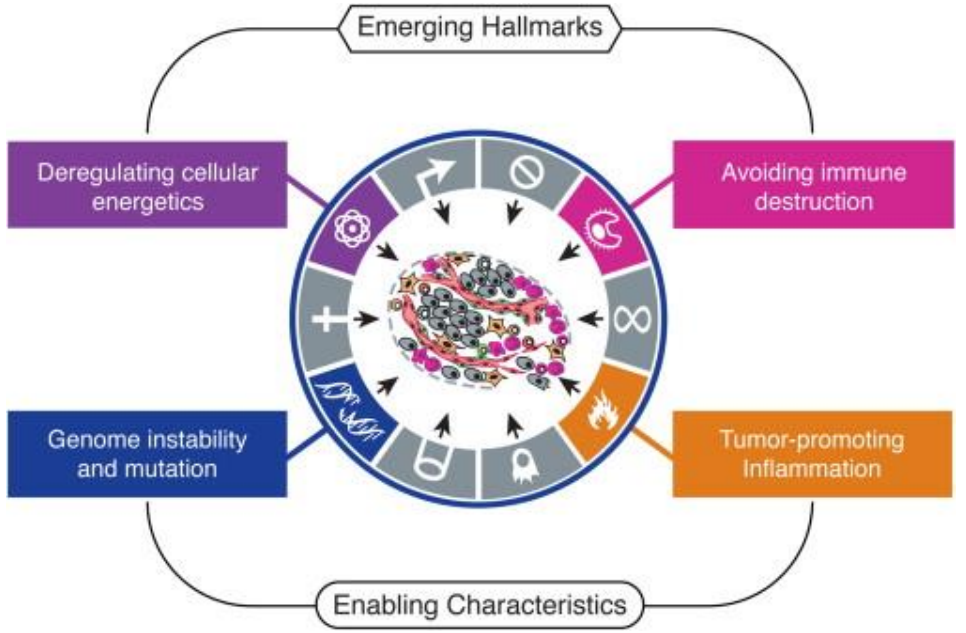
19-20 novembre 2024

Le proprietà di un tumore

2001



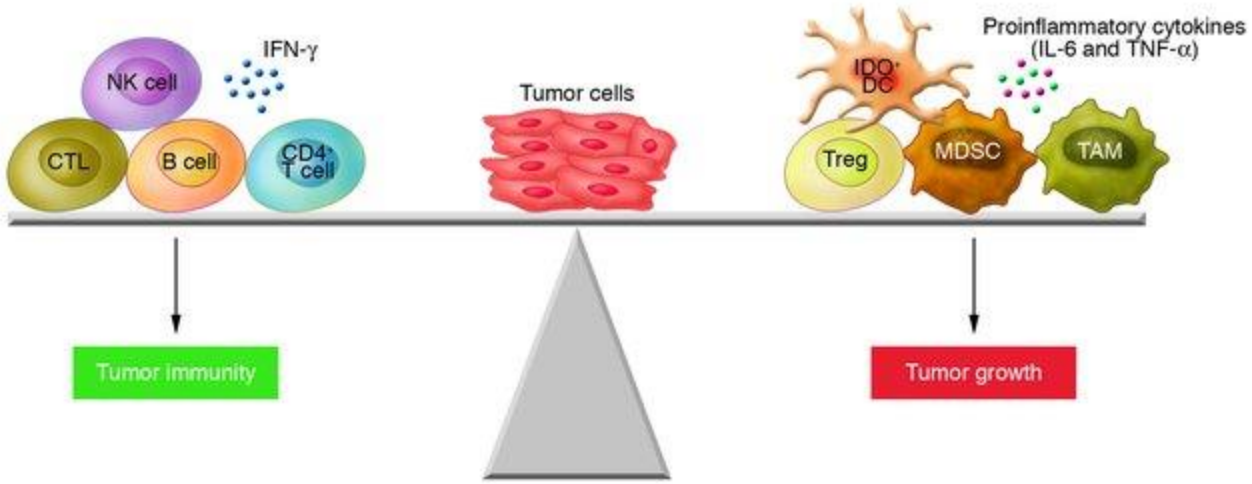
2011



10 anni dopo emergono nuove proprietà…

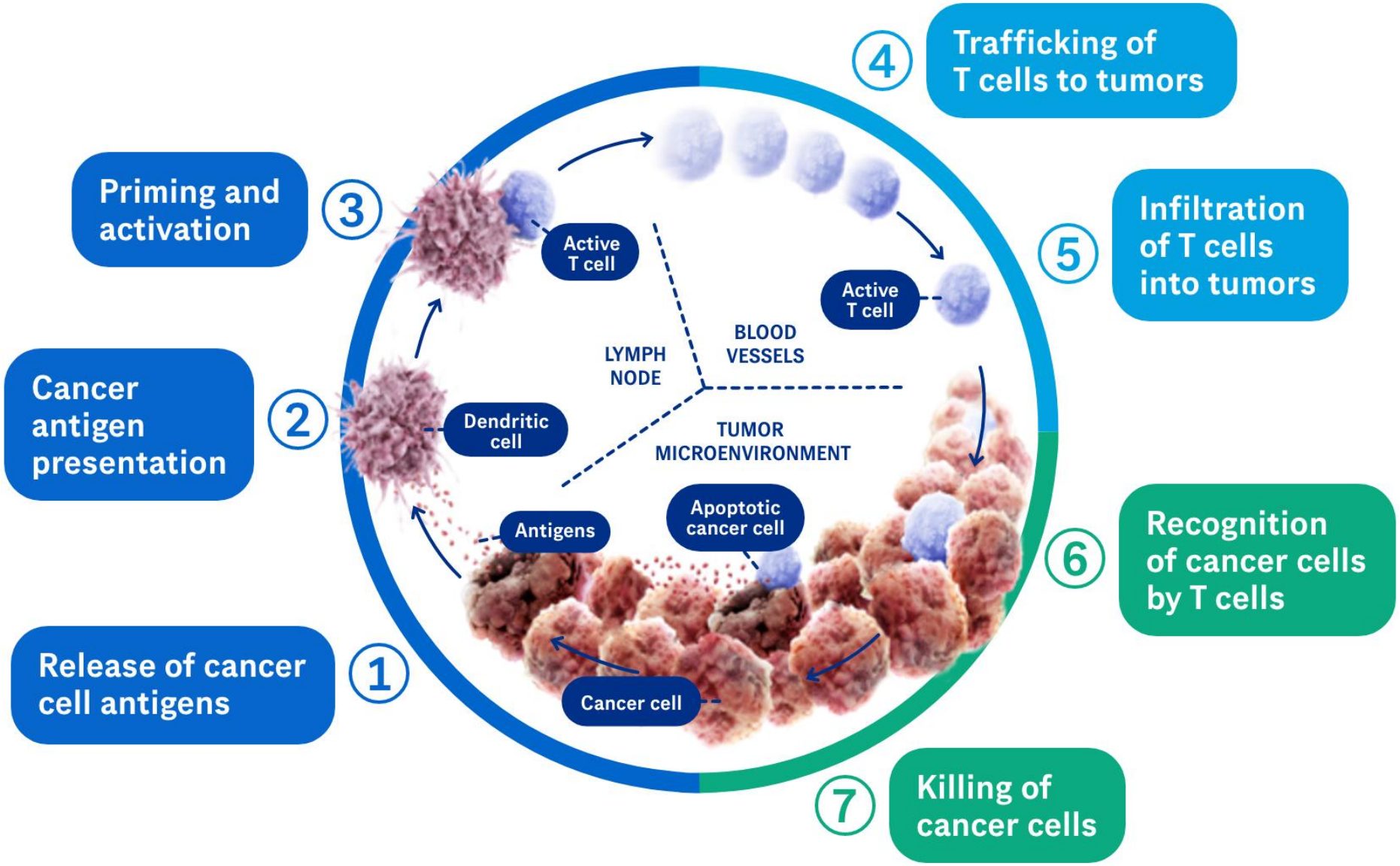
The Hallmarks of Cancer
Hanahan D and Weinberg RA, Cell 2011

Immunità e tumori

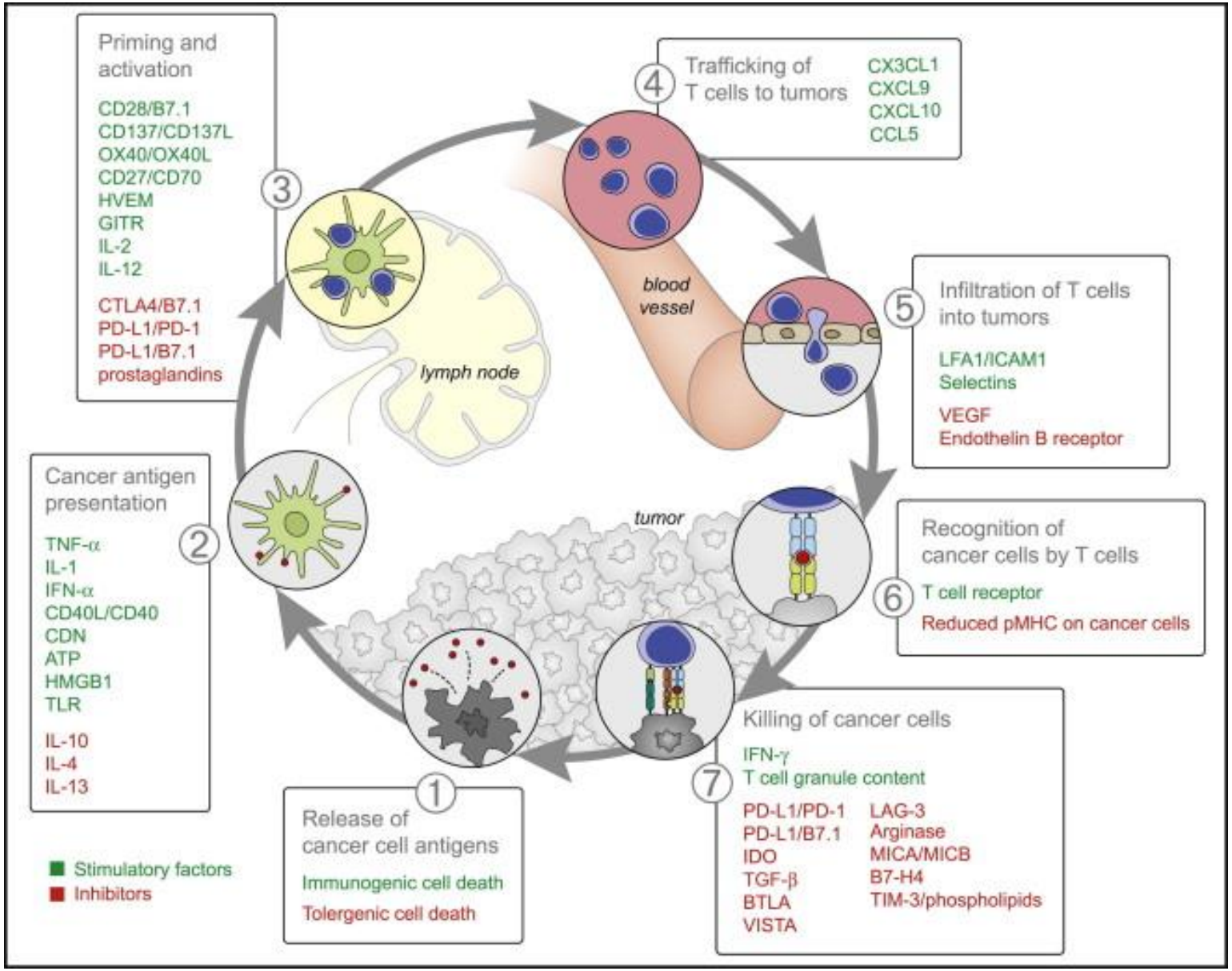


Treg: regulatory T cells
MDSC: myeloid-derived suppressor cells
TAM: tumor-associated macrophages

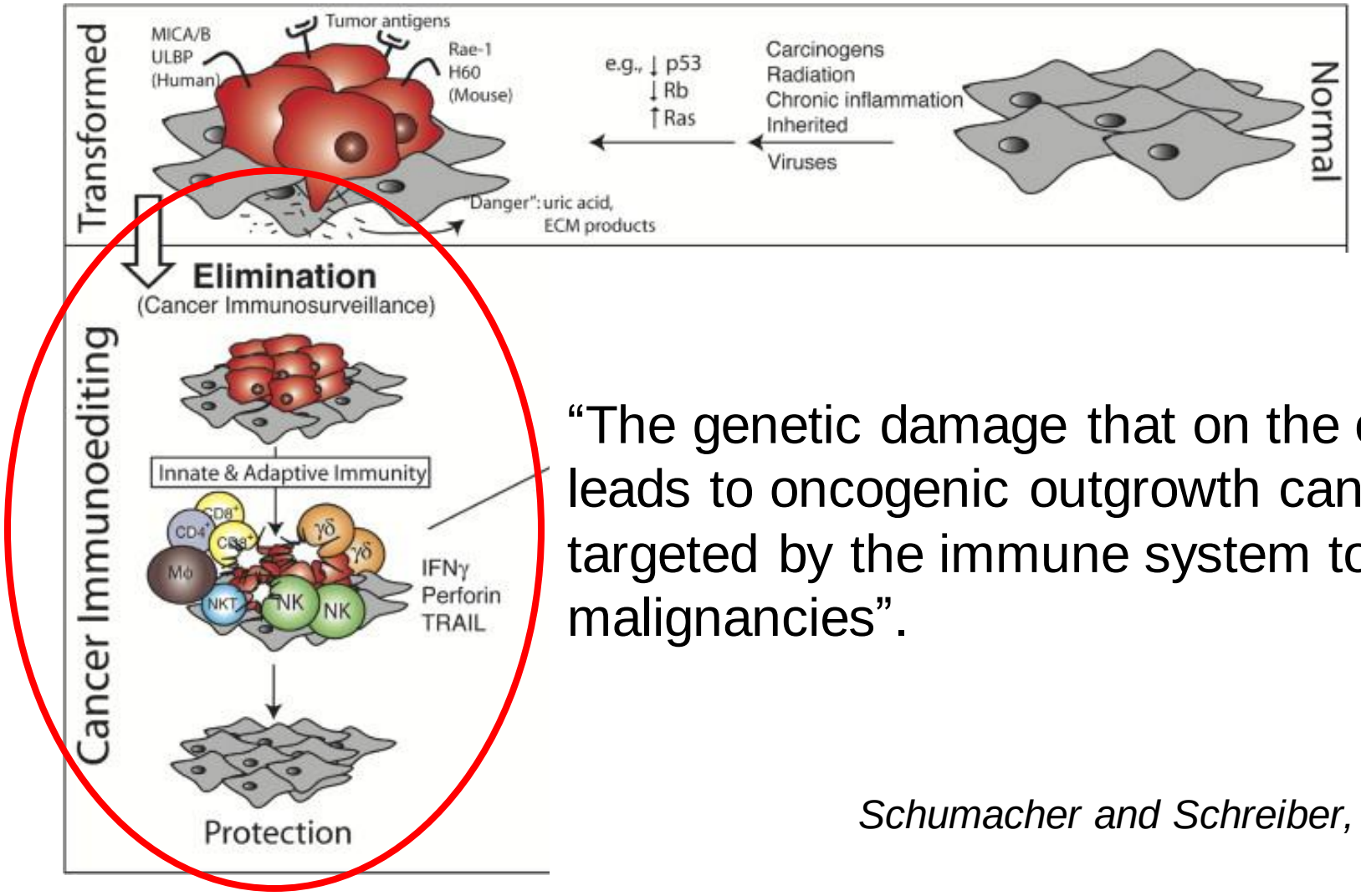
The Cancer-Immunity Cycle



The cancer-immunity cycle with stimulatory and inhibitory factors



The immune system establishes a dynamic interaction with the tumour: cancer immunoediting

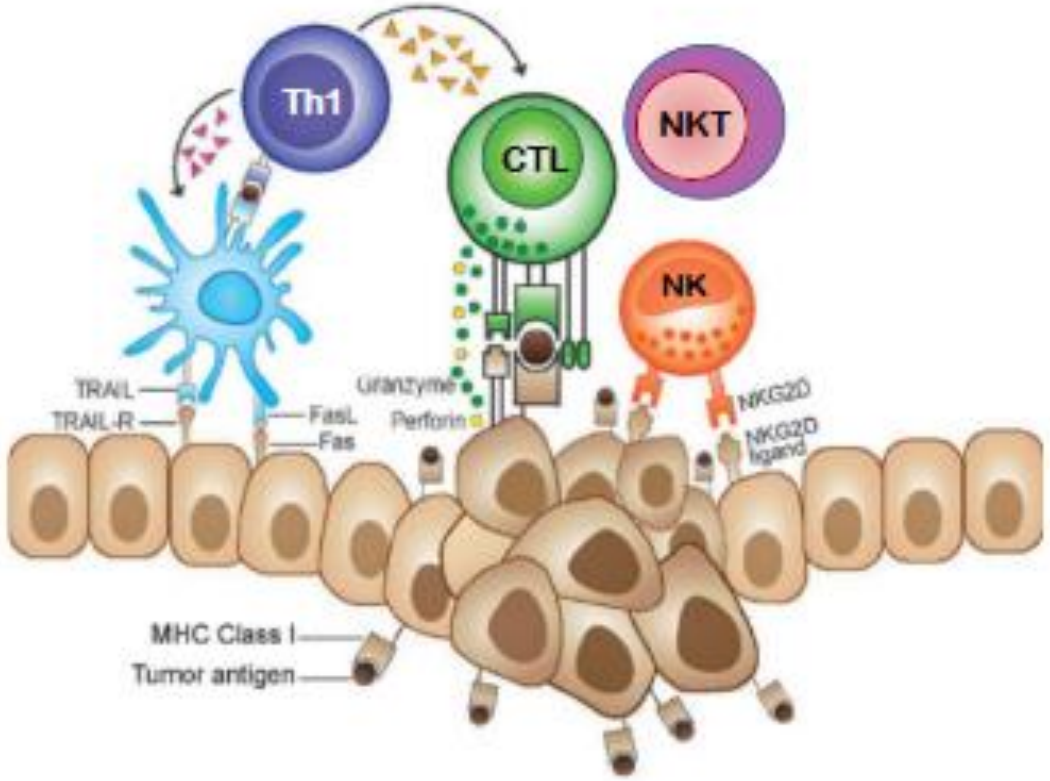


"The genetic damage that on the one hand leads to oncogenic outgrowth can also be targeted by the immune system to control malignancies".

