Corso di Biologia cellulare del Cancro 2020/21

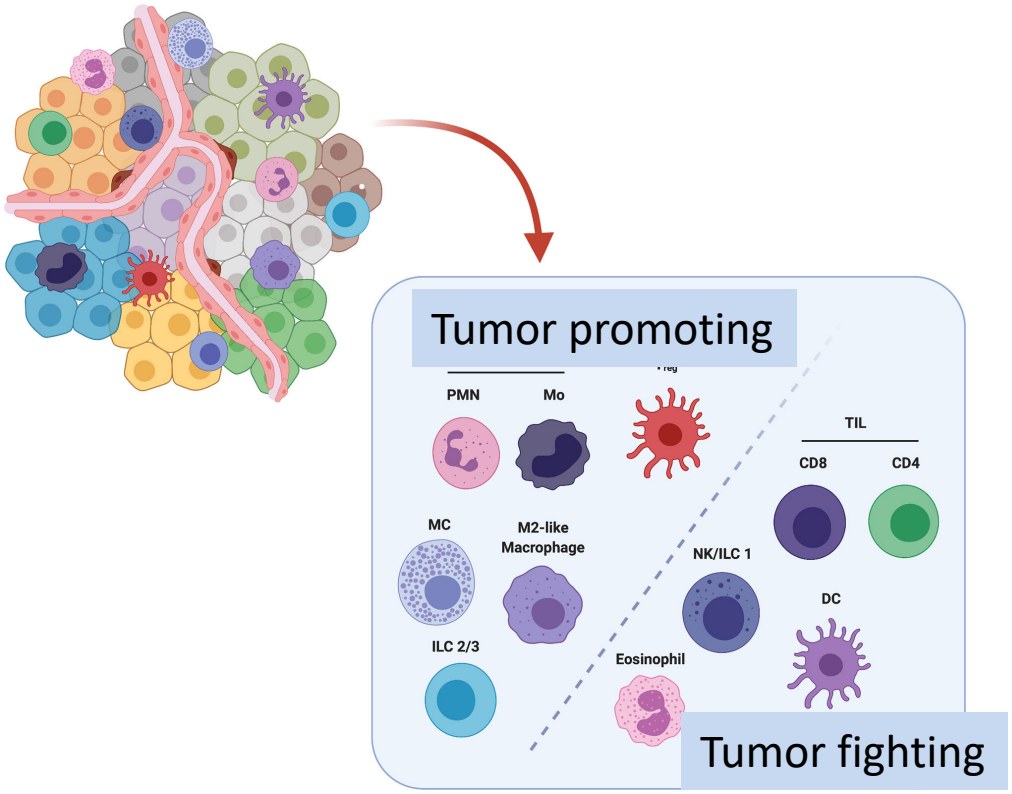
Cancer immunoediting from immune surveillance to immune escape

Federica Benvenuti

International centre for Genetic Engineering and Biotechnology
Area Science Park
040 3757389
benvenut@icgeb.org

Dual role of the immune system in cancer

- Inflammation (by immune cells) can promote tumorigenesis
- The imune system has potent anti-cancer properties



Interplay between Immune system and cancer cells

Intrinsic and extrinsic tumor suppression mechanism

INTRINSIC

Correct genetic mutation
Induce senescence or apoptosis

Elimination of preneoplastic cells

EXTRINSIC

Environmental signals that prevent cell cycle progression :
-Cell-matrix interactions/polarity proteins
-Cell-cell junctions

Elimination/containment of tumor cells by effector cells of the Immune systems

Interplay between immune system and cancer cells

The immune system protects from tumor development INDIRECTLY

1. Eliminating tumor promoting viruses (HPV, EBV, HCV)

2. Resolution of infection to limit inflammation
(reparative mechanism, anti-inflammatory molecules)

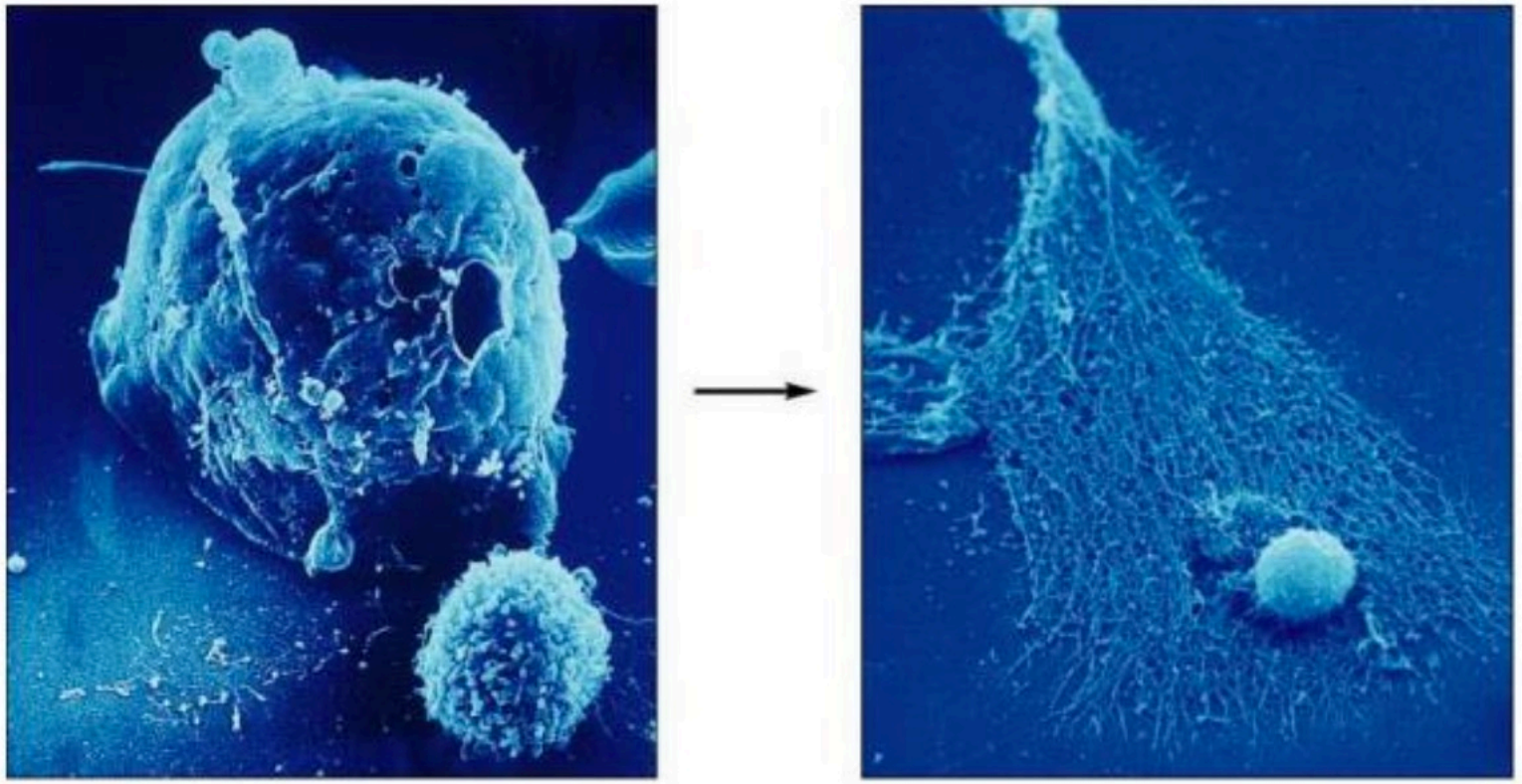
Interplay between Immune system and cancer cells

- The immune system protects from tumor development DIRECTLY by recognition and elimination of transformed cells

- Cancer cells possess tumor associated antigens (mutated proteins that are different from the "self")

- Tumor antigens can be recognized as foreign by T cells and NK cells and the cells carrying the foreign antigens can be destroyed

Killing by cytotoxic T cells



Immunological surveillance

Paul Ehrlich (1909) Concept of cancer immunosurveillance.
Predicted that cancer would occur at "incredible frequency" if host defenses did not prevent the outgrowth of continuously arising cancer cells

Lewis Thomas (1957) "primary function of cellular immunity….is to protect from neoplastic disease"

Macfarland Burnet (1957) "It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provide an effective immunological reaction with regression of this tumor and no clinical hint of its existence"

Evidences of immune surveillance: humans

Increased incidence of EBV+ B cell lymphomas in transplant patients treated with immunosuppressive drugs

Increased incidence of Kaposi's sarcoma & EBV+ B cell lymphomas in AIDS patients

Evidences of immune surveillance: animal models

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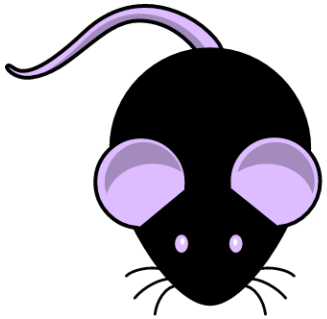


CARCINOGEN INDUCED TUMORS
(MCA SARCOMAS)

SPONTANOUS TUMOR DEVELOPMENT
(IN AGING ANIMALS)

GENETIC MODELS OF CANCER
p53 -/+

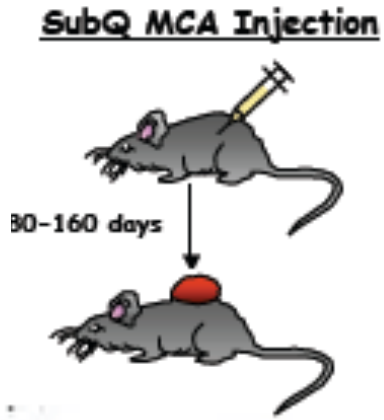
Animals lacking defined
Immune subsets or pathways

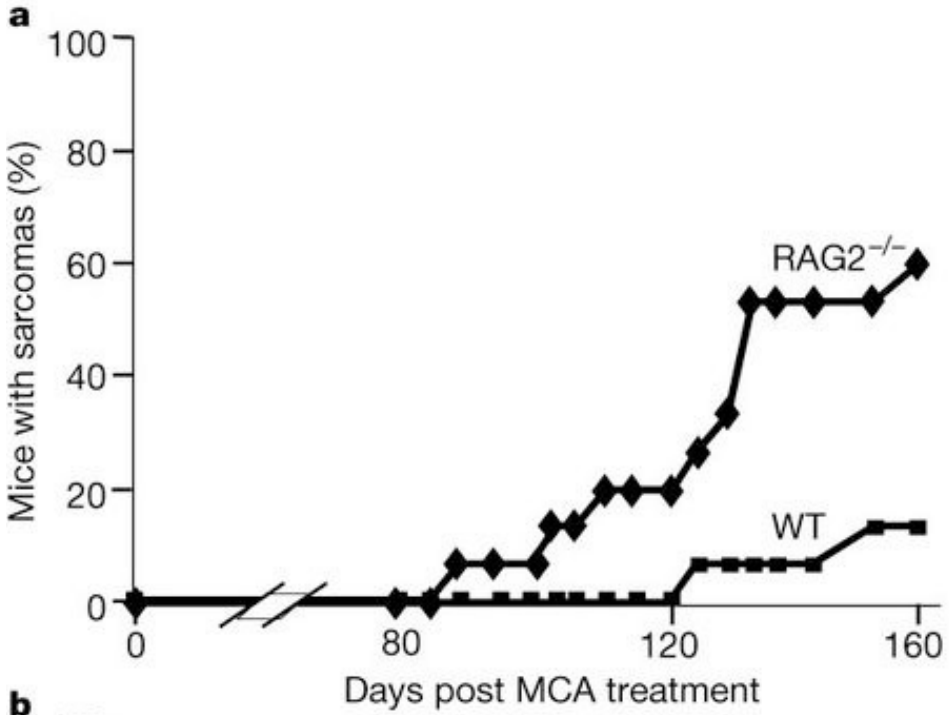
→ INCREASED TUMOR INCIDENCE

Immunological surveillance

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

Vijay Shankaran, Hiroaki Ikeda, Allen T. Bruce, J. Michael White, Paul E. Swanson, Lloyd J. Old & Robert D. Schreiber





