Corso di Biologia cellulare del Cancro 2019/20

Cancer immunoediting from immune surveillance to immune escape

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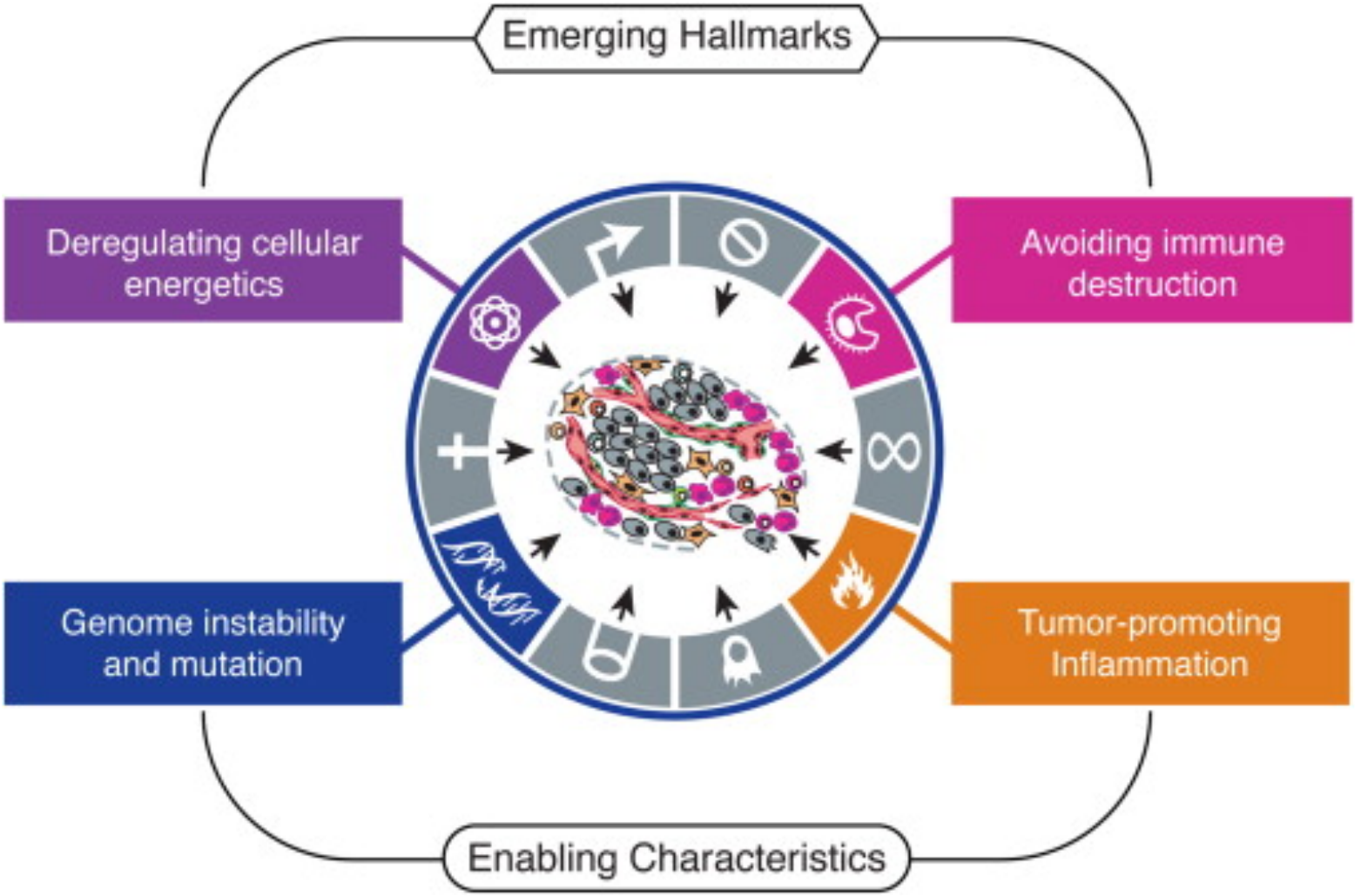
The seventh hallmark of cancer: avoiding immune recognition



Cell , Volume 144, Issue 5, Pages 646-674

Immunological surveillance

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

Immunological surveillance

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)

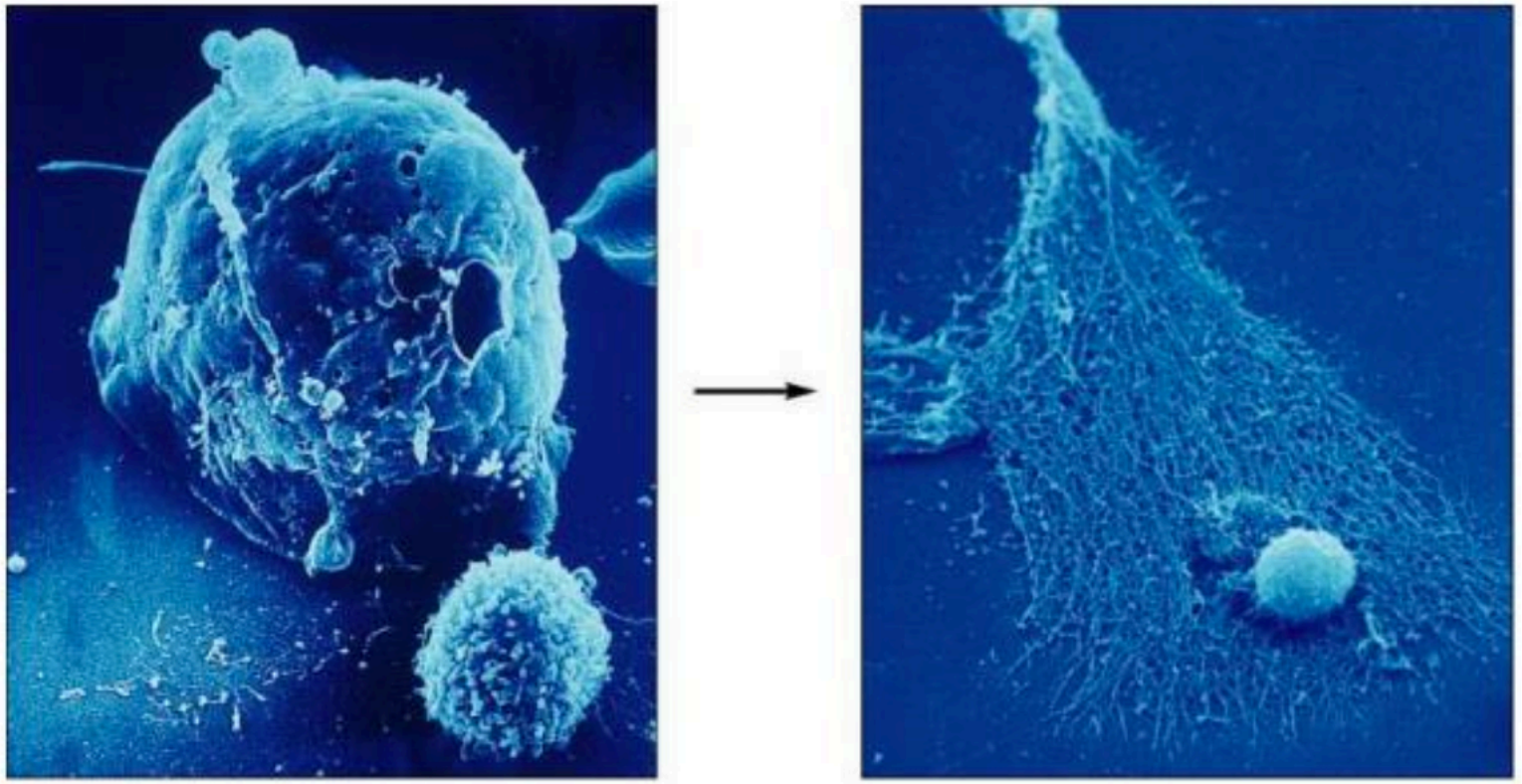
Immunological surveillance

- 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"

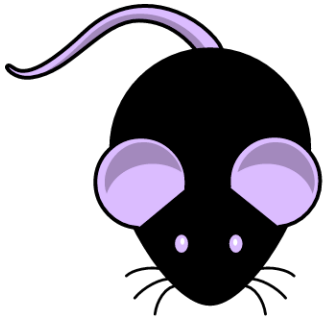
Evidences of immune surveillance: humans

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

X



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

Evidences of immune surveillance: animal models

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*

Nature 410:1107, 2001

Immunological surveillance

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

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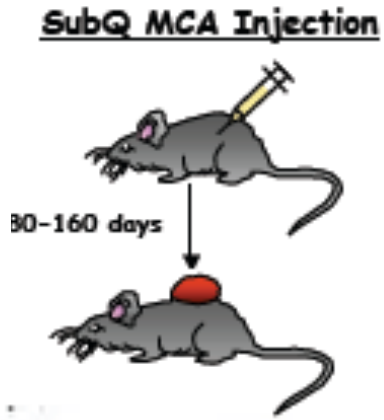