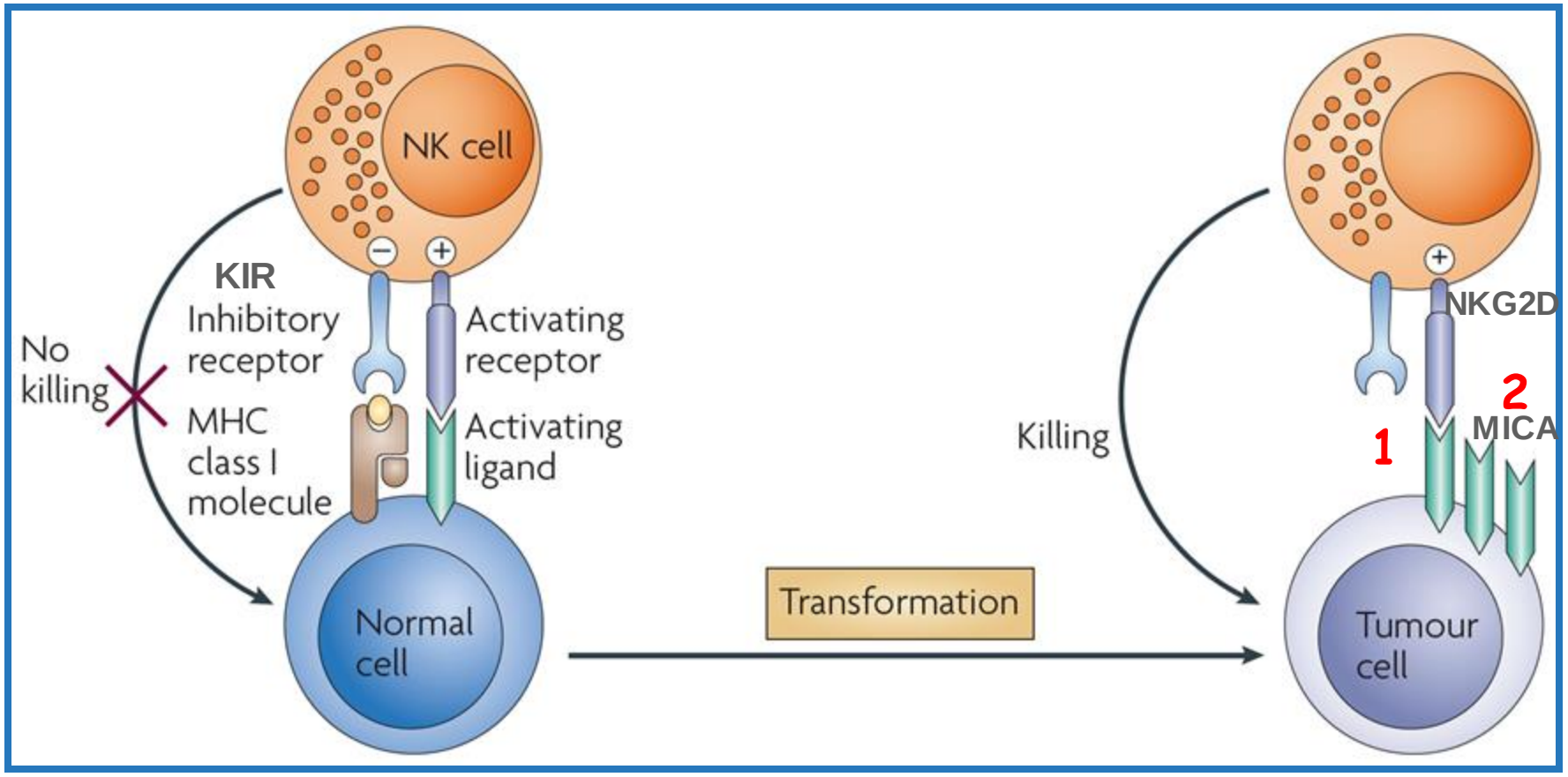
Schumacher and Schreiber, Science 2015

Dunn et al Immunity 2004

ELIMINATION



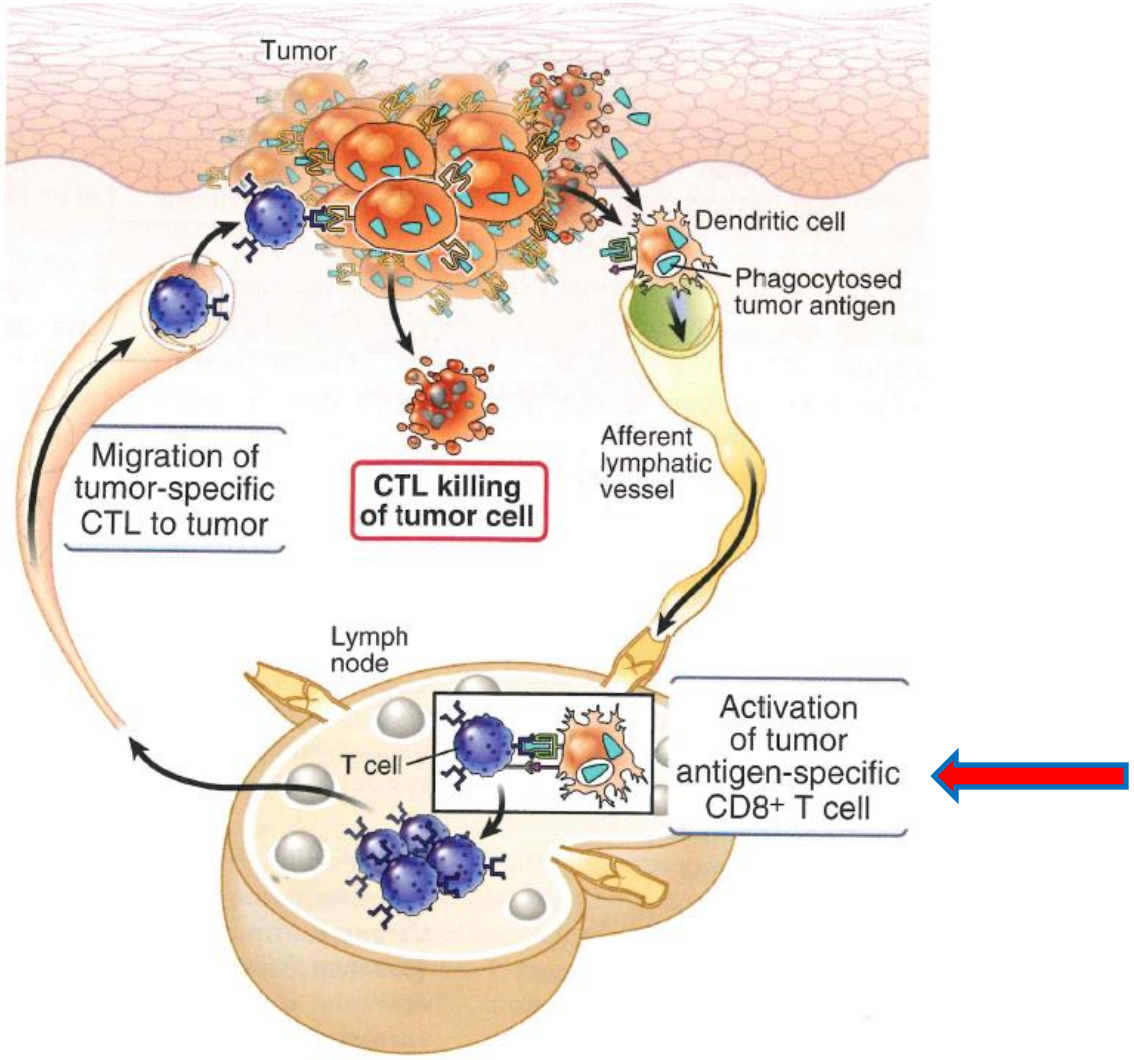
Le cellule NK eliminano una cellula tumorale attraverso il *missing-self* (1) e l'*induced-self* (2)



il *missing-self* (1) è la perdita di inibizione (MHC-I);
l'*induced-self* (2) è una "super-attivazione" dovuta all'aumento di espressione di molecole attivatorie (MICA, ULBPs)

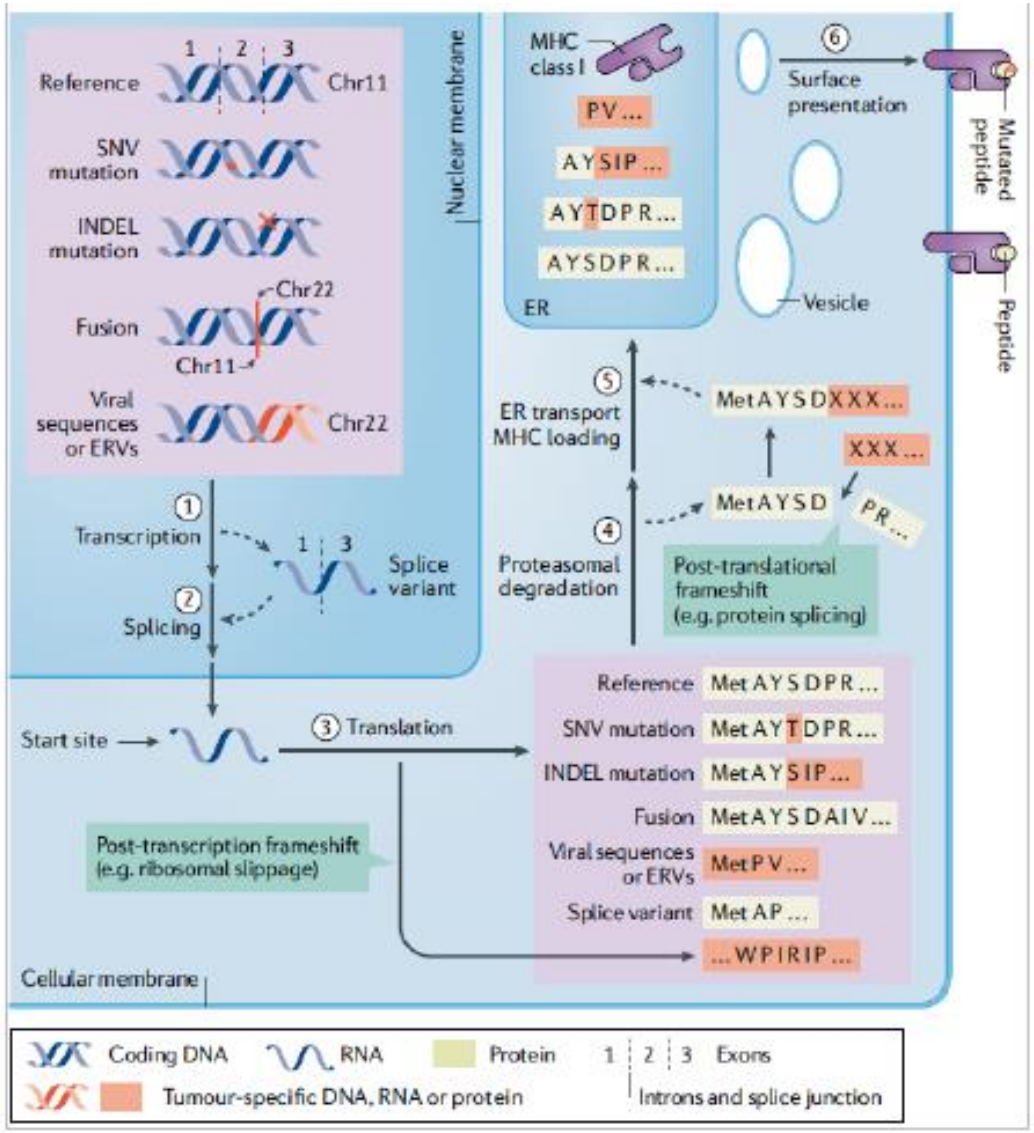
Immunità adattativa

The principal mechanism of immune protection against tumors is killing of tumor cells by CD8+ CTLs



Gli antigeni tumorali

La generazione di antigeni tumorali



Chr, chromosome;
ERV, endogenous retrovirus;
INDEL, insertion or deletion;
SNV, single-nucleotide variant

Smith CC Nature Rev Cancer 2019

What type of antigens can be expressed?

1. Tumor-specific antigens (TSA) are only expressed by the tumor

2. Tumor-associated antigens (TAA) which can also be found in other normal cell types

1a. Unique TSA: result from somatic point mutations (possibly induced by carcinogens) and, therefore, occur in **a single** tumor of one patient; bone fide TSA are not expressed by any normal tissue.

Can be:

Neoantigens: antigens encoded by mutated genes (can be driver mutation or not)

Antigens of Oncogenic Viruses

1b. Shared TSA expressed in different tumors but not in healthy tissues. The most prominent antigens among this group are the cancer-testis family of antigens including MAGE, BAGE, LAGE, GAGE, and NY-ESO-1, which in normal tissues are restricted only to testis and placenta.

2. Shared TAA This category of antigens, although not tumor specific, is overexpressed in different types of tumors.

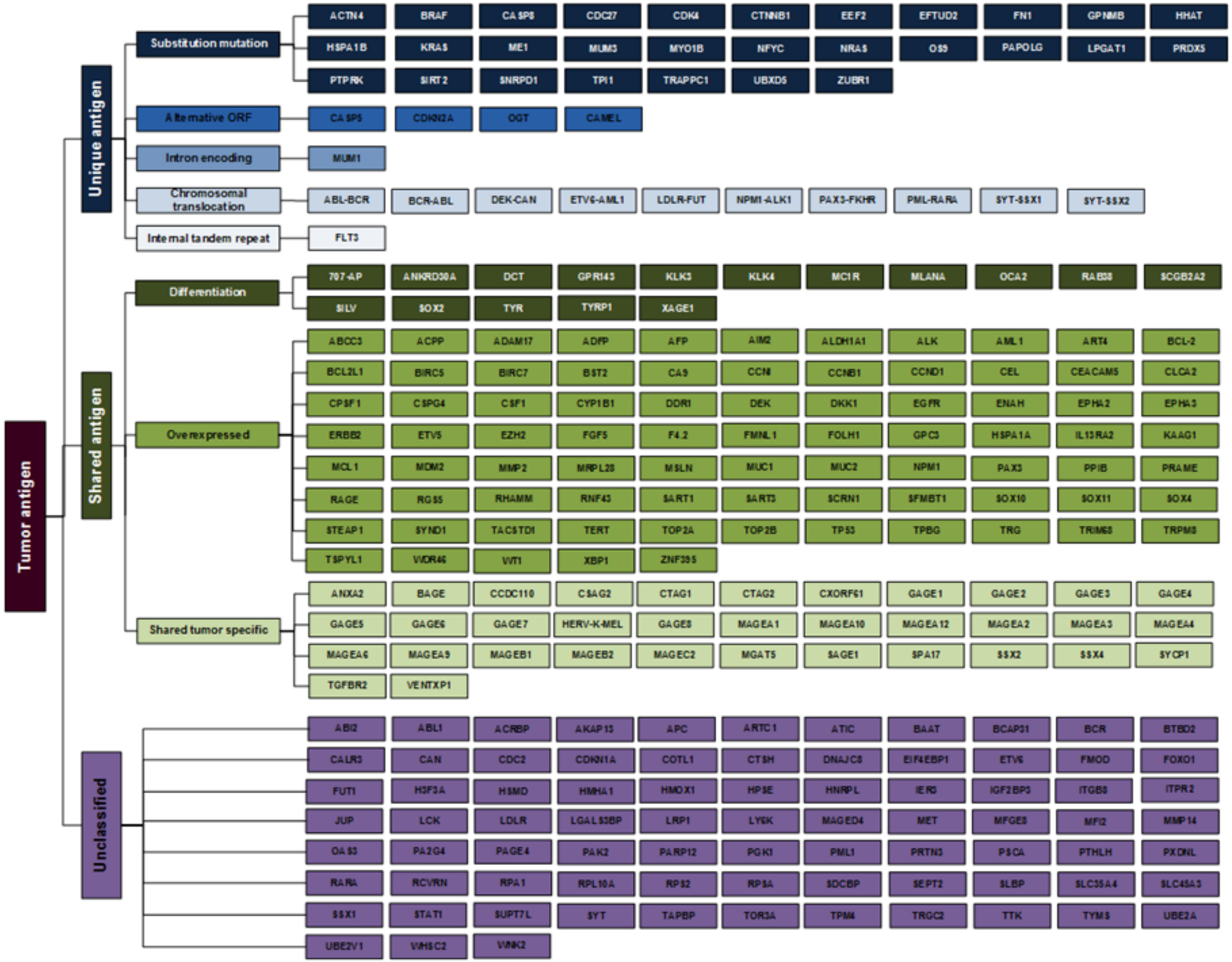
What type of antigens can be expressed?

