SAPIENZA
UNIVERSITÀ DI ROMA

Tumor Immunity

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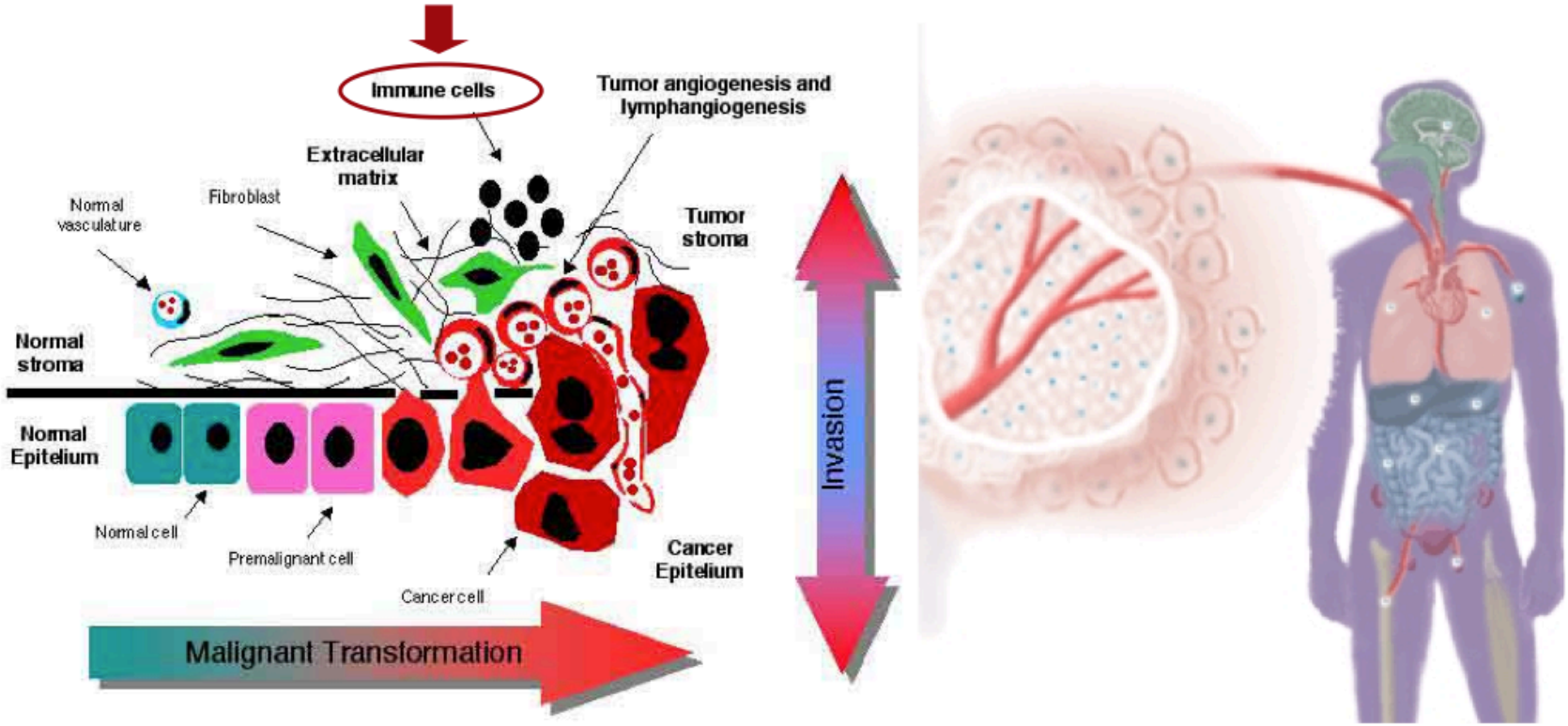
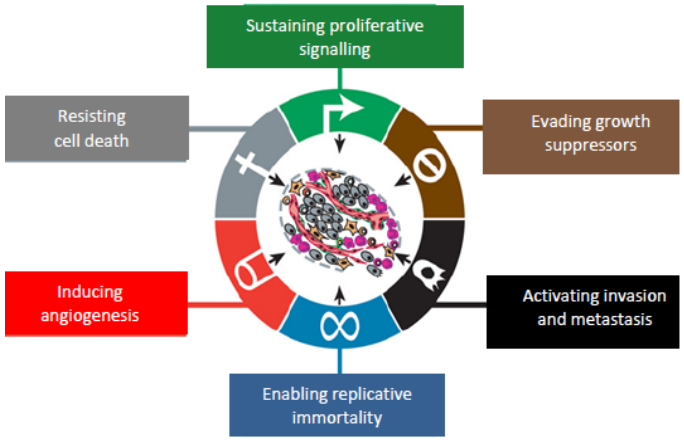
Natural History of Tumors

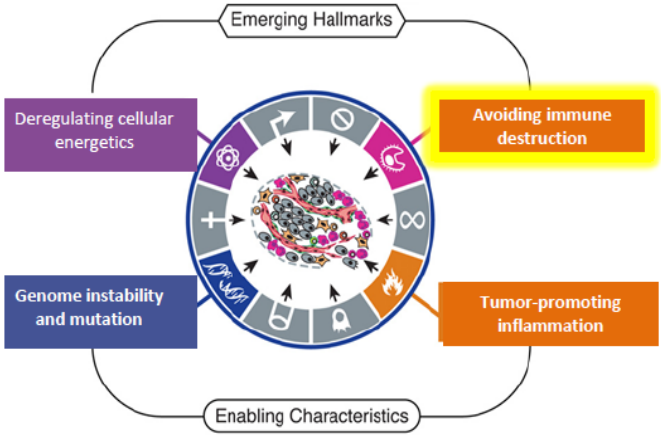


Cancer as failure of the immune system to eradicate tumor cells

Tumor immunity is an acknowledged hallmark of cancer cells



Hanahan and Weinberg, Cell, 2000



Hanahan and Weinberg, Cell, 2011

1909 Erhlich P *predicted that:*

The immune system represses the growth of carcinomas that he envisaged would otherwise occur with great frequency

1957 Burnet FM *hypothesized that:*

Tumor cell-specific neo-antigens could provoke an effective immunologic reaction that would eliminate developing cancers

1959 Thomas L *theorized that:*

Complex long-lived organisms must possess mechanisms to protect against neoplastic disease similar to those mediating homograft rejection

1967 Burnet FM *coined the term* ***"immunosurveillance"***

The cancer immunosurveillance hypothesis *stated that:*

"Sentinel thymus-dependent cells of the body constantly surveyed

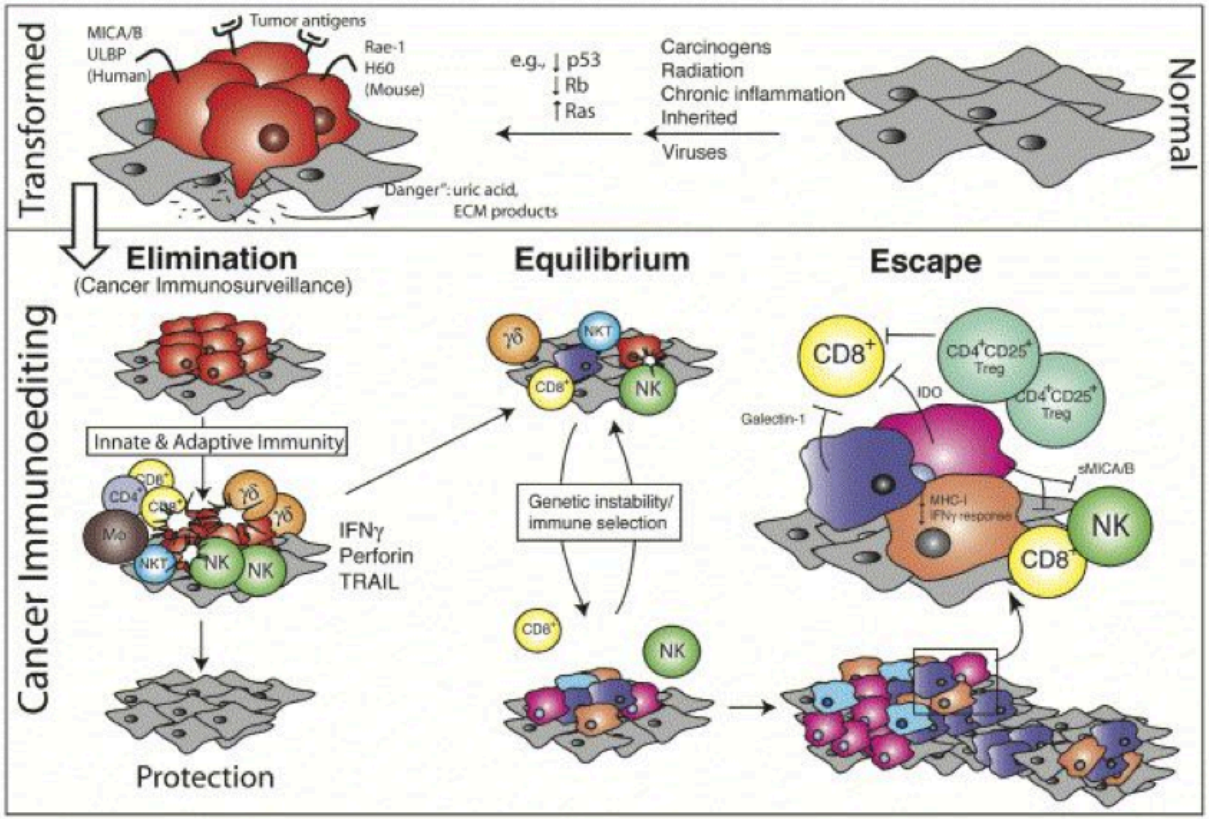
From "CANCER IMMUNOSURVEILLANCE"
Why recognition fails to resolve in protection?

To "CANCER IMMUNOEDITING"

Host protective vs tumor sculpting actions of immunity

Robert D. Schreiber
Lloyd J. Old

Immunoediting

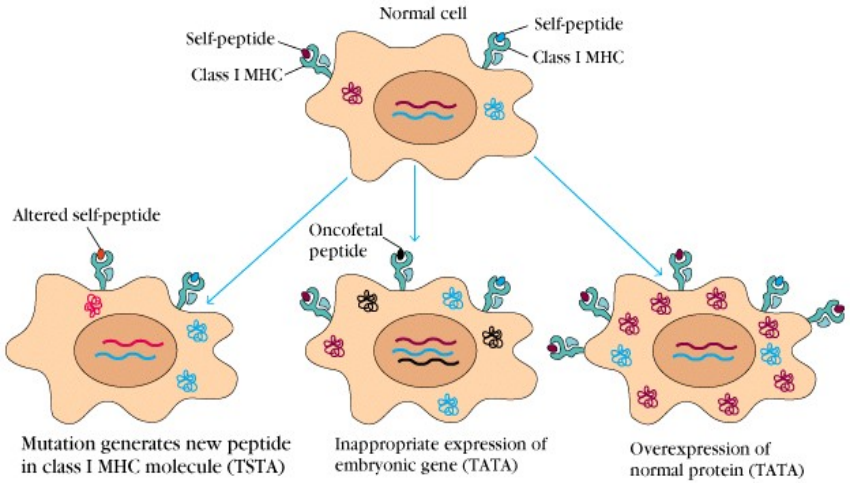


Dunn et al Immunity 2004

Tumor Antigens

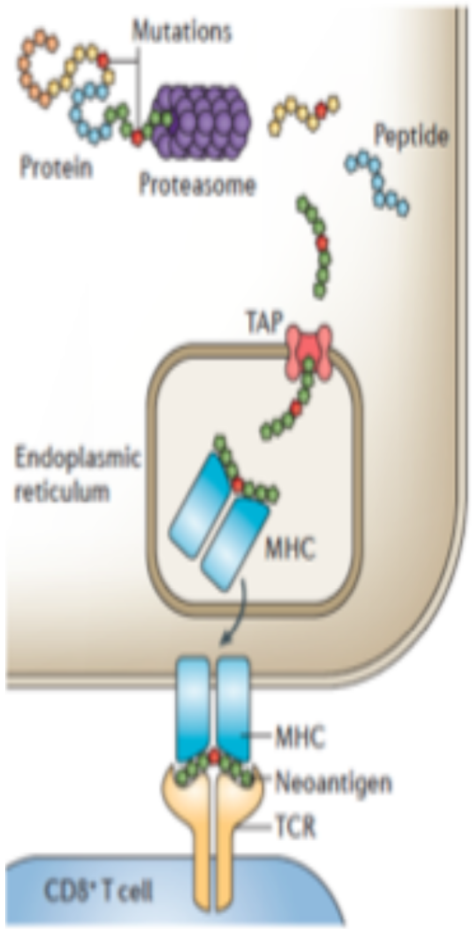
Human Cancer Antigens

- Differentiation antigens
- Cancer-testis
- Mutational antigens
- Amplified or overexpressed antigens
- Splice variant antigens
- Viral antigens
- etc