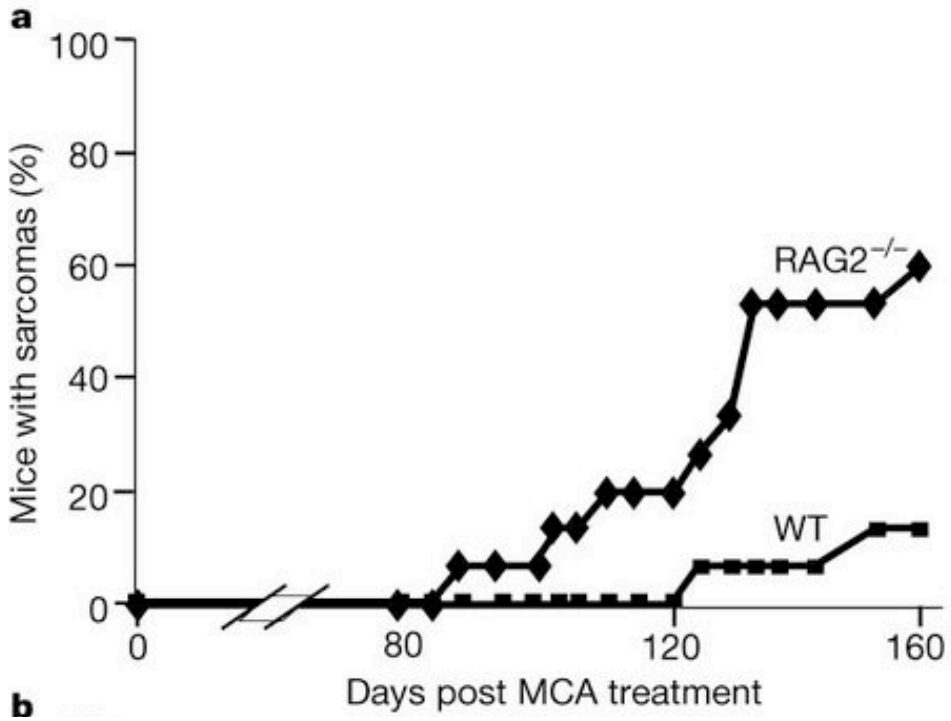

No T, no B cells

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

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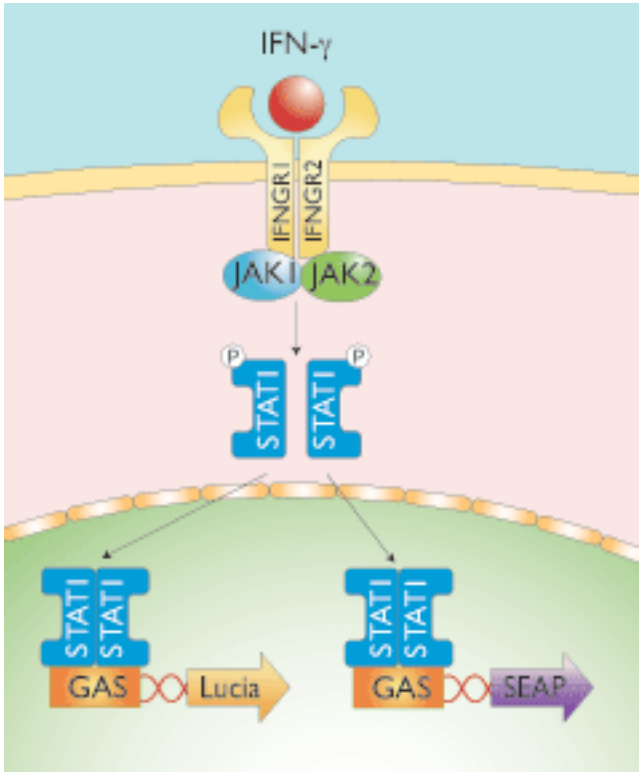
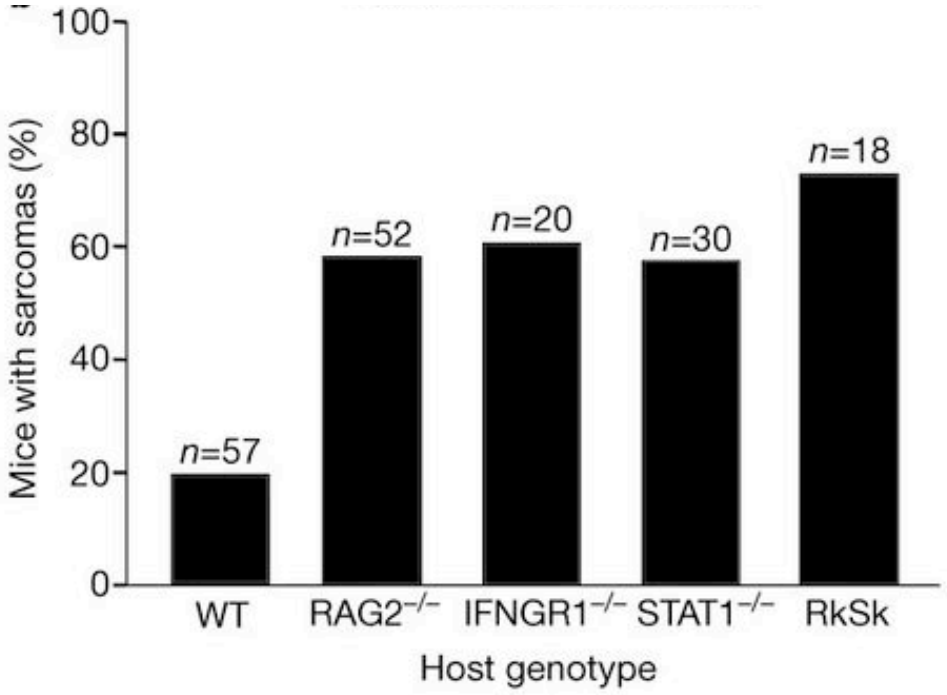
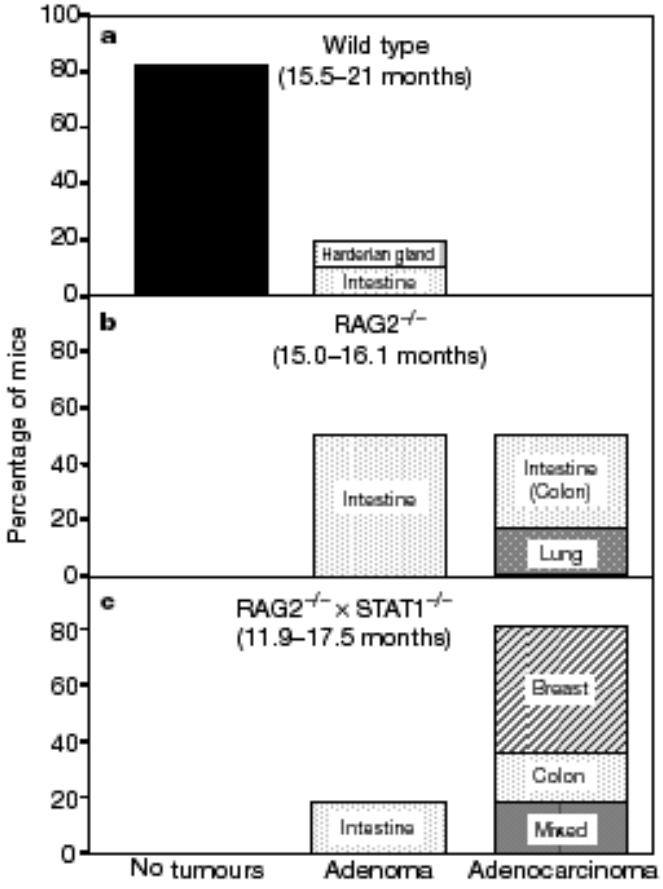




Immunological surveillance

HIGH INCIDENCE OF SPONTANEOUS TUMORS IN IMMUNODEFICIENT MOUSE MODELS

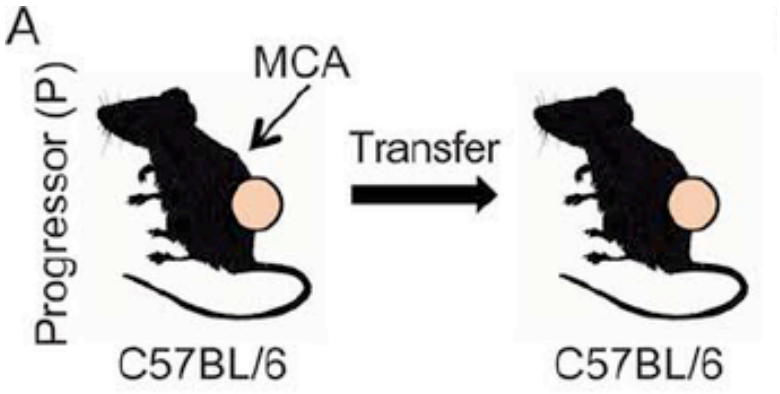


The immune system eliminates nascent tumors

Immune 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

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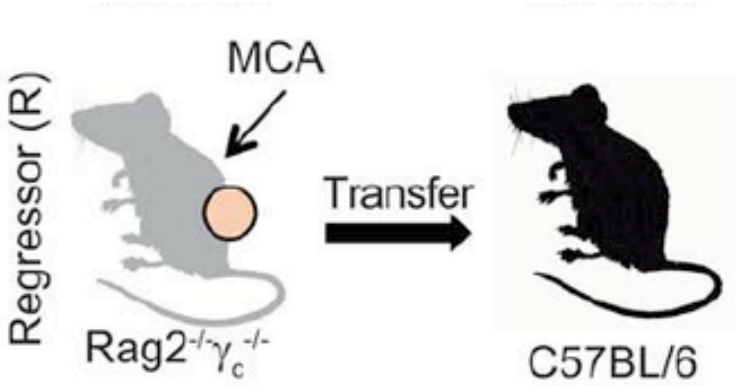