Antigen type	Description	Examples of antigen type
Tumour-specific antigens[8,9] TSA	• Completely absent from normal host cells • Arise in cancer cells from oncogenic viral proteins or nonsynonymous somatic mutations	• HPV oncoproteins E6 and E7 (HPV-associated cancers of the cervix, anus and oropharynx)[11,12] • Individual KRAS mutations (pancreatic, colon, lung and various other cancers)[10,19]
Tumour-associated antigens[9] TAA	• Low levels of expression on normal host cells • Disproportionately expressed on tumour cells • Often result from genetic amplification or post-translational modifications • Can be selectively expressed by the cell lineage from which the cancer evolved	• ERBB2 (some breast cancers and various other cancers)[158] • Mesothelin (pancreatic cancer and mesothelioma)[159–161] • CD19 on B cell malignancies[27,28]
Cancer/testis antigens[13,14] CTA (Shared TSA)	• Absent on normal adult cells, except in reproductive tissues (e.g. testes, fetal ovaries and trophoblasts) • Selectively expressed by various tumour types	• MAGE (various cancers)[162] • NY-ESO-1 antigen (various cancers)[163]

Yarchoan M et al. Nature Rev Cancer 2017

ANTIGENI TUMORALI UMANI (alcuni esempi)

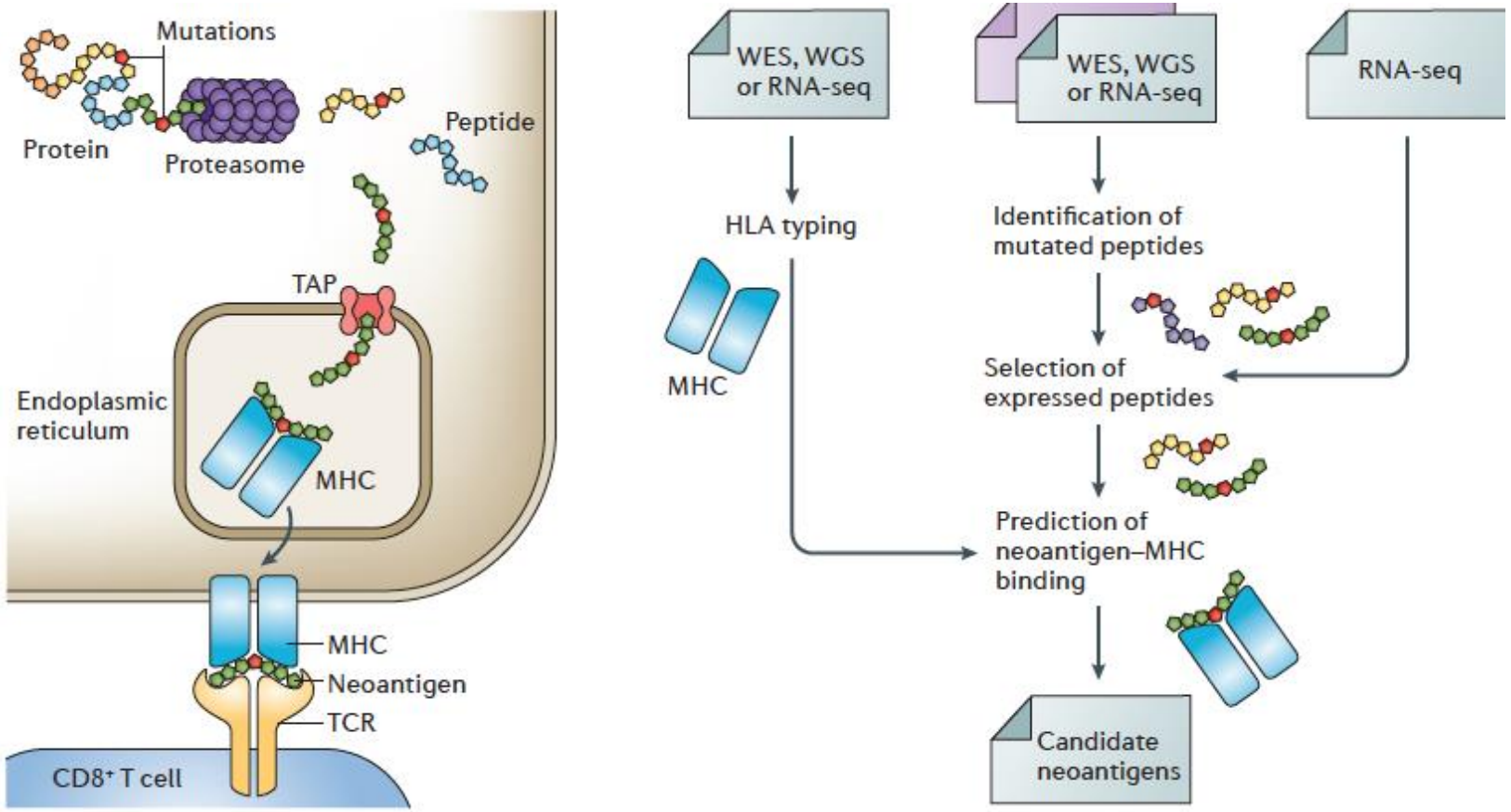
- **Prodotti di geni amplificati o mutati (HER-2/neu).**
- **Prodotti di oncogeni o geni onco-soppressori (Ras, Bcr-Abl, p53).**
- **Prodotti di virus oncogeni (E6 ed E7 del papilloma virus; EBNA-1 del virus di Epstein-Barr).**
- **Antigeni tumorali/testicolari: normalmente silenti nei tessuti normali (tranne testicolo e trofoblasto), ma espressi da molti tumori (MAGE).**
- **Antigeni oncofetali: espressi nei tessuti fetali in via di sviluppo e da molti tumori nell'adulto, ma non dai tessuti normali (CEA, AFP).**
- **Antigeni di differenziazione tissutale (tirosinasi dei melanociti, antigene prostatico specifico/PSA, CD10, CD20).**
- **Glicolipidi e glicoproteine alterate (MUC-1).**



TANTIGEN: Classification of tumor antigens

Developed by Bioinformatics Core at Cancer Vaccine Center, Dana-Farber Cancer Institute.

Bioinformatic platform for tumor neo-antigen identification

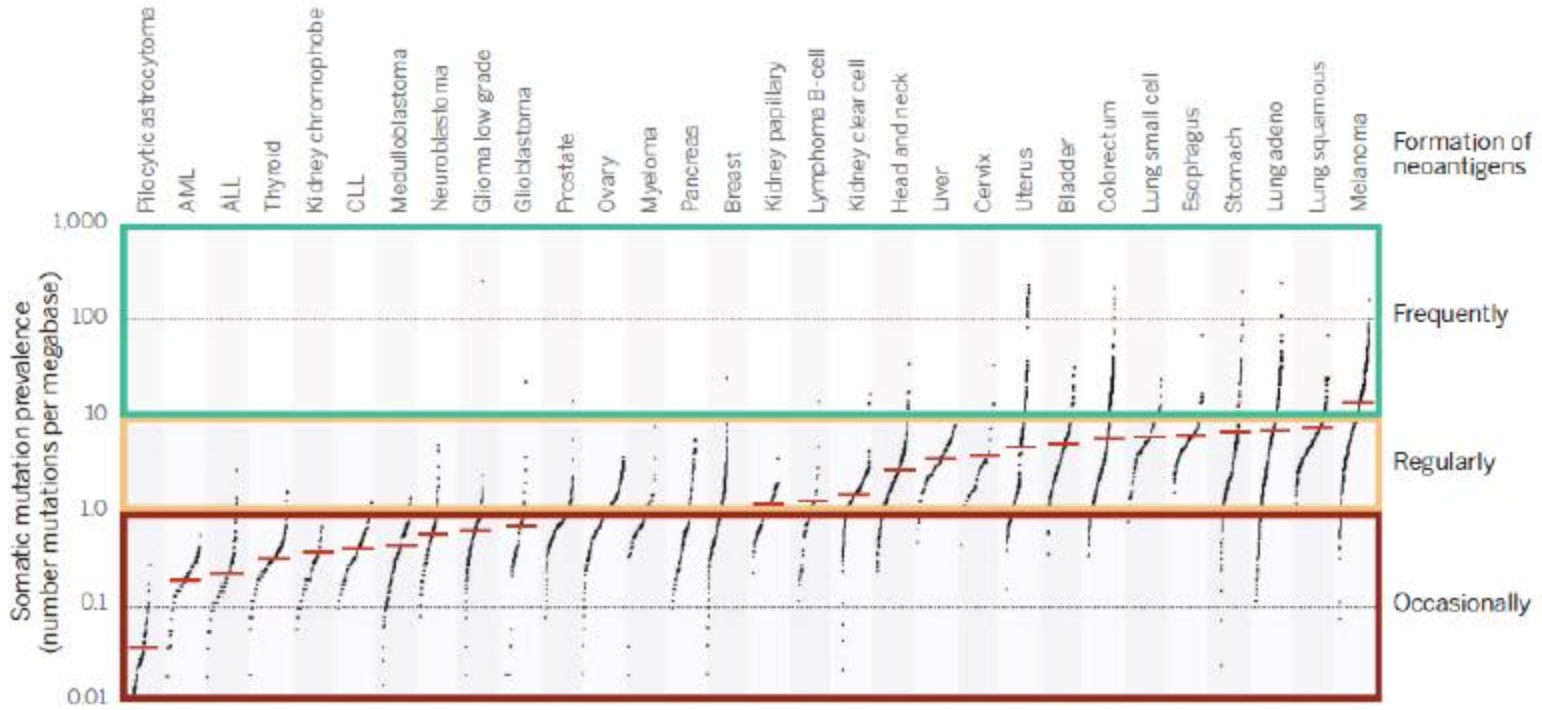


Cancer whole exome sequencing

Mutations

Neoantigens

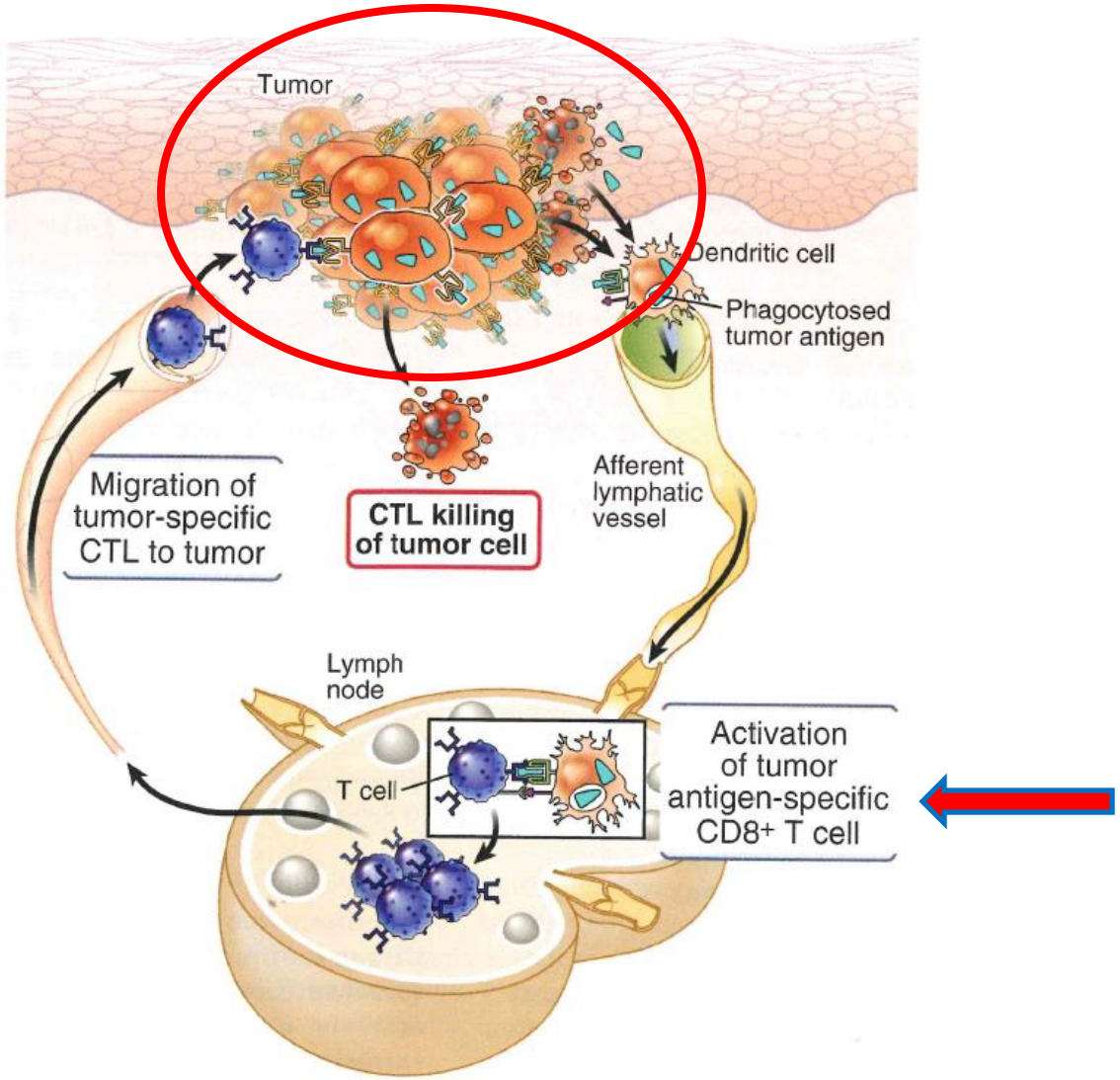
Estimate of the neoantigen repertoire in human cancers



Schumacher TN and Schreiber RD, Science 2015

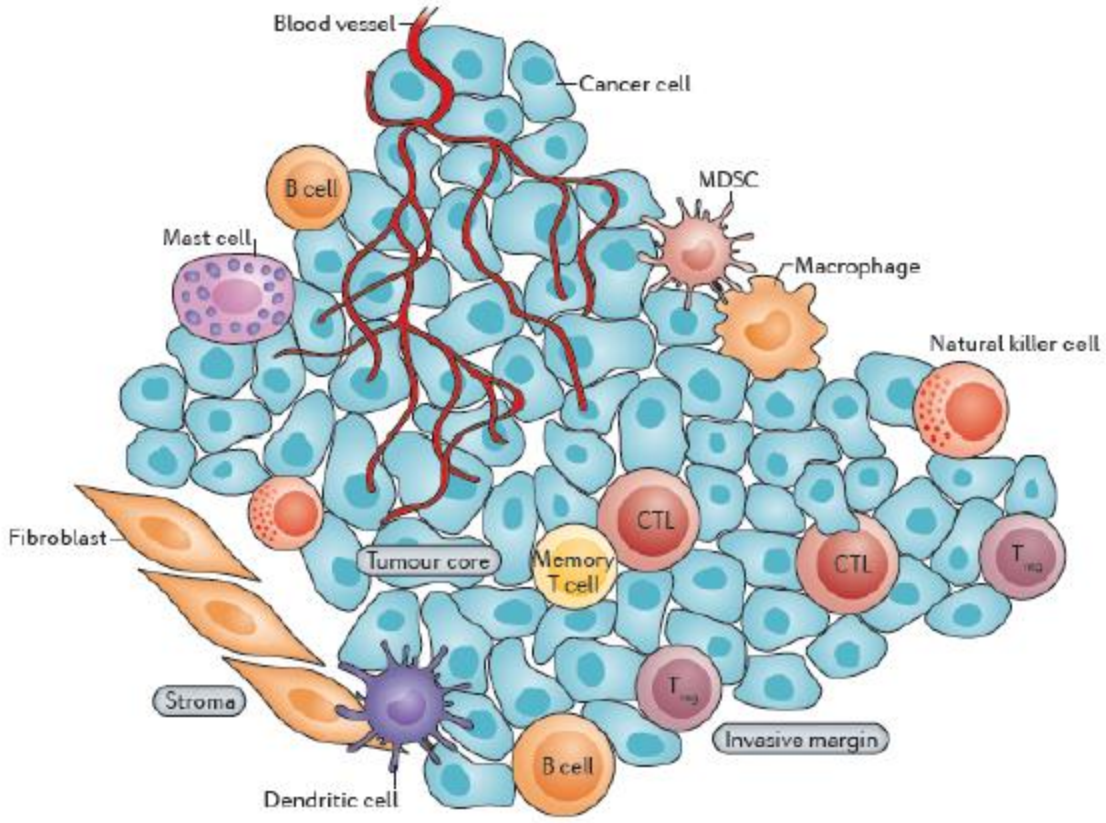
Immunità adattativa

The principal mechanism of immune protection against tumors is killing of tumor cells by CD8+ CTLs



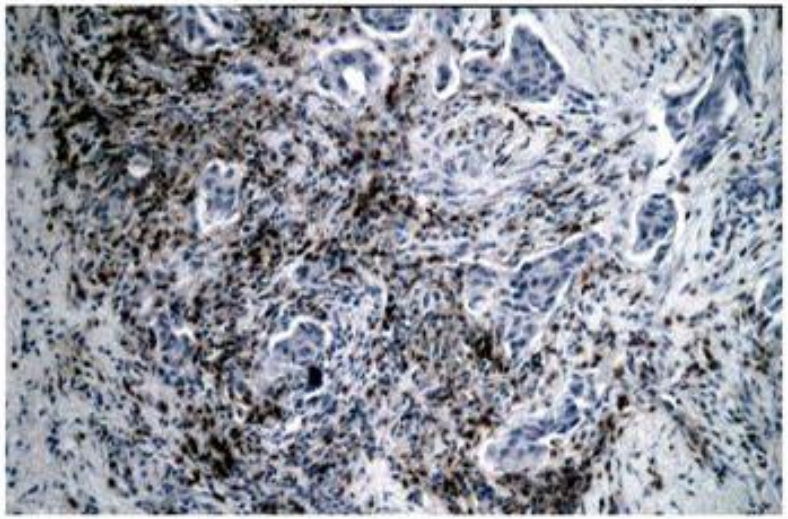
The immune contexture of the tumor

If an immune response is ongoing, we should be able to detect effector adaptive immune cells in the tumor

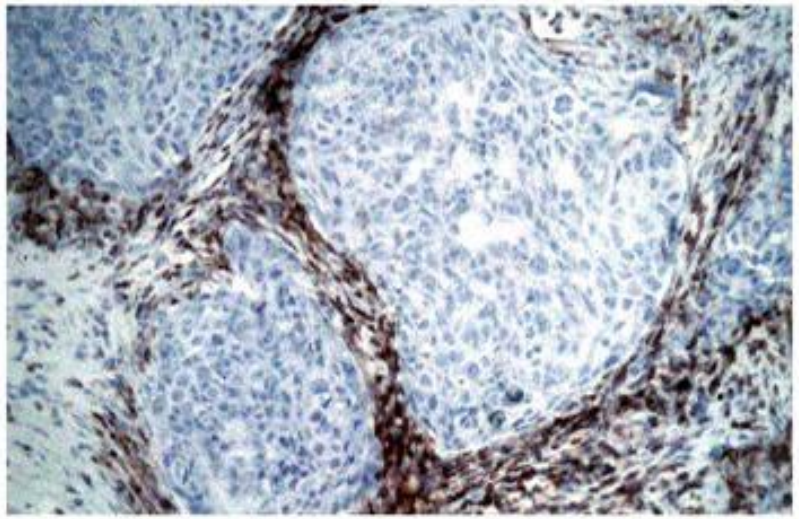


Is it possible to stratify tumor level of malignancy on the basis of immune-related parameter?

I linfociti T devono essere localizzati nel posto giusto!