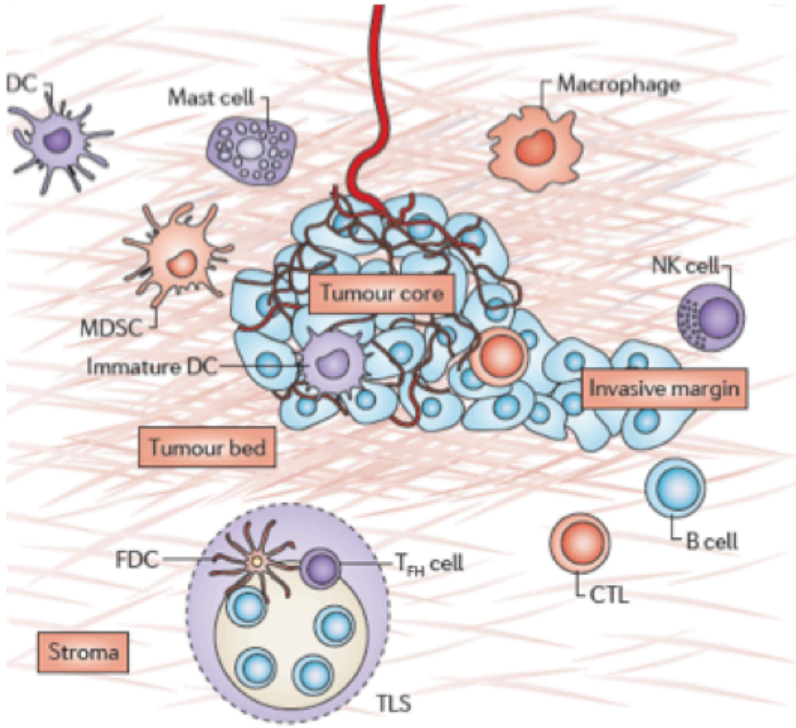


1. **Altered peptides-**
2. **Products of fetal genes**
3. **Over-expressed proteins**

Neoantigens



The immune contexture in human cancers: impact on clinical outcome



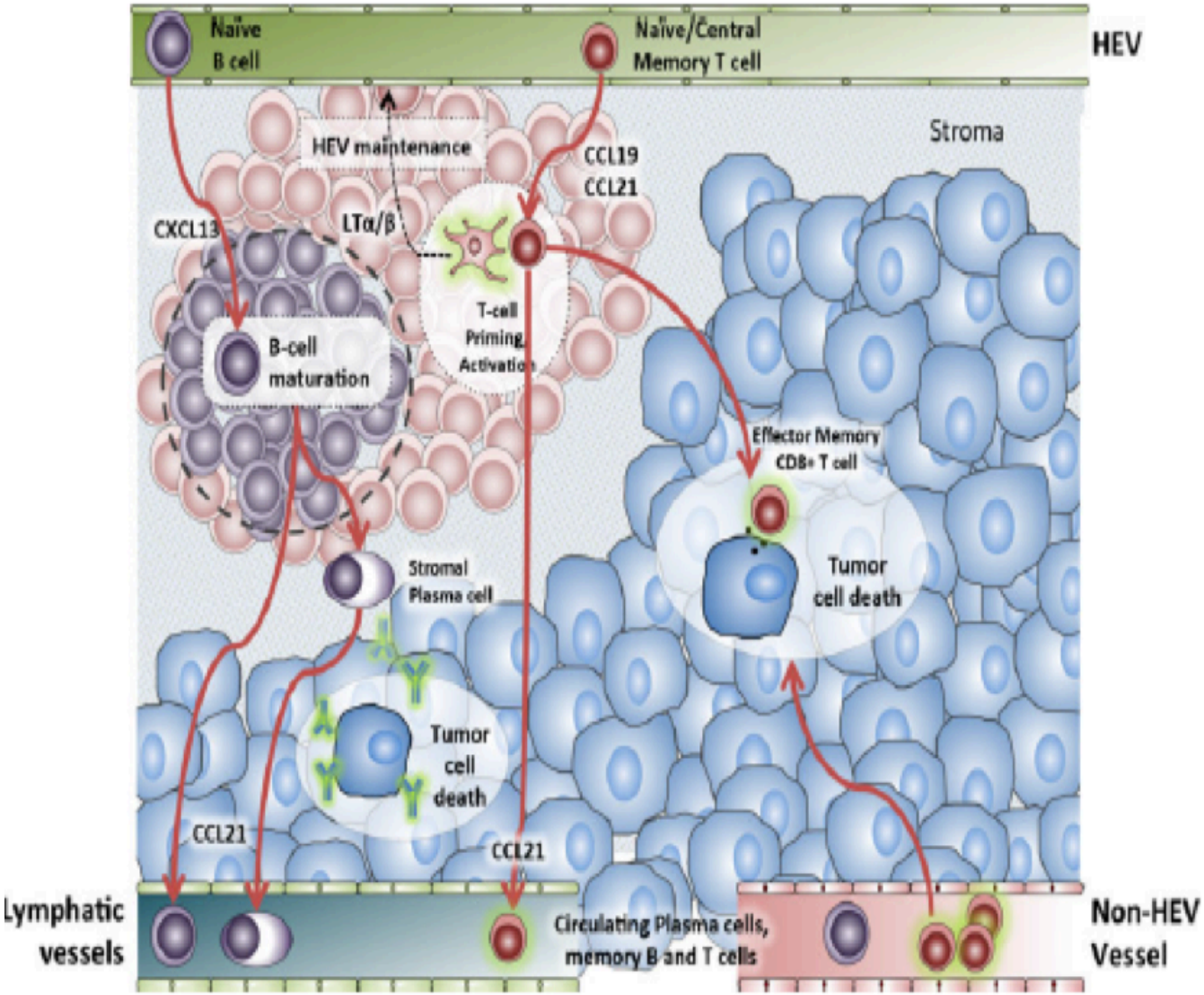
Immune contexture	Parameters: positive association with survival
Type	CTLs ($CD3^+CD8^+$)
	Memory T cells ($CD45RO^+$)
Location	Core of the tumour
	Invasive margin
Density	Number of cells per mm^2: 1, 10, 100, 1,000, 10,000 — $CD3^+_{CT}$, $CD3^+_{IM}$, $CD8^+_{CT}$, $CD8^+_{IM}$, $CD45RO^+_{CT}$, $CD45RO^+_{IM}$
Functional orientation	T_H1 cell-associated factors (IFNγ, IL-12, T-bet and IRF1)
	Cytotoxic factors (granzymes, perforin and granulysin)
	Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2)
	T_H17 cells, T_{Reg} cells and T_H2 cells have a variable effect on survival, depending on tumour type
TLS	Presence and quality

Fridman WH et al Nature Rev Cancer 2012

Cancers in which T cell infiltration is associated with favorable prognosis

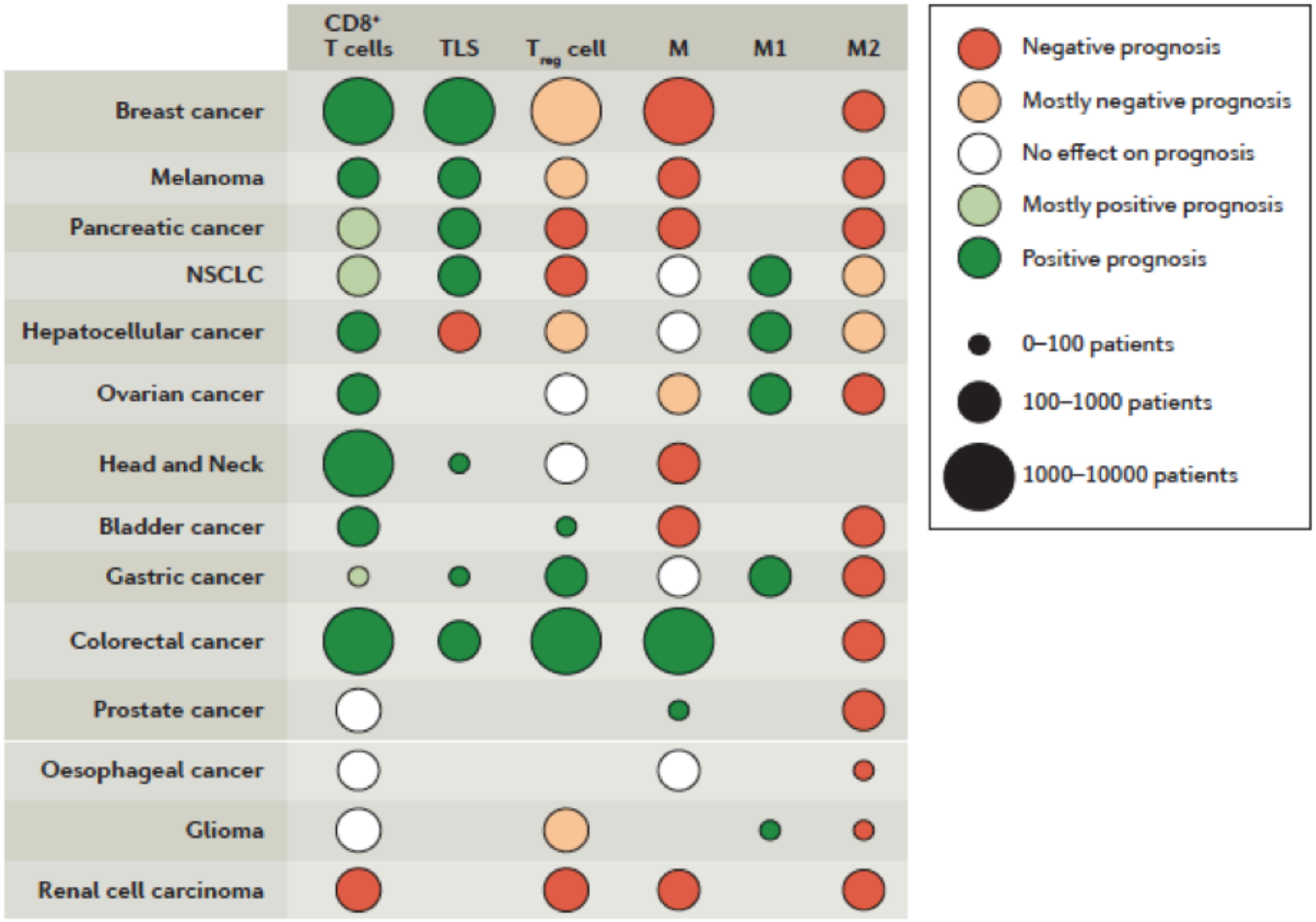
Cancers	*References*
Melanoma	Clark *et al.* (1989); Tefany *et al.* (1991); Mackensen *et al.* (1993); Clemente *et al.* (1996)
Head and neck cancers	Reichert *et al.* (2001); Shibuya *et al.* (2002); Badoual *et al.* (2006)
Breast cancer	Marrogi *et al.* (1997); Menegaz *et al.* (2008)
Bladder cancer	Sharma *et al.* (2007)
Ovarian cancer	Zhang *et al.* (2003); Sato *et al.* (2005)
Esophageal cancer	Schumacher *et al.* (2001); Cho *et al.* (2003)
Colorectal cancer	Jass (1986); Graham and Appelman (1990); Harrison *et al.* (1994); Ropponen *et al.* (1997); Baier *et al.* (1998); Naito *et al.* (1998); Dalerba *et al.* (2003); Diederichsen *et al.* (2003); Prall *et al.* (2004); Pages *et al.* (2005, 2009); Galon *et al.* (2006); Salama *et al.* (2009)
Renal cell carcinoma	Nakano *et al.* (2001)
Prostatic adenocarcinoma	Vesalainen *et al.* (1994); Karja *et al.* (2005); Richardsen *et al.* (2008)
Lung carcinoma	Ito *et al.* (2005); Hiraoka *et al.* (2006a); Al-Shibli *et al.* (2008); Dieu-Nosjean *et al.* (2008); Kawai *et al.* (2008)