REJECTION

Immunological surveillance

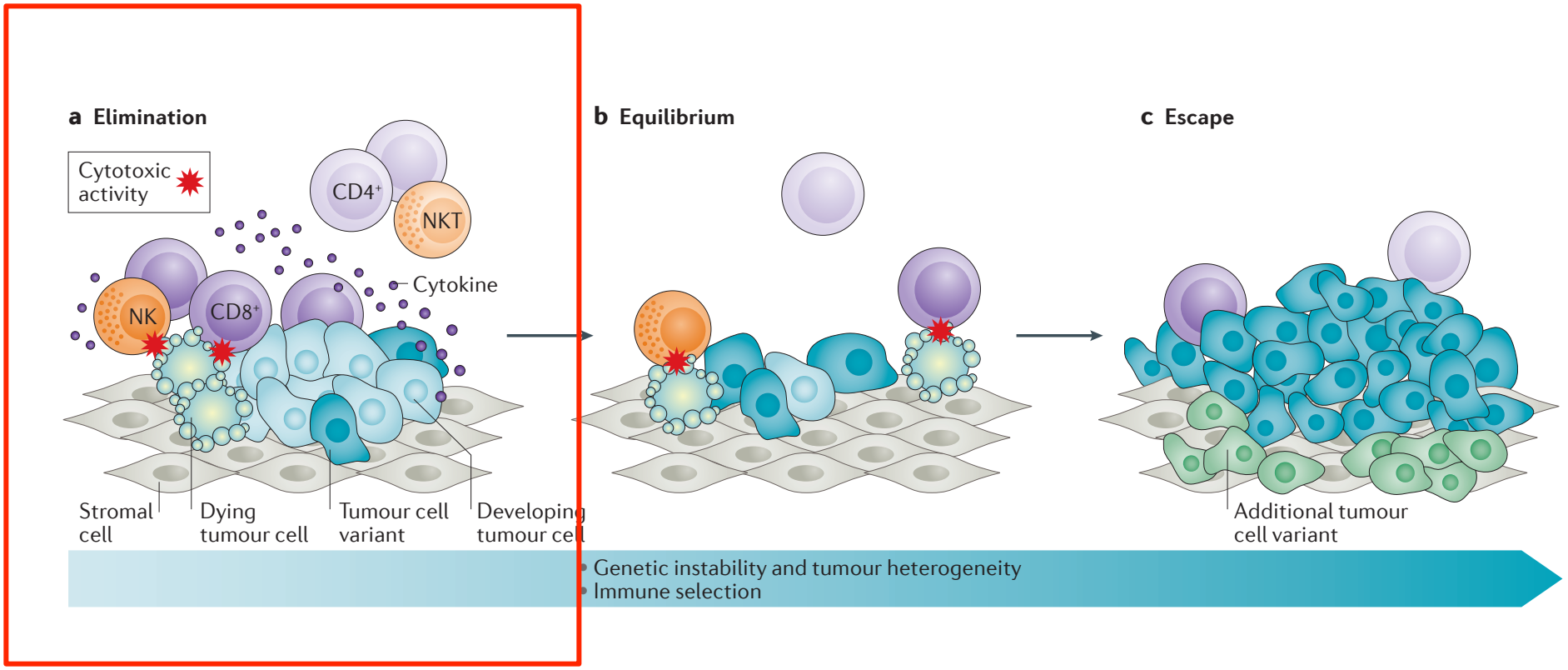
THE IMMUNE SYSTEM DESTROYS EMERGING TUMORS AND SHAPES TUMORS SELECTING FOR MORE AGGRESSIVE VARIANTS

"CANCER IMMUNOEDITING"

CANCER IMMUNOEDITING

A DYNAMIC PROCESS IN THREE PHASES:

ELIMINATION-EQUILIBRIUM-ESCAPE



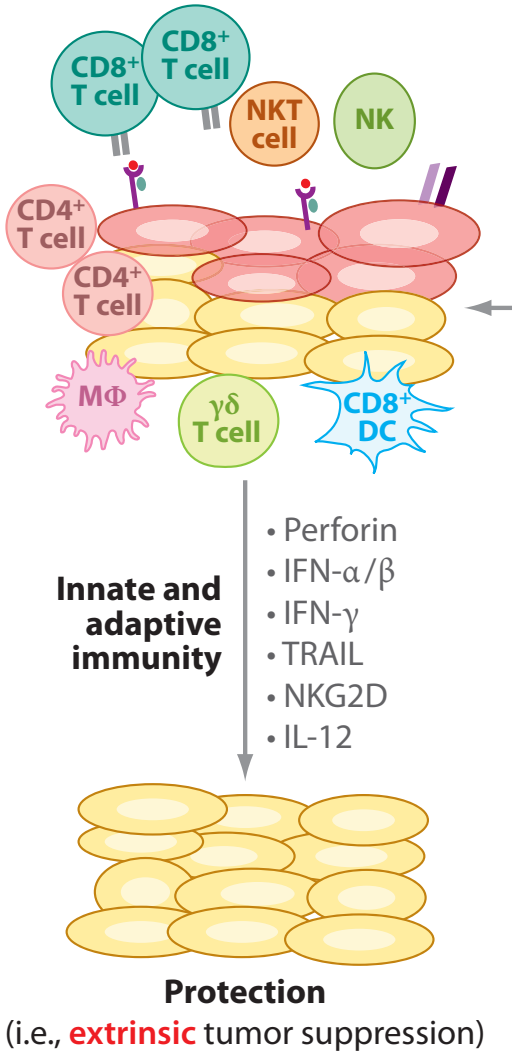
ELIMINATION REQUIRES ADAPTIVE AND INNATE IMMUNE CELLS

INNATE CELLS:

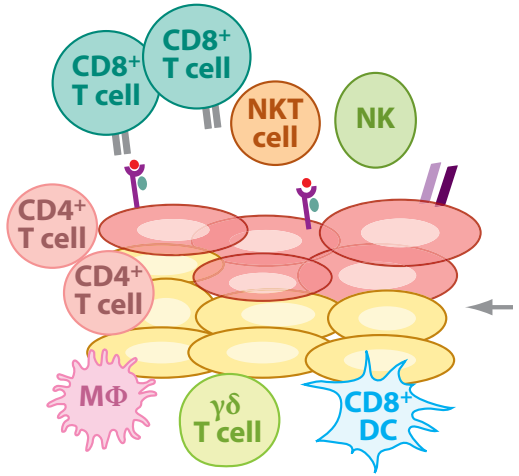
Myeloid cells, NK CELLS, γδ T CELLS
Recognize not polymorphic receptors expressed by tumor cells

ADAPTIVE CELLS:

CD8 AND CD4 ARE ANTIGEN SPECIFIC

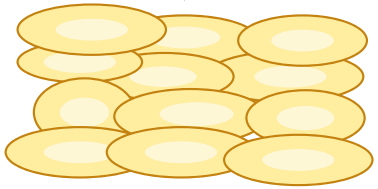


Pathways involved in tumor elimination



Innate and adaptive immunity

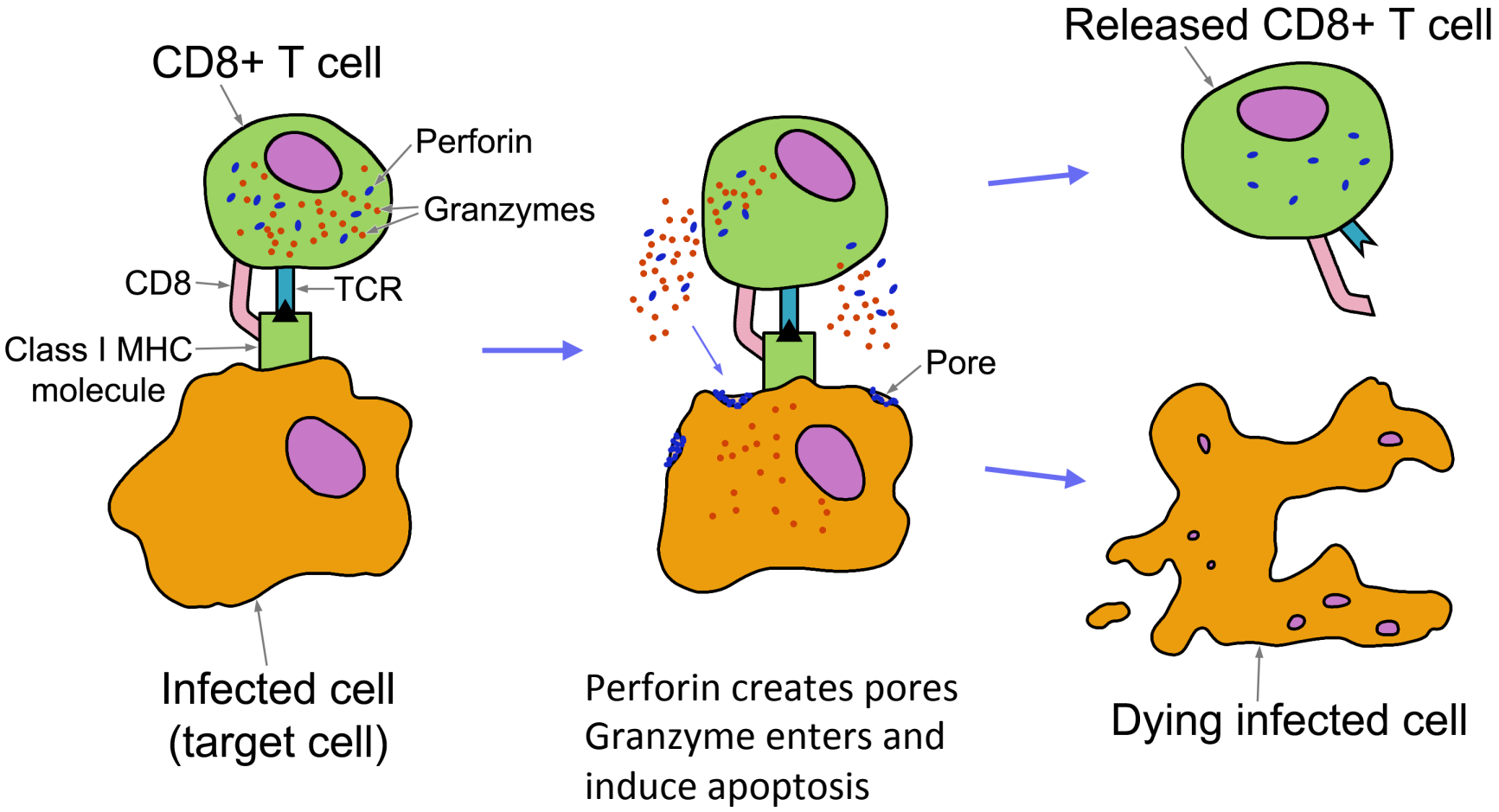
- Perforin
- IFN-α/β
- IFN-γ
- TRAIL
- NKG2D
- IL-12