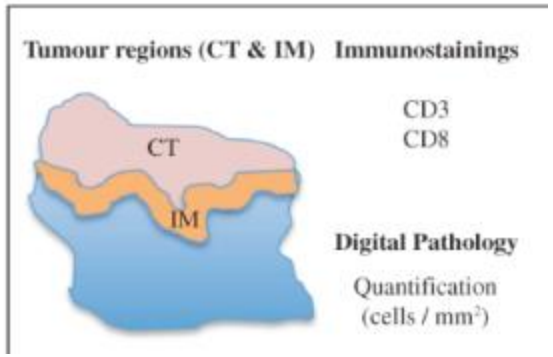


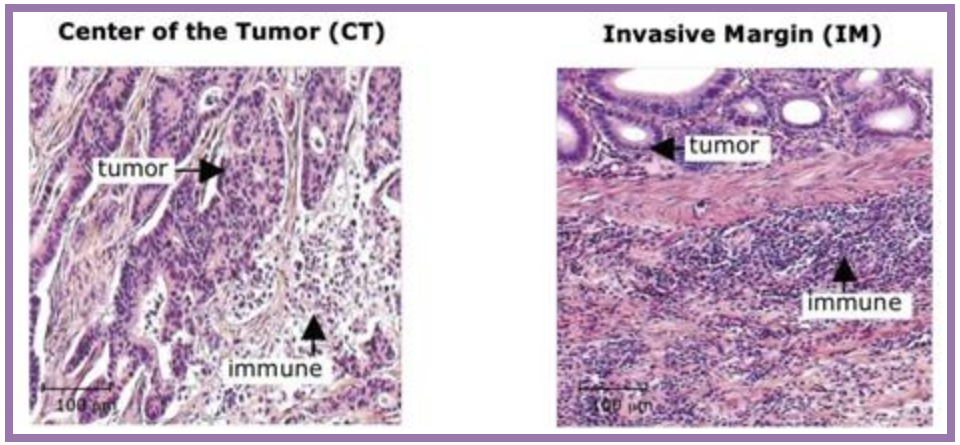
Linfociti CD3+ INTRATUMORALI

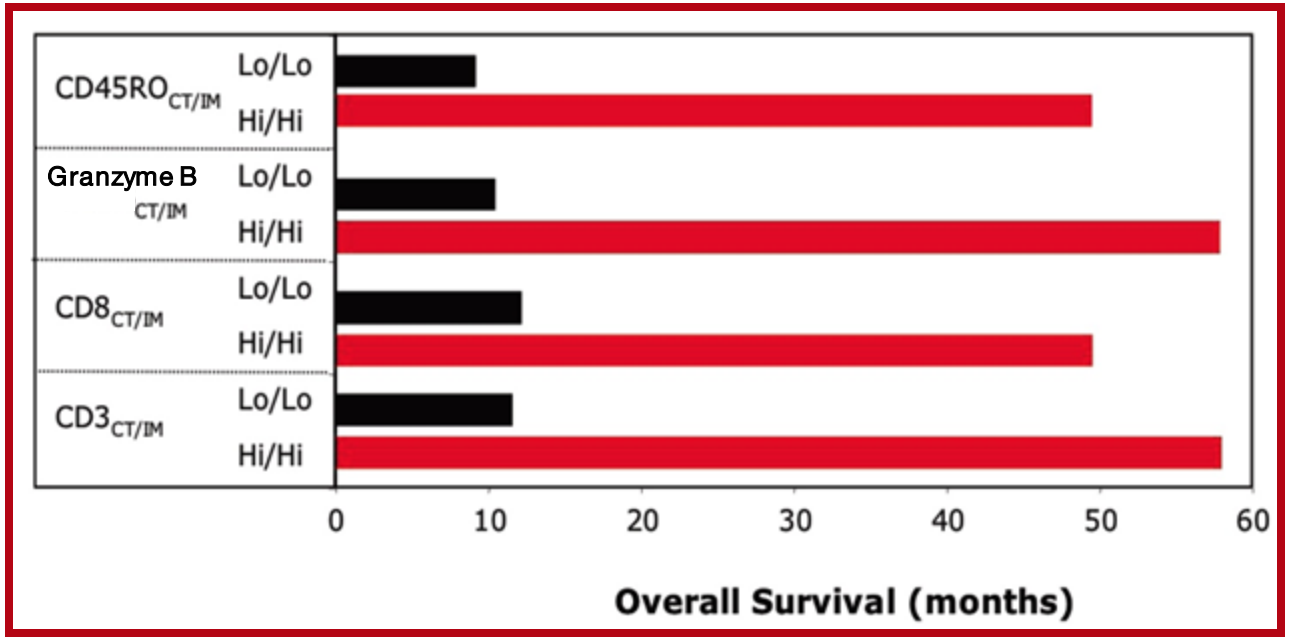


Linfociti CD3+ PERITUMORALI

Tanti, di buona qualità e nel posto giusto: come la presenza dei linfociti T correla con una prognosi migliore nel cancro del colon-retto





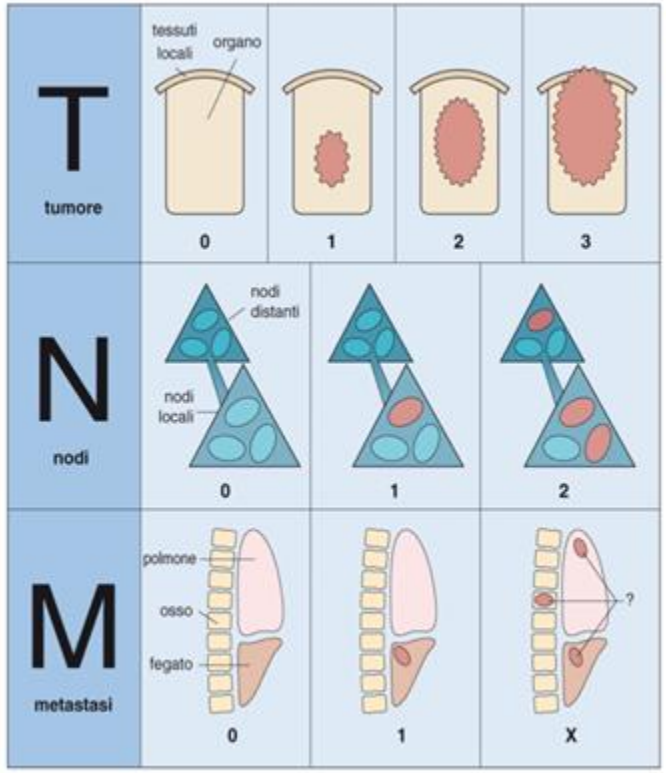


Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[3*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]

29 SEPTEMBER 2006 VOL 313 SCIENCE www.sciencemag.org

Galon J et al, NEJM 2005 & Science 2006



Stadiazione e (staging)

A. Stevens, J. Lowe, I. Scott Patologia, terza edizione

T cells → **TNM staging: a new view?** ← **Memory**

TNM staging: a new view?

- **T**umor
- **N**ode
- **M**etastasis

A new view in cancer staging?
T is for T cells and M is for Memory

4

immuno-score (IS)

Density and location of immune cells within tumors

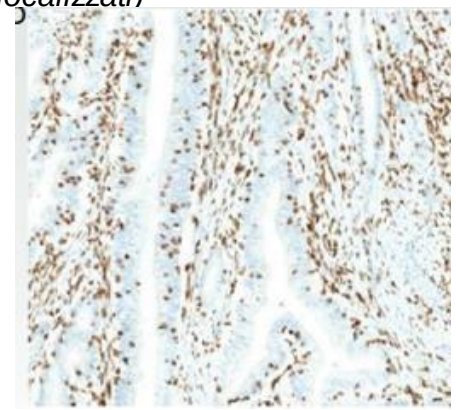
0

Low density
«Bad»

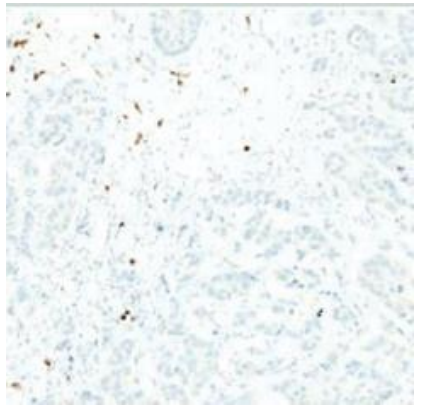
(tumori invasivi, metastasi)

High density
«Good»

(tumori in situ, o localizzati)



CD3 staining



CD3 staining

Immuno score: CD8+/CD45+RO+/GRZB+ in CT (center of the tumour) e IM (invasive margin)

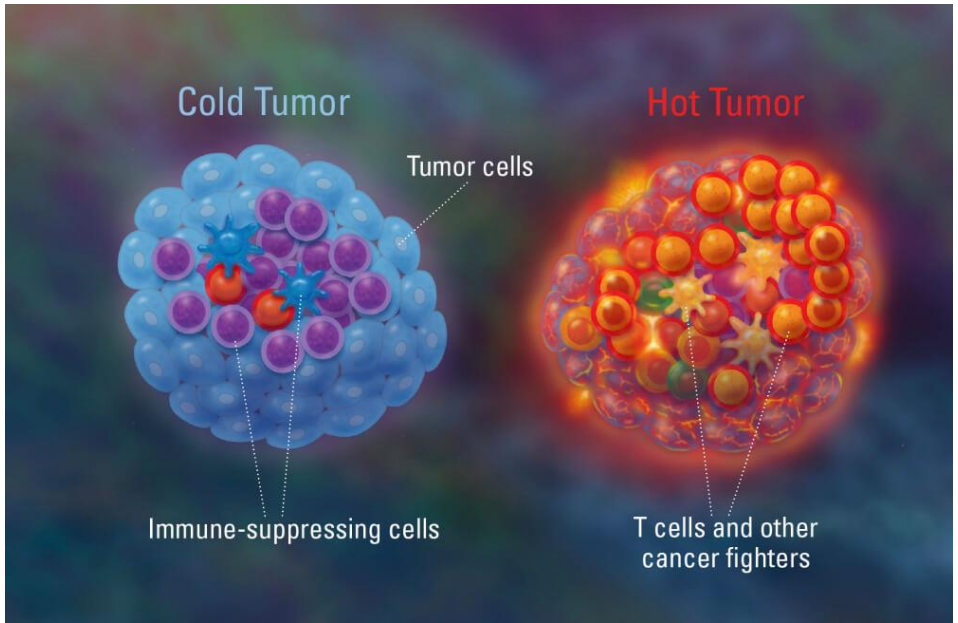
Capability of a tumor to correctly present immunogenic antigens has also been linked to the tumor's capacity to attract immune cells

Quantity and distribution of immune cells within a tumor have been proposed as broad measurements of tumor immunogenicity, with three typical scenarios being recognized:

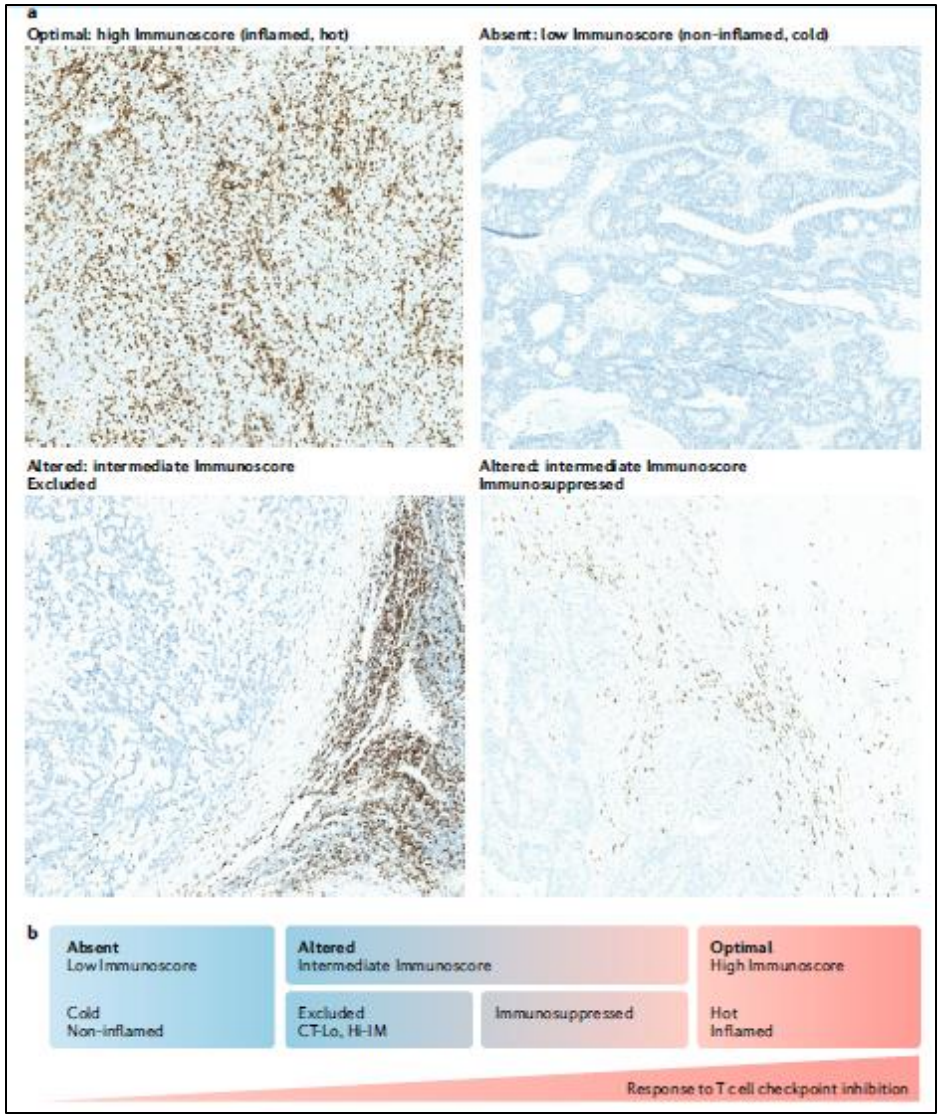
1- inflamed tumors (''hot'', immune infiltration)

2- immune-excluded tumors (presence of T cells at the tumor margins but not in the tumor core)

3- immune-desert tumors (''cold'', no immune infiltration)



Defining ‘hot’, ‘altered’ and ‘cold’ immune tumors: Immunoscore as a new approach for the classification of cancer

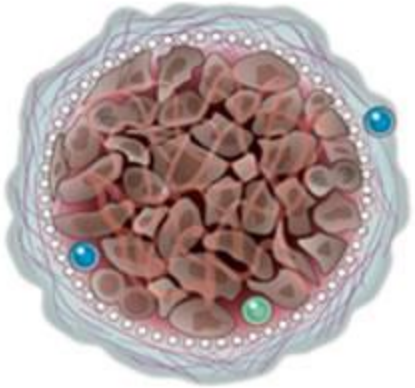


Immunoscore:
immune cell infiltrate

Galon Nature Review Drug Dicovery 2019

Trasformare un tumore “freddo” in uno “caldo”

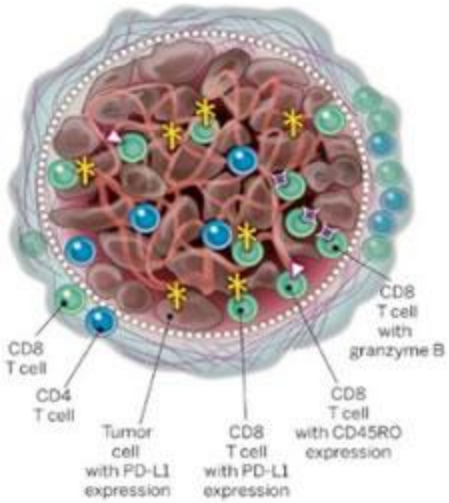
Cold tumors



Nonimmunogenic tumor microenvironment

Combination therapies with agents that create immunogenic tumor microenvironment and immune checkpoint therapy