No T, no B cells

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

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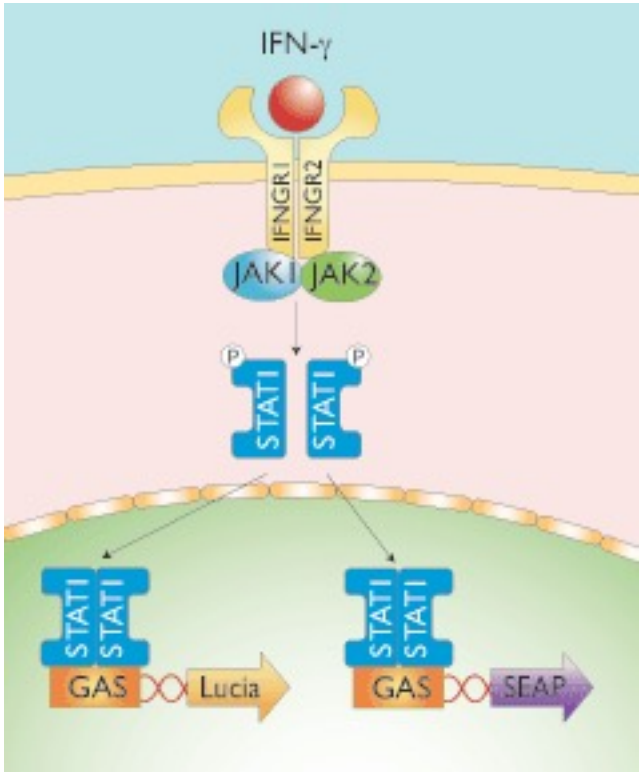
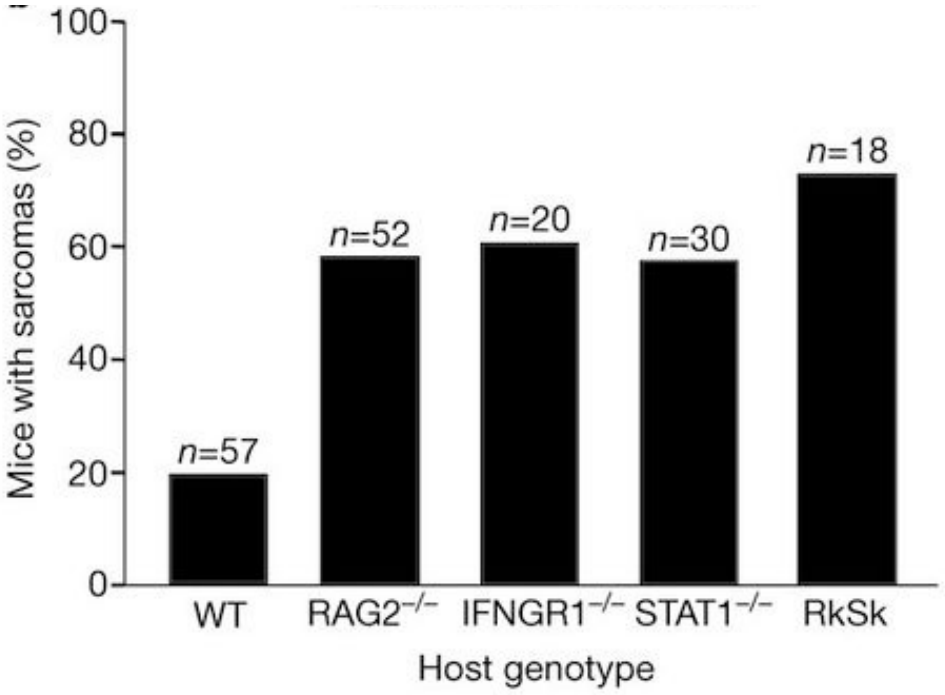
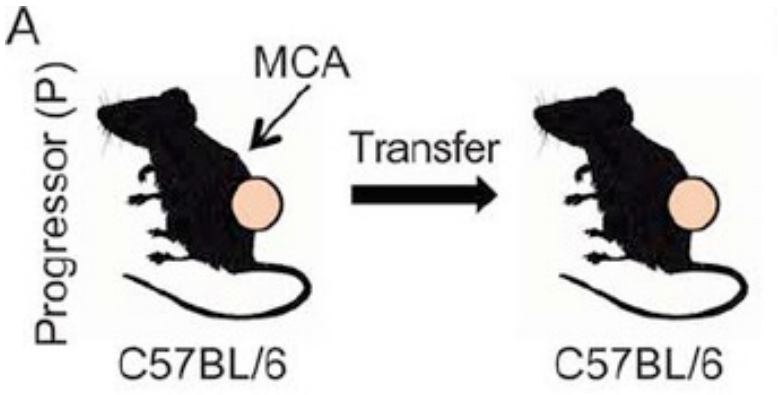




Immuno EDITING: the immune system shapes nascent tumor

TUMORS GROWING IN IMMUNOCOMPETENT HOST

TRANSPLANTED
IN IMMUNOCOMPETENT HOST

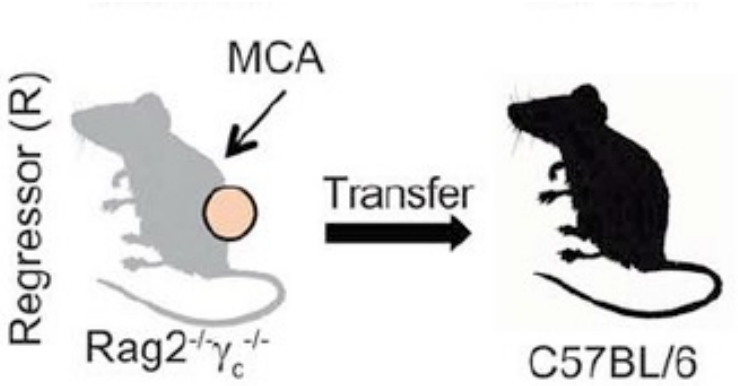


TUMOR GROWTH

Immunological Surveillance

TUMORS GROWING IN IMMUNODEFICIENT HOST

TRANSPLANTED
IN IMMUNOCOMPETENT HOST



REJECTION

Immunological Surveillance

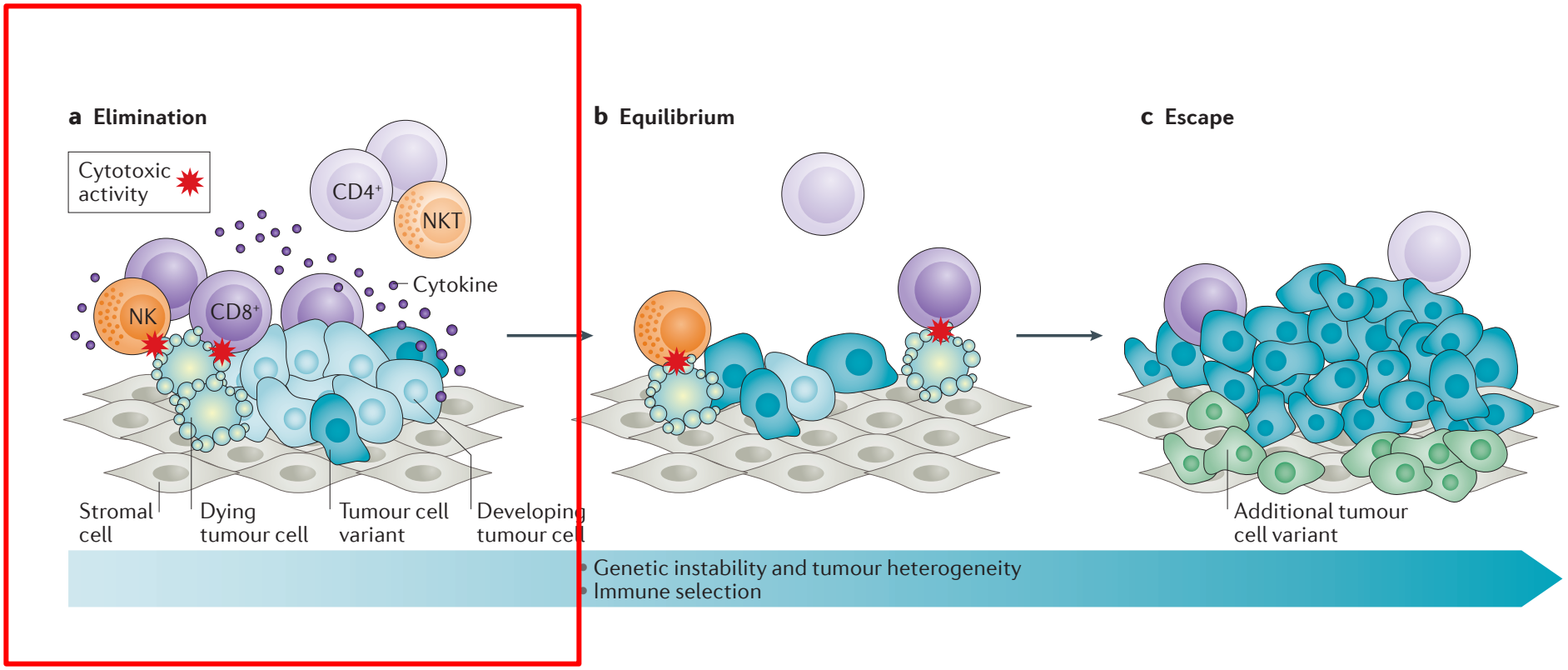
THE IMMUNE SYSTEM DESTROYS EMERGING TUMORS AND SHAPES TUMORS SELECTING FOR MORE AGGRESSIVE VARIANTS

"CANCER IMMUNOEDITING"

CANCER IMMUNOEDITING

A DYNAMIC PROCESS IN THREE PHASES:

ELIMINATION-EQUILIBRIUM-ESCAPE



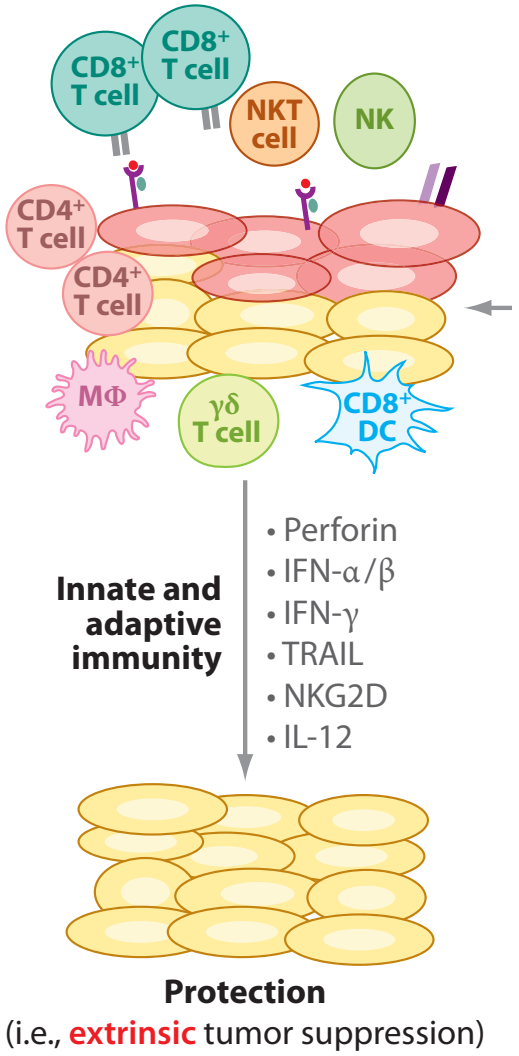
ELIMINATION REQUIRES ADAPTIVE AND INNATE IMMUNE CELLS

INNATE CELLS:

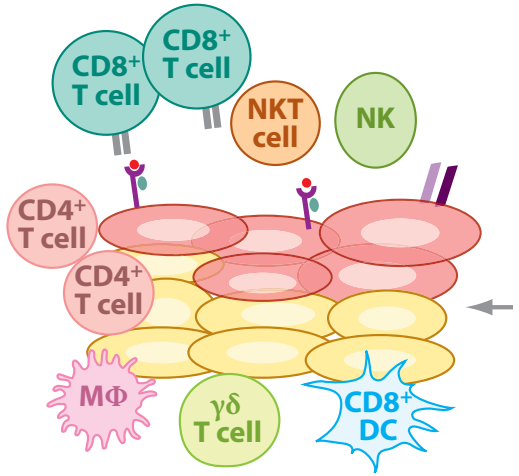
Myeloid cells, NK CELLS, γδ T CELLS
Recognize not polymorphic receptors expressed by tumor cells

ADAPTIVE CELLS:

CD8 AND CD4 ARE ANTIGEN SPECIFIC

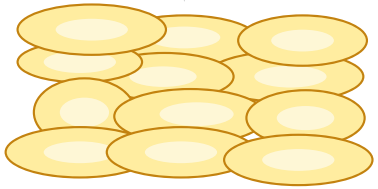


Pathways involved in tumor elimination



Innate and adaptive immunity

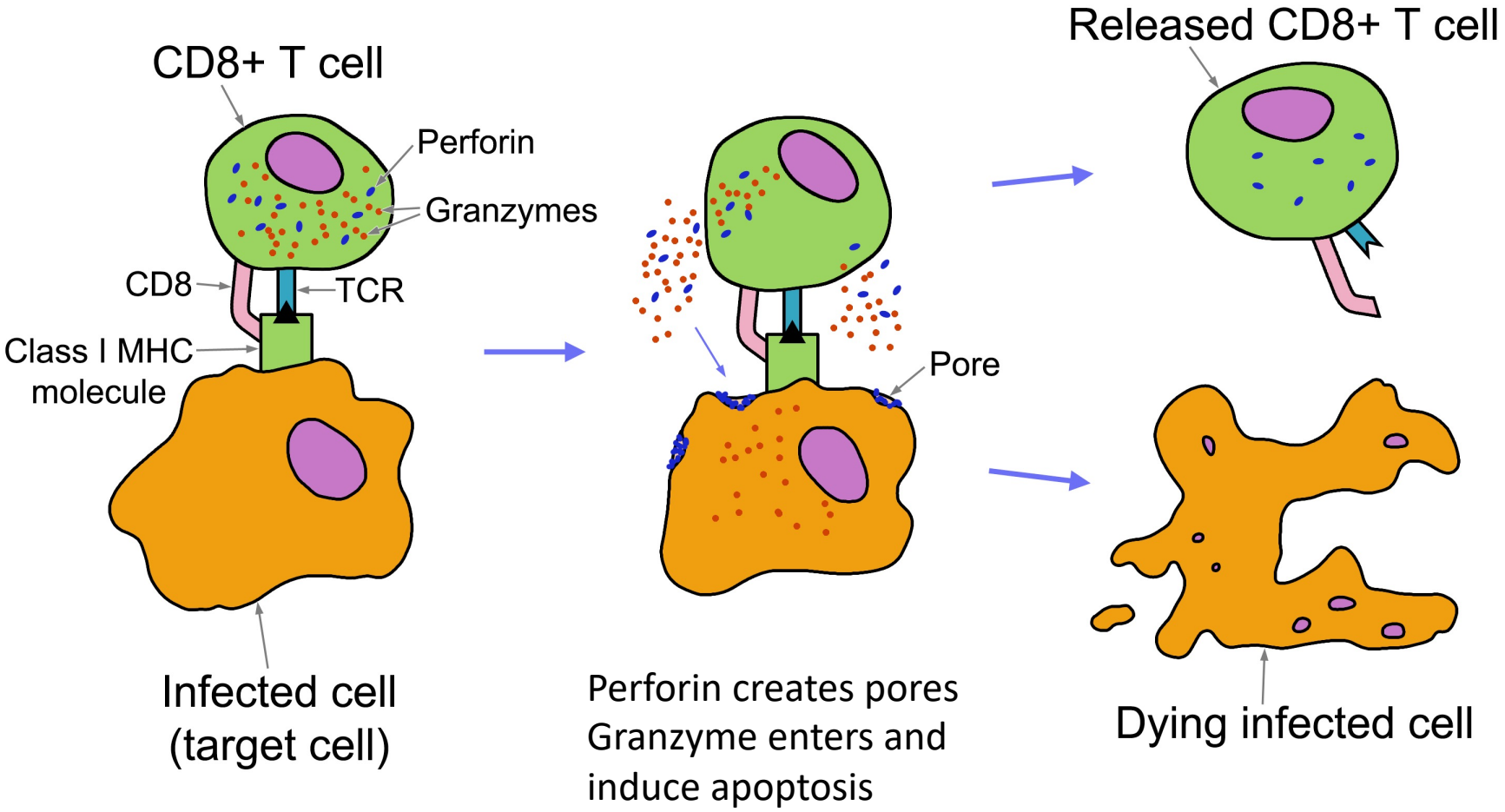
- Perforin
- IFN-α/β
- IFN-γ
- TRAIL
- NKG2D
- IL-12



Protection

(i.e., **extrinsic** tumor suppression)

Perforin kills target cells (infected or transformed)



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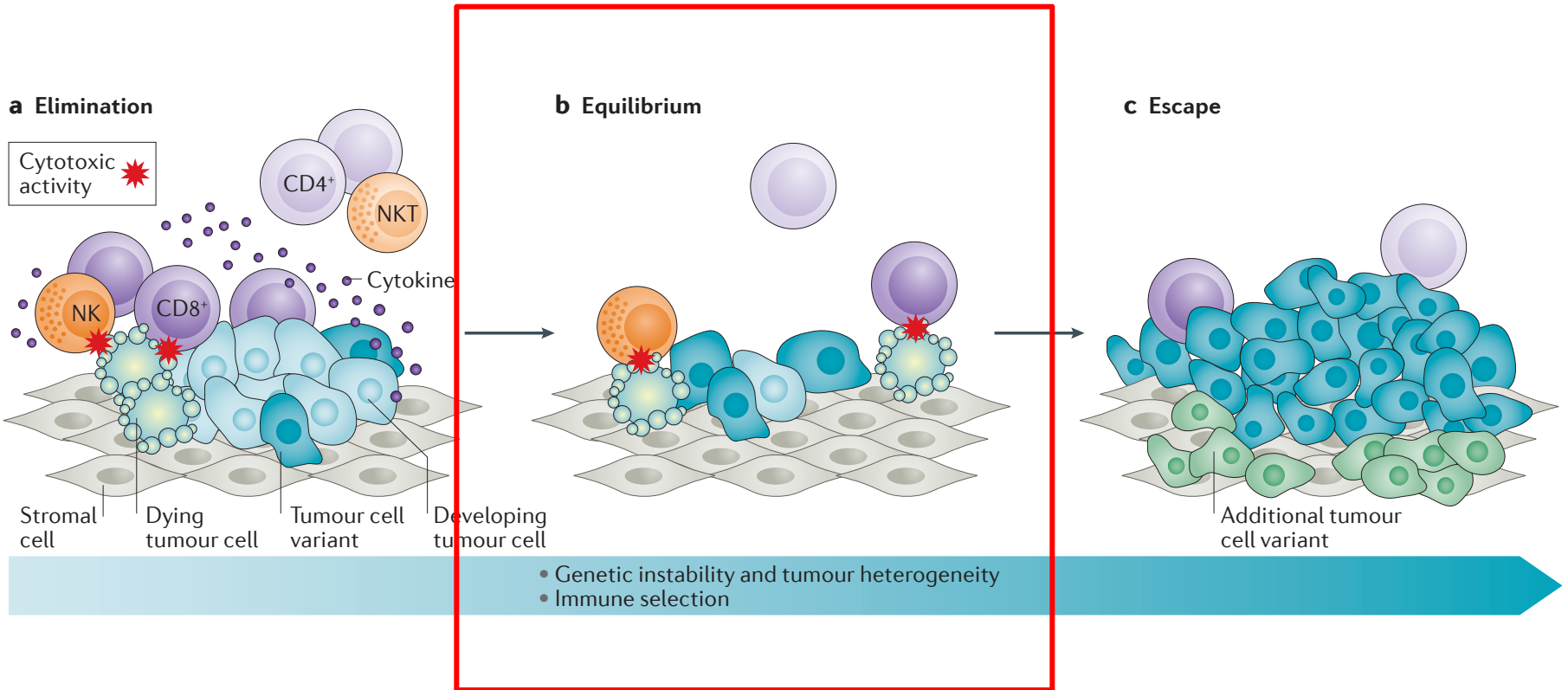
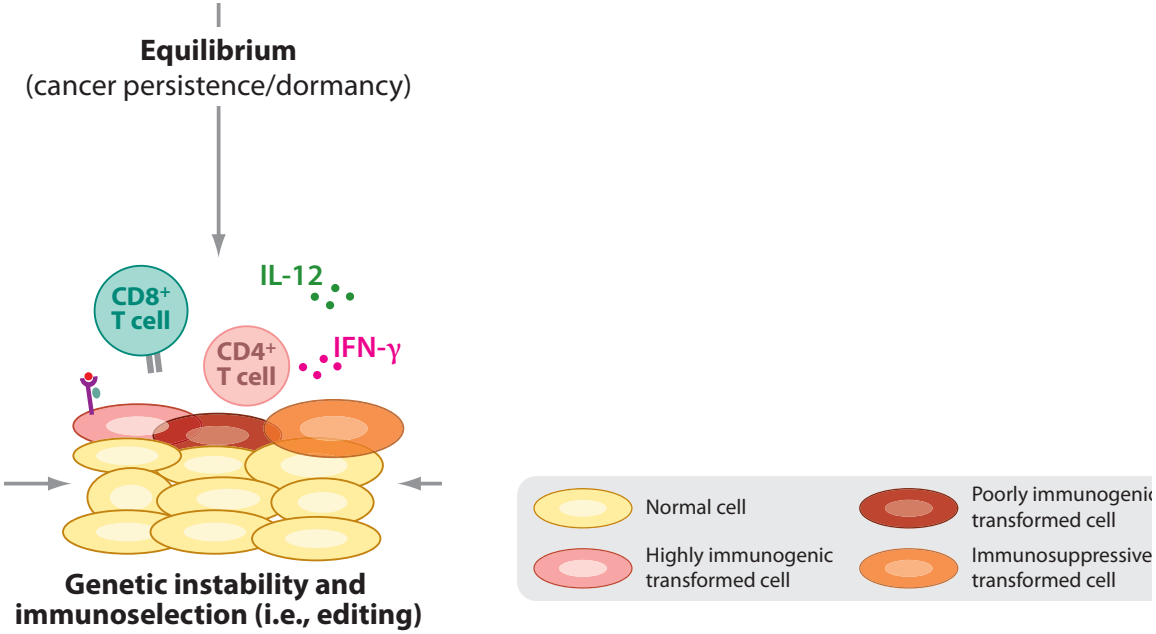


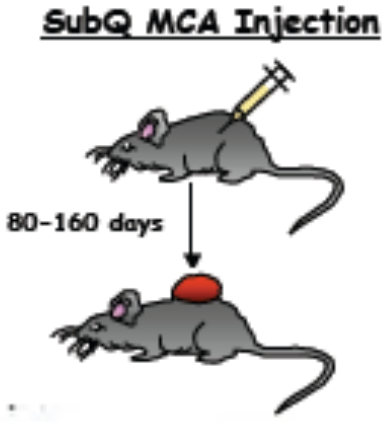
EQUILIBRIUM: CD8 T and CD4 T cells keep tumor cells under control

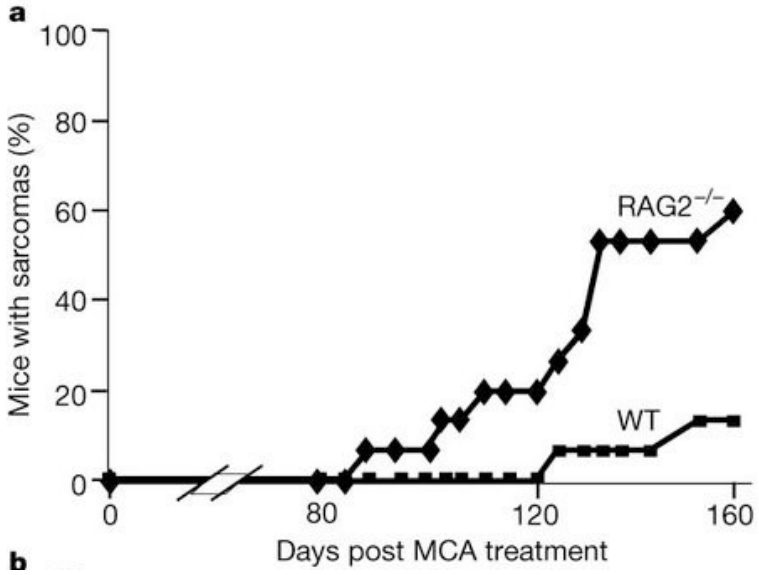


Tumors may remain dormant for long periods (more than 10 years).
During this phase antitumor immunity contains but does not completely eradicates an heterogenous population of tumor cells. Among these cells some acquire the capacity to evade immune recognition.