Protection

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

Perforin kills target cells (infected or transformed)



CANCER IMMUNOEDITING

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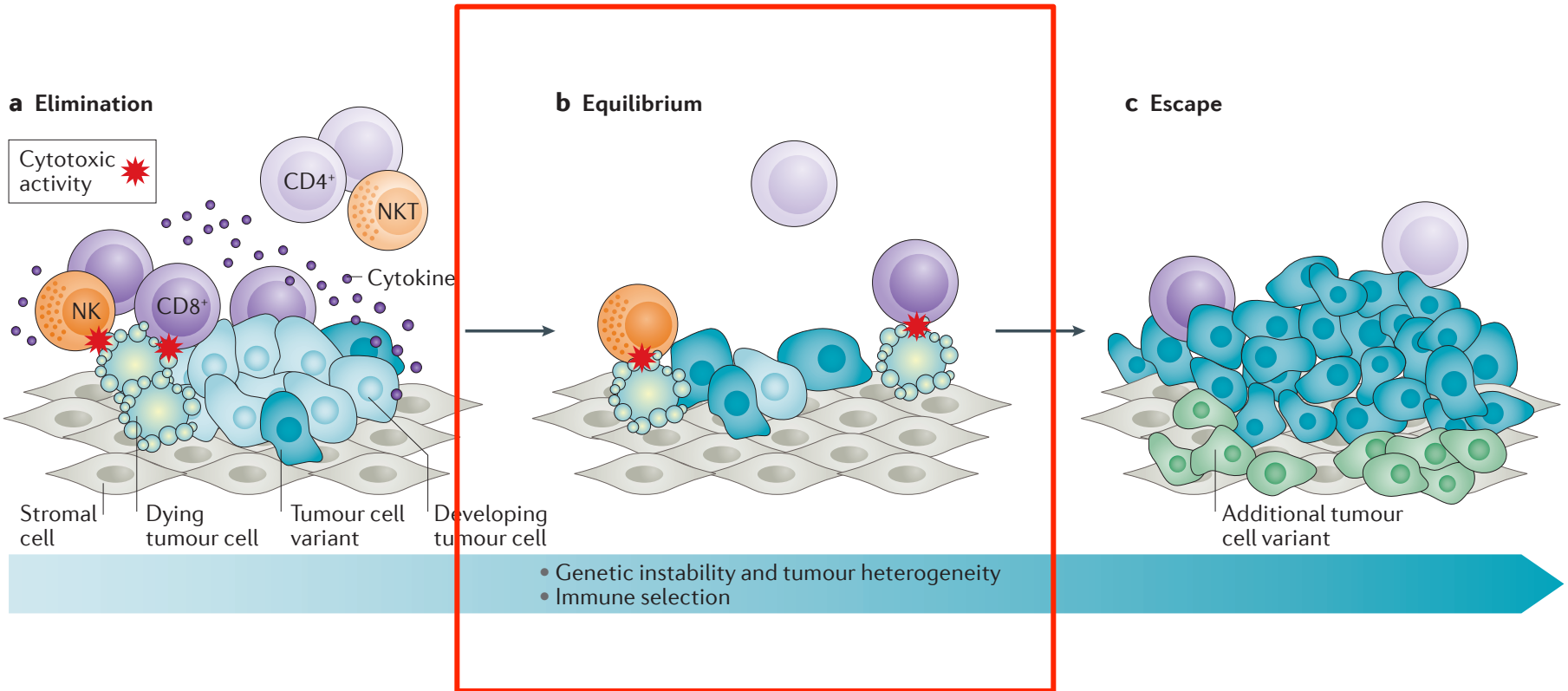
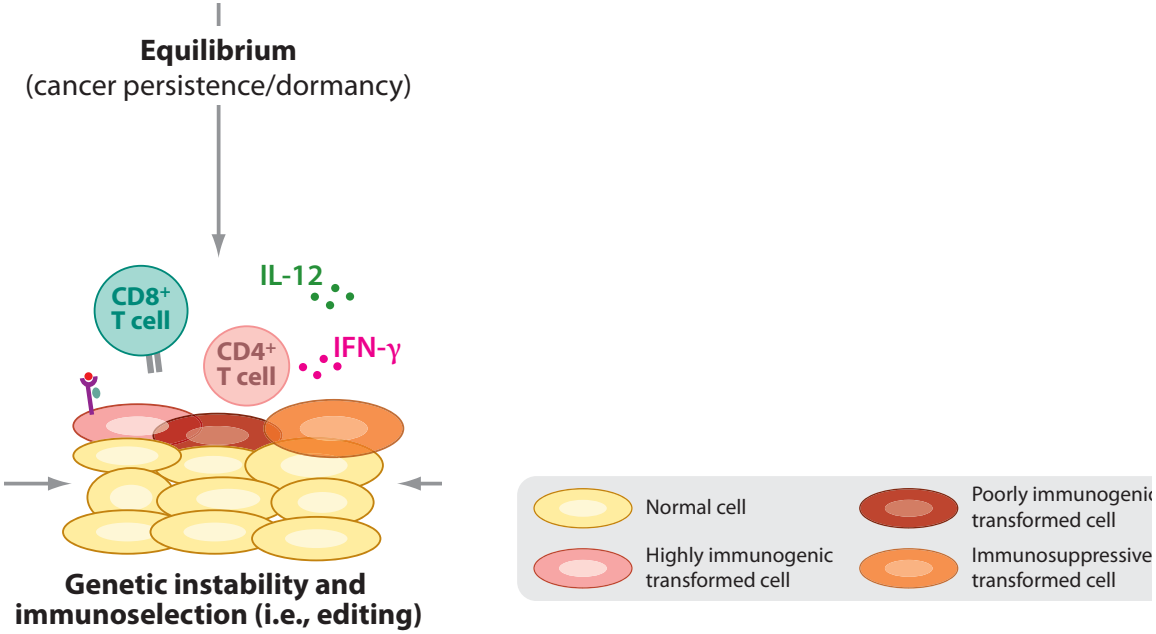


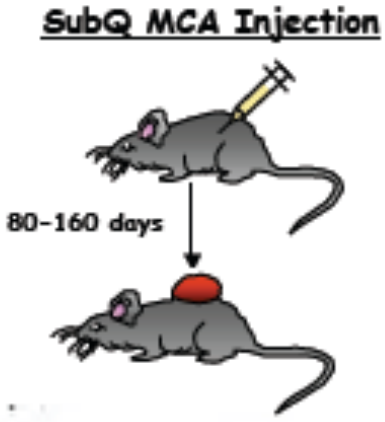
EQUILIBRIUM: CD8 T and CD4 T cells keep tumor cells under control

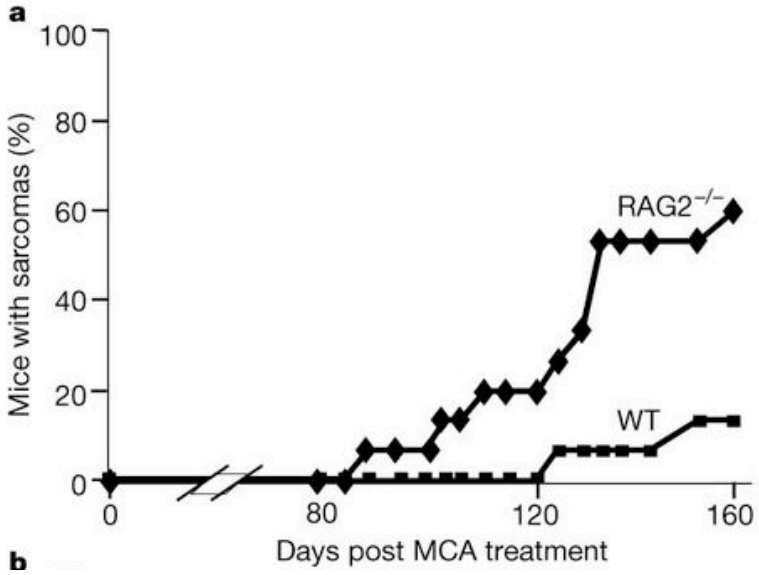


Tumors may remain dormant for long periods (more than 10 years).
During this phase antitumor immunity contains but does not completely eradicates an heterogenous population of tumor cells. Among these cells some acquire the capacity to evade immune recognition.

