Primer on Macrophages, Dendritic Cells and Other Myeloid Cells in Cancer

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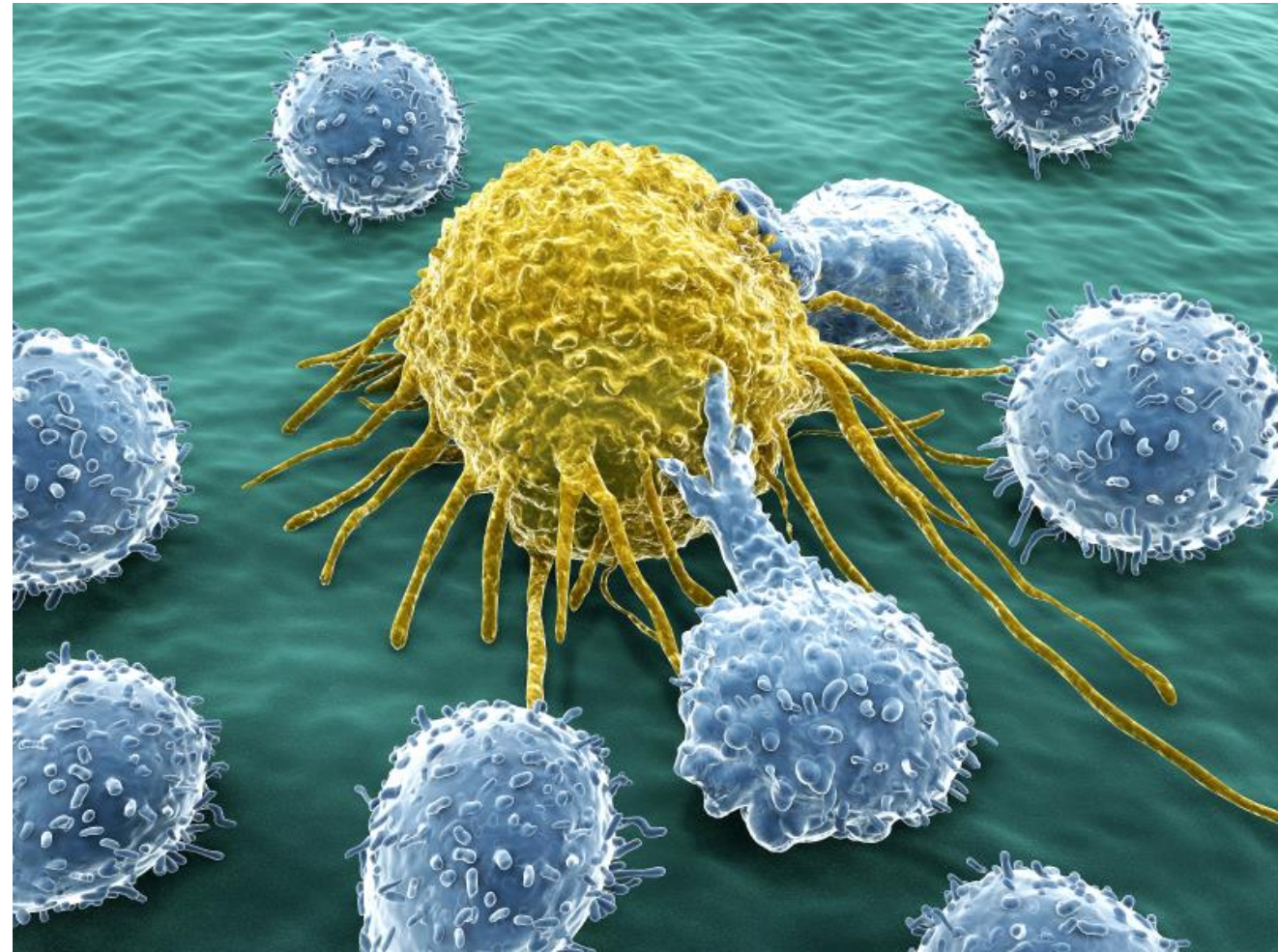**curielt@uthscsa.edu**