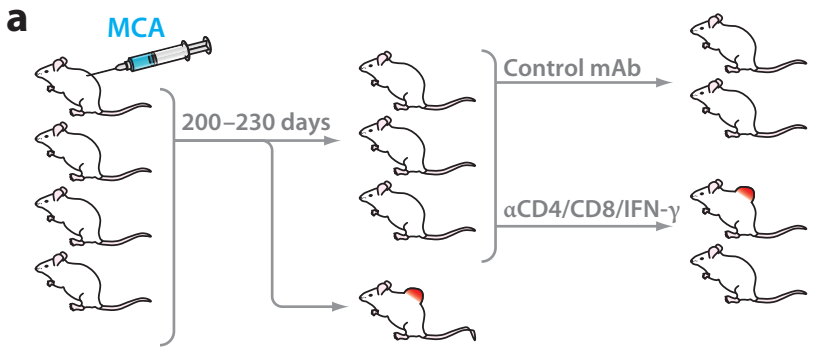
TUMOR SCULPTING PHASE

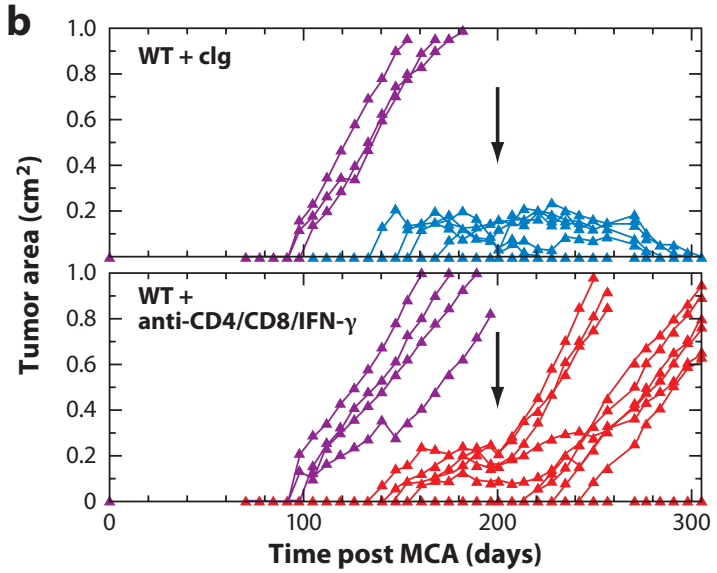
EQUILIBRIUM: experimental evidences

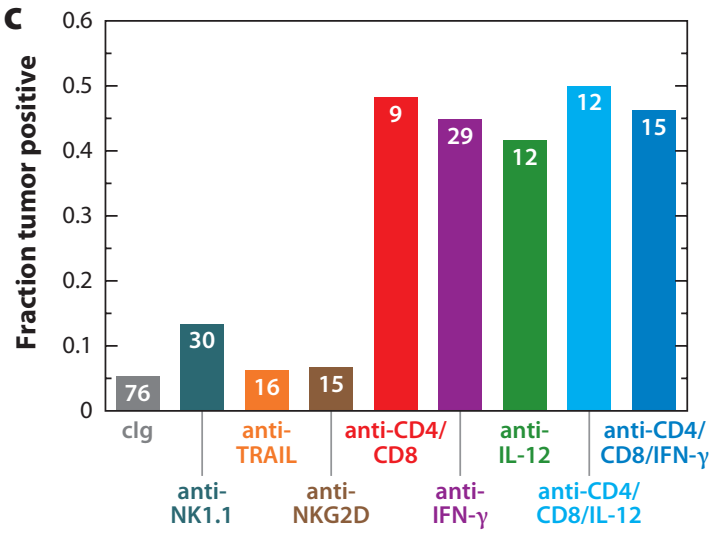




EQUILIBRIUM: experimental evidences

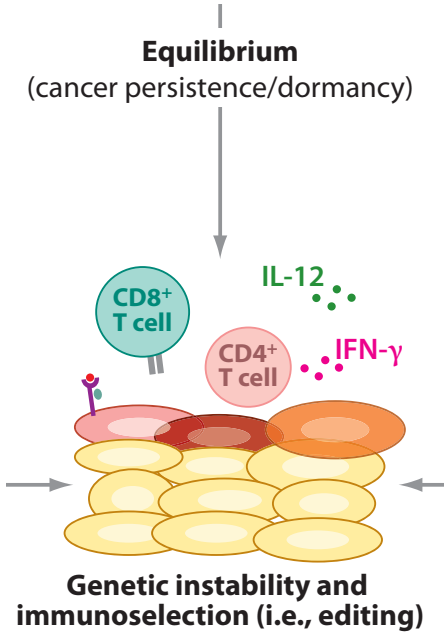






Equilibrium depends on adaptive immunity

EQUILIBRIUM: experimental evidences



Equilibrium depends on adaptive immunity

CANCER IMMUNOEDITING

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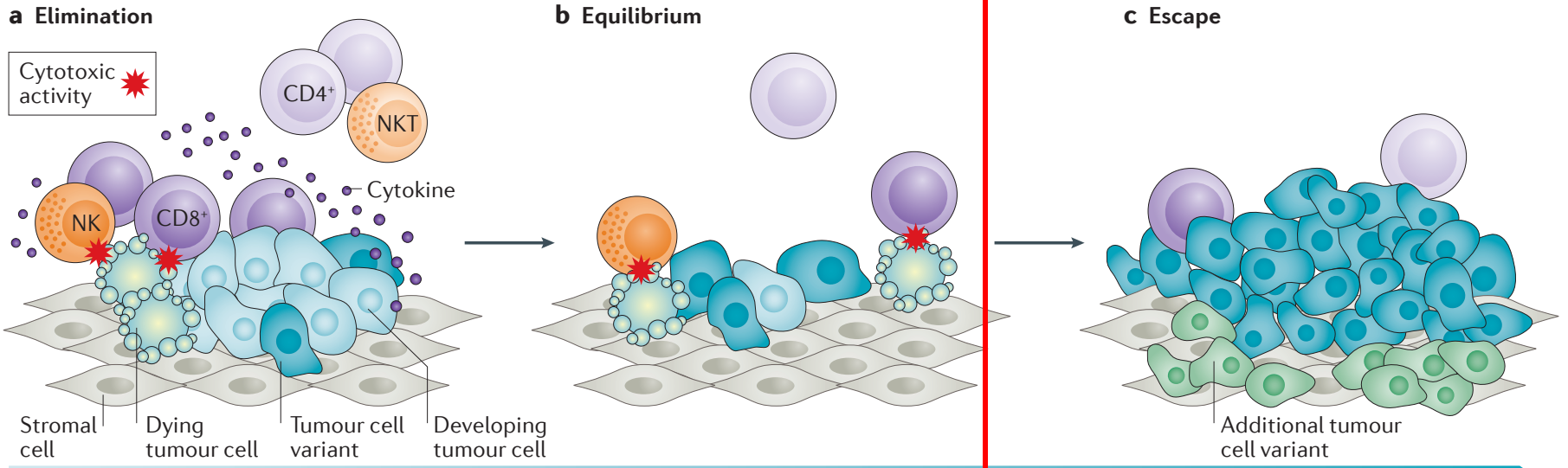
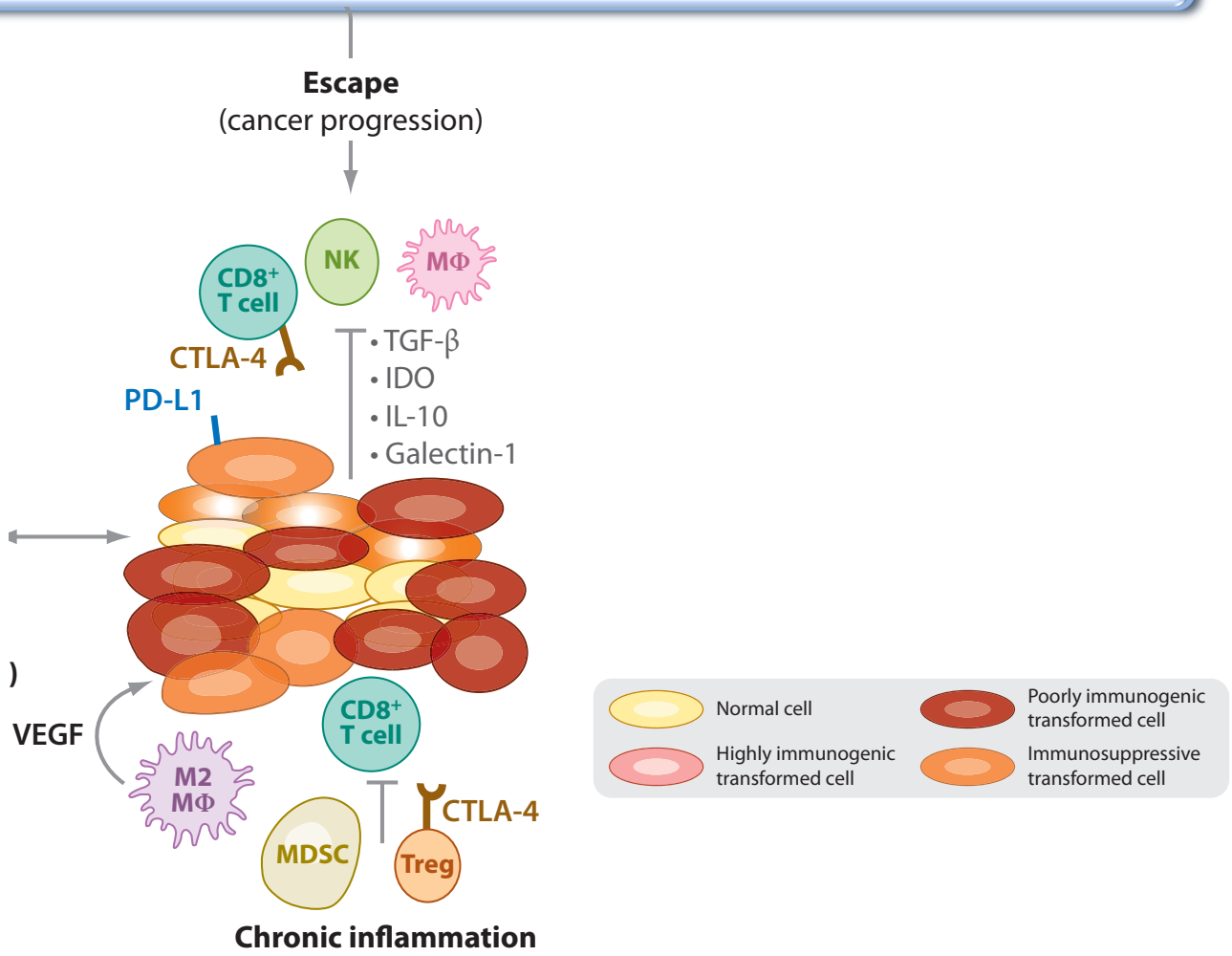


ESCAPE: aggressive clones escape immune system control



APPERANCE OF POORLY IMMUNOGENIC CELLS THAT HAVE UNDERGONE EDITING

AND

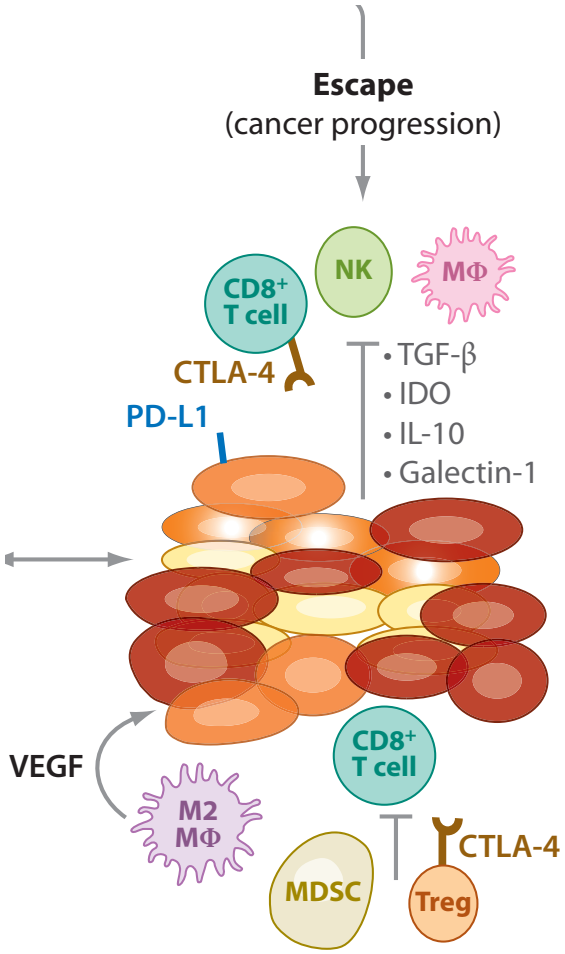
ESCAPE IMMUNE SYSTEM CONTROL

TUMOR ESCAPE: A DARWINIAN SELECTION PROCESS

Stochastic appearance of variants capable to avoid immune recognition

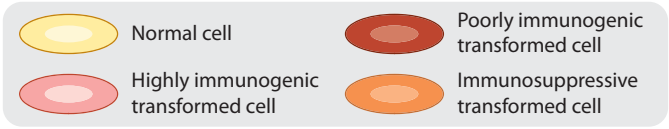
+

evolutionary pressure to select for more aggressive variants



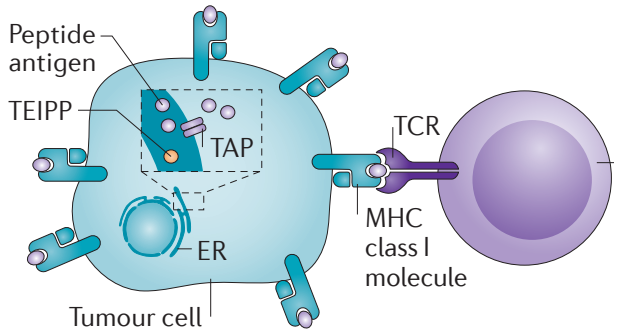
1.Inhibition of anti-tumor responses

2.Induction of immunosuppressive mechanism

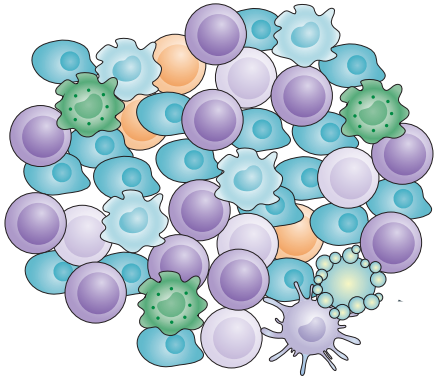


Mechanism of immune escape

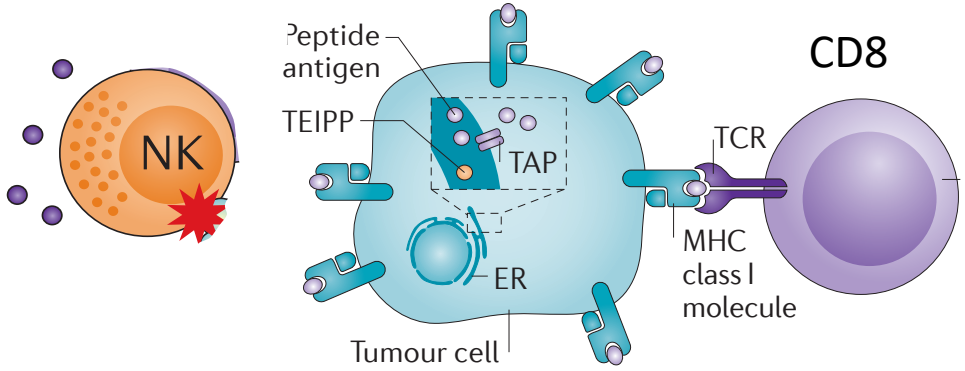
CELL AUTONOMOUS MODIFICATIONS



CHRONIC INFLAMMATION AND IMMUNE SUPPRESSIVE NETWORK



Cancer cell autonomous mechanism of escape (passive)