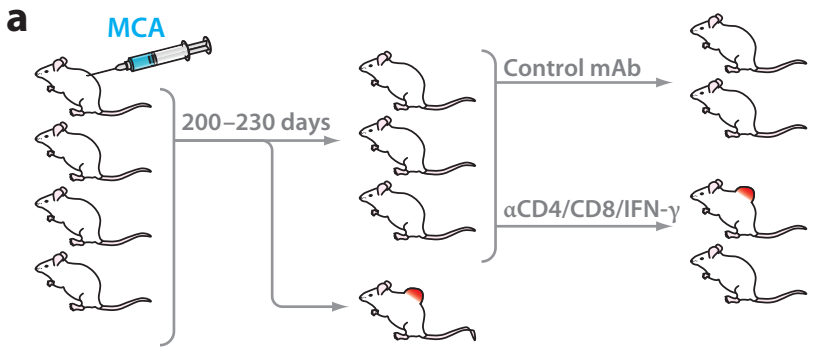
TUMOR SCULPTING PHASE

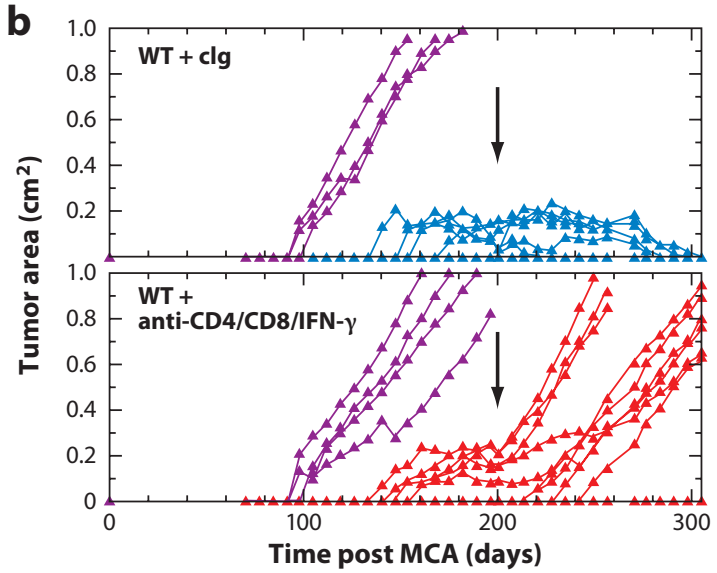
EQUILIBRIUM: experimental evidences

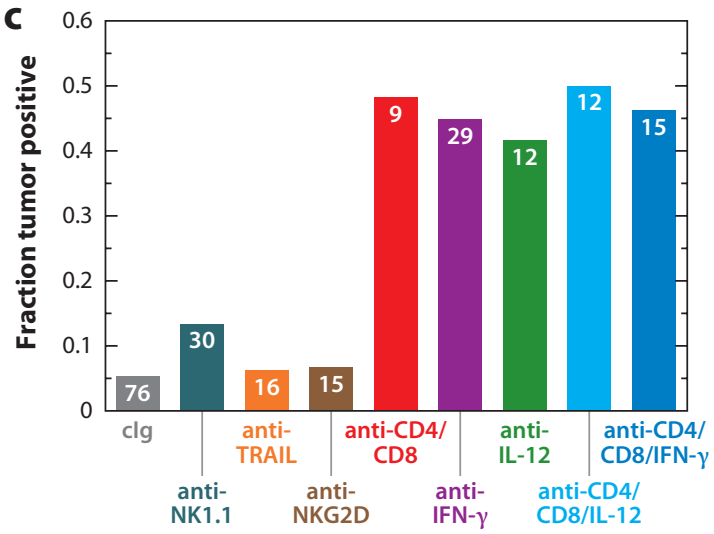




EQUILIBRIUM: experimental evidences

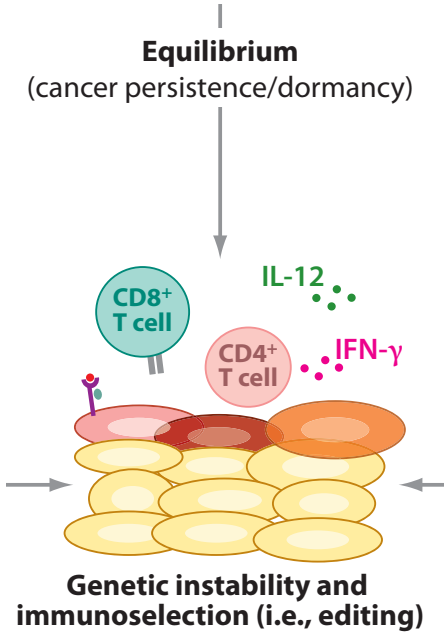






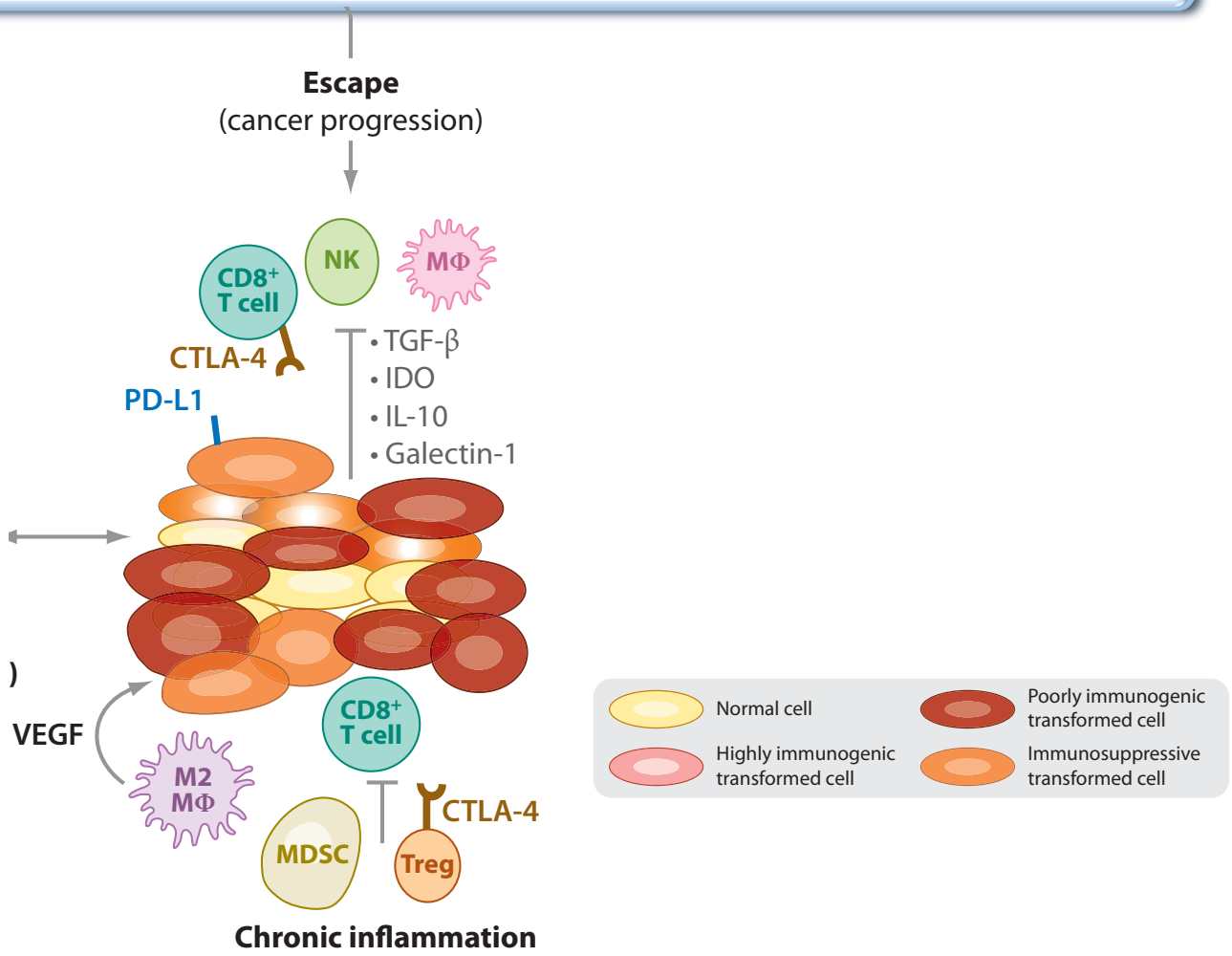
Equilibrium depends on adaptive immunity