Hot tumors

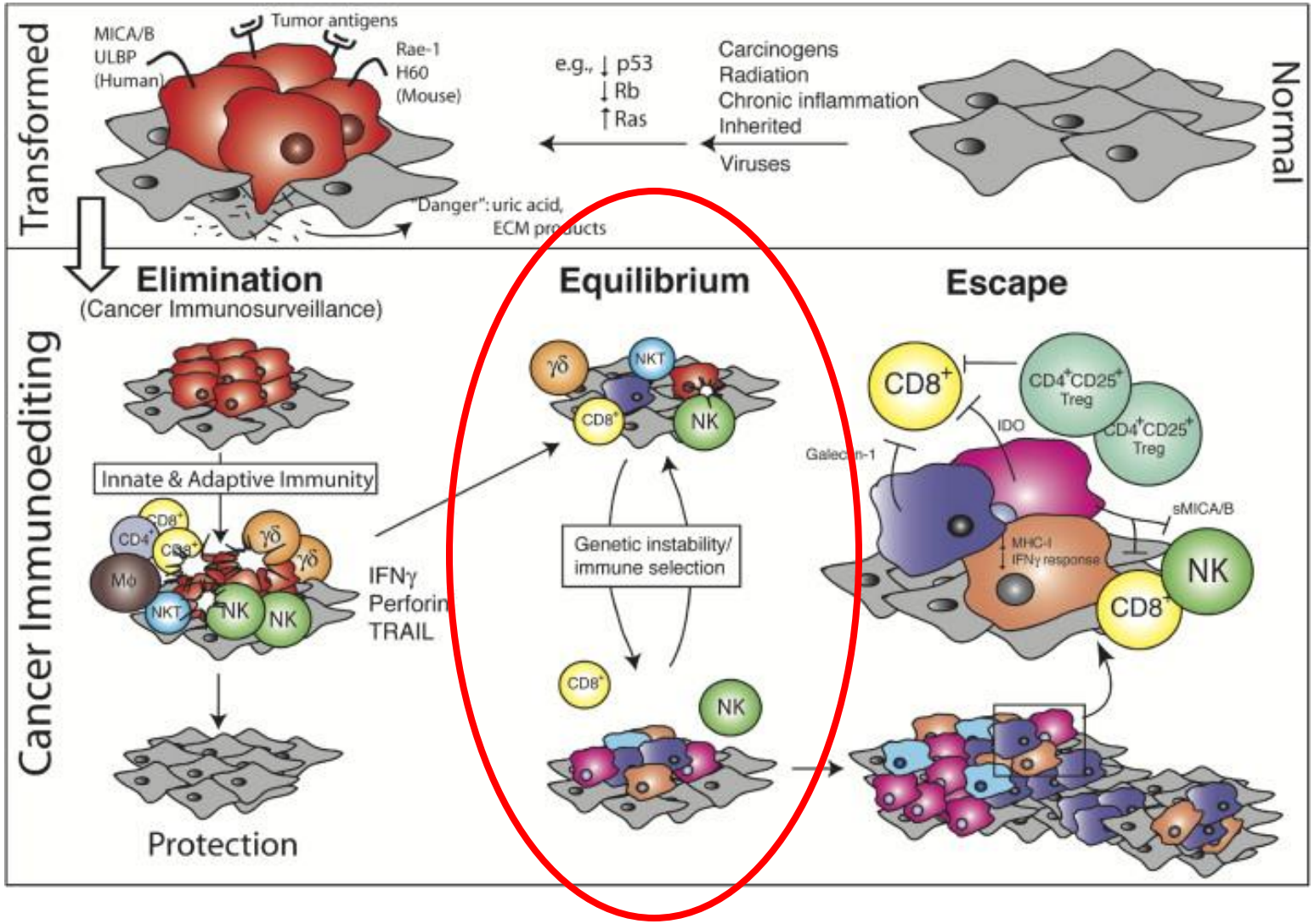


Immunogenic tumor microenvironment

Immune checkpoint therapy and durable clinical benefit

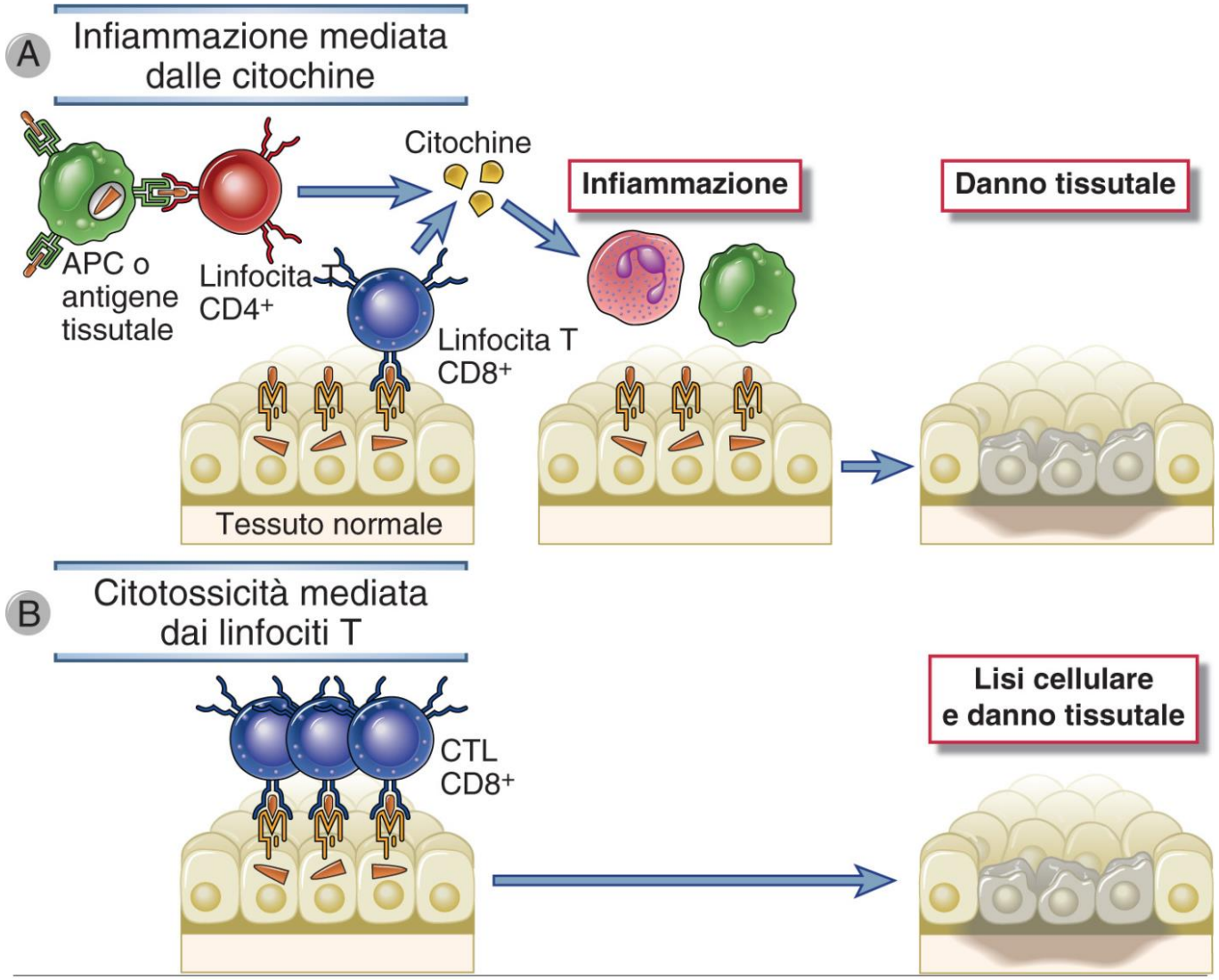
(Science 03 Apr 2015: 348, 56-61)

The immune system establishes a dynamic interaction with the tumour: cancer immunoediting



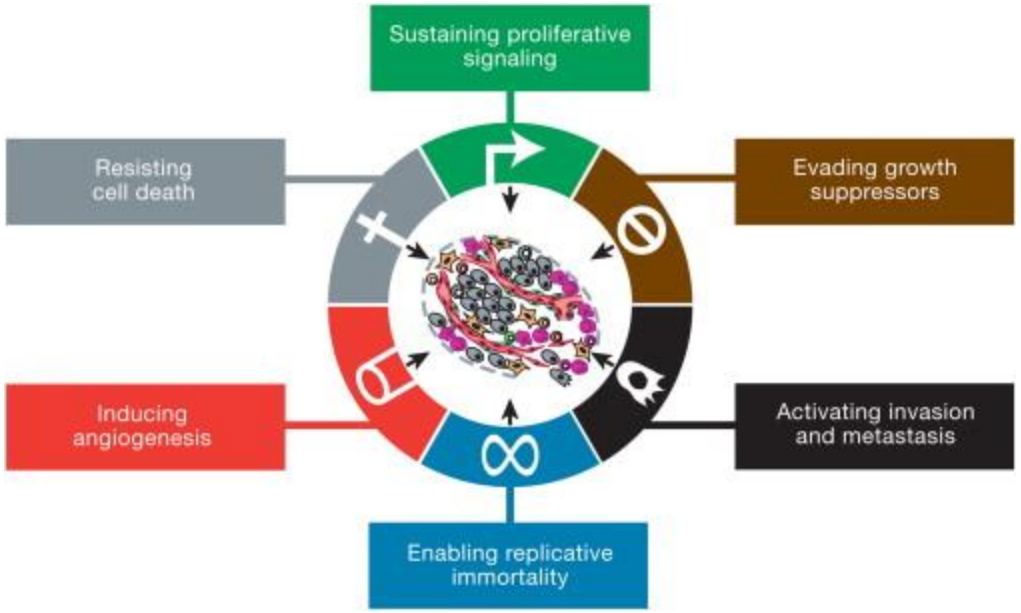
Dunn et al Immunity 2004

Il perpetuarsi della risposta infiammatoria porta a danno tissutale

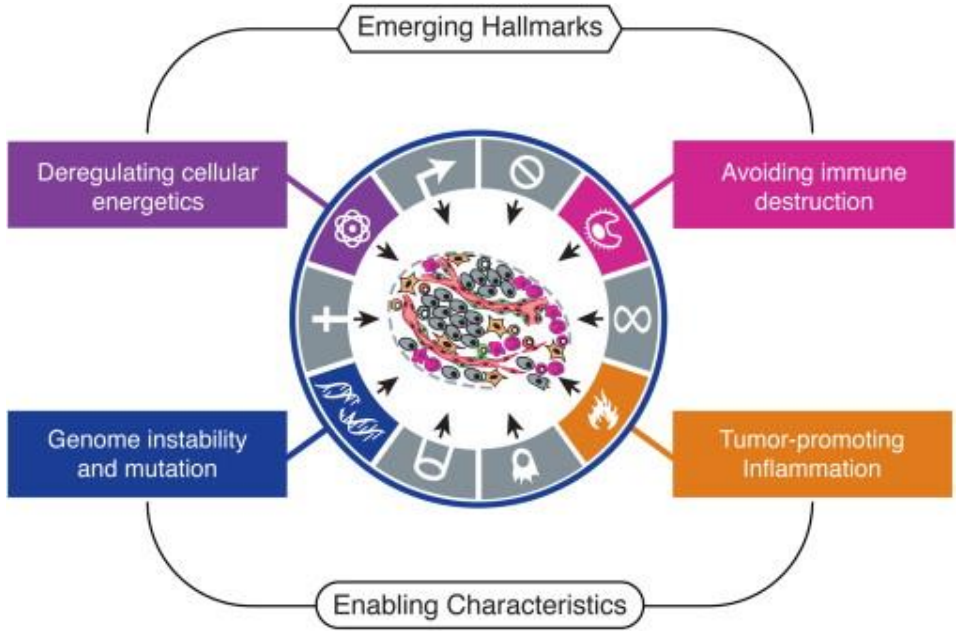


Le proprietà di un tumore

2001



2011



10 anni dopo emergono nuove proprietà…

The Hallmarks of Cancer
Hanahan D and Weinberg RA, Cell 2011

Infiammazione e cancro: evidenze a favore

Virchow, 1863

- **Le malattie infiammatorie dell'intestino (colite ulcerosa, malattia di Crohn) sono associate ad un alto rischio di cancro del colon-retto. Individui con la colite ulcerosa hanno un rischio dieci volte maggiore di sviluppare un cancro del colon-retto, rispetto al resto della popolazione.**

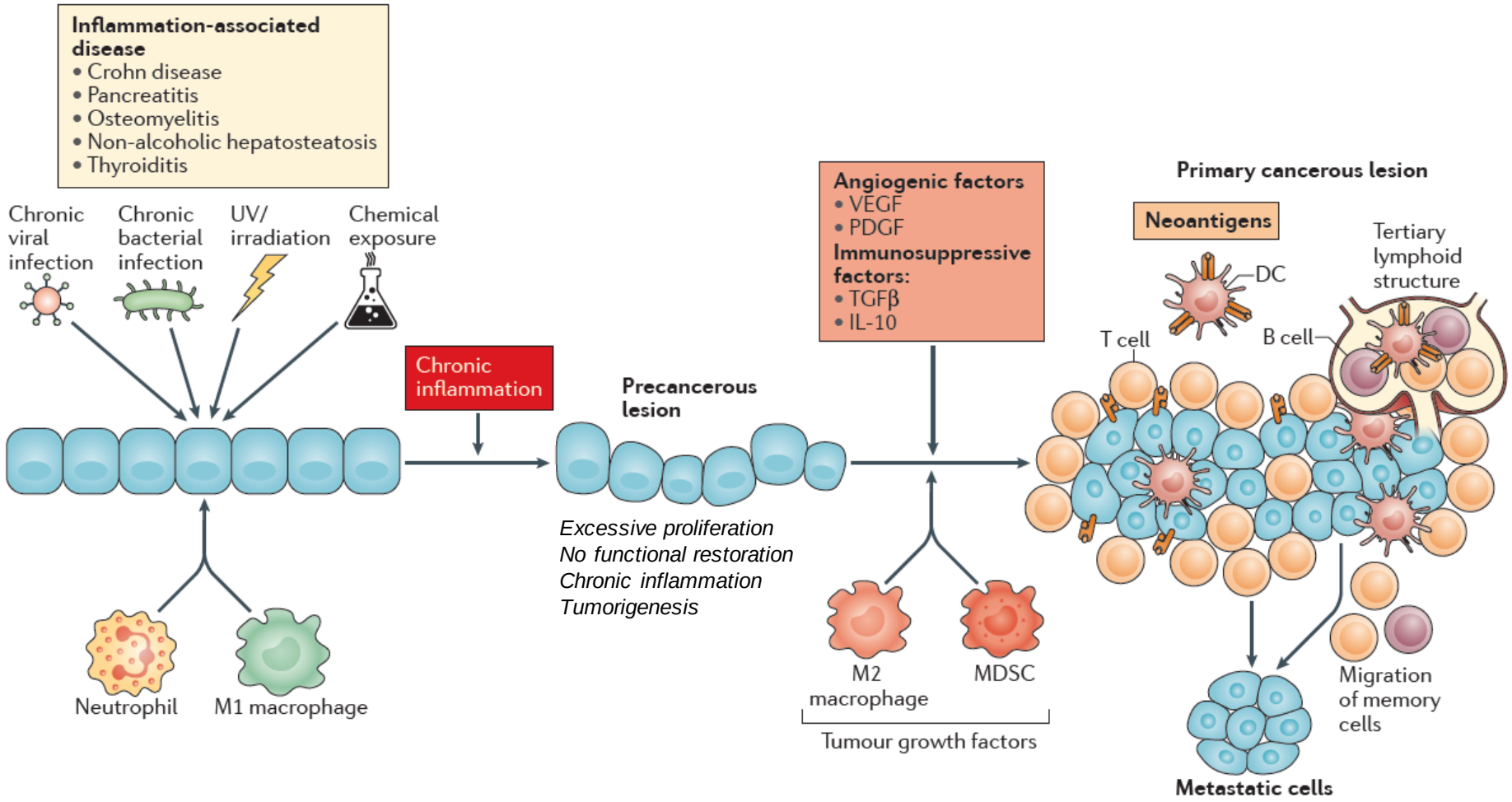
- **L'esposizione cronica a sostanze irritanti che causano un'infiammazione dei bronchi (es., sigarette, asbesto, silice) è associata ad un elevato rischio di cancro del polmone.**

- **L'esposizione eccessiva ai raggi UV aumenta il rischio di melanoma.**

- **Molti tumori sono correlati ad una esposizione cronica ai patogeni (es., cancro dello stomaco ed *Helicobacter pylori;* epatocarcinoma e HCV; cancro della cervice e HPV).**

Inductor	Inflammation	Cancer
Gut pathogens	Inflammatory bowel disease	Colorectal cancer
Tobacco smoke	Bronchitis	Bronchial lung cancer
Helicobacter pylori	Gastritis	Gastric cancer
Human papilloma virus	Cervicitis	Cervical cancer
Hepatitic B/C virus	Hepatitis	Hepatocellular carcinoma
Bacteria, gall bladder stones	Cholecystitis	Gall bladder cancer
Tobacco, genetics, alcohol	Pancreatitis	Pancreatic cancer
Epstein-Barr virus	Mononucleosis	Burkitt's lymphoma
Ultraviolet light	Sunburn	Melanoma
Asbestos fibers	Asbestosis	Mesothelioma
Gram-uropathogens	Schistosomiasis (Bilharzia)	Bladder cancer
Gastric acid, alcohol, tobacco	Esophagitis	Esophageal adenocarcinoma

Infiammazione e cancro



Chronic inflammation associated with infections or autoimmune disease precedes tumor development and can contribute to it through induction of oncogenic mutations, genomic instability, early tumor promotion, and enhanced angiogenesis.