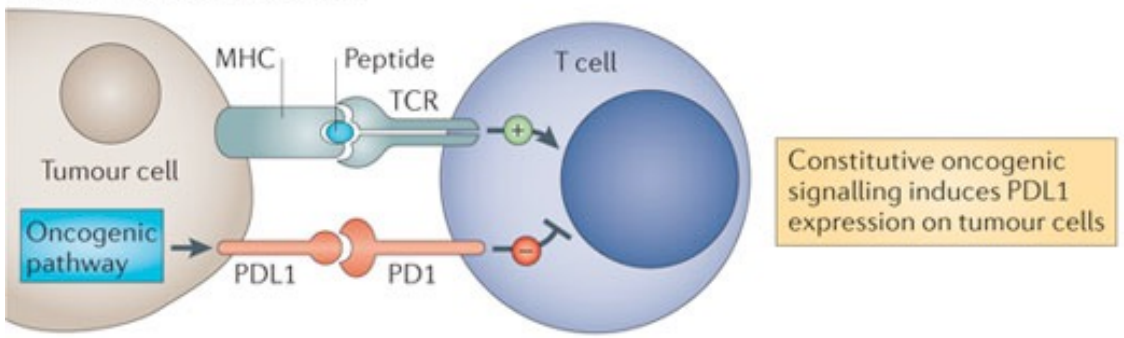
1. AVOID DETECTION:

downregulation of MHC class-I, TAP, LMP2-LMP7, IFN-γ insensitivity
Loss of ligand for NKG2D

2. AVOID IMMUNE MEDIATED KILLING

Upregulation of antiapoptotic molecules (FLIP, BCL-XL)
Expression of mutated forms of death receptor (TRAIL, DR), normally inducing apoptosis.

Immune checkpoint inhibitors
(active mechanism of immune escape)



3. EXPRESSION OF IMMUNE INHIBITORY LIGANDS

Implicated in modulating duration and amplitude of immune responses to pathogens, important to maintain tolerance

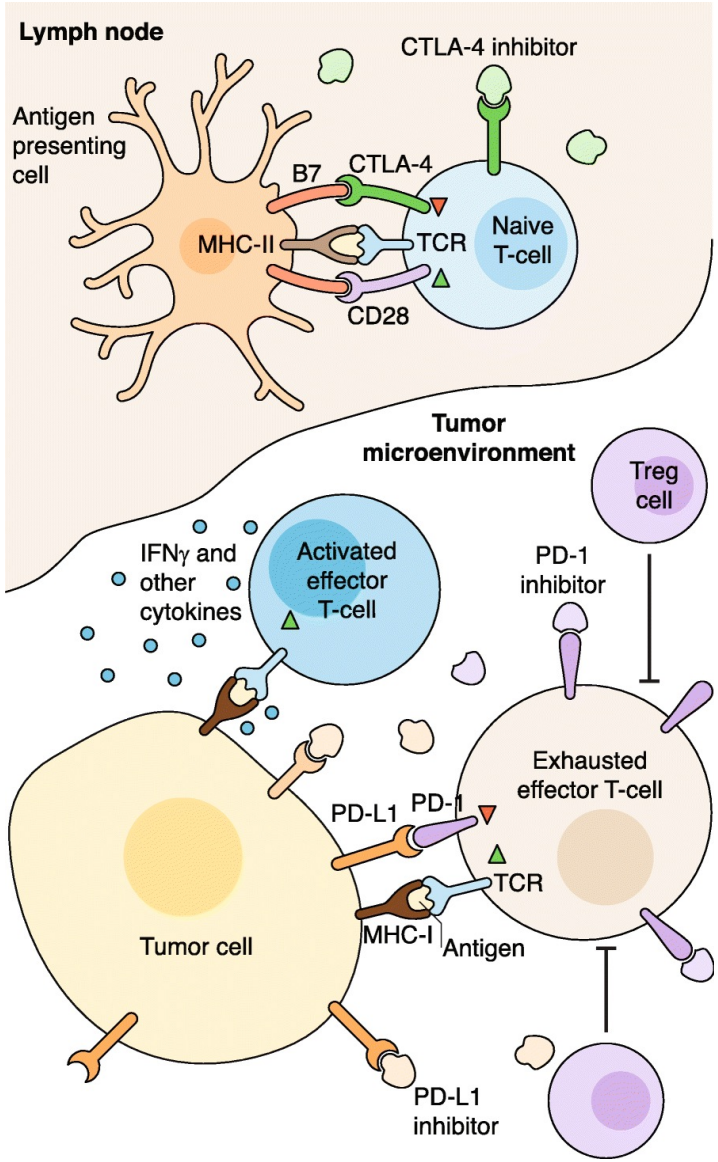
⬇

subverted by tumor cell

PDL1-PD1

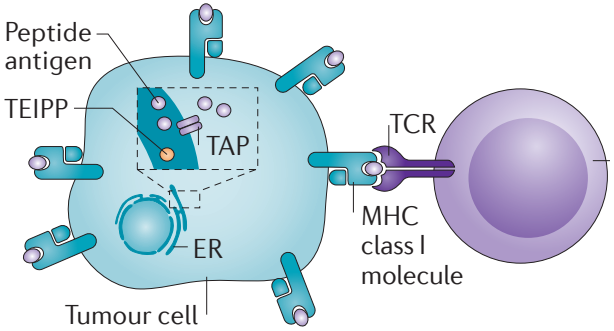
Reduce T cell survival and induce T cells apoptosis
Induce exhaustion, increase T regulatory function

Immune checkpoint inhibitors
(active mechanism of immune escape)

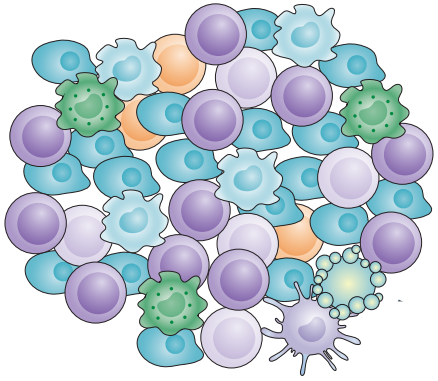


Generation of a tumor promoting/immuno suppressive environment

CELL AUTONOMOUS MODIFICATIONS



INFLAMMATION AND IMMUNE SUPPRESSIVE NETWORK



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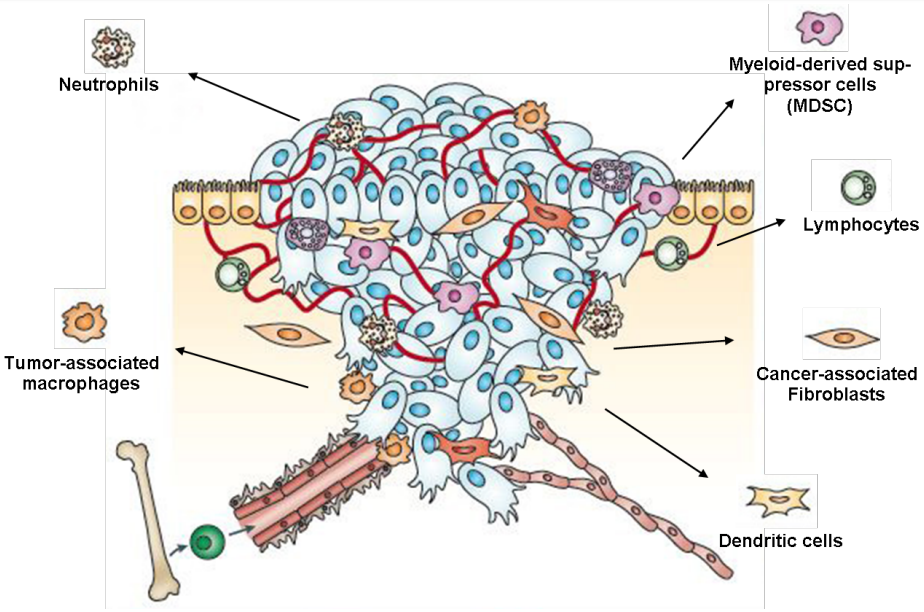
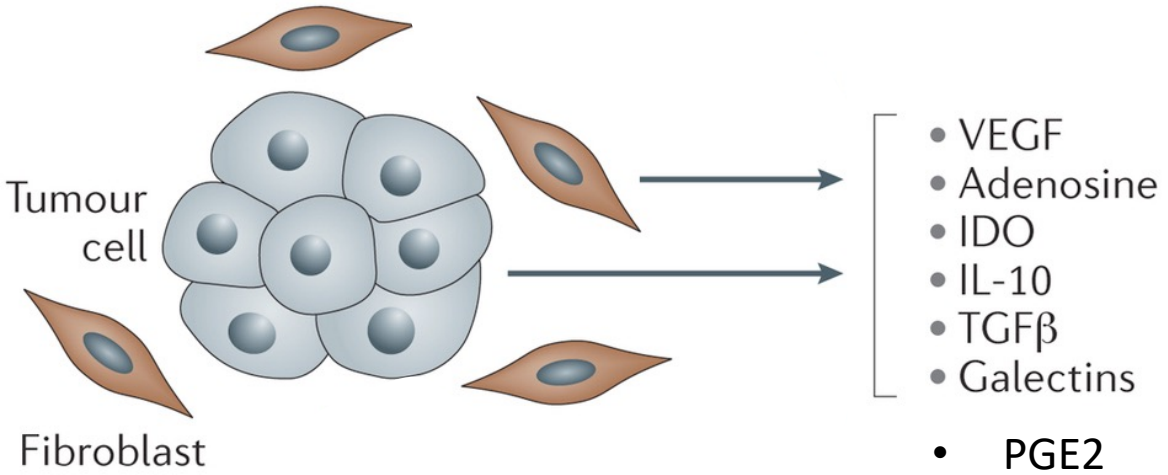


1. Malignant cells stimulate stromal and immune cells to secrete inflammatory cytokines . Chronic inflammation directly promotes tumor growth (matrix remodeling,angiogenesis, proliferative molecules)
2. Tumor derived factors recruit immune cells with protumorigenic functions
3. Tumor derive factors subvert the function of anti tumorigenic immune cell types (T cells and dendritic cells)

Tumor derived factors directly inhibits the function of cytotoxic T cells



- PGE2
- Lactic acid

Tumor derived factors directly inhibits the function of cytotoxic T cells

- IDO: catabolism of Triptophan , production of metabolites that inhibits
- T cell proliferation

- TGF-β: multiple tumor promoting effects and inhibition of T cells and NK cell functions

- **Adenosine:** induced by hypoxia: adenosine receptor on CD8 T cells blocks T cell
- proliferation and NK cells function

- **Galectins**: lectins that play a direct a role in neoplastic transformation and
- modulate immune responses. Block T cell activation, induce T cell apoptosis, impair
- secretion of proinflammatory cytokines