EQUILIBRIUM: experimental evidences



Equilibrium depends on adaptive immunity

ESCAPE: FAILURE OF IMMUNE SURVEILLANCE



APPERANCE OF POORLY IMMUNOGENIC CELLS THAT HAVE UNDERGONE EDITING

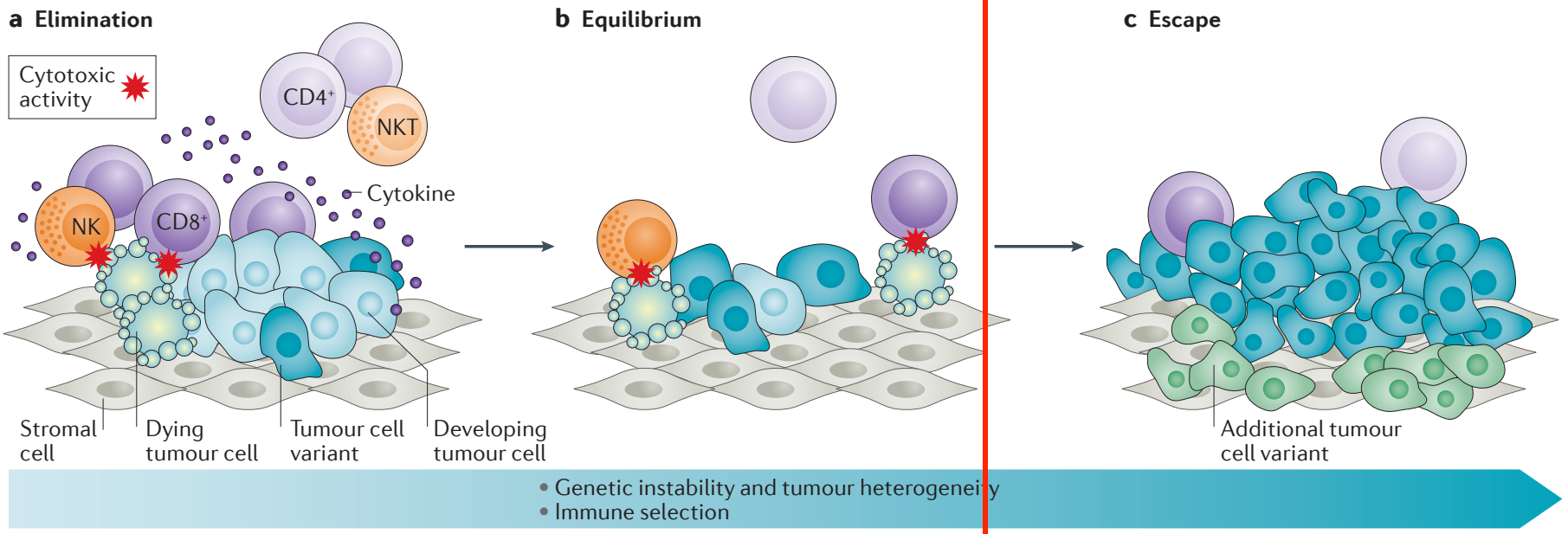
AND

ESCAPE IMMUNE SYSTEM CONTROL

CANCER IMMUNOEDITING

A DYNAMIC PROCESS IN THREE PHASES:

ELIMINATION-EQUILIBRIUM-ESCAPE

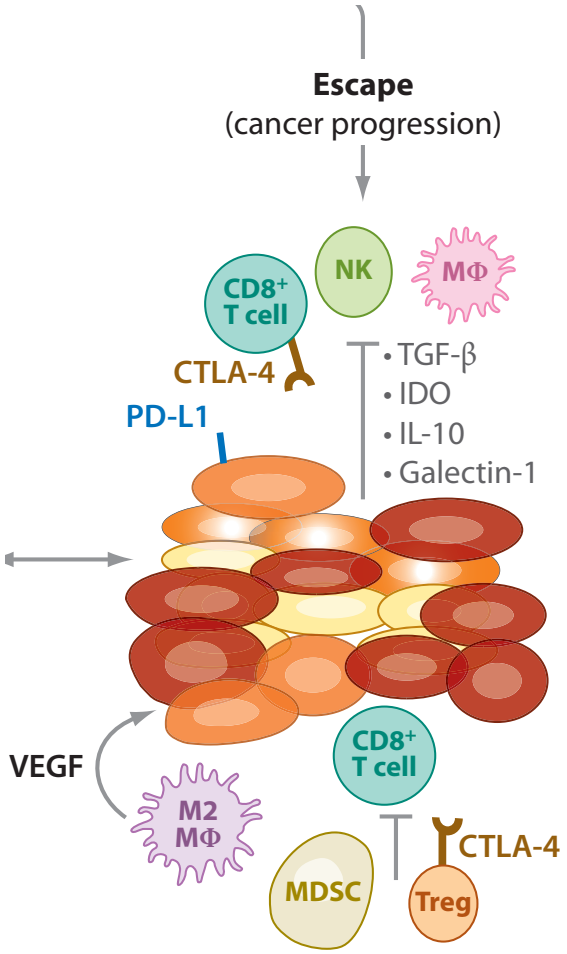


TUMOR ESCAPE: A DARWINIAN SELECTION PROCESS

Stochastic appearance of variants capable to avoid immune recognition

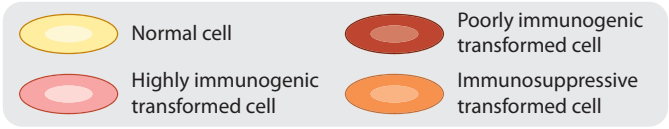
+

evolutionary pressure to select for more aggressive variants



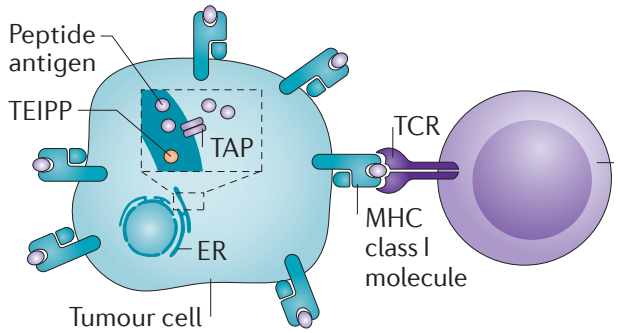
1.Inhibition of anti-tumor responses

2.Induction of immunosuppressive mechanism

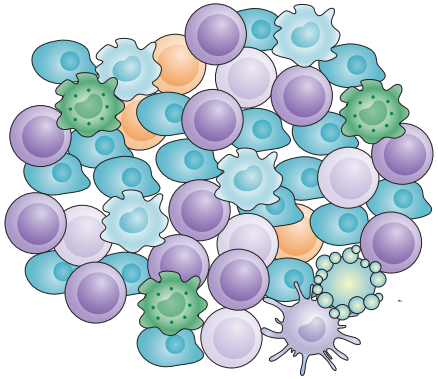


Mechanism of immune escape

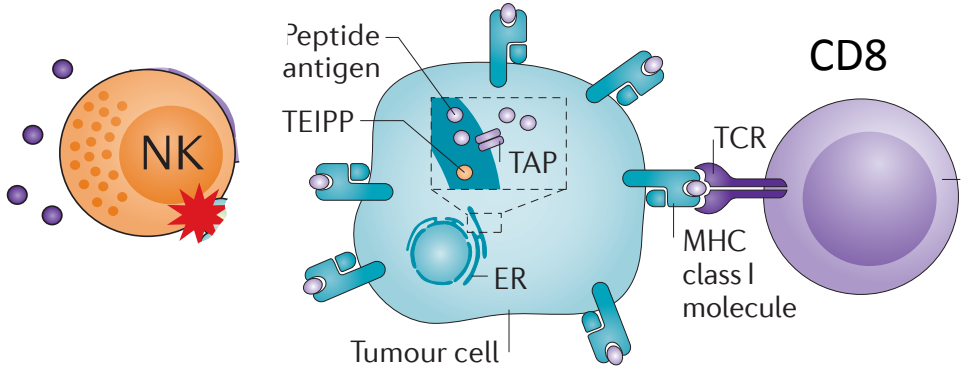
CELL AUTONOMOUS MODIFICATIONS



GENERATION OF AN IMMUNE SUPPRESSIVE NETWORK



CELL AUTONOMOUS MECHANISM OF ESCAPE (passive)



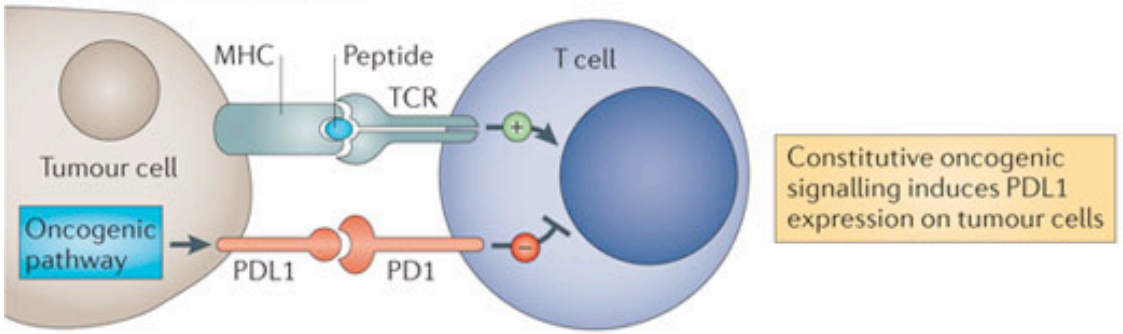
1. AVOID DETECTION:

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.

CELL AUTONOMOUS MECHANISM OF ESCAPE (active)



3. EXPRESSION OF IMMUNE INHIBITORY LIGANDS

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

↓

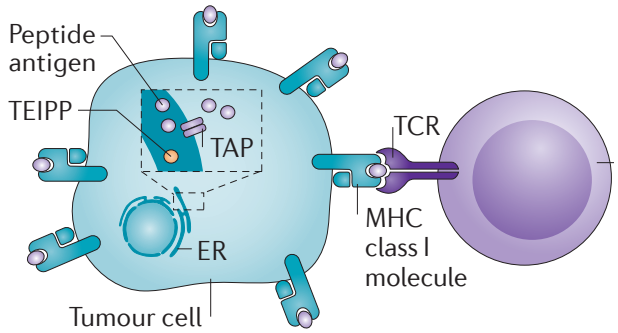
subverted by tumor cell

PDL1-PD1

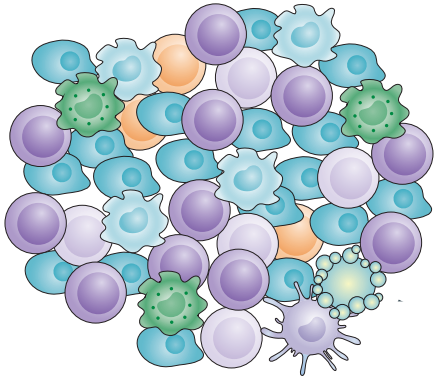
Reduce T cell survival and induce T cells apoptosis
Induce exhaustion, increase T regulatory function