Galon J et al Oncogene 2010

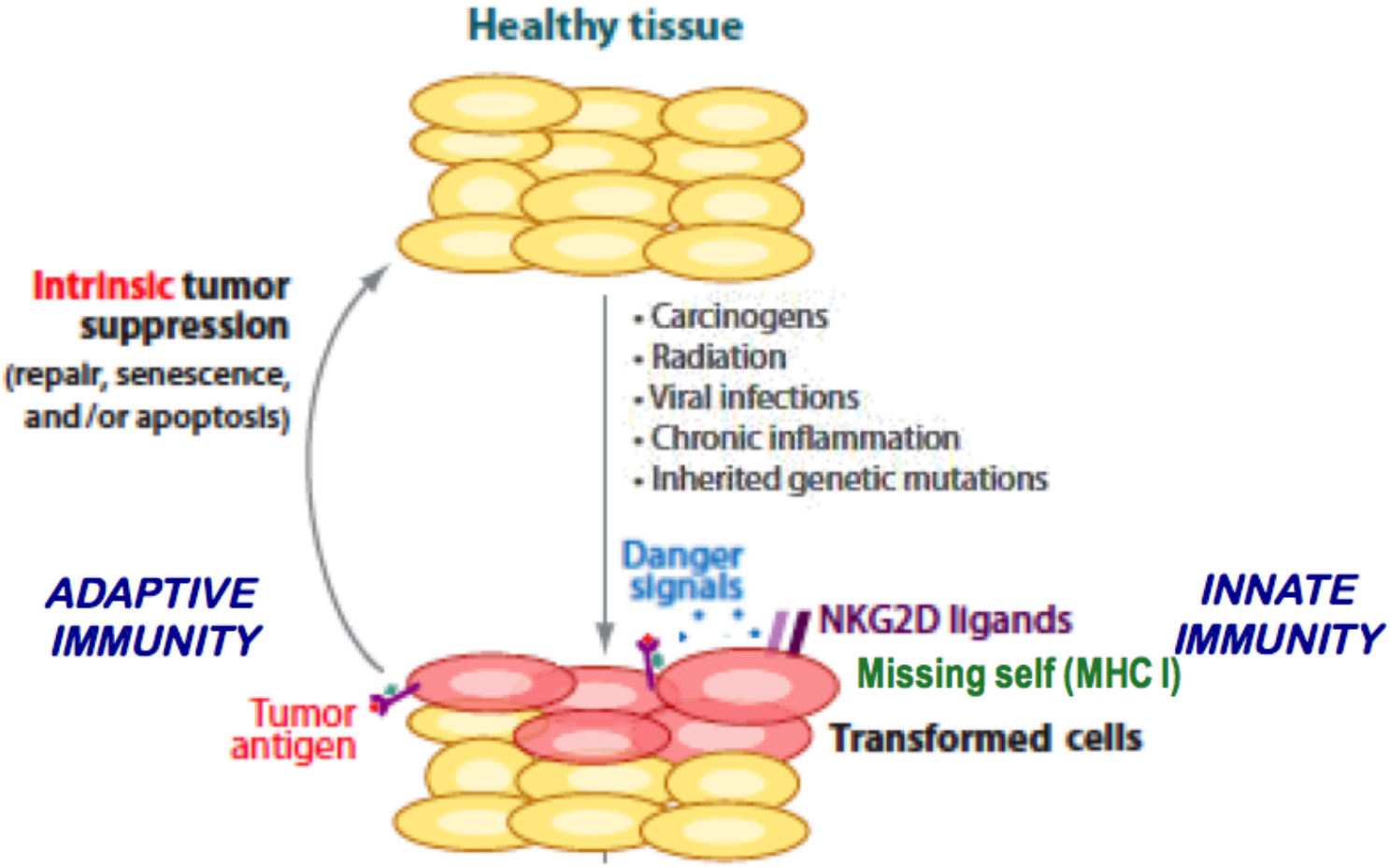


Dieu-Nosjean MC et al Immunol Rev 2016

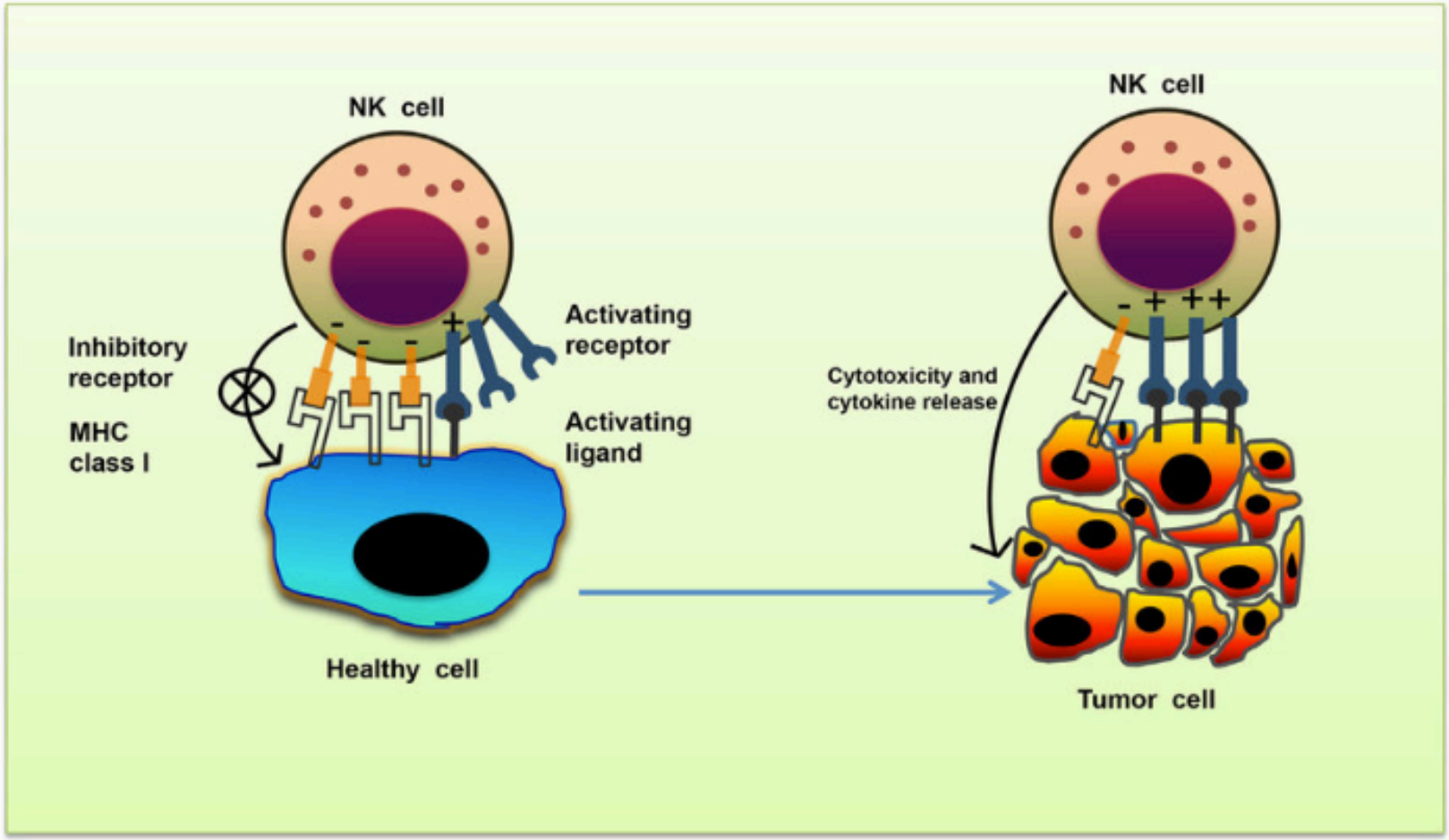
Effect of immune cell infiltrates on cancer patient prognosis



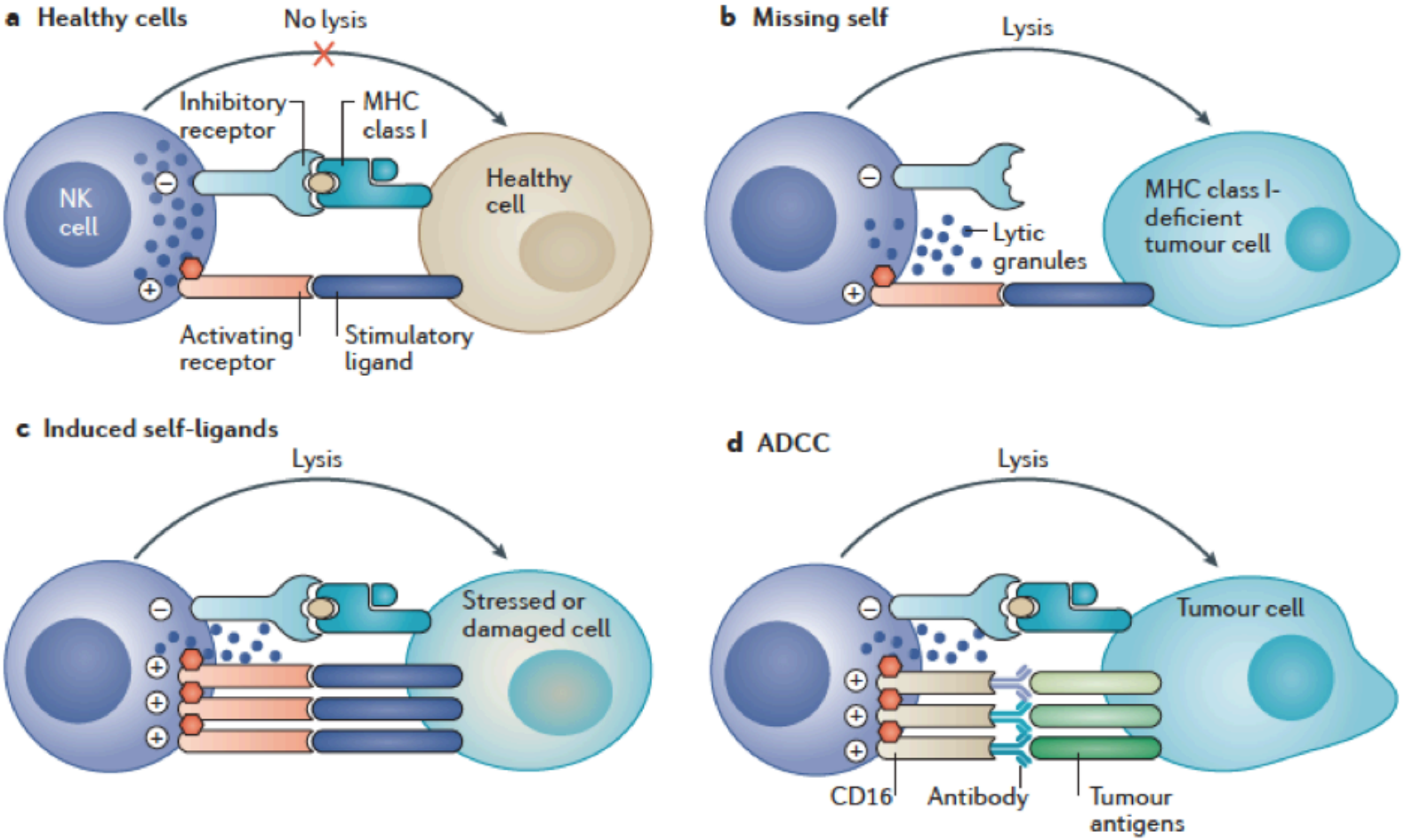
What cells protect the host from tumor development and what are the critical effector functions of the immune system in cancer surveillance?