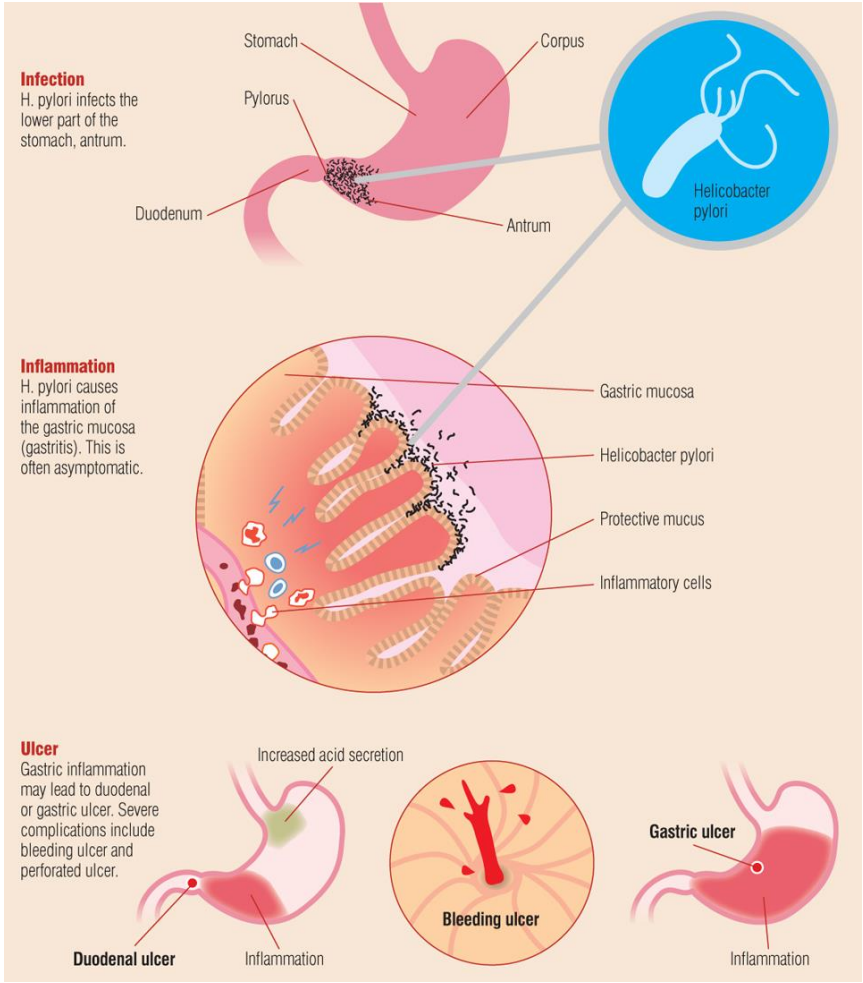
Fridman et al. Nat. Rev Clin Onc 2017

Helicobacter Pylori and ulcer disease

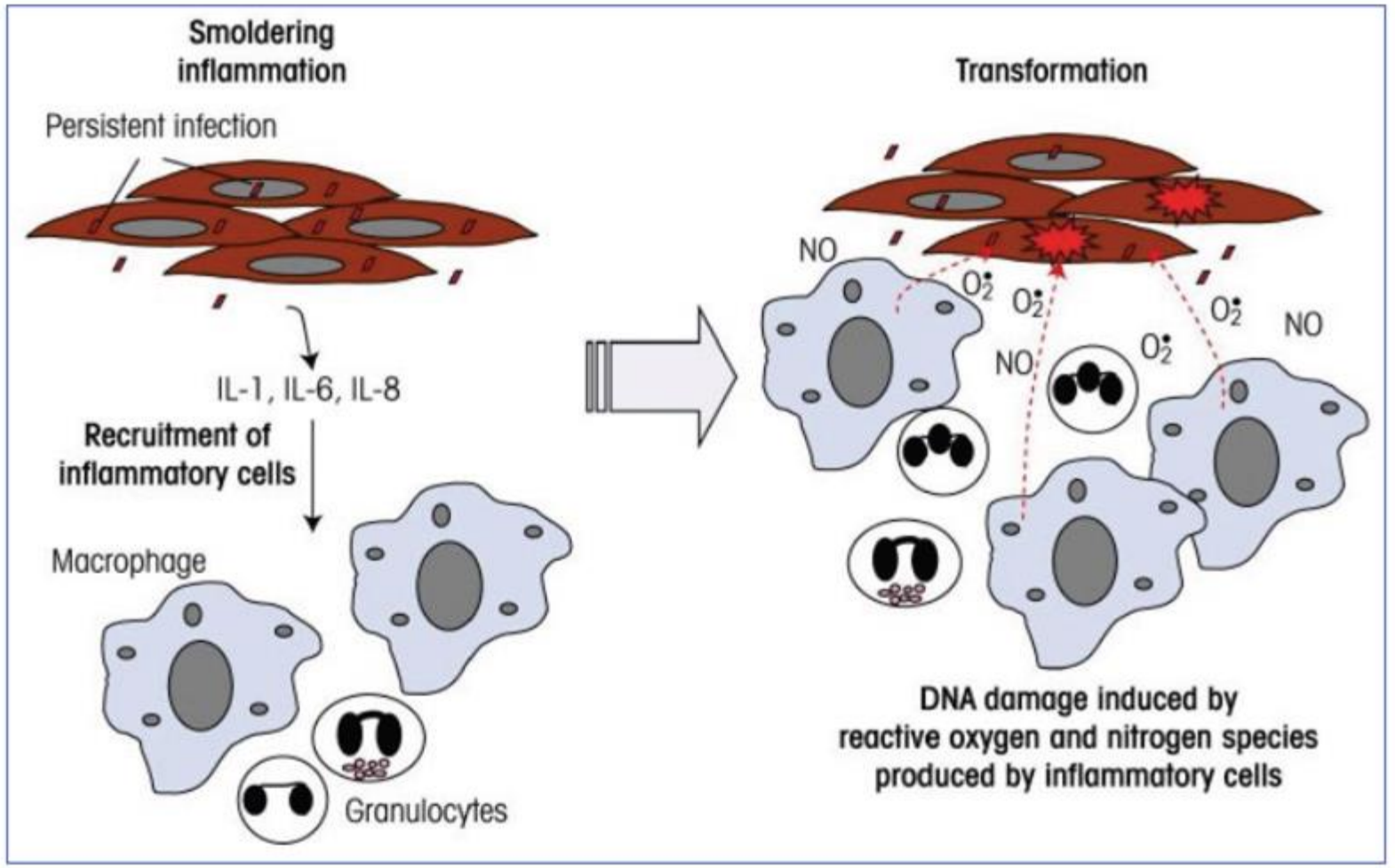
infection

inflammation

ulcer

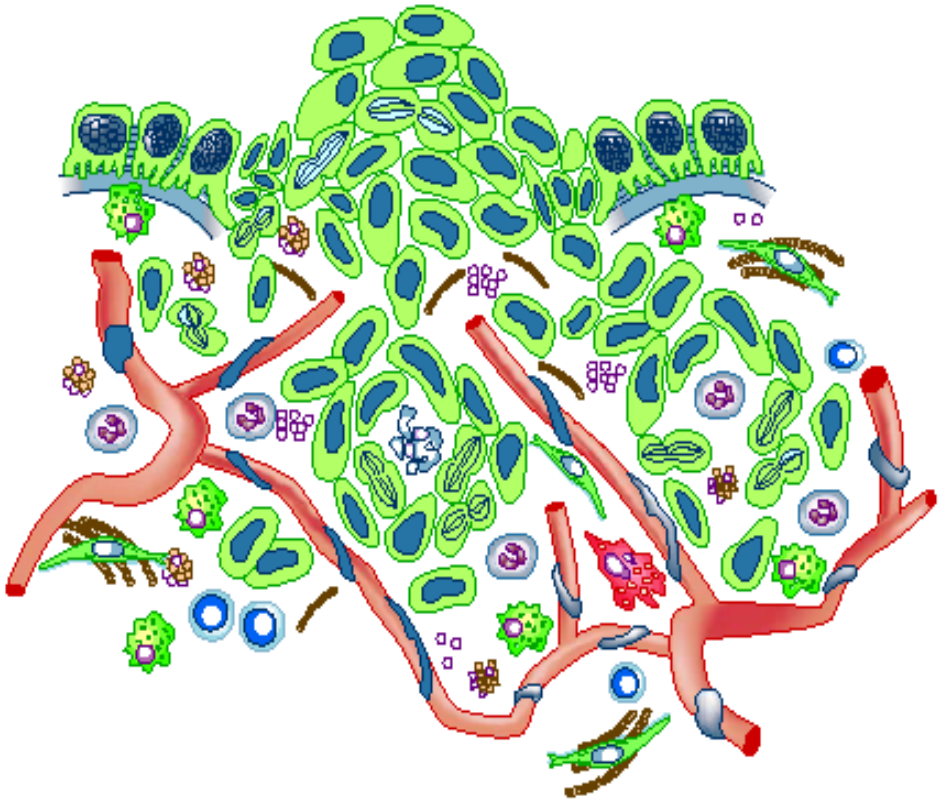


Chronic inflammation can promote malignant transformation



Il microambiente è importante!

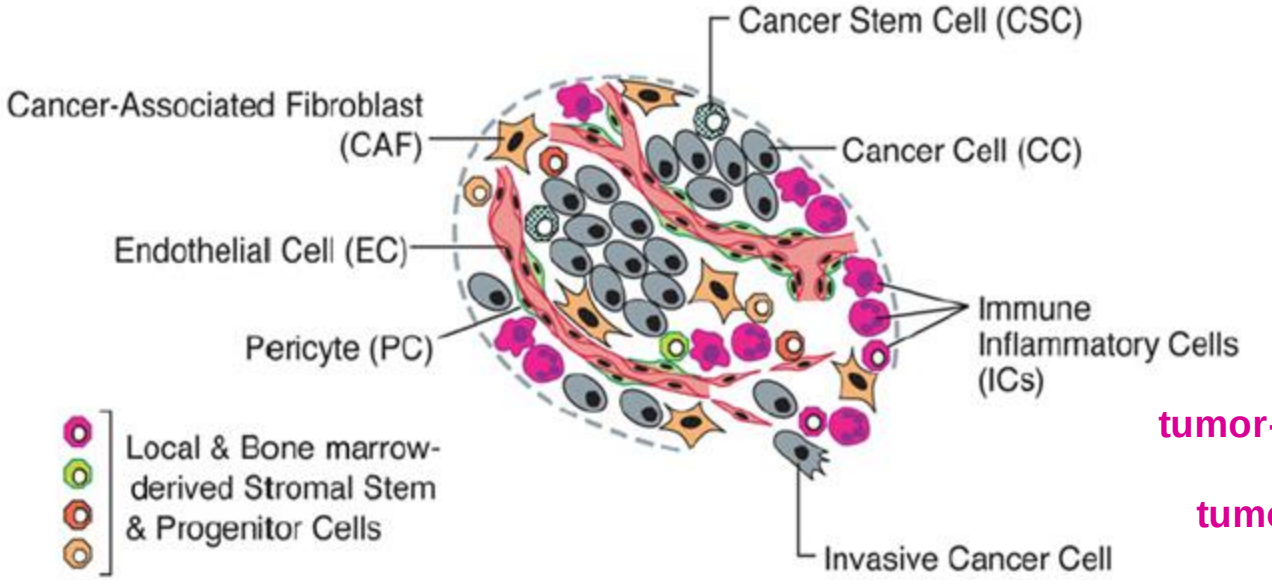
… il terreno…



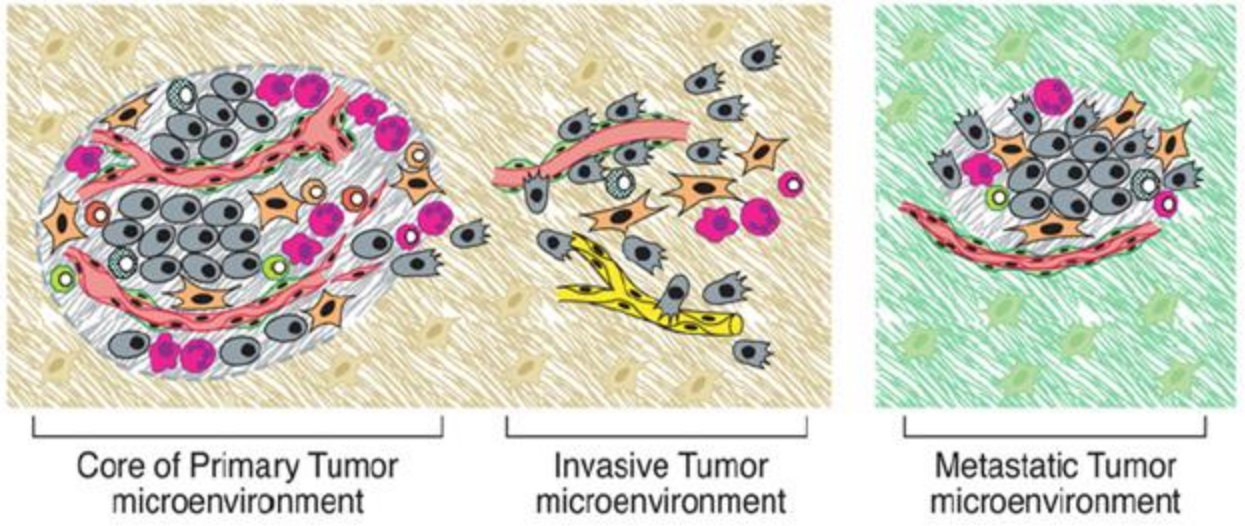
Il microambiente tumorale è un protagonista indispensabile del processo neoplastico, poiché favorisce la proliferazione, la sopravvivenza e la migrazione delle cellule tumorali.

Coussens LM and Werb Z Nature 2002

Un tumore è costituito da diversi tipi di cellule…



tumor-promoting & tumor-killing



…e da diversi microambienti

Hanahan and Weinberg, Cell 2010

Quali sono le cellule infiammatorie nel microambiente tumorale che favoriscono lo sviluppo e la progressione tumorale?

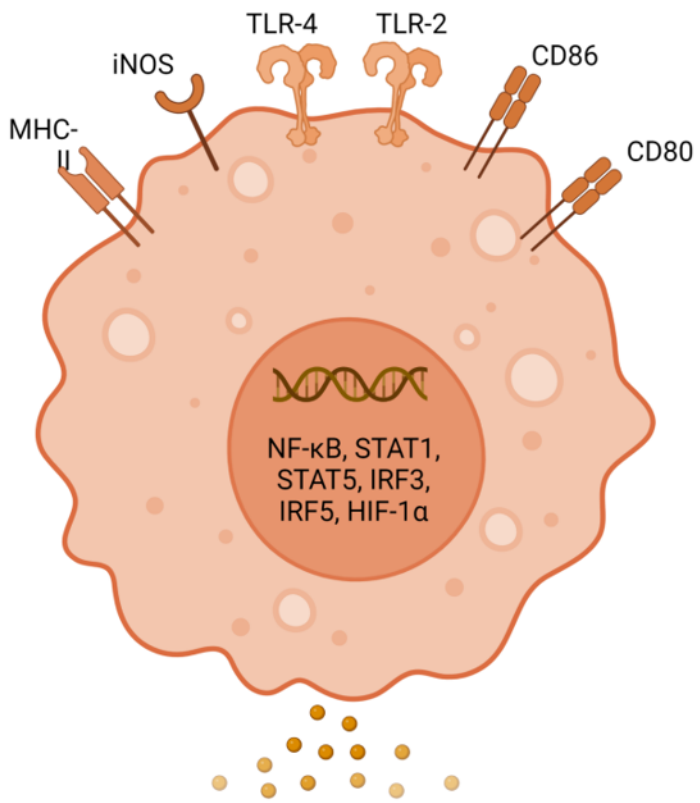
- Macrofagi associati al tumore (TAM) ⟶
- Cellule dendritiche (DC)
- Mastociti
- Neutrofili
- Eosinofili

Cosa fanno?

- Inibiscono la risposta anti-tumorale.
- Promuovono la proliferazione cellulare, la deposizione dello stroma, l'angiogenesi.
- Inducono o aumentano il danno al DNA.

I macrofagi associati al tumore (TAM)

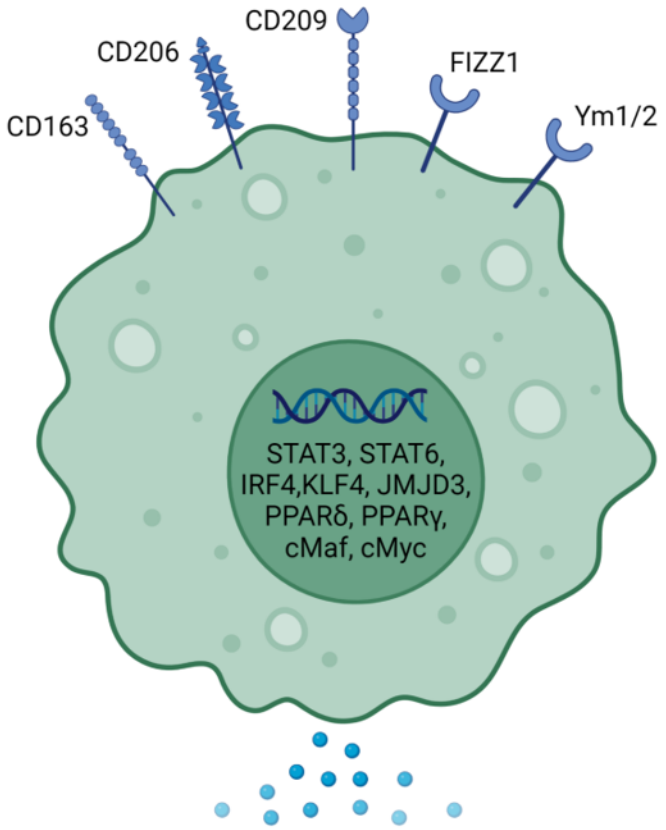
M1 Macrophage



TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-23, CXCL9, CXCL10, CXCL11, CXCL16, CCL5

Function:
Proinflammatory activity
Microbial and tumoral activity
Tissue damage

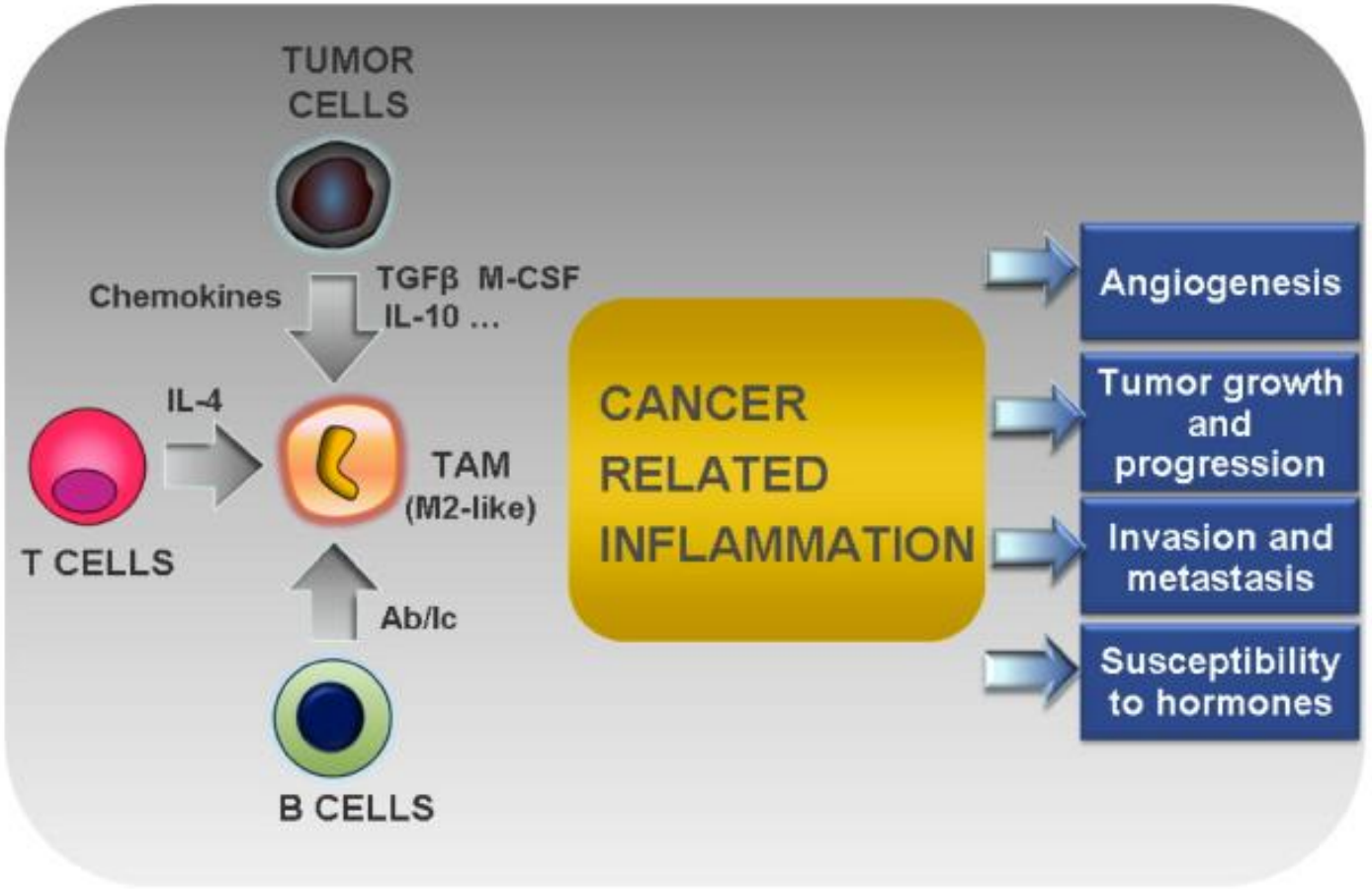
M2 Macrophage



IL-10, TGF-β, CCL1, CCL17, CCL18, CCL22, CCL24, CXCL13, VEGF

Function:
Anti-inflammatory activity
Phagocytosis capacity
Tissue regeneration and repair
Angiogenesis and immunomodulation
Tumor formation and progression