- **VEGF and IL-10:** blocks T cells and antigen presenting cells

Tumor derived factors determine the composition of the microenvironment

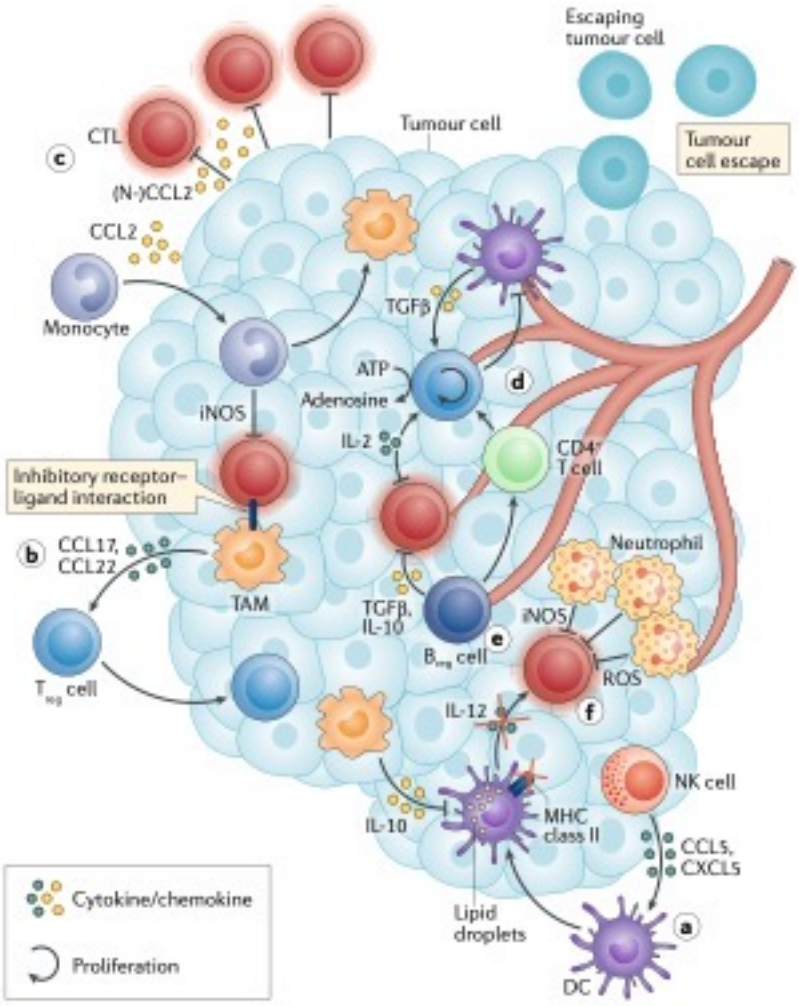
Recruitment/accumulation of immune cells with suppressive functions:

- MYELOID DERIVED SUPPRESSOR CELLS
- REGULATORY T CELLS

MDSC

heterogeneous class of myeloid derived cells with a common ability to suppress T cell functions and to promote tumor growth

Multipli meccansimi di blocco della risposta anti tumorale



a. Dc can be recruited by CCL5 secreted by NK cells, but their fucntions of antigen presenting cells is inhibited

b. Monocytes differentiate into tumor-associated macrophages that recruits Treg via CCL17/CCL22

c. CTLs recruited via CCL2, iNOS can nitrate CCL2 trapping T cells outside the tumor mass

d. Dc can produce TGFb that leads to T regs differentiation Tregs convert ATP in adenosine, immunosuppressive

Open questions:

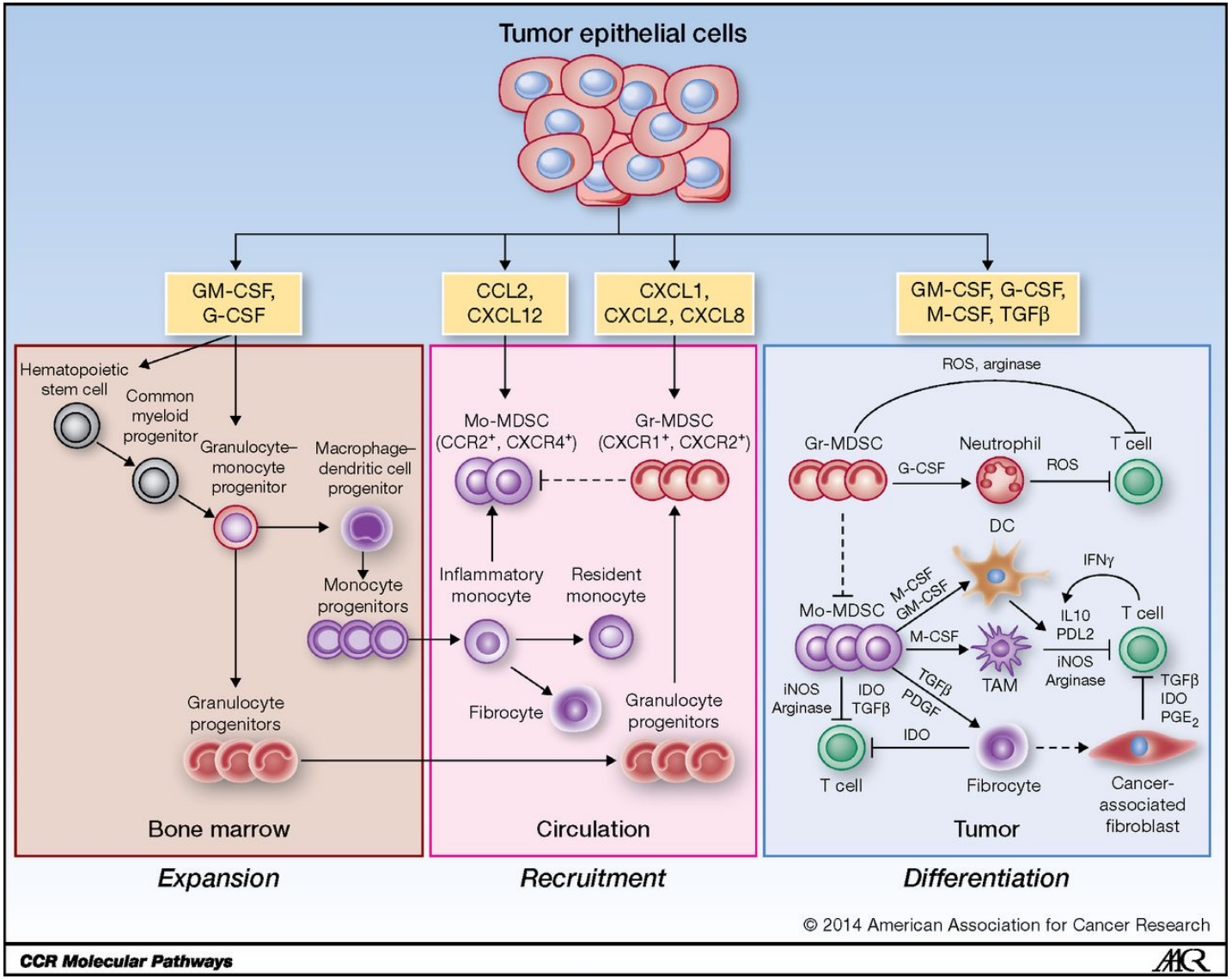
Tumor specificity-timing

Model used

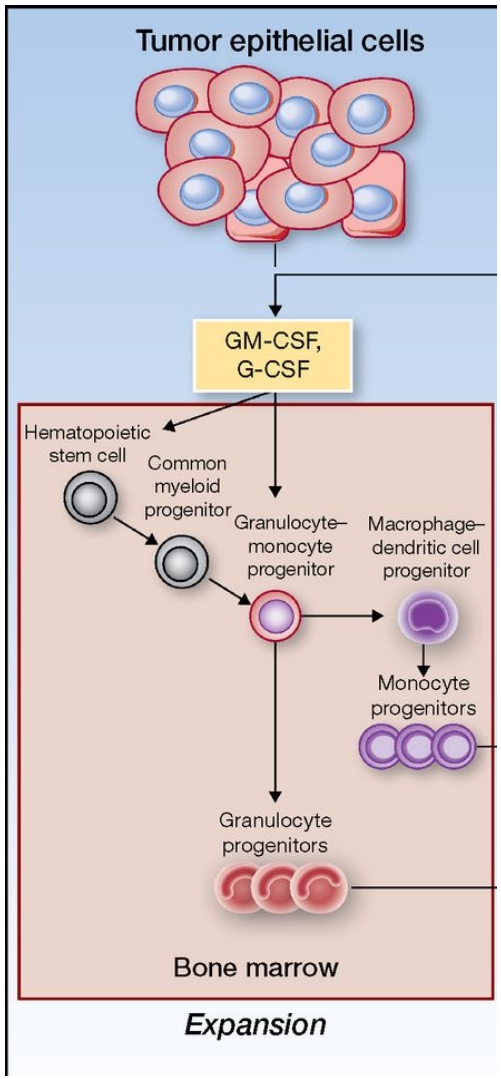
What mechnims prevails in quantity and quality

What is the ideal target?

Mechanism of accumualtion of MDSC



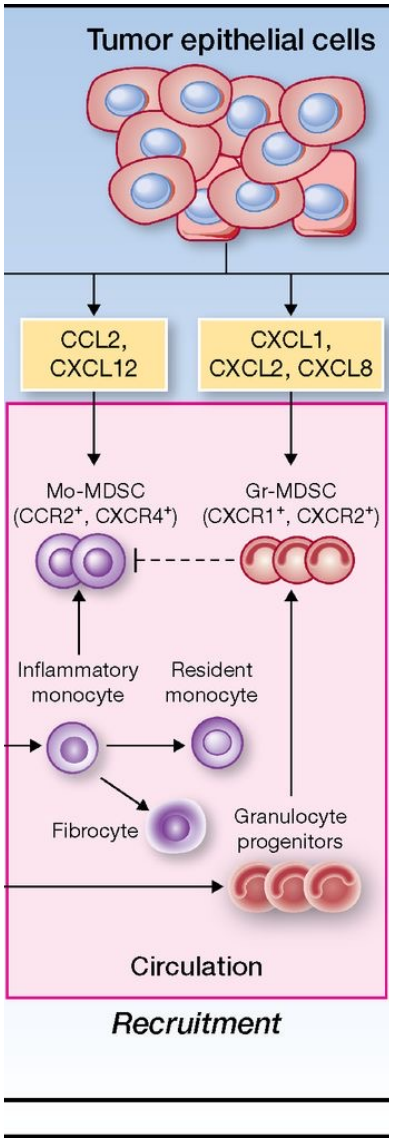
Mechanism of expansion of MDSC



Carcinoma cells overexpress cytokines implicated in differentiation of myeloid cells

Expansion and accumulation of immature myeloid cells

Mechanism of recruitment of MDSC



Overexpression of chemokines by cancer cells

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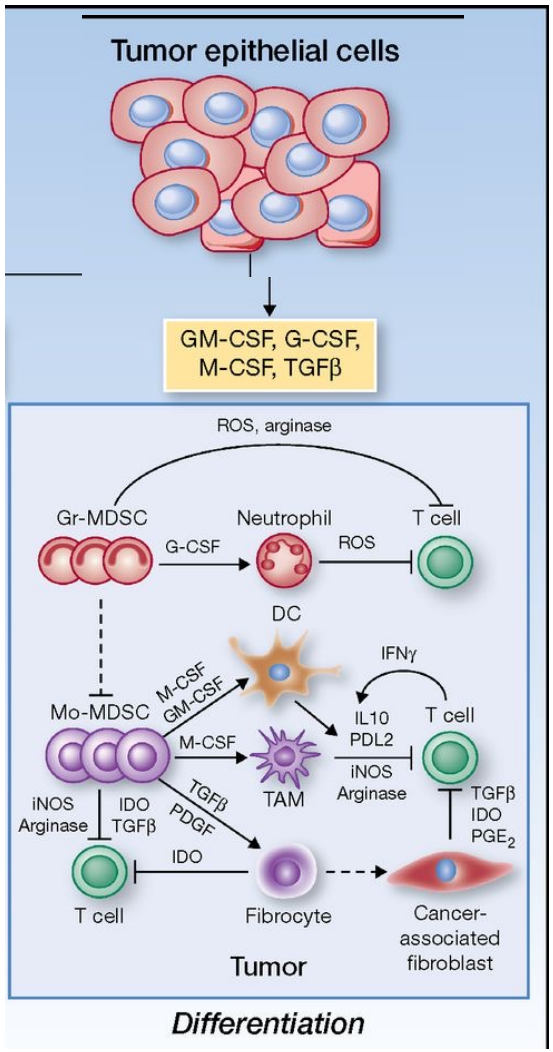
Recruitment of immature and inflammatory monocytes