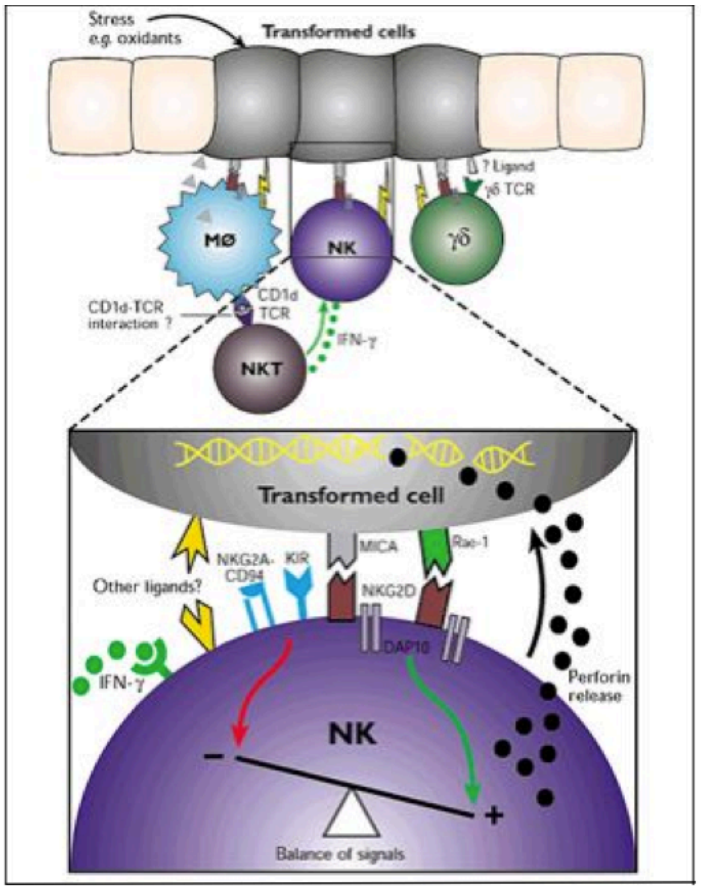
NK: missing self recognition of tumor cells



NK cell recognition of tumour cells

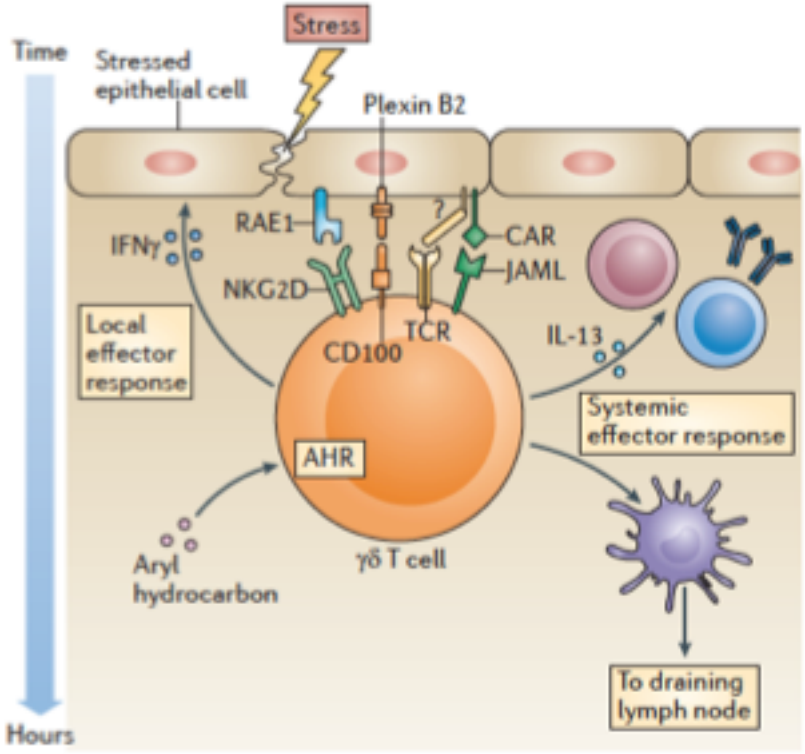


Recognition of tumor cells by innate immune system



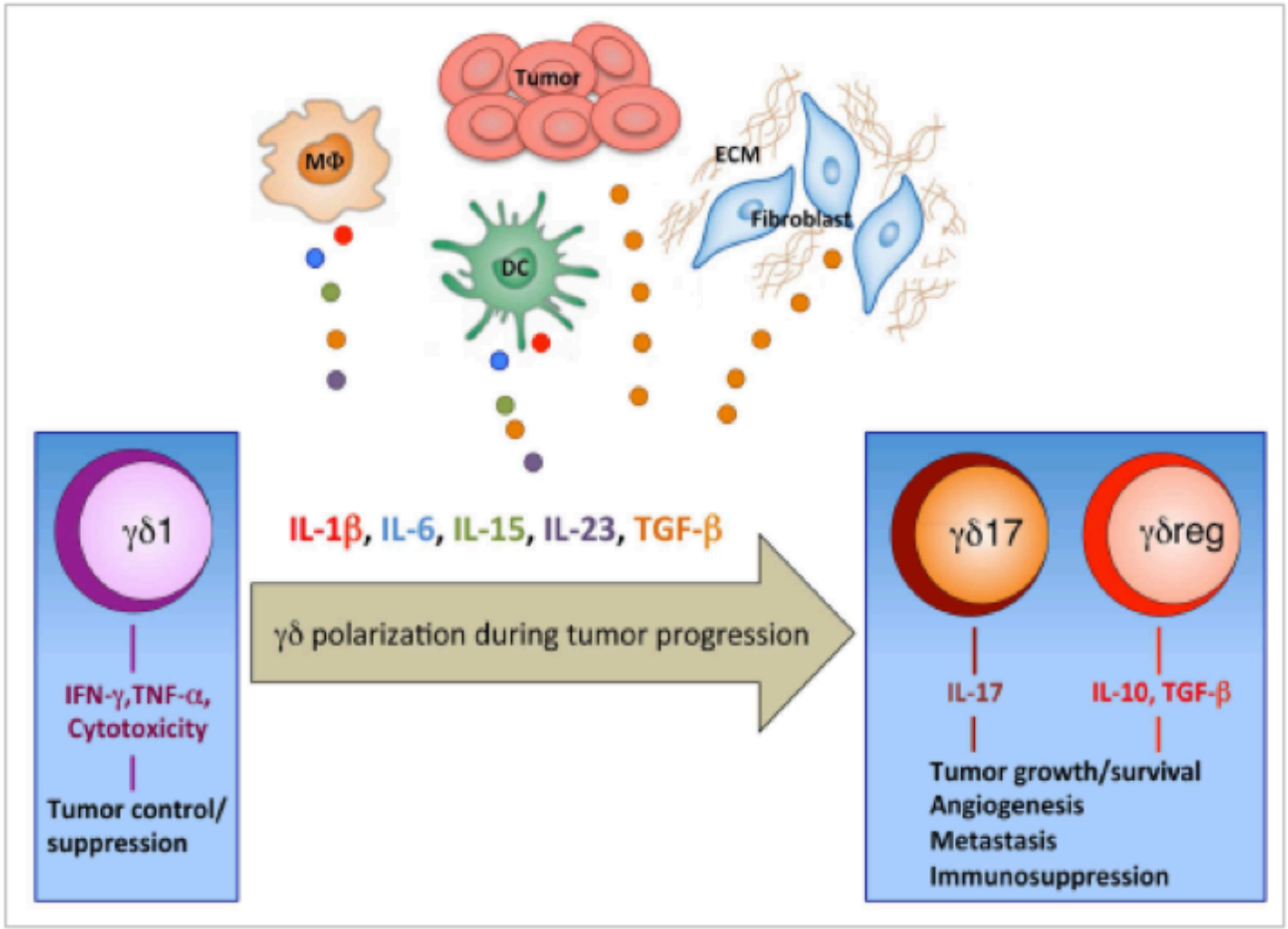
Smyth MJ et al Nat Immunol 2001

γδ cells respond to stressed cell antigens

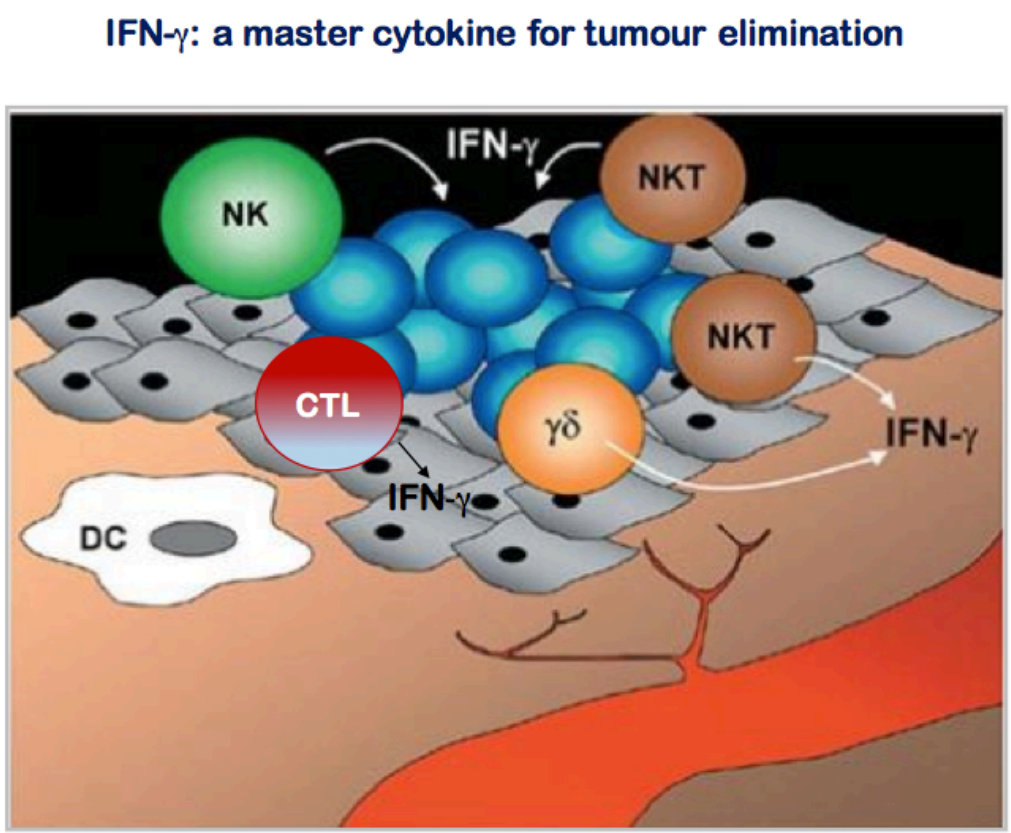


- The frequency of γδ cells is higher than that of ag specific αβ cells
- γδ cells recognize a broad range of tumor cell antigens not only proteins.
- γδ activation does not require co-stimulatory signals