South Texas Research Facility

The Alamo
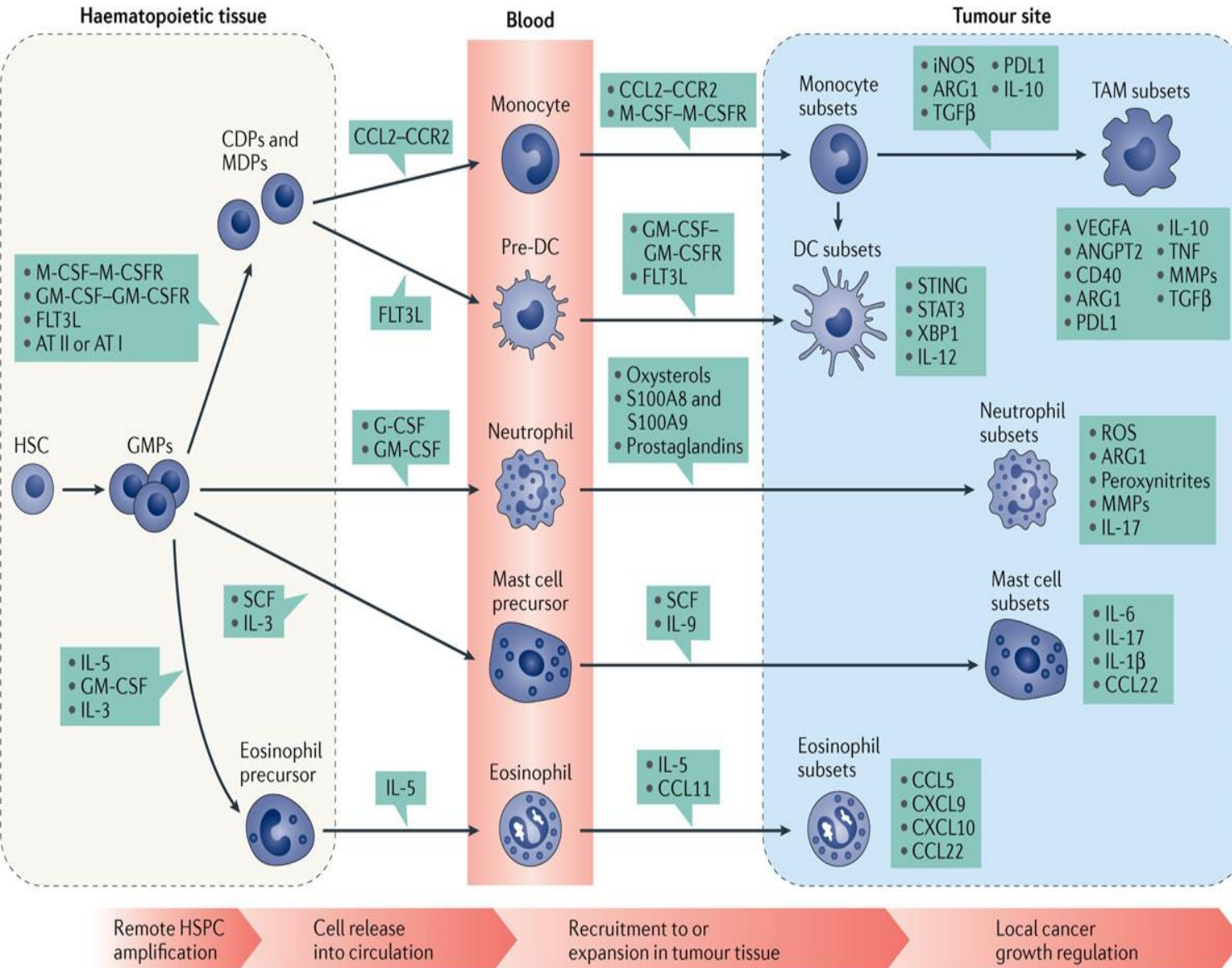
North Star Mall

Disclosures

- Agenus, Xencor

Overview

- **Normal myeloid cells and differentiation**
- **Myeloid subsets in cancer**
- **Tumor microenvironment factors**
- **Tumor myeloid cell defects**
- **Translational considerations**