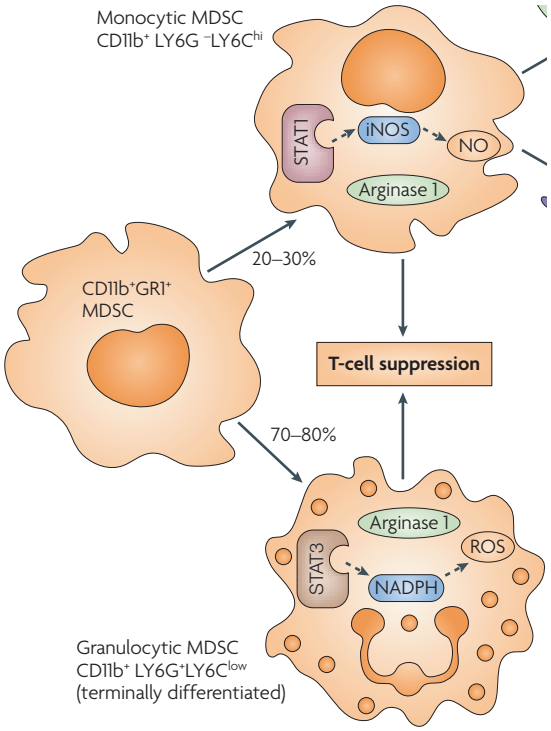
Mechanism for accumulation of MDSC: differentiation



Expanded precusors attracted in the tumor tissue

Differentiation into immuno suppressive populations

Mechanism of T cell suppression by MDSC



High expression of and Arginase /iNOS

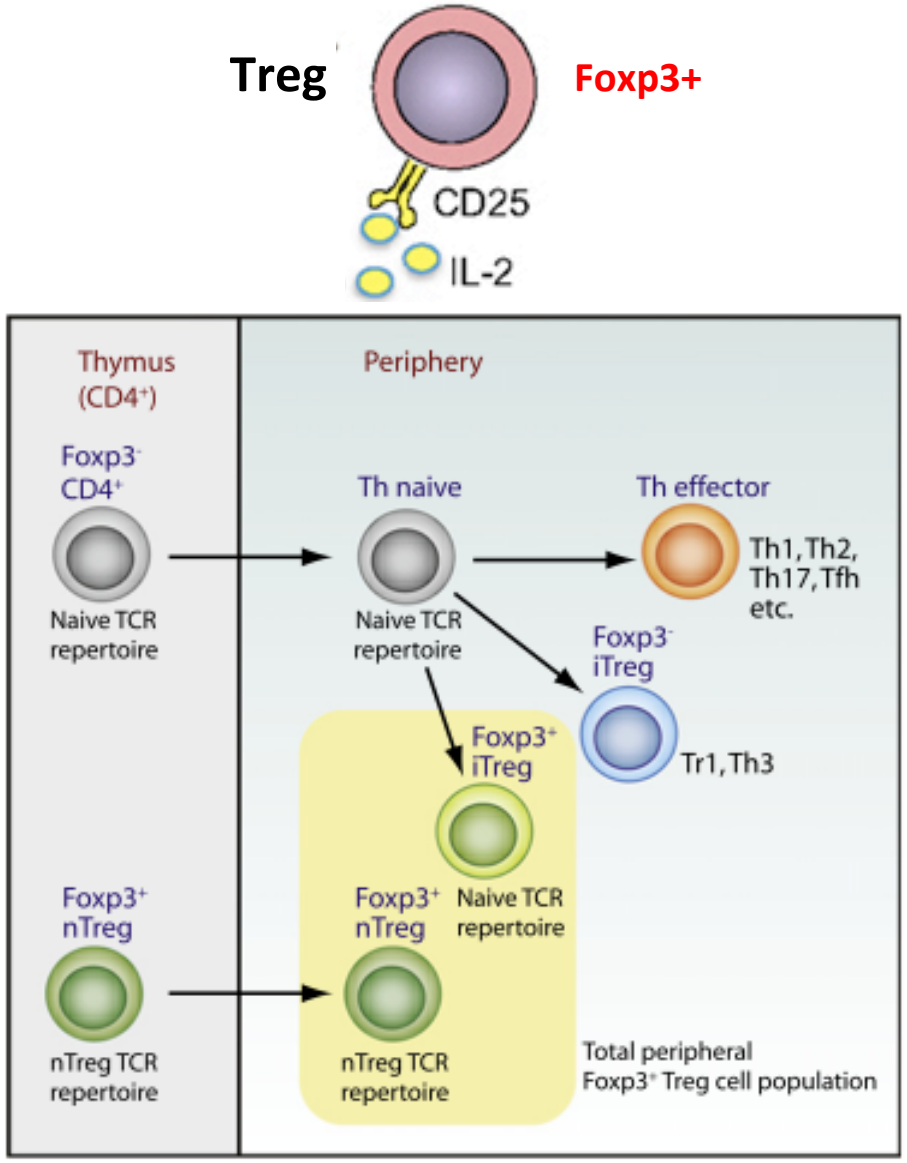
T cell suppression via:

1. depletion of arginine (essential for proliferation)
2. Modification of TCR signaling
3. Induction of T cell apoptosis
4. Interfering with IL-2 signaling (Jack/STAT)
5. Nitrosylation of cysteine in key signaling molecules

ROS

Modification of T cell receptor, T cell unresponsiveness

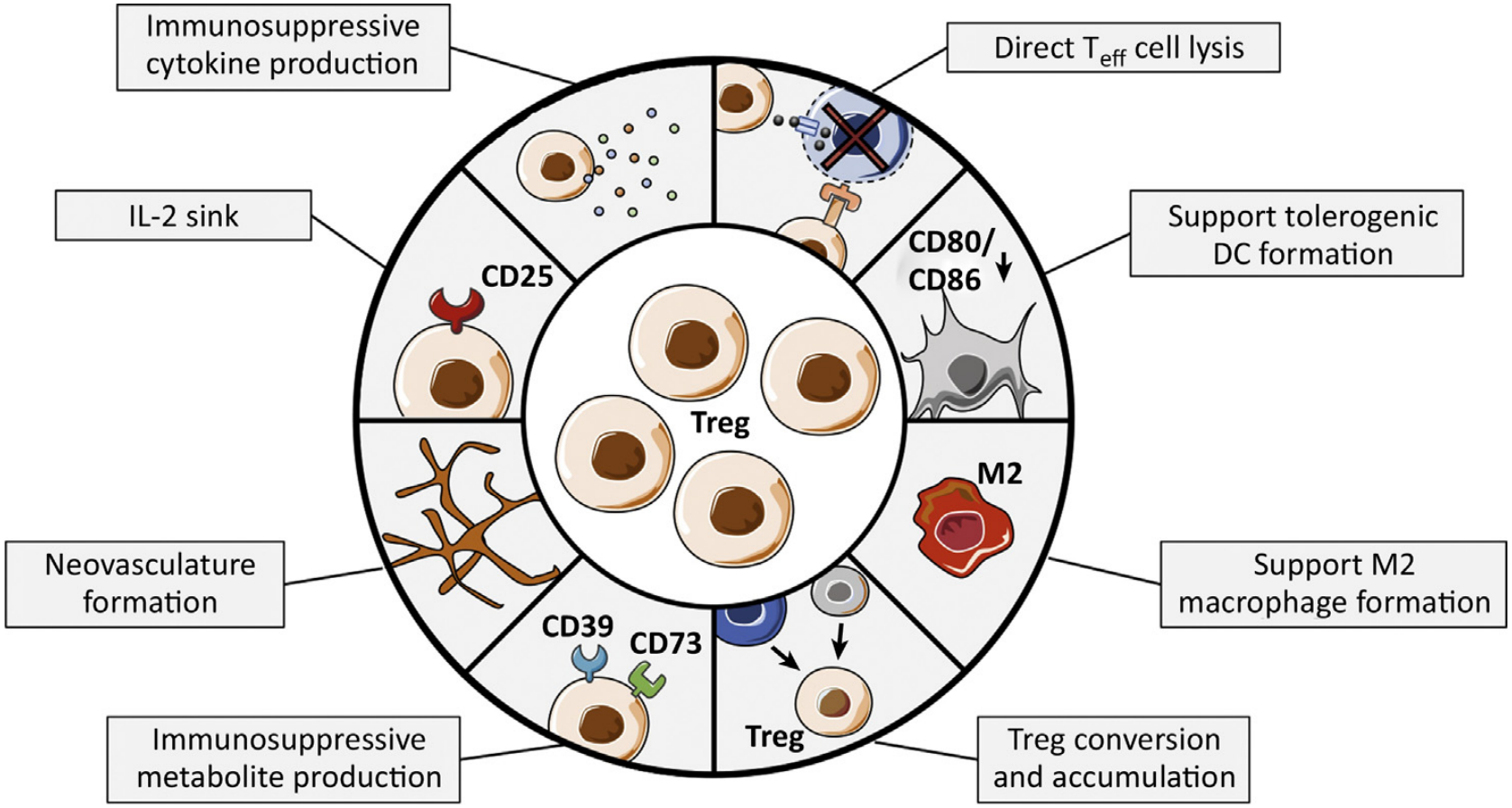
Regulatory T cells are crucial to maintain immune homeostasis



Peripheral T reg **(iTreg)** are mostly directed against non-pathogenic peripheral antigens (most are generated in the gut)

Thymus derived **(nTreg)** have high affinity for self antigens

T reg accumulate in cancer and exert multiple immune suppressive functions



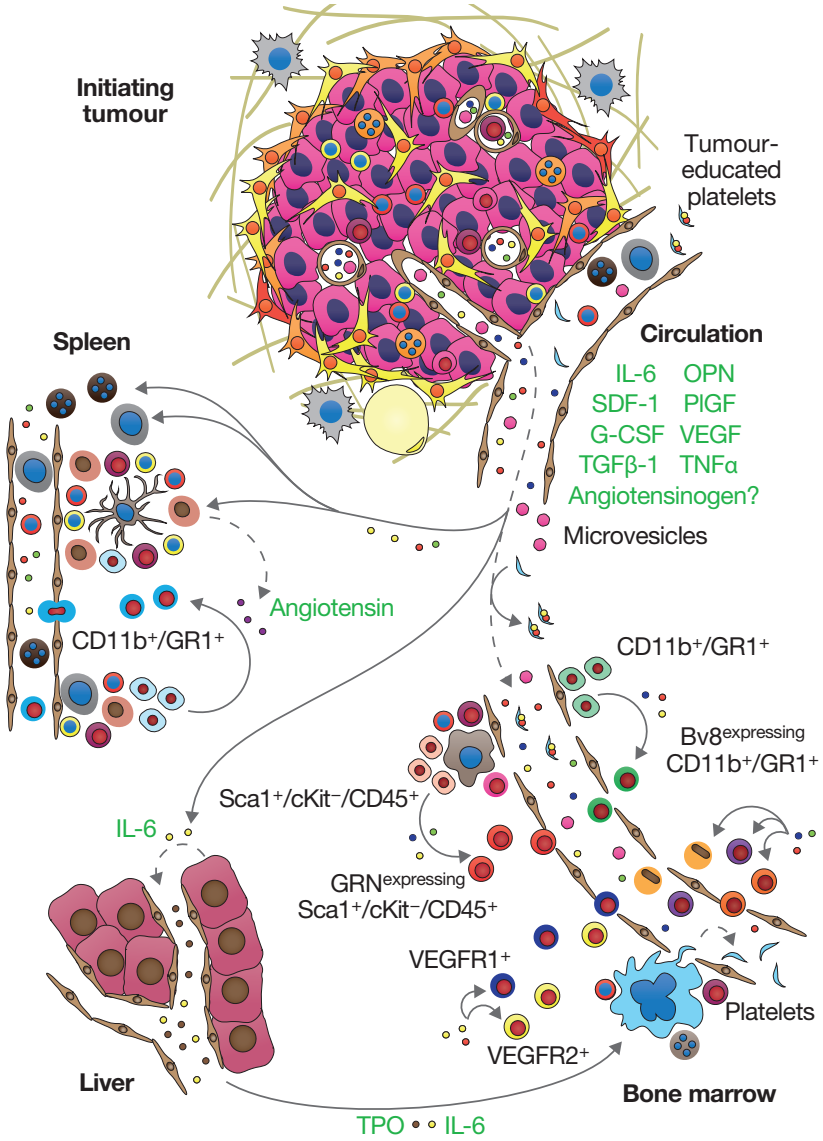
Trends in Cancer

Mechanism of T reg accumulation in cancer

Selective accumulation of T regs in cancer is not yet fully understood and the proposed mechanisms include:

- Production of the chemokine CCL22 by tumor cells, recruit cells via CCR4 chemokine receptor expressed on Tregs
- Hypoxia stimulates CCL28 and Treg accumulation via the CCL28-CCR10 pathway
- VEGF, TGF-b and IL-10 promote differentiation of iTreg
- Altered cancer cell metabolism favor Treg over effector T cells (as Treg rely on fatty acid oxidation and oxidative phosphorylation to support their survival and proliferation)