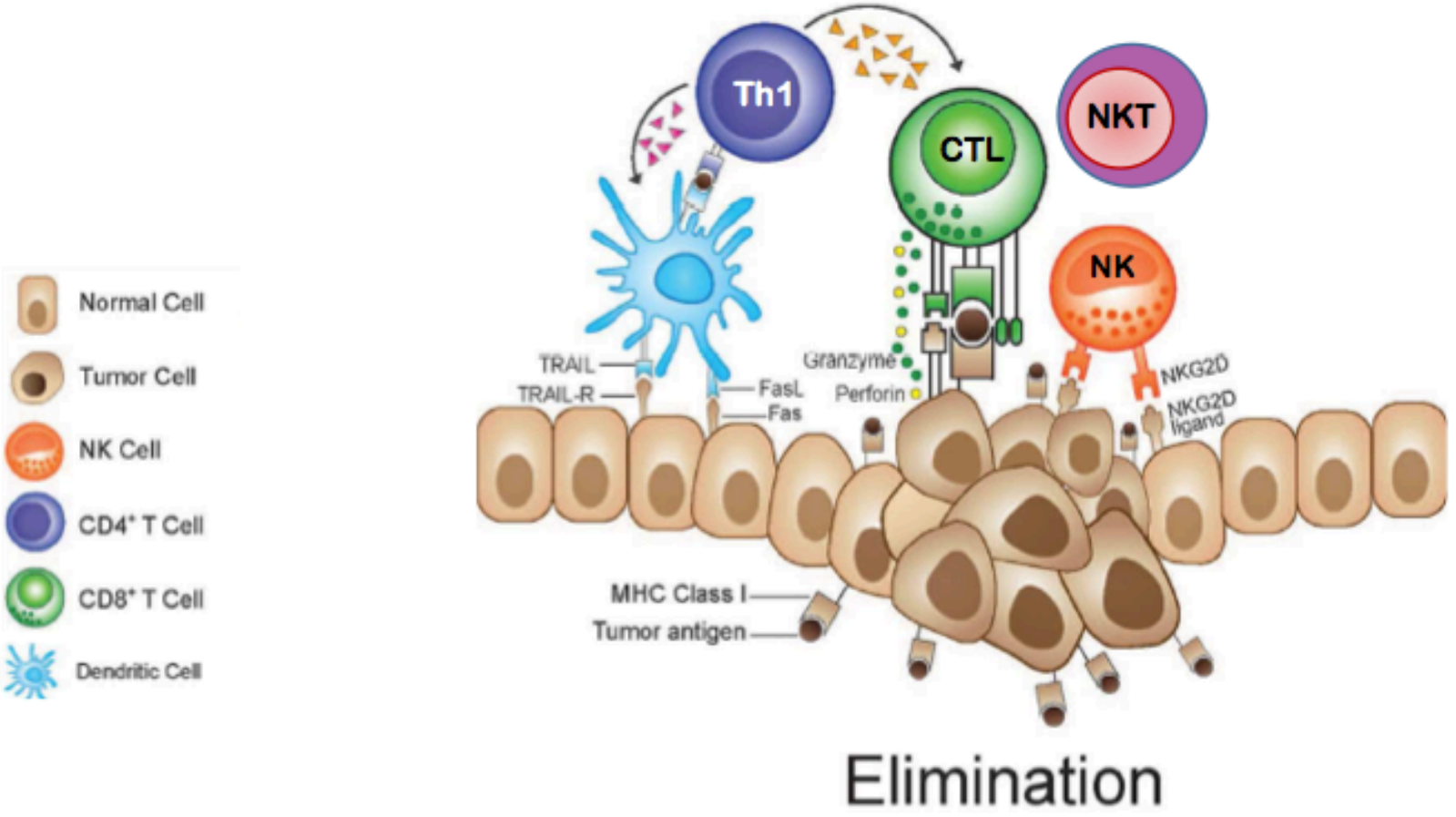
Polarization of γδ cells in tumor progression



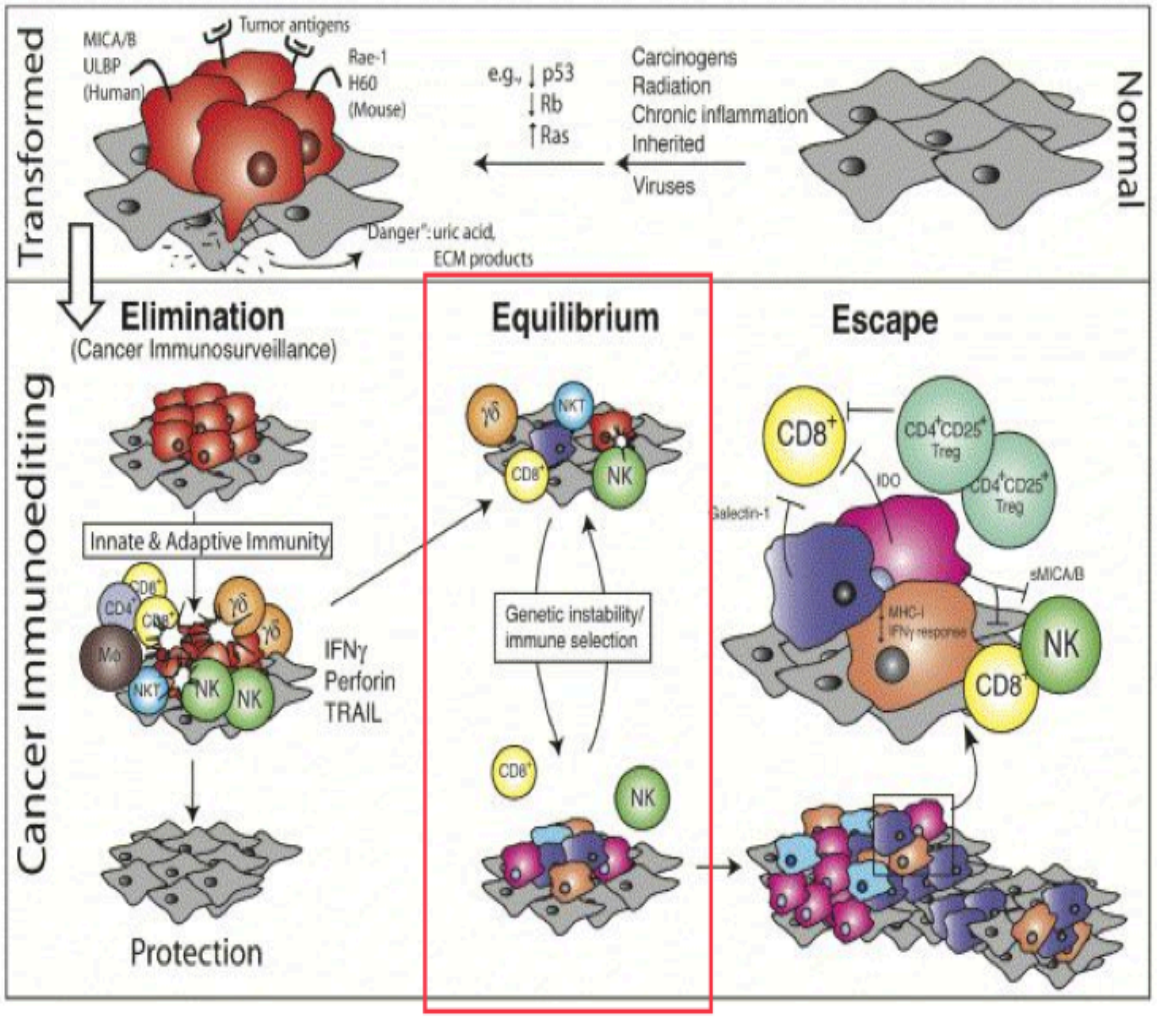
NK s, Th 1, CTLs and DC, secrete IFNγ



Dunn GP et al Nat Immunol 2002

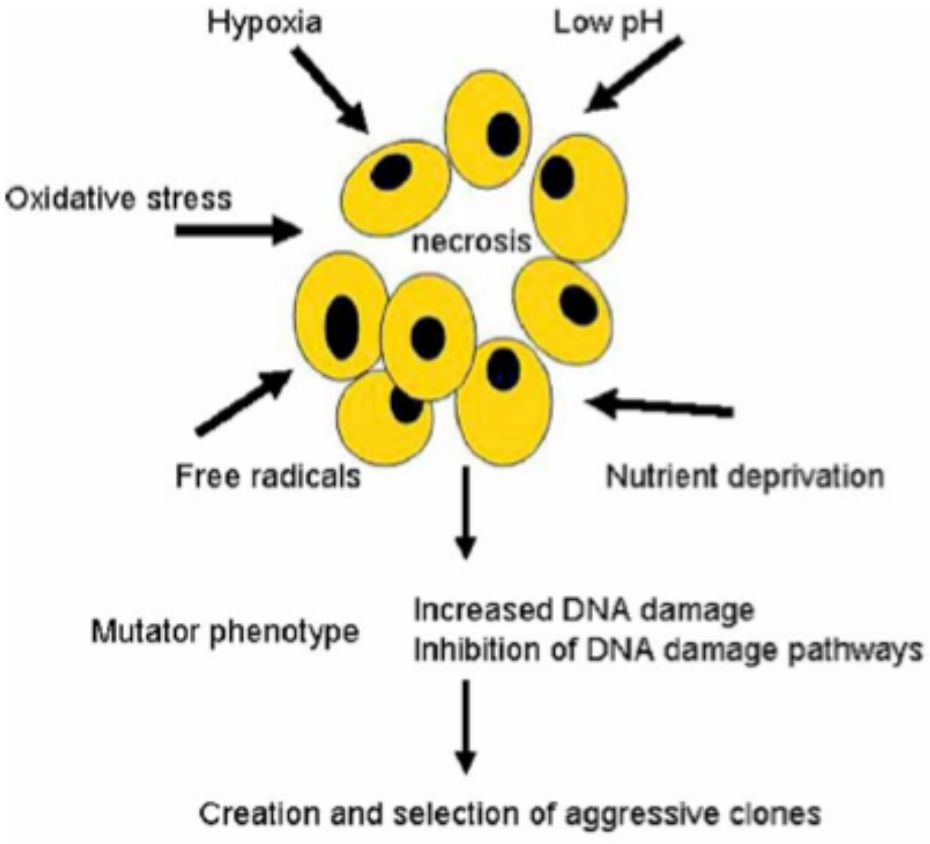

Normal Cell
Tumor Cell
NK Cell
CD4+ T Cell
CD8+ T Cell
Dendritic Cell
Th1
CTL
NKT
NK
TRAIL
TRAIL-R
FasL
Fas
Granzyme
Perforin
NKG2D
NKG2D ligand
MHC Class I
Tumor antigen
Elimination