Mechanism of immune escape

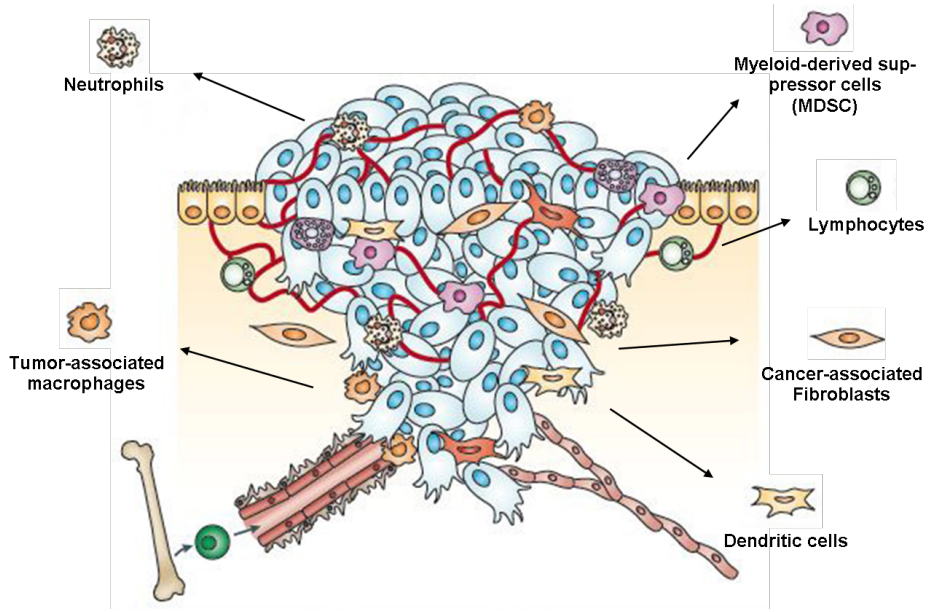
CELL AUTONOMOUS MODIFICATIONS



GENERATION OF AN IMMUNE SUPPRESSIVE NETWORK



Immune cells in the tumor microenvironement

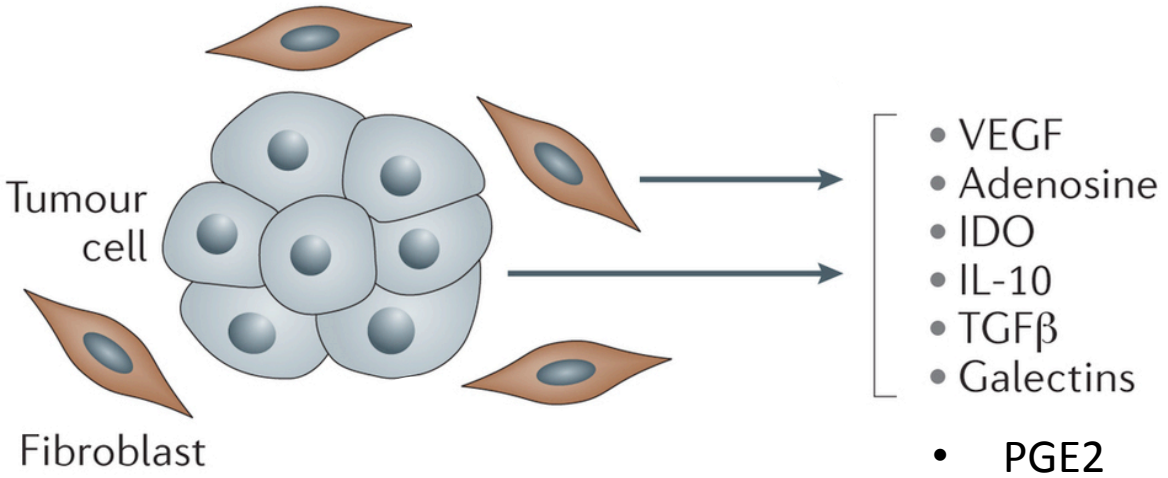


1. Tumor cells derived factors directly inhibit the function of immune cells

2. Tumor cells recruit immune cells with regulatory and suppressive functions

Immune cells in the tumor microenvironement

1. Tumor derived factors that inhibit immune cell function



- PGE2
- Lactic acid

Immune cells in the tumor microenvironment

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

Immune cells in the tumor microenvironement

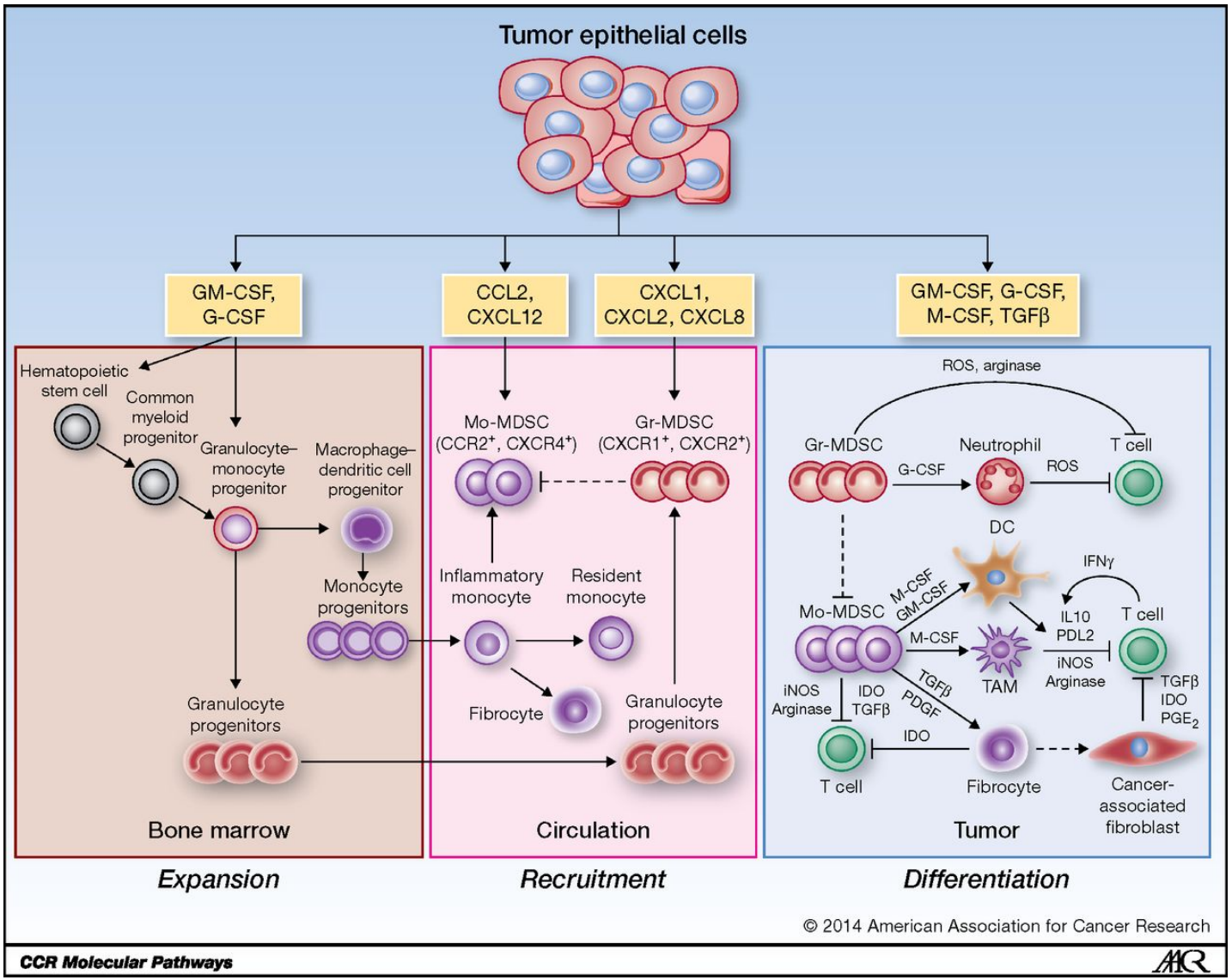
2. Tumor cells recruit immune cells with suppressive functions:

One major pathway of immune suppression is the accumulation of

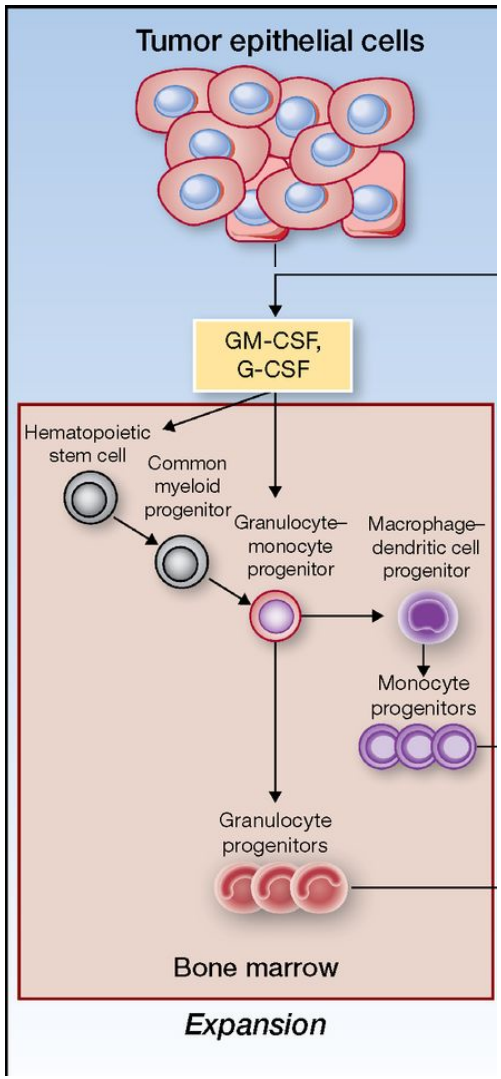
MYELOID DERIVED SUPPRESSOR CELLS

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

Mechanism for accumulation of MDSC



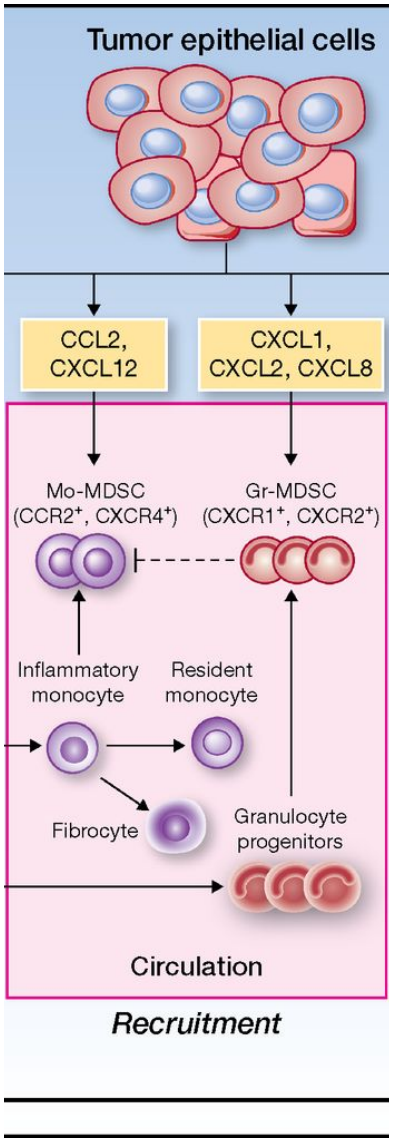
Mechanism for accumulation of MDSC:expansion



Carcinoma cells overexpress cytokines implicated in differentiation of myeloid cells

Expansion and accumulation of immature myeloid cells

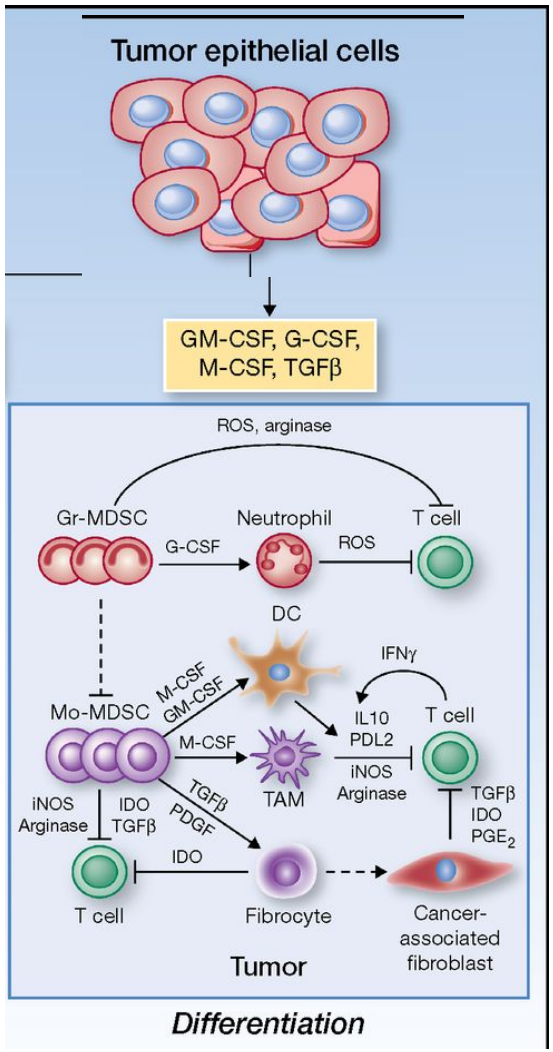
Mechanism for accumulation of MDSC:recruitment



Overexpression of chemokines in cancer

Recruitment of immature and inflammatory monocytes

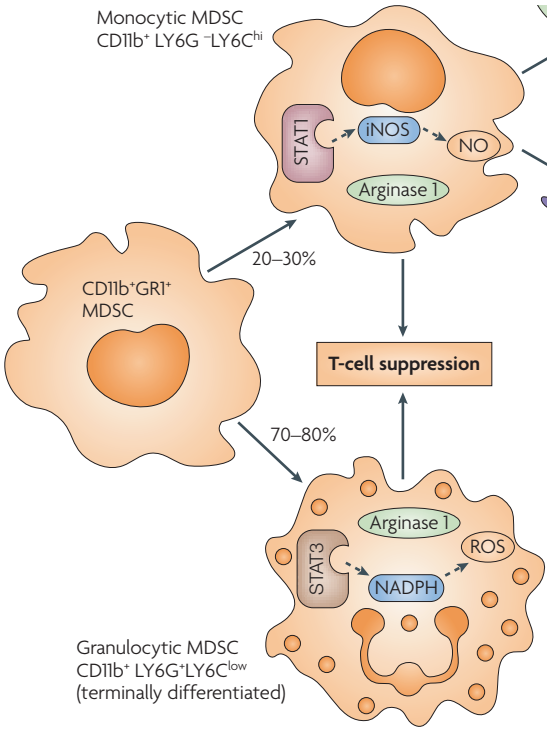
Mechanism for accumulation of MDSC: differentiation



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

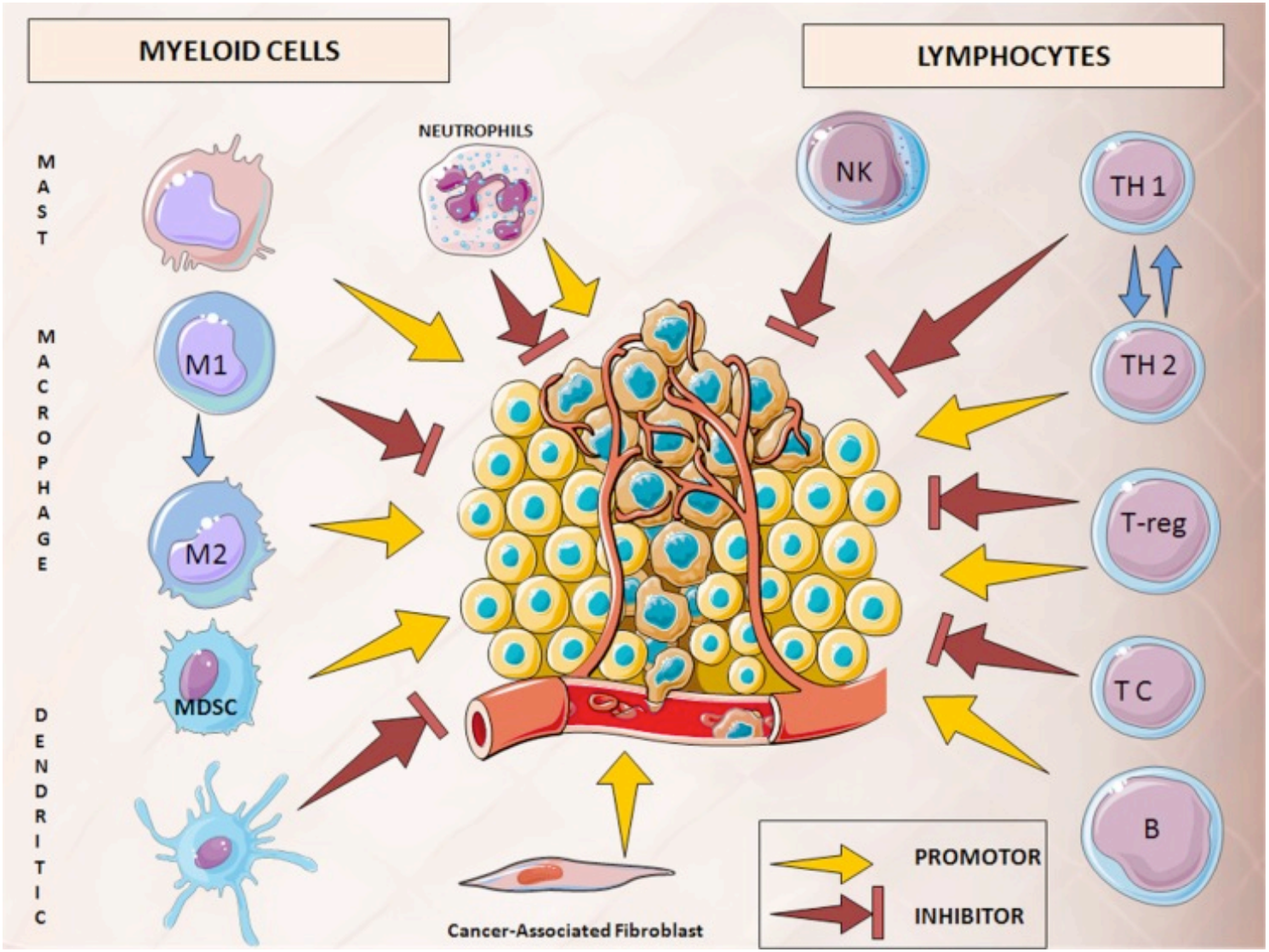
T cell suppression via:

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

Next:
Antigenic landscape of tumors and immune checkpoint blockade


MYELOID CELLS
LYMPHOCYTES
MAST
NEUTROPHILS
NK
TH 1
MACROPHAGE
M1
TH 2
M2
T-reg
MDSC
TC
DENDRITIC
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