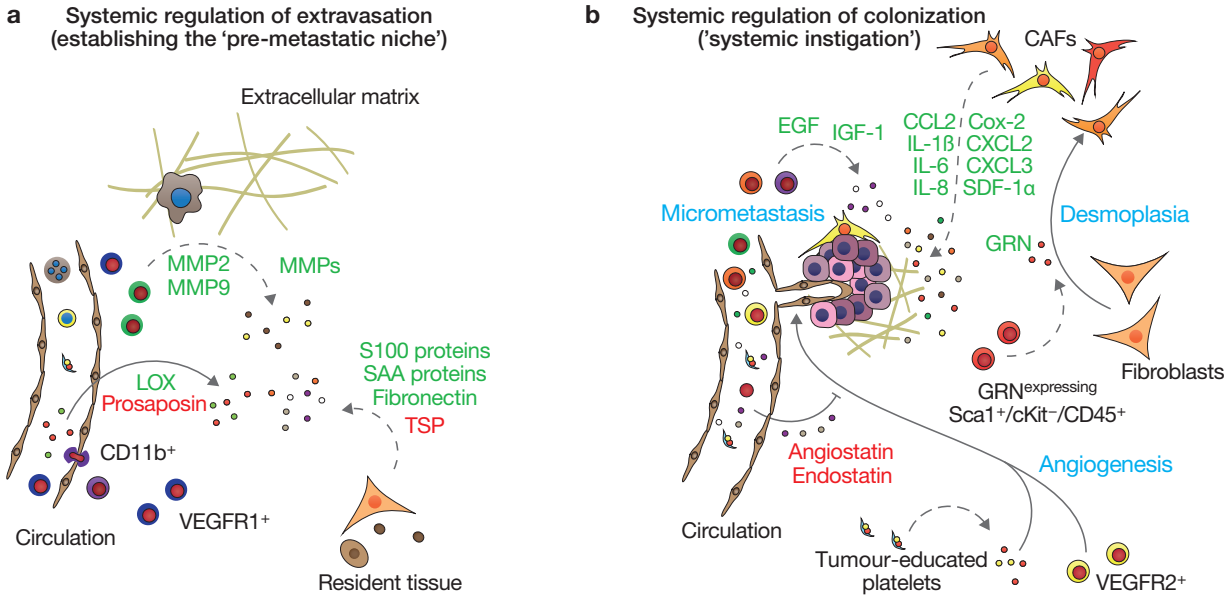
Generation of a tumor promoting/immuno suppressive environment is a systemic event



Systemic perturbation
that mobilize cells that become recruited at the tumor site
Tumor derived cytokines modified distant sites like the spleen and the bone marrow

G-CSF mobilize bone marrow precursors

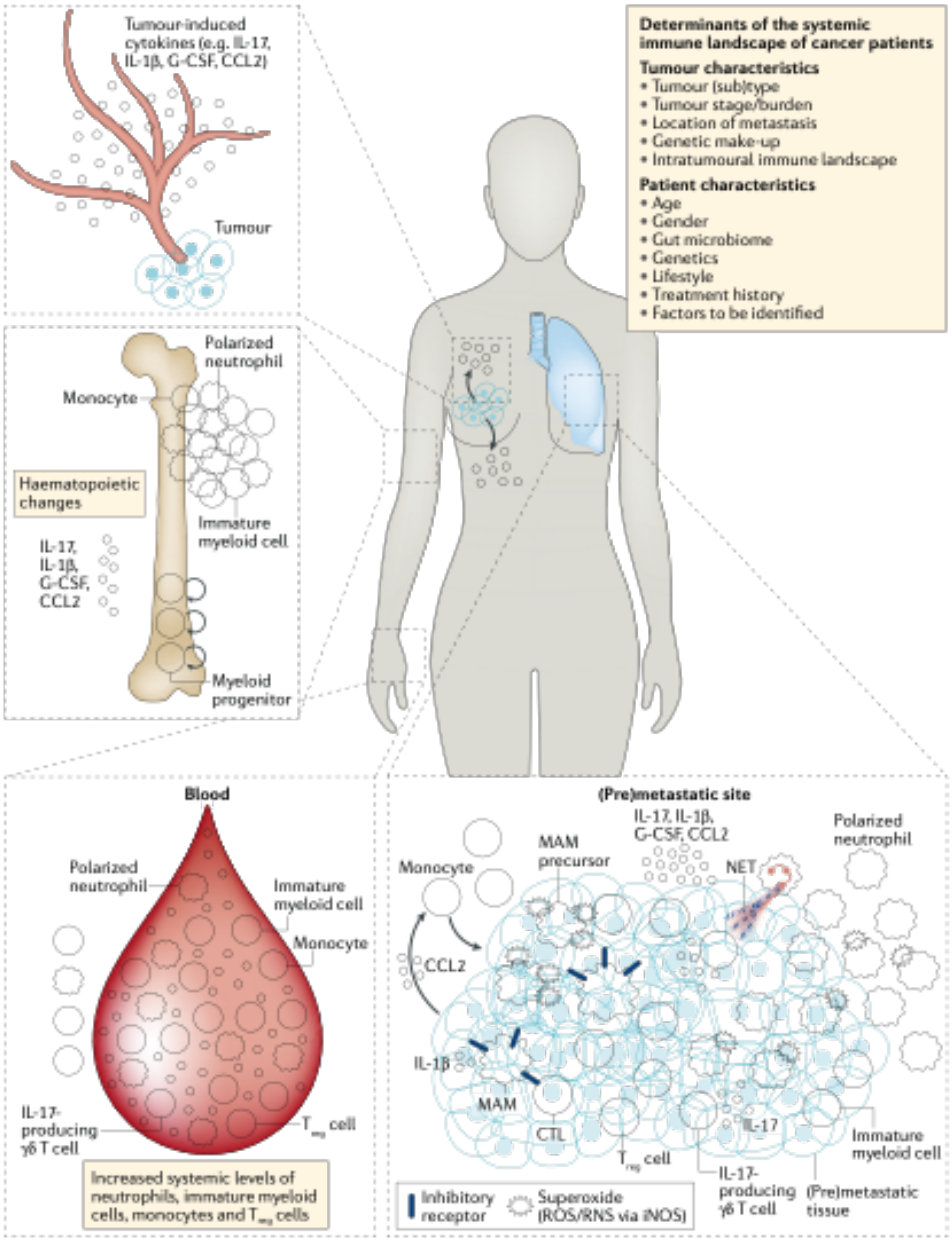
Inflammation spreads to distant tissues and contribute to create the metastatic niche



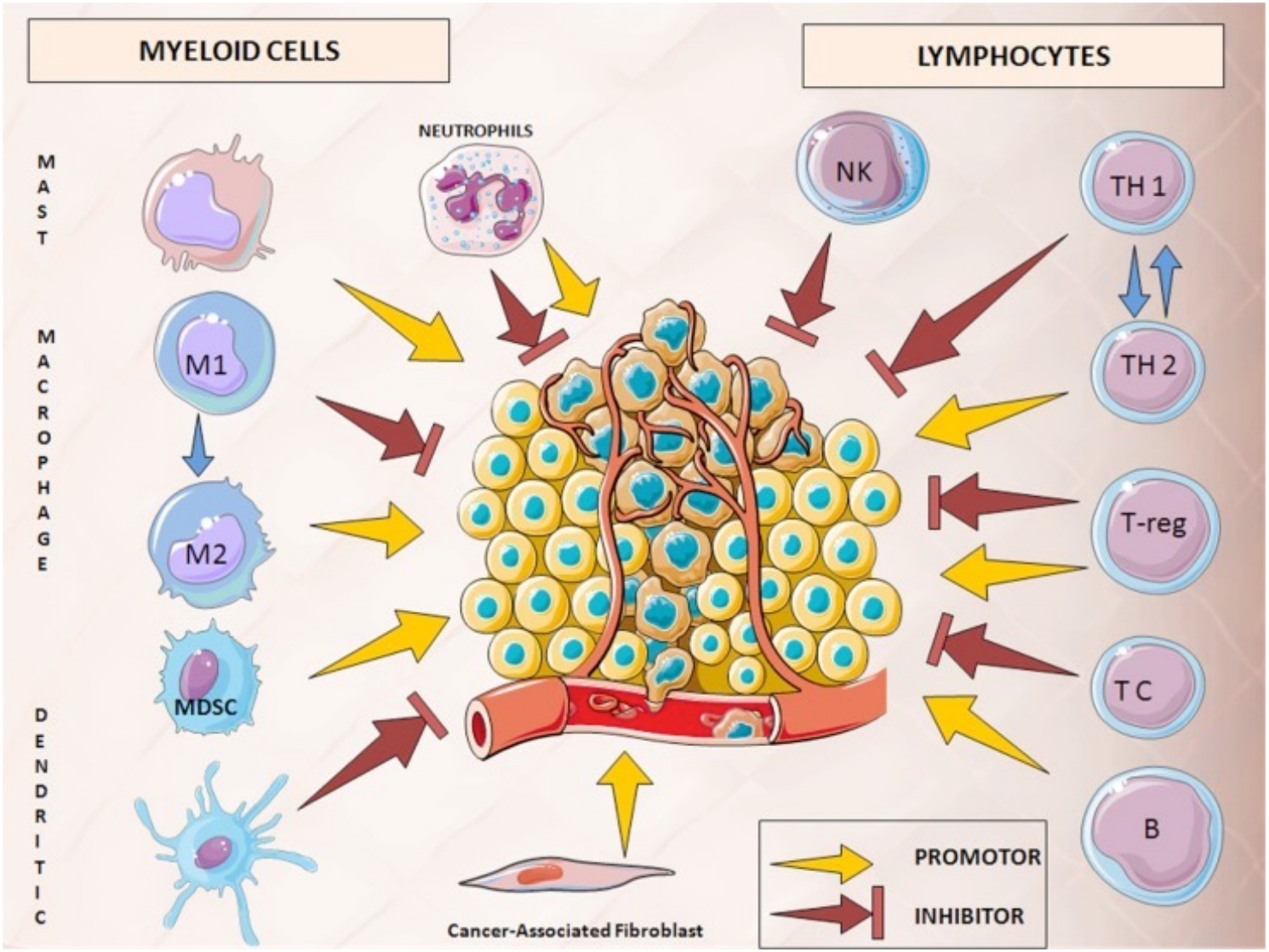
Systemic regulation of metastatic extravasation and clolonization.
Tissue derived factors conditioned the parechima and mobilize bone marrow cells That form an environement prone to colonization

Circulating factors and bone marrow cells can affect micrometastasis promoting the growth into metastasis (promotion of vascularization, proliferation). Some factors can also inhibit vascularization and prevent metastatic growth
Blue:promote colonization
Green:protumorigenic
Red: tumor inhibitors

Immune environment impact on metastasis



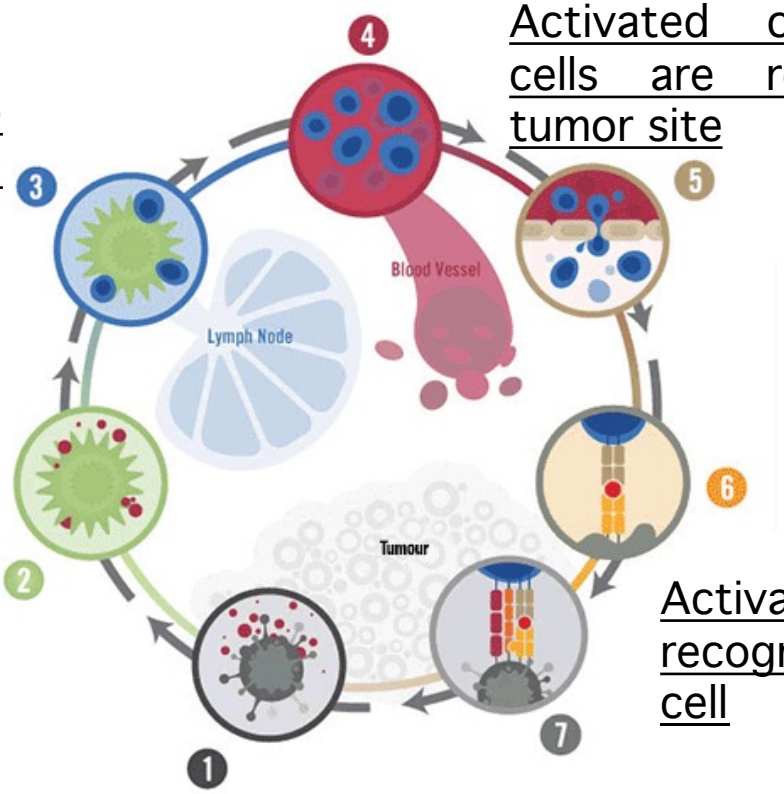
Next: neoantigens, immunotherapy


MYELOID CELLS
LYMPHOCYTES
MAST
MACROPHAGE
DENDRITIC
NEUTROPHILS
NK
TH 1
TH 2
M1
M2
T-reg
MDSC
TC
B
Cancer-Associated Fibroblast
PROMOTOR
INHIBITOR

Cancer-immunity cell cycle and immunotherapy

Activated cytotoxic T cells are recruited at tumor site

APC present neo-Ags to cytotoxic T cells



APC phagocyte apoptotic tumor cells and process the neo-antigens

Activated cytotoxic T cells recognize and eliminate cancer cell

Mutations in cancer cells cause release of neo-antigens