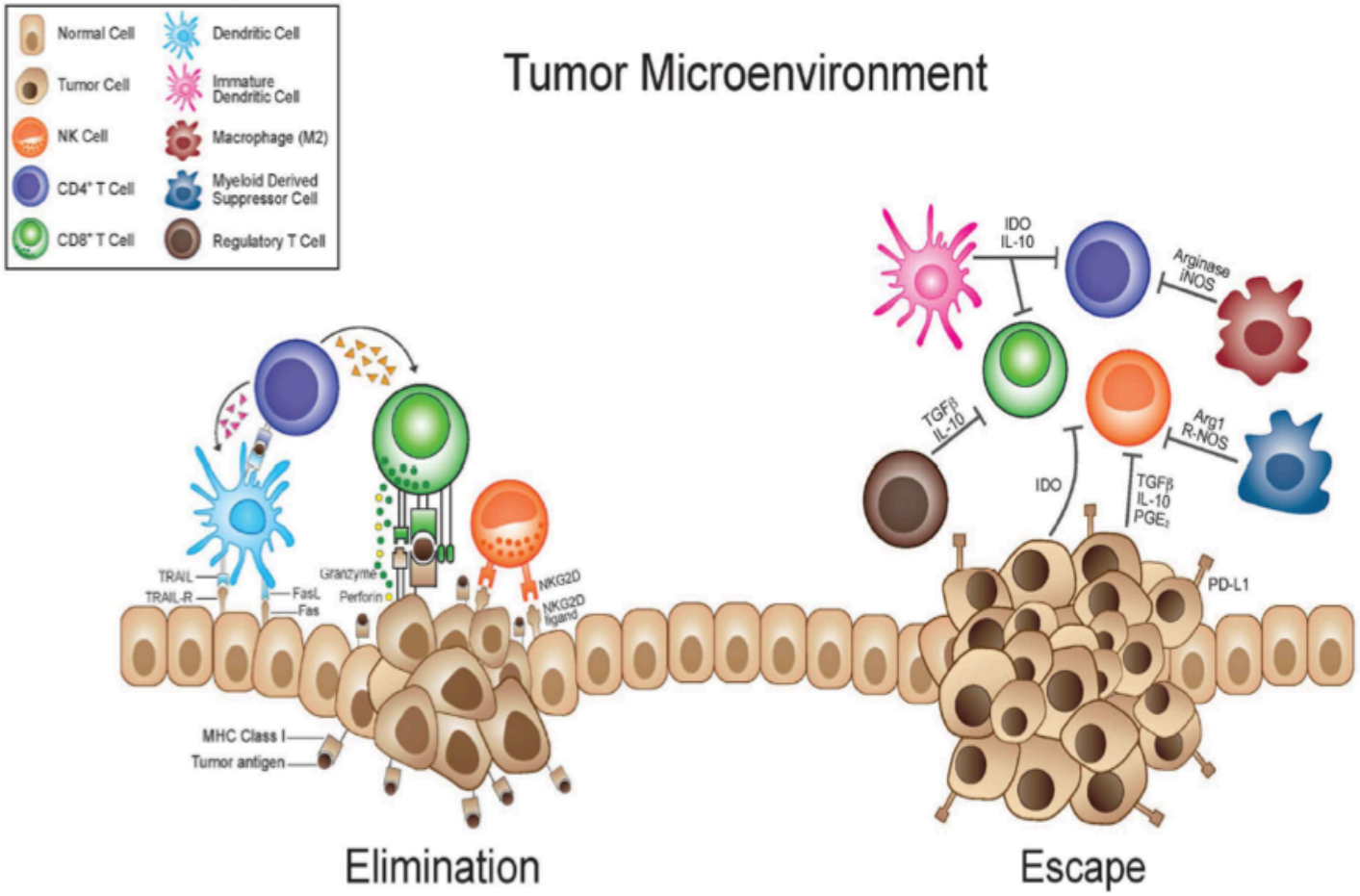
CANCER IMMUNOEDITING:
host protective vs tumor sculpting actions of immunity



Dunn et al Immunity 2004

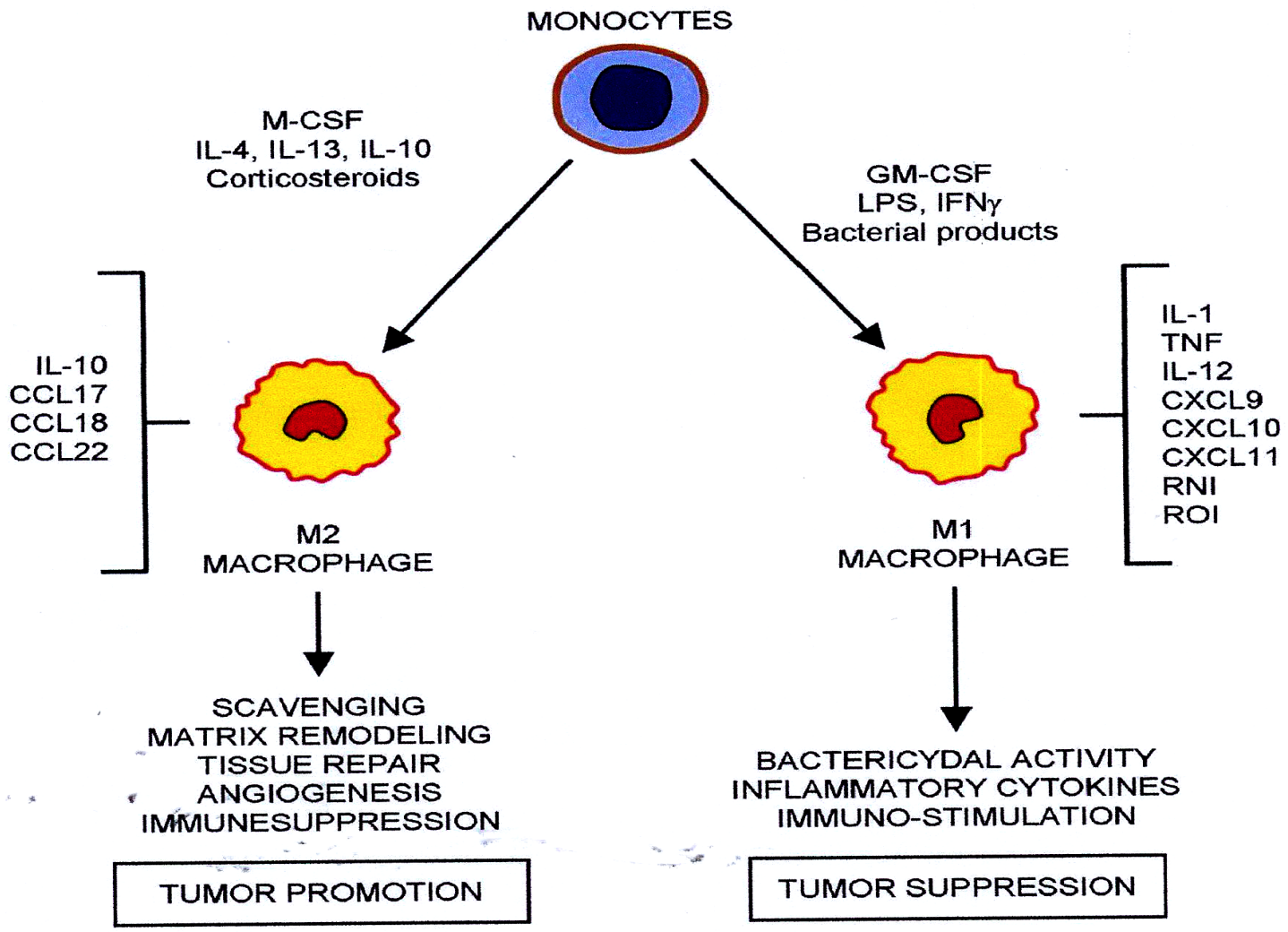
Tumor microenvironment promotes tumor progression



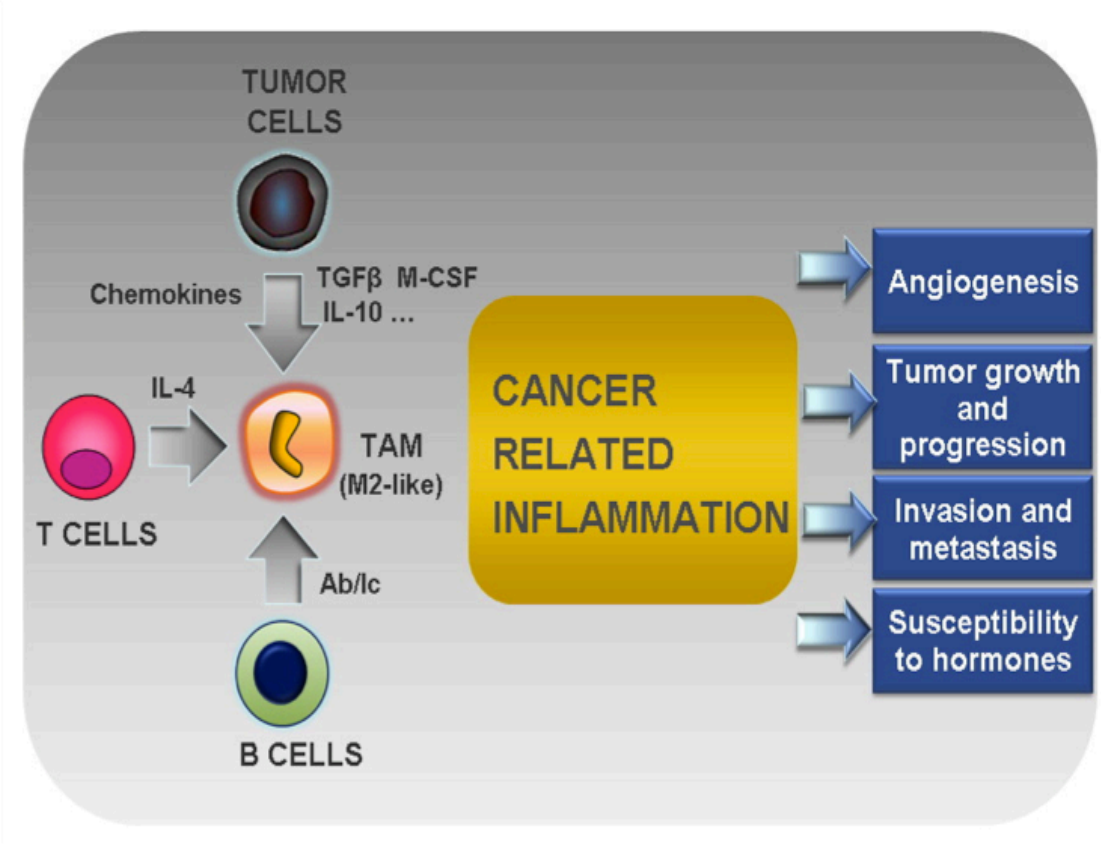


Monjazeb et al. Front Oncol 2013

M1/ M2 macrophages

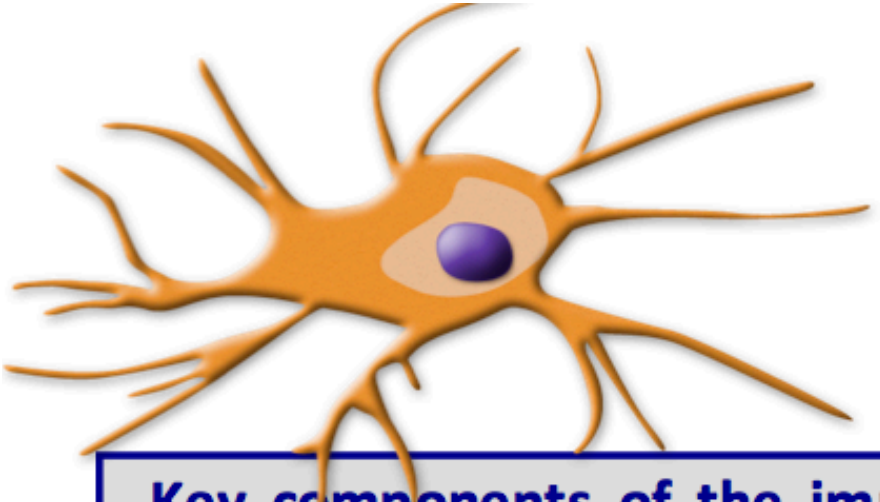


Orchestration of TAM in cancer-promoting inflammation



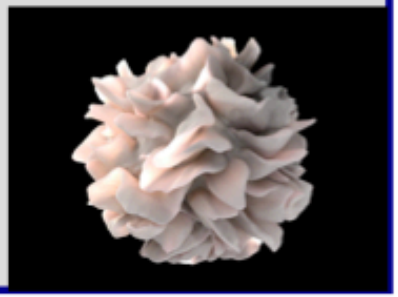
Mantovani A and Sica A Curr Opin Immunol 2010