General myeloid cell features
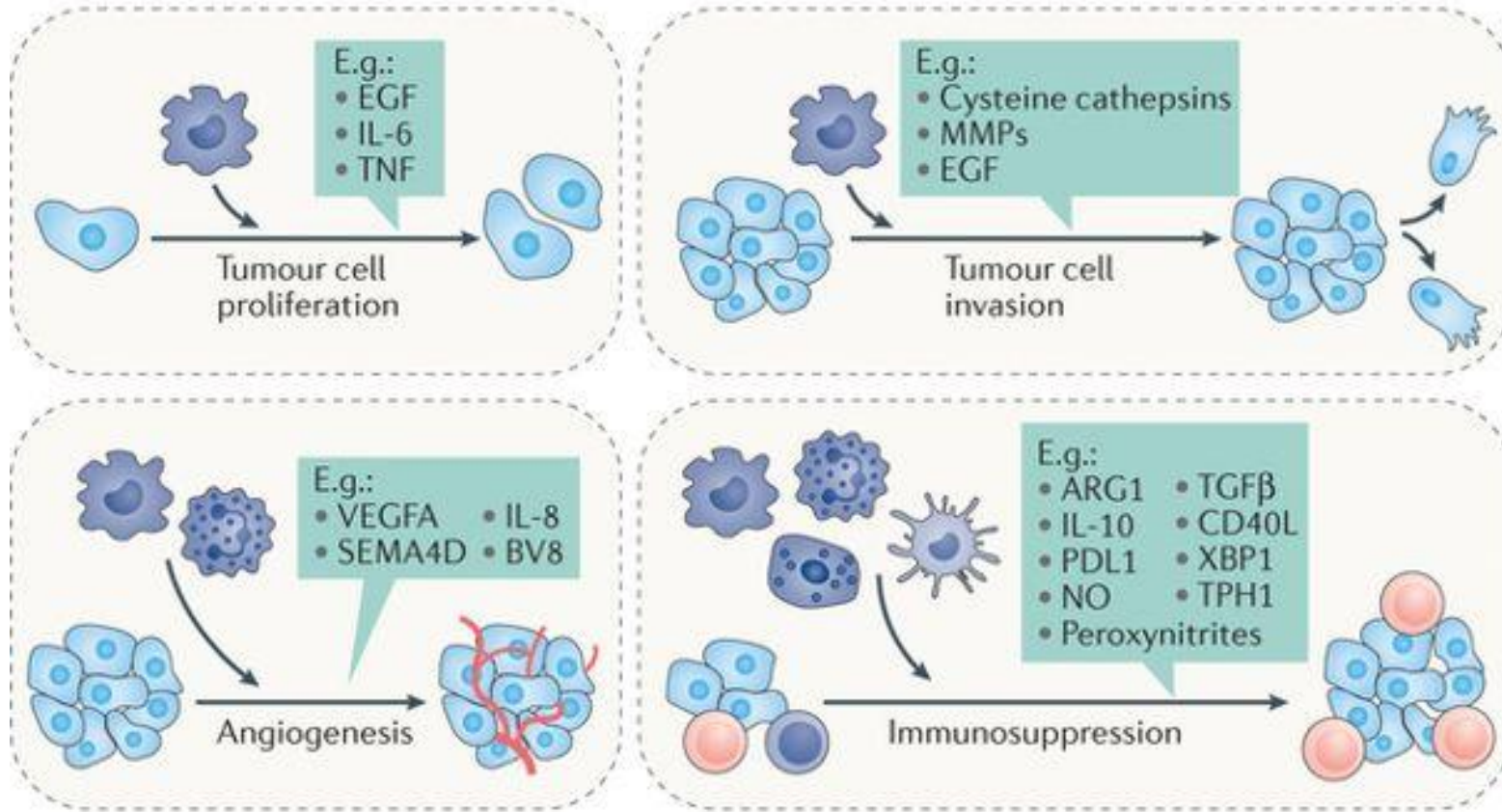
Myeloid cell differentiation is complex