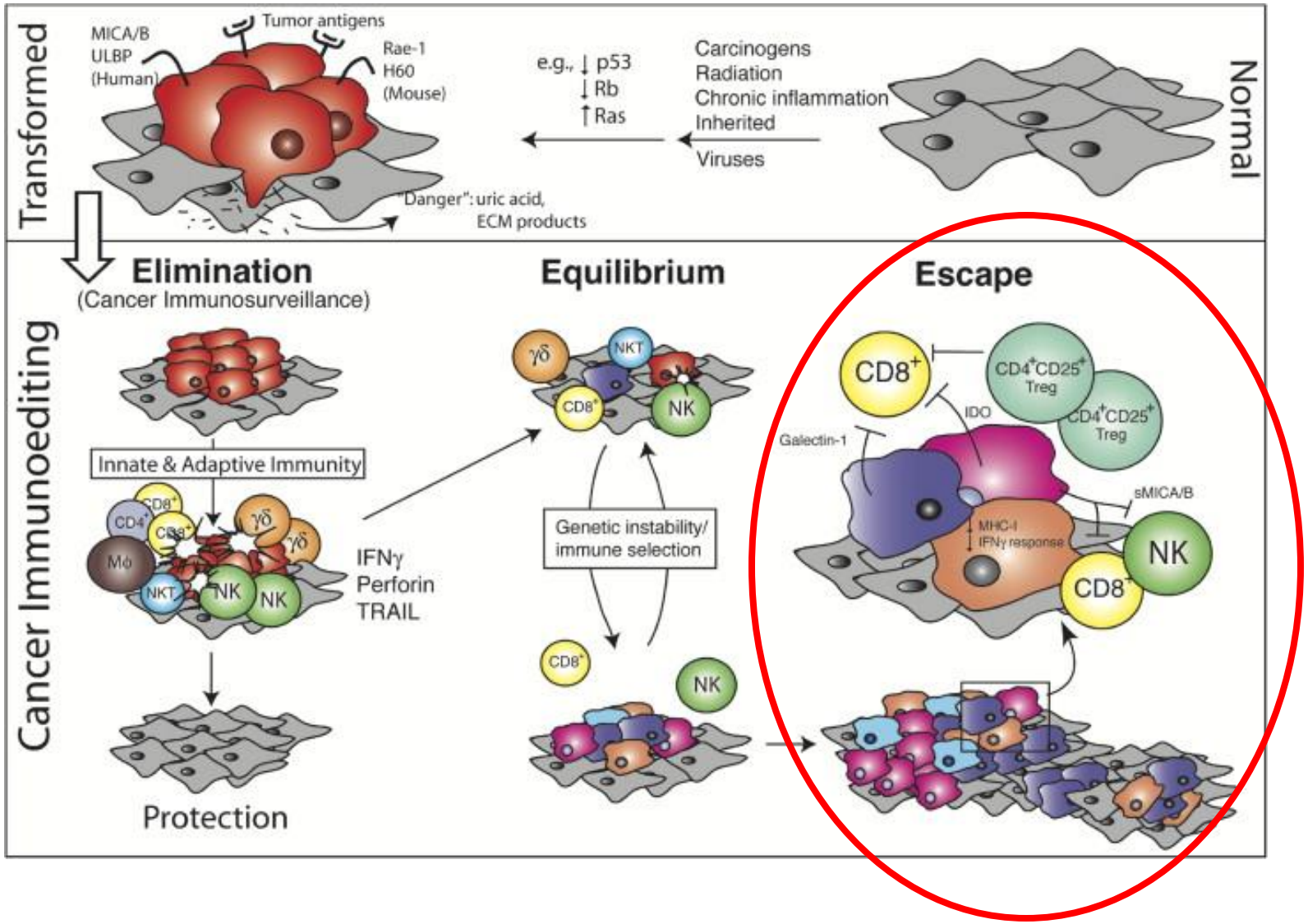
Il ruolo dei TAM nell'infiammazione e cancro



Mantovani and Sica Curr Opin Immunol 2010

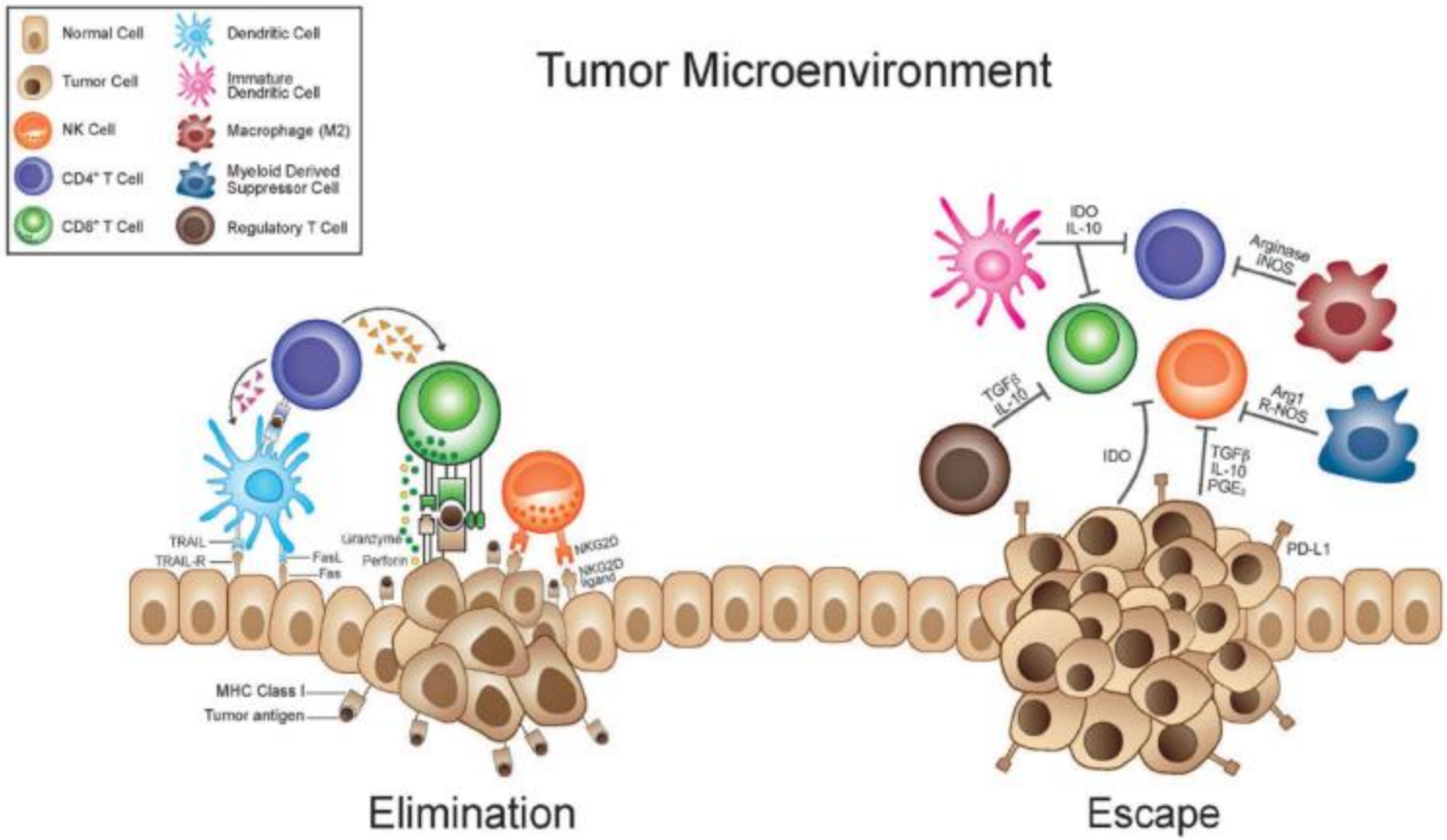
Although cancer is described as a disease of genetic mutations, it is clear the important, but multifaceted role of the host.

The immune system establishes a dynamic interaction with the tumour: cancer immunoediting



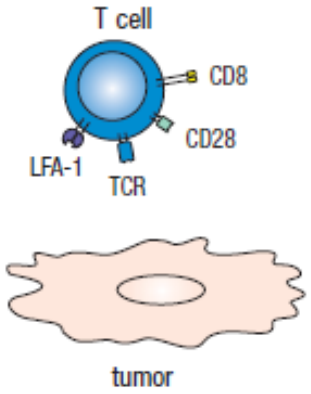
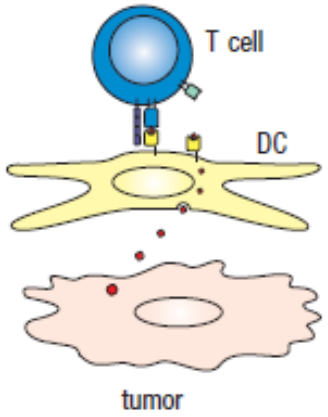
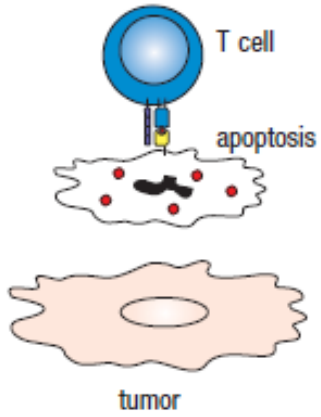
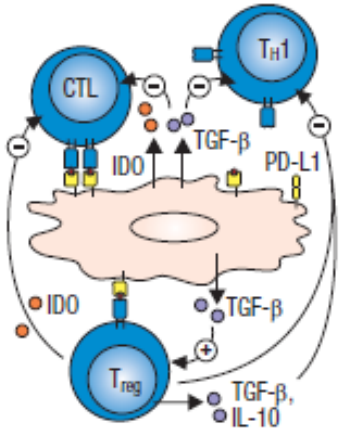
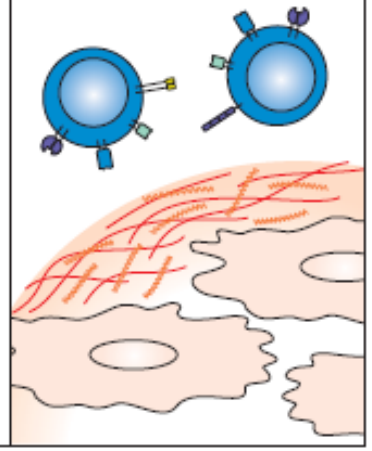
Dunn et al Immunity 2004

Escape



Monjazeb et al. Front Oncol 2013

Alcuni meccanismi con cui i tumori sfuggono al riconoscimento da parte del sistema immunitario

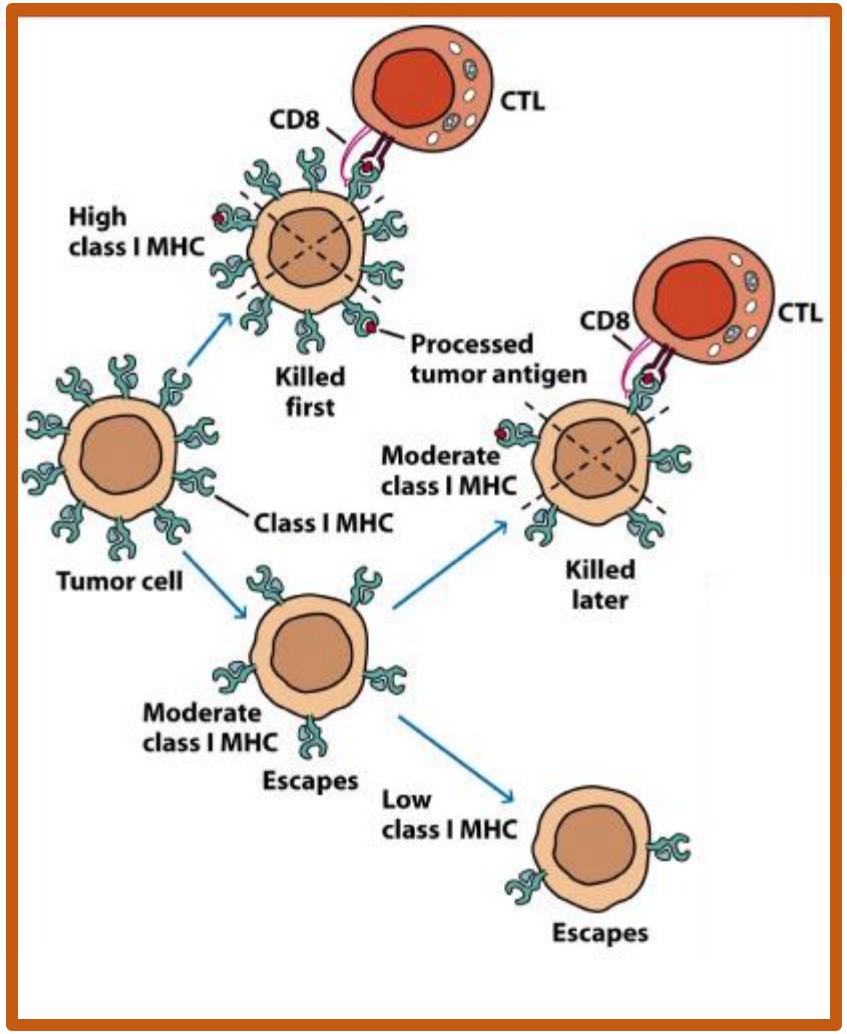
Low immunogenicity	Tumor treated as self antigen	Antigenic modulation	Tumor-induced immune suppression	Tumor-induced privileged site
No peptide:MHC ligand No adhesion molecules No co-stimulatory molecules	Tumor antigens taken up and presented by APCs in absence of co-stimulation tolerize T cells	T cells may eliminate tumors expressing immunogenic antigens, but not tumors that have lost such antigens	Factors (e.g.,TGF-β, IL-10, IDO) secreted by tumor cells inhibit T cells directly. Expression of PD-L1 by tumors	Factors secreted by tumor cells create a physical barrier to the immune system
				

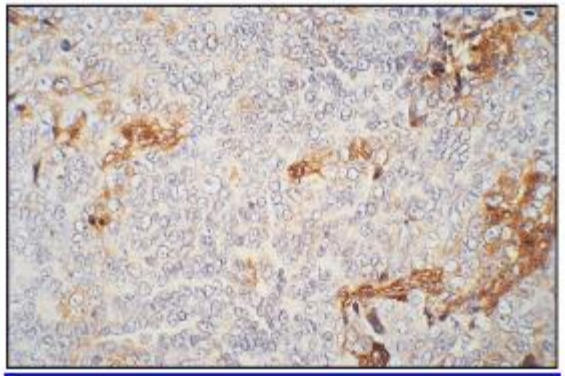
During the equilibrium phase tumor cell variants may emerge that

(i) are no longer recognized by adaptive immunity (antigen loss variants or tumors cells that develop defects in antigen processing or presentation),
(ii) become insensitive to immune effector mechanisms, or
(iii) induce an immunosuppressive state within the tumor microenvironment.

IDO : Indoleamine-pyrrole 2,3-dioxygenase

HLA class I down-modulation as a tumor evasion strategy against CD8+ T cell recognition

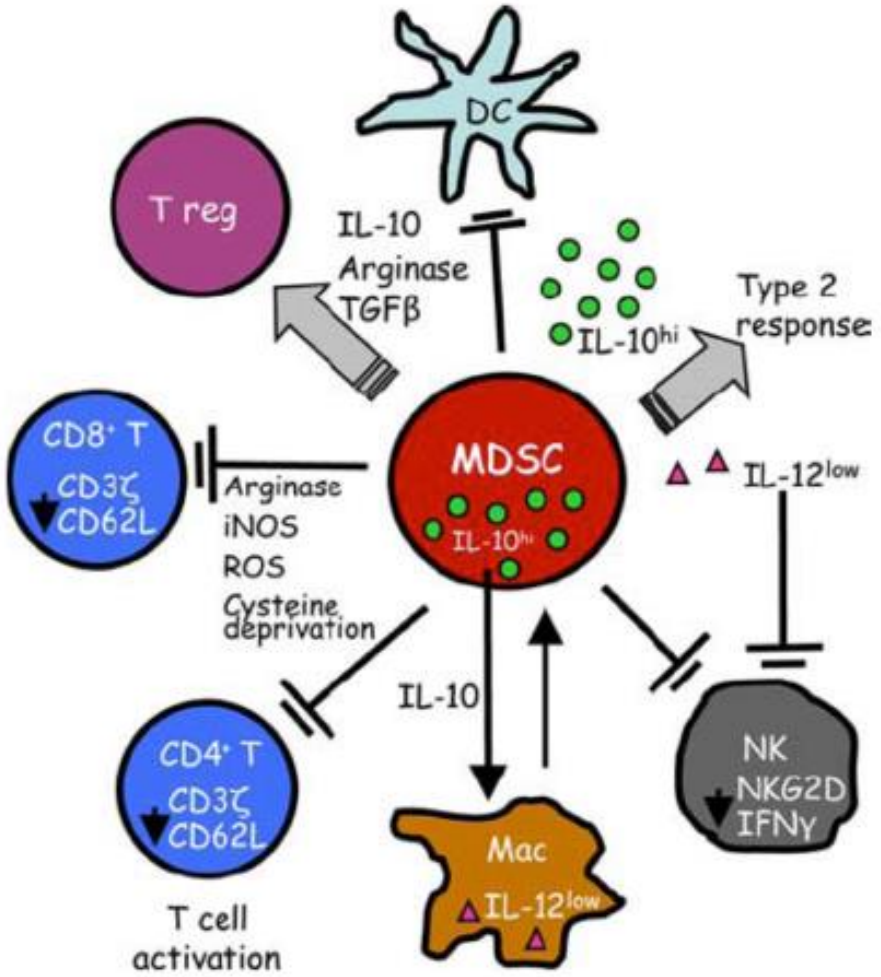


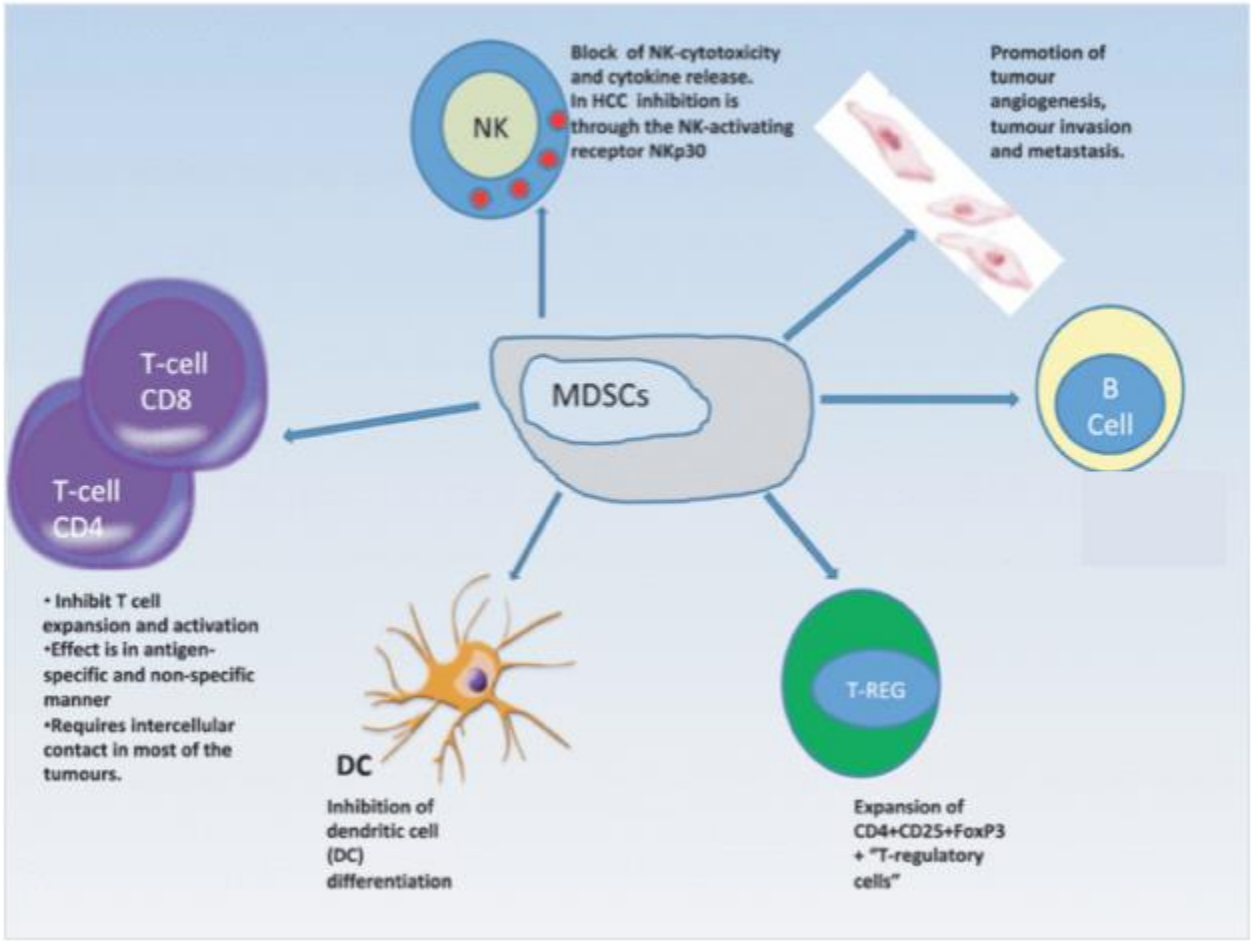


HLA-I- prostate cancer, with HLA-I+ stroma and infiltrating cells

Frequency (%) of HLA-I altered phenotypes in invasive tumors

MDSC suppress anti-tumor activity through different mechanisms

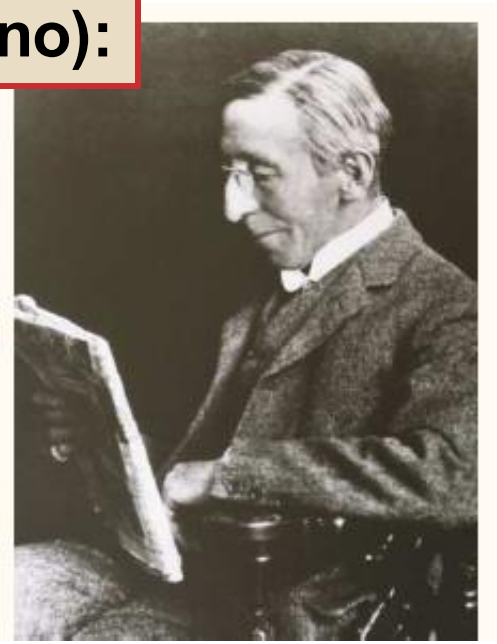




Il processo di formazione delle metastasi

1889 Stephen Paget
L'ipotesi "Seed and Soil" (Il seme e il terreno):

Le metastasi si sviluppano solo se il seme e il terreno sono compatibili!