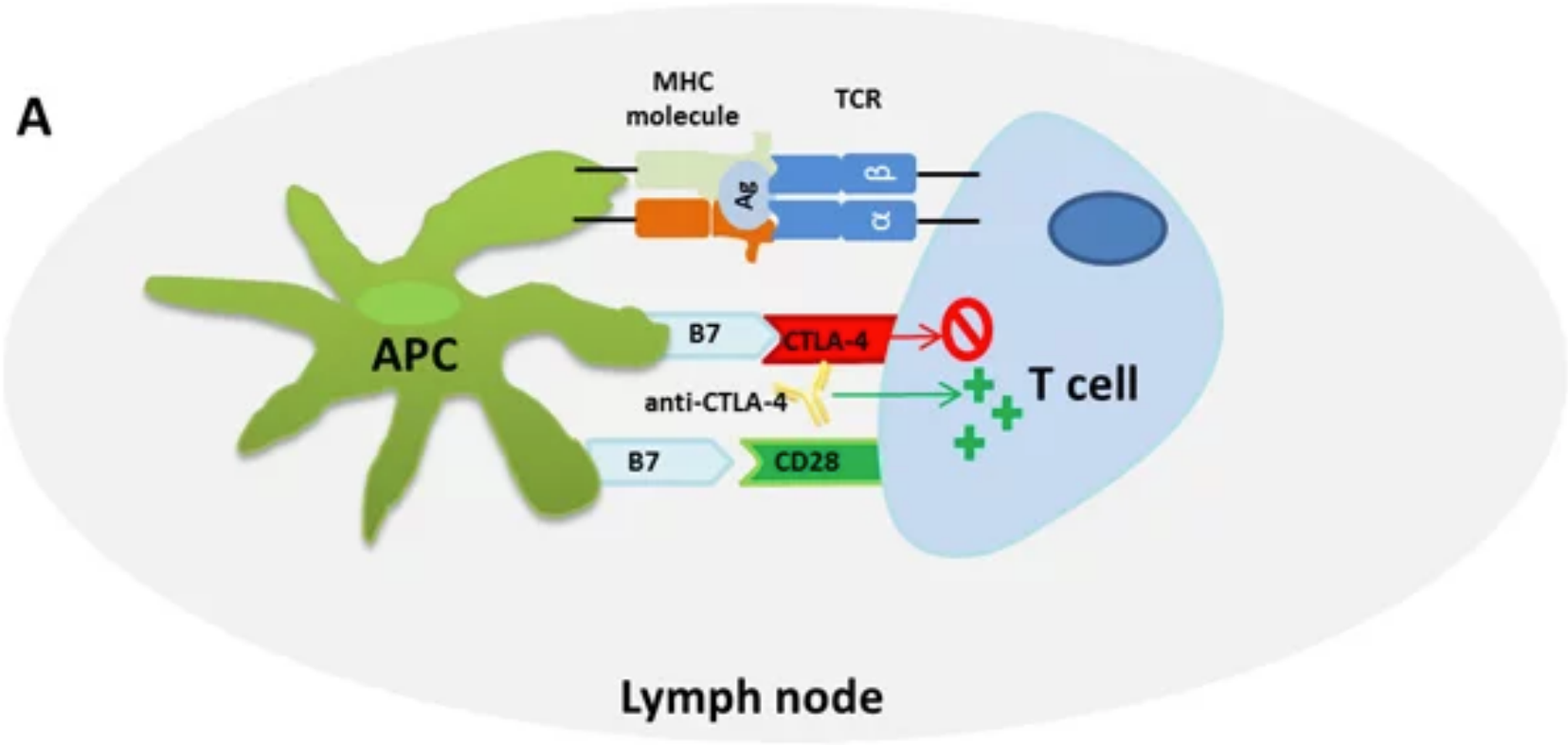
Dendritic cells

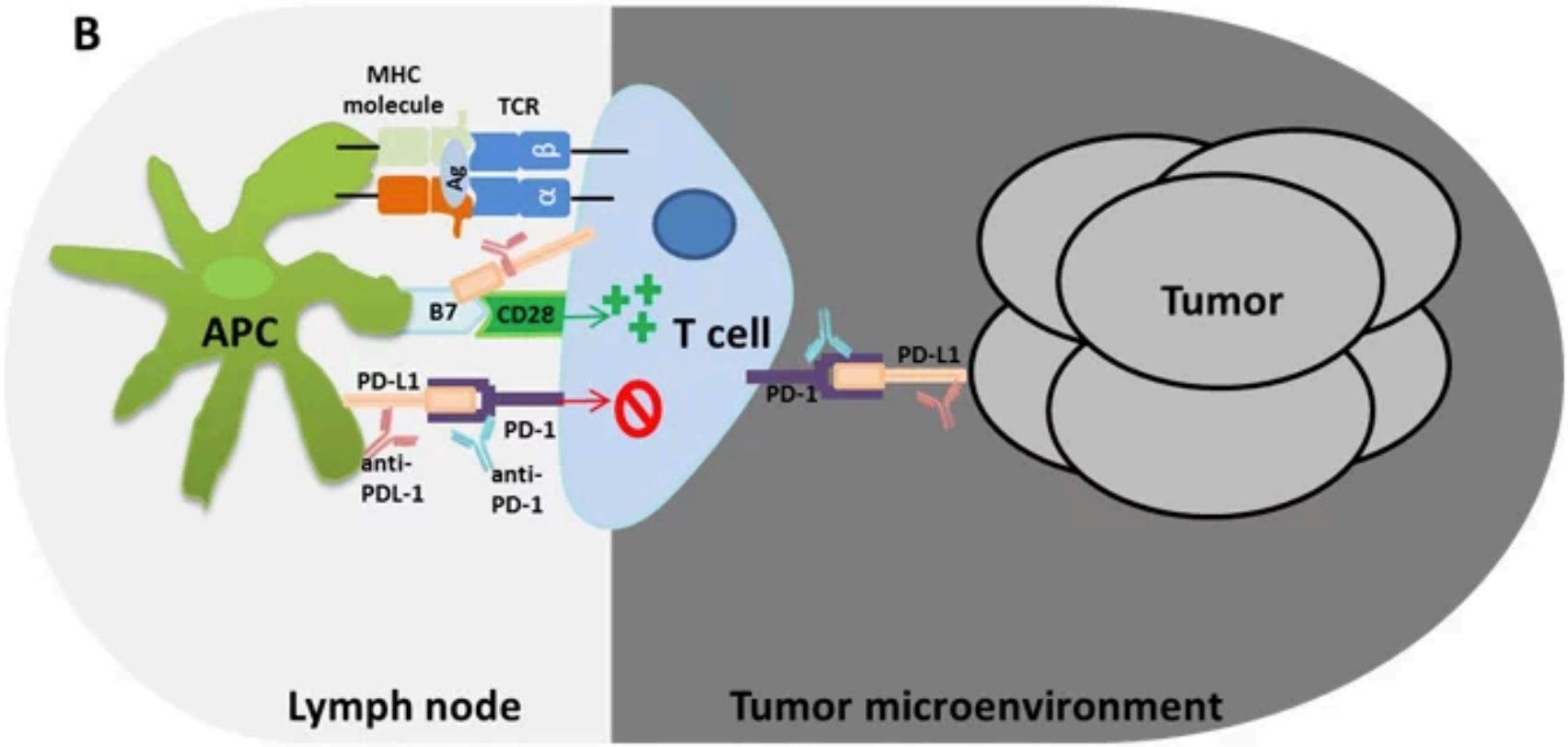


Key components of the immunosuppressive network in the tumor microenvironment are DC with:

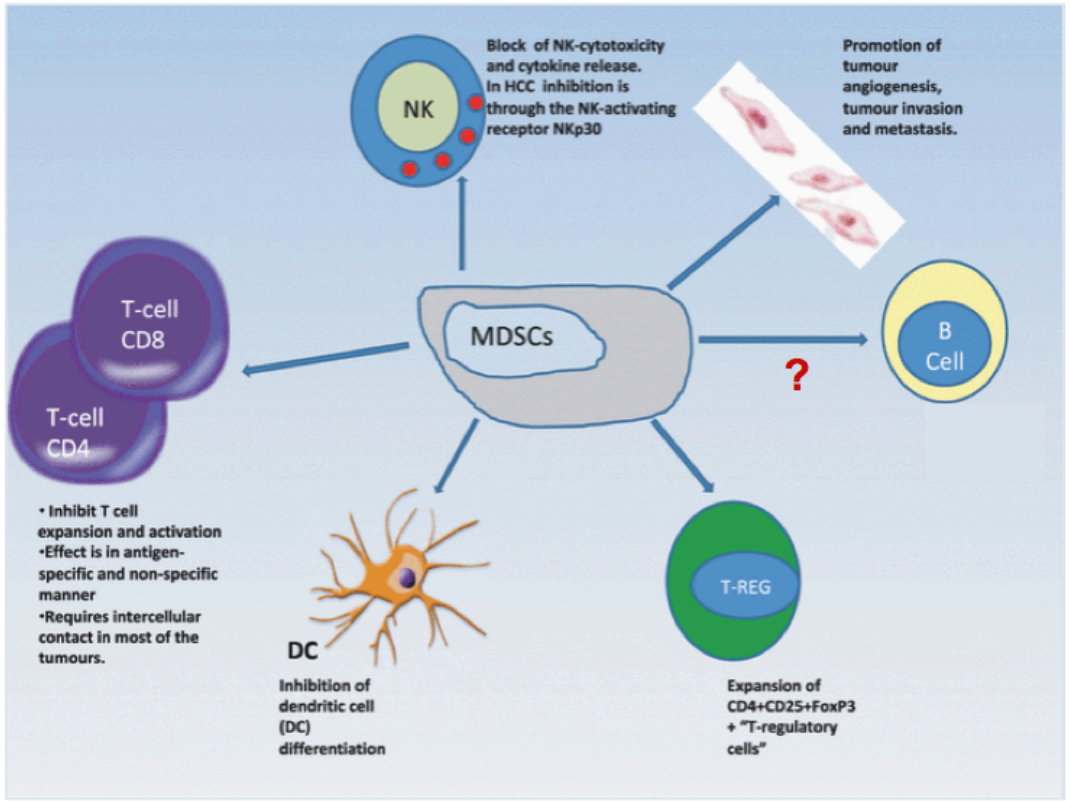
- **immature phenotype**
- **immunosuppressive phenotype (PDCs)**
- **vascular**




A
MHC molecule
TCR
Ag
β
α
APC
B7
CTLA-4
anti-CTLA-4
T cell
B7
CD28
Lymph node

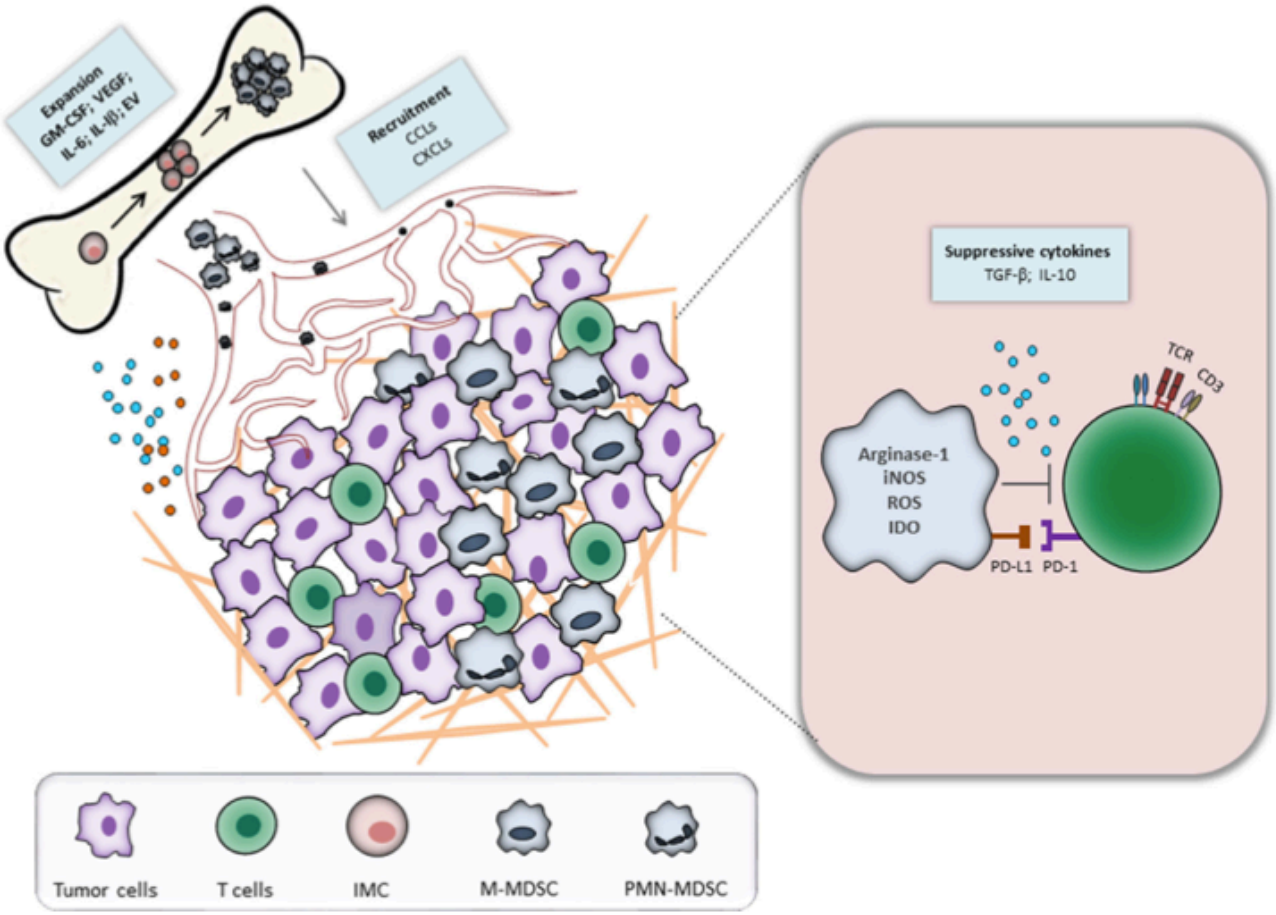

B
MHC molecule
TCR
Ag
β
α
APC
B7
CD28
T cell
PD-L1
PD-1
anti-PDL-1
anti-PD-1
PD-L1
PD-1
Tumor
Lymph node
Tumor microenvironment

Myeloid-derived suppressor cells (MDSC)-mediated activities

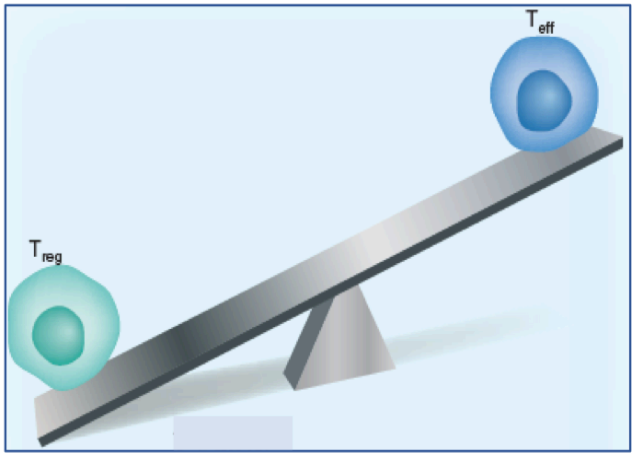


Tadmor T et al British J Hematol 2011

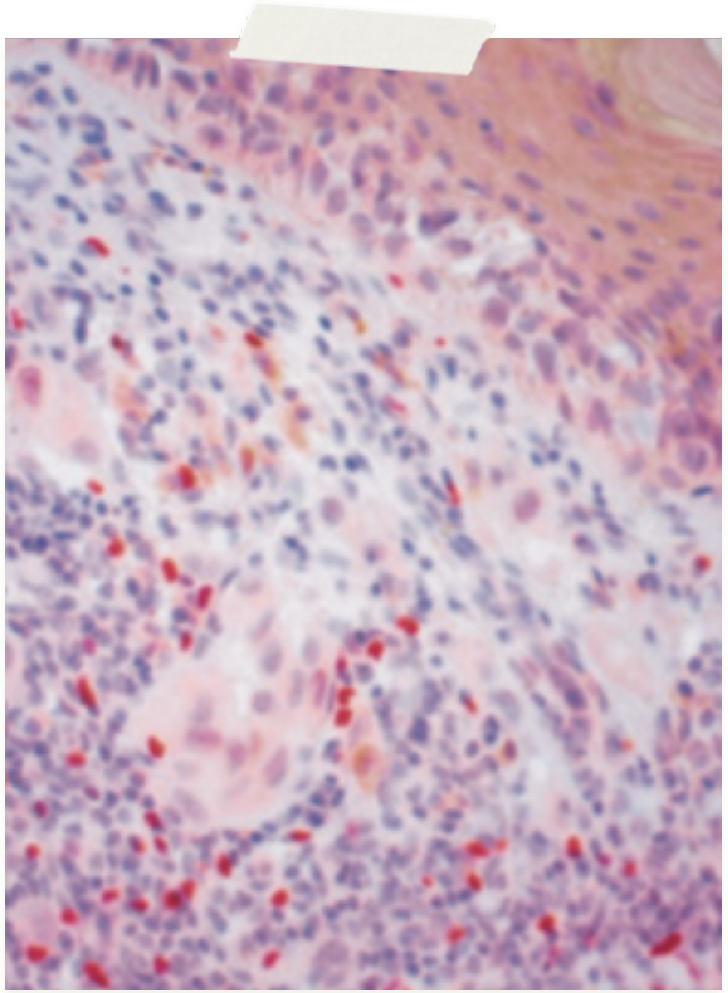
MDSC myeloid derived suppressor cells



T regs infiltration in melanoma



Melanoma is treated with immune therapy

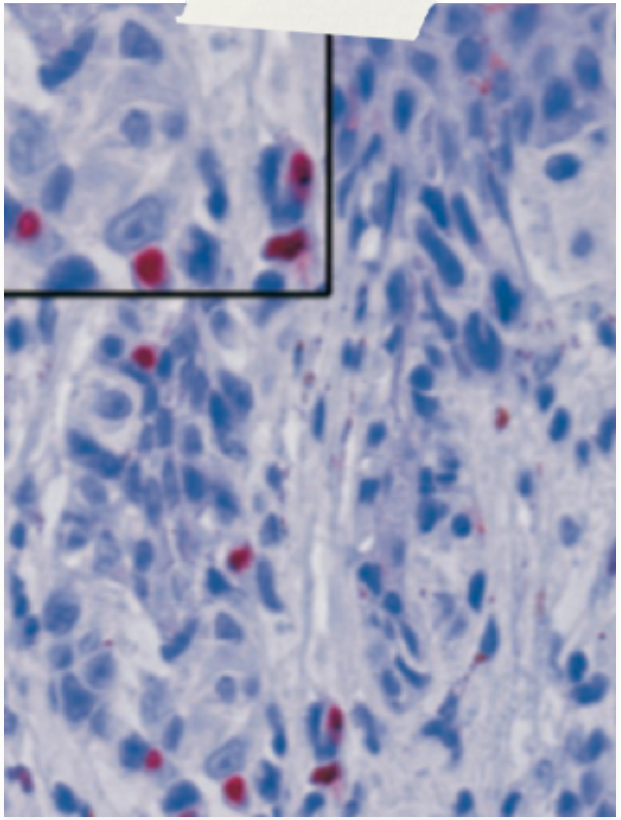


Foxp3+:red

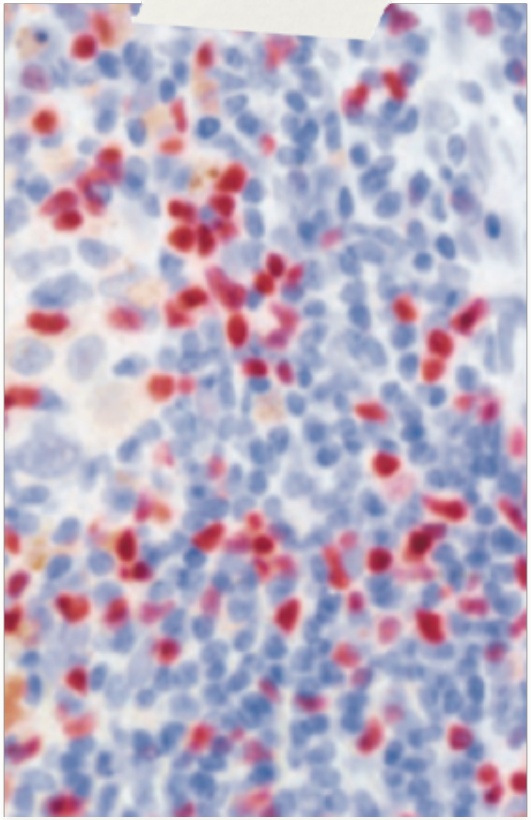
Mourmouras et al. Evaluation of tumour-infiltrating Cd4+Cd25+Foxp3+ regulatory T cells in human cutaneous benign and atypical naevi, melanomas and melanoma metastases Dermatopathology 2007

Look at the difference...

Red: Fox P3 cells

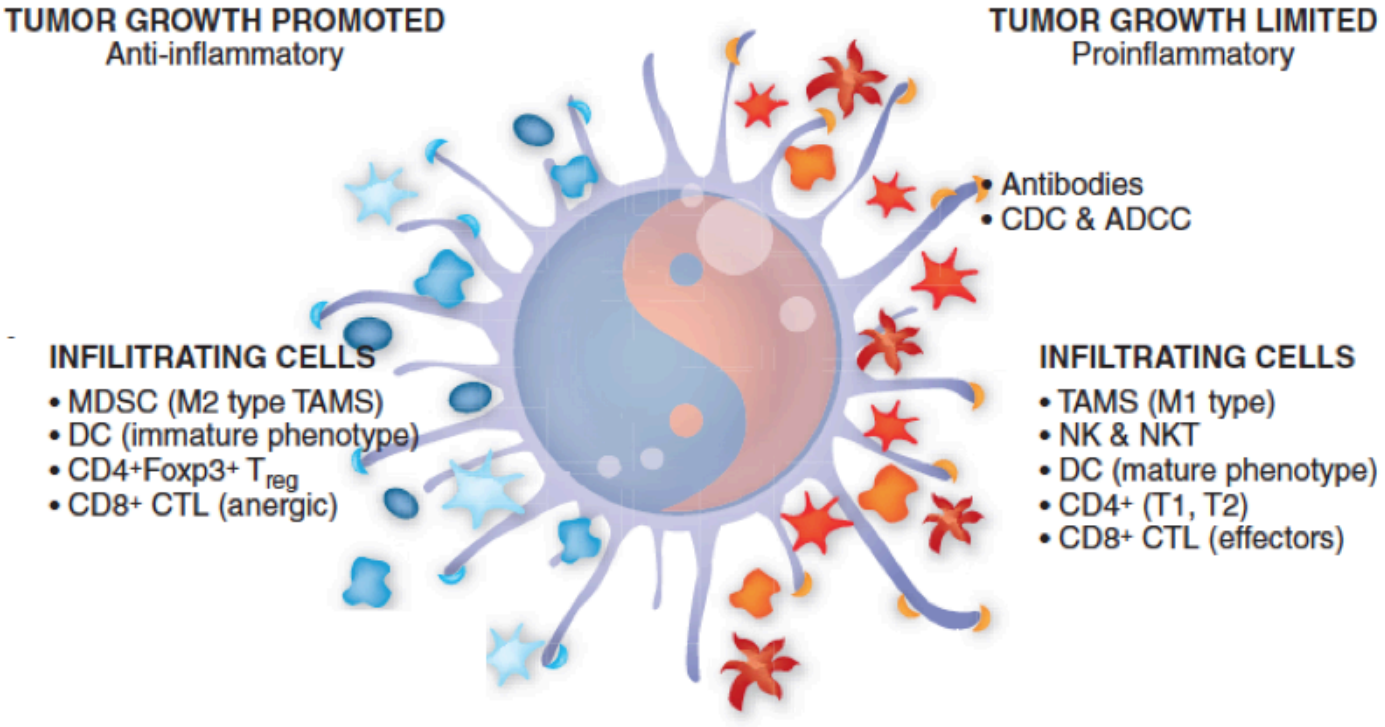


Melanoma in radial growth



Melanoma in vertical growth

The 'yin and yang' of immune response in the tumor microenvironment



Monoclonal antibodies