In his paper, Paget analyzes 735 fatal cases of breast cancer, complete with autopsy, as well as many other cancer cases from the literature and argues that the distribution of metastases cannot be due to chance, concluding that although "the best work in pathology of cancer is done by those who… are studying the nature of the seed…" [the cancer cell], but the "observations of the properties of the soil" [the secondary organ] "may also be useful"...

The Lancet, 1889

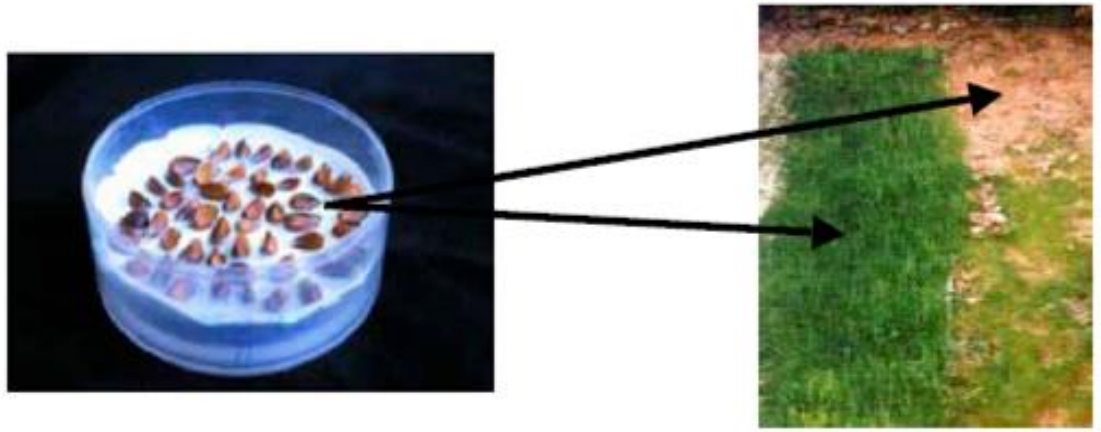
"When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil."

Seed and Soil

I semi vanno in tutte le direzioni, ma cresceranno solo quelli che cadranno dove il terreno gli è congeniale

Teoria postulata nel 1889 dal Dr. Stephen Paget: "seed and soil"

la cellula metastatica (**the seed**) necessita di un appropriato microambiante (**the soil**) per crescere e svilupparsi in un'altra regione corporea diversa da quella di origine.



IFOM
ISTITUTO FIRC DI ONCOLOGIA MOLECOLARE

Le cellule tumorali (seed) hanno affinità per alcuni organi (soil).
Si formano metastasi solo quando seed & soil sono compatibili

I fatti sono…

1. **Gli organi bersagliati dalle metastasi sono spesso sempre gli stessi**

2. **I reni, che ricevono il 25% della gittata cardiaca, sono raramente sede di metastasi**

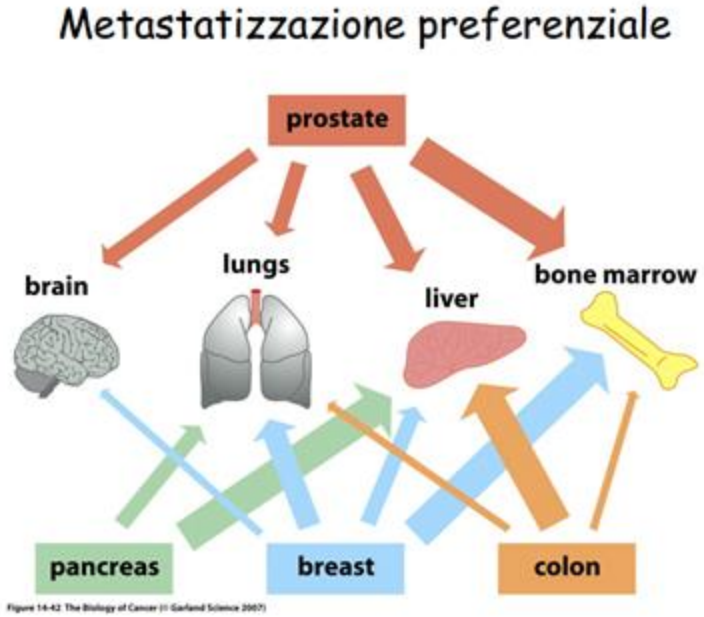
3. **Il miocardio, con tutto il sangue che riceve….. non è quasi mai sede di metastasi**

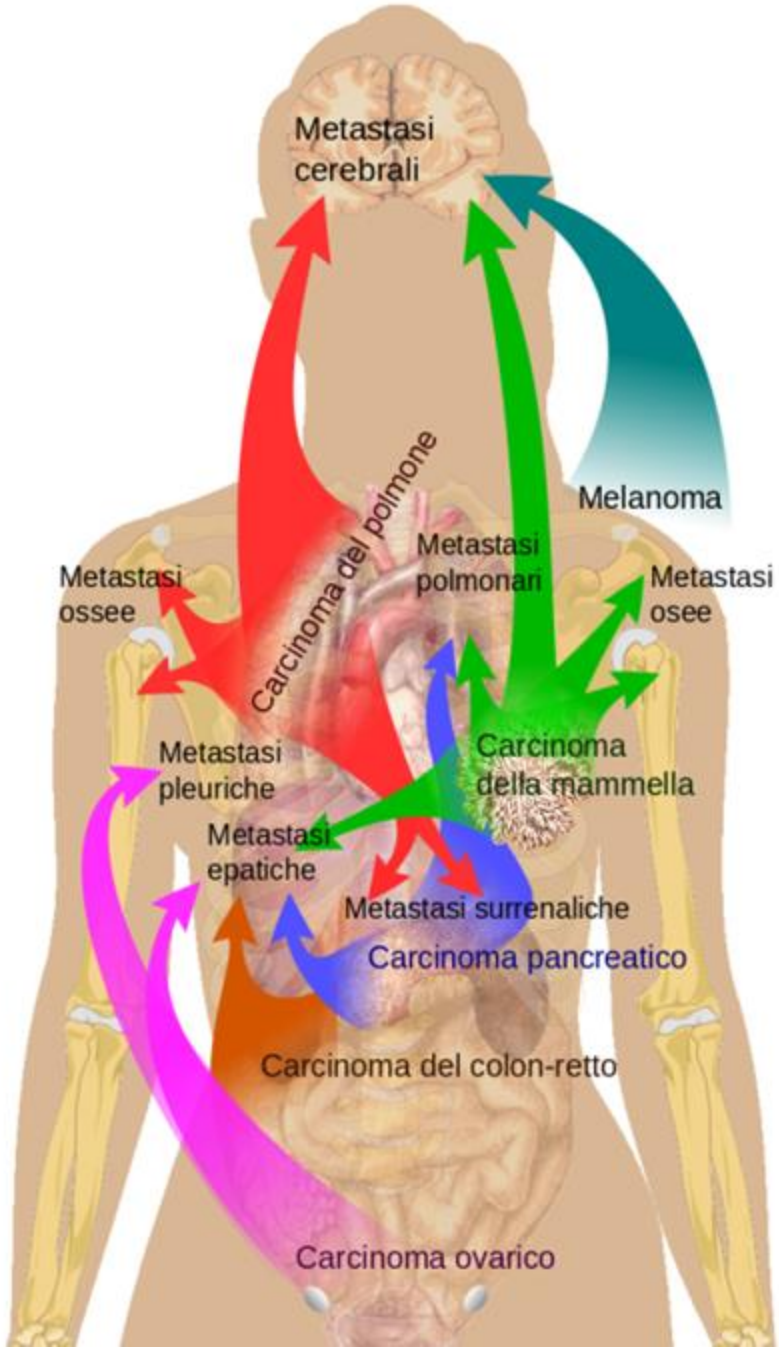
4. **Non sempre le metastasi seguono "regole anatomiche"**

Quindi i tumori hanno "particolari" preferenze d'organo non sempre spiegabili su base anatomica

Organotropismo delle localizzazioni metastatiche

localizzazione preferenziale delle metastasi in determinati organi





se una metastasi crescerà o meno in un tessuto dipende da:

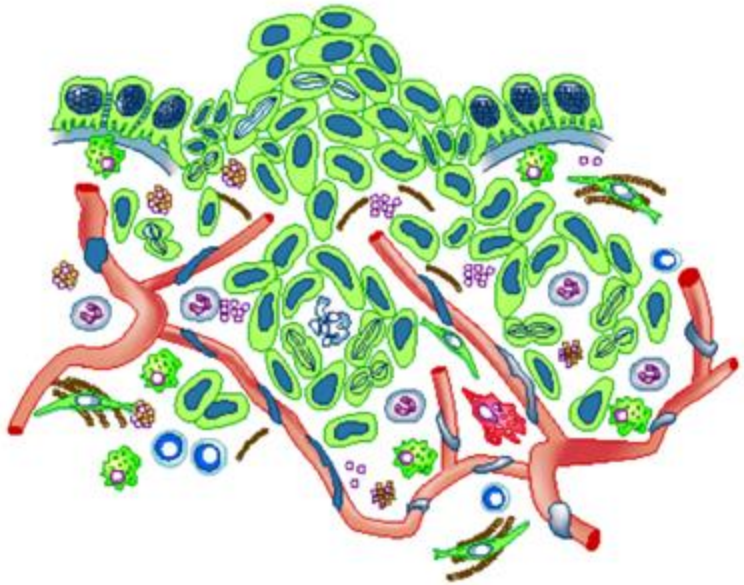
chemochine

citochine

fattori di crescita

recettori

Il microambiente è importante!

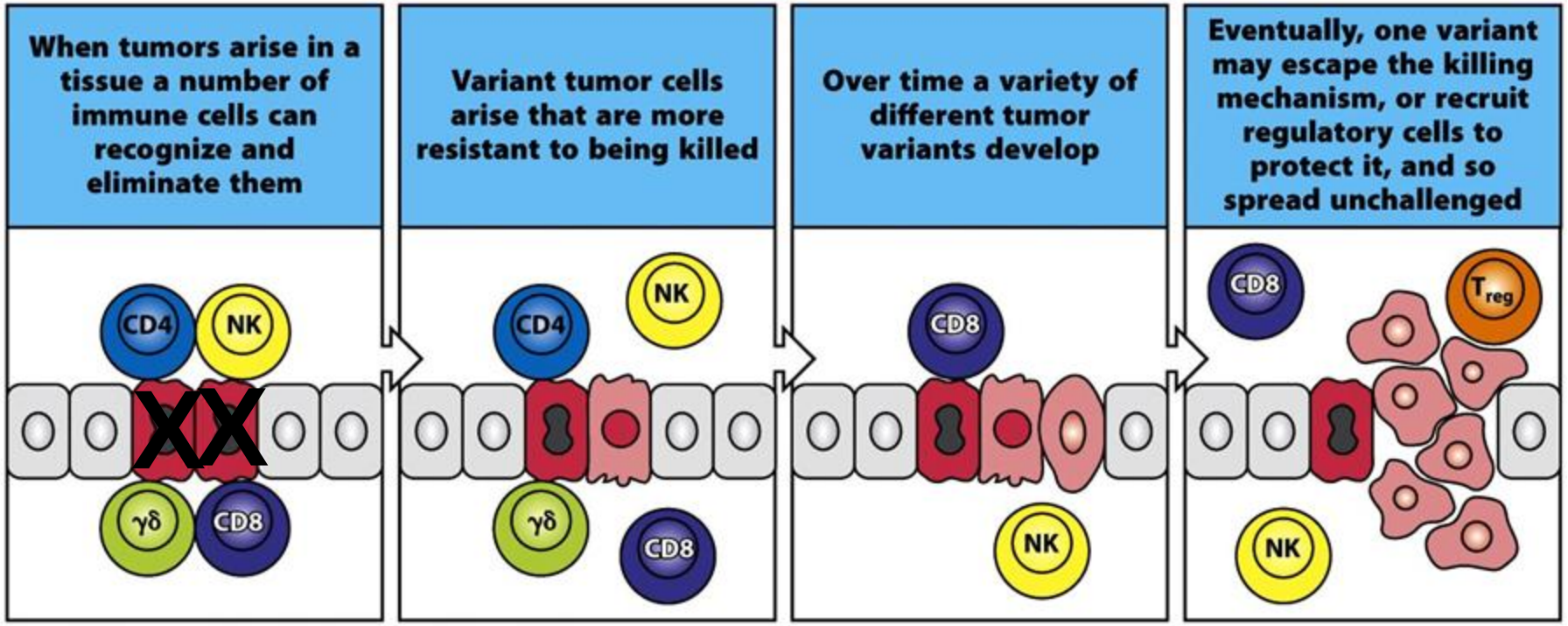


Il microambiente tumorale è un protagonista indispensabile del processo neoplastico, poiché favorisce la proliferazione, la sopravvivenza e la migrazione delle cellule tumorali.

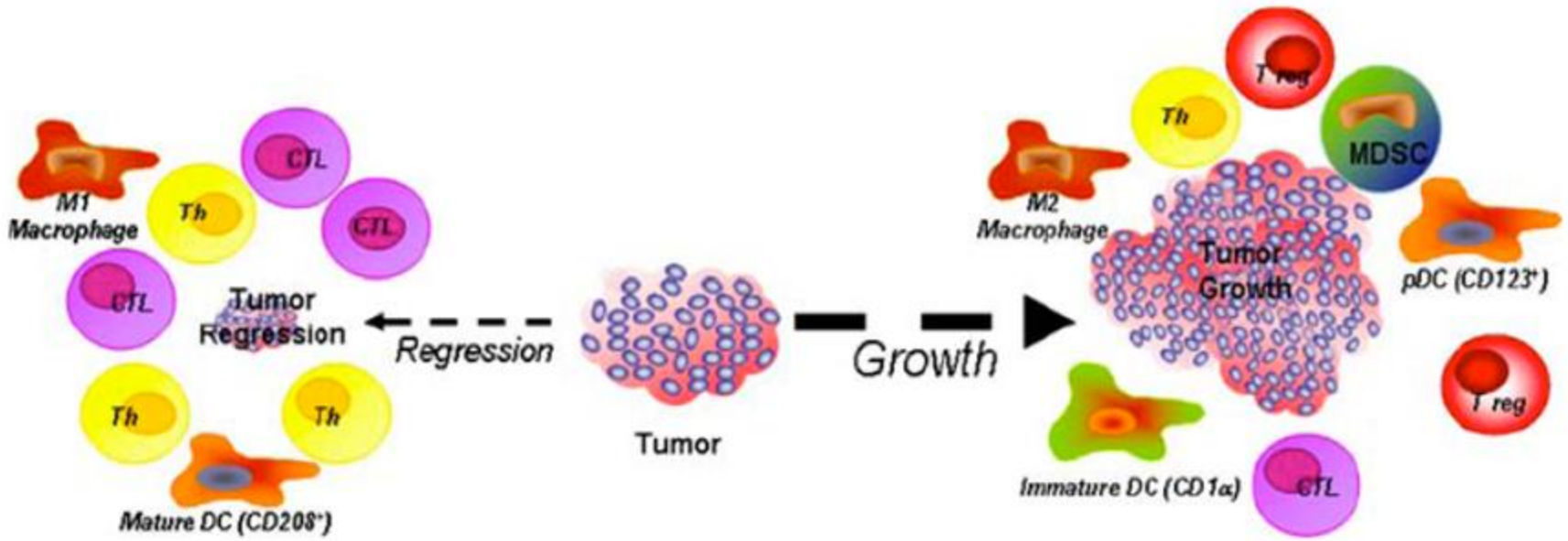
Coussens LM and Werb Z Nature 2002

"Immunoediting" del tumore: le 3 E

Eliminazione | Equilibrio | Evasione



Il sistema immunitario è come “un’arma a doppio taglio”



THE IMMUNE SYSTEM IS A “DOUBLE-EDGED SWORD”

- It can destroy tumor cells, and yet paradoxically also promote and sustains cancer.

- The complexity of the immune system-cancer relationship depends on tumor cellular origin, mode of transformation, anatomic location, stromal response, cytokine production profile, inherent immunogenicity….etc.

Talmadge JE et al, Cancer Metastasis Rev 2007