- Cell states are plastic
- Functions depend on tumor type
- Functions depend on intratumor location
- Many myeloid cell phenotypes are not firmly established

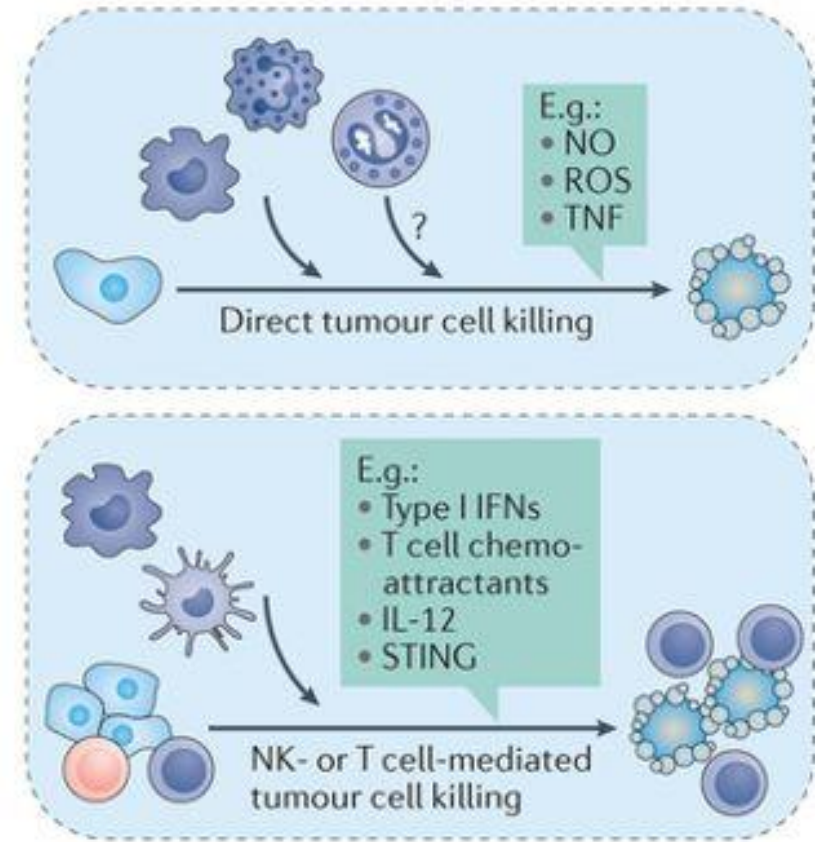Engblom, *et al., Nat Rev Cancer* **16**:447–462 (2016)

Myeloid cells exert both pro- and anti-tumor effects


a The tumour-promoting functions of myeloid cells

E.g.:
• EGF
• IL-6
• TNF

Tumour cell proliferation

E.g.:
• Cysteine cathepsins
• MMPs
• EGF

Tumour cell invasion

E.g.:
• VEGFA • IL-8
• SEMA4D • BV8

Angiogenesis

E.g.:
• ARG1 • TGFβ
• IL-10 • CD40L
• PDL1 • XBP1
• NO • TPH1
• Peroxynitrites

Immunosuppression

b The antitumour functions of myeloid cells

E.g.:
• NO
• ROS
• TNF

Direct tumour cell killing

E.g.:
• Type I IFNs
• T cell chemo-attractants
• IL-12
• STING

NK- or T cell-mediated tumour cell killing

Tumour cell | TAM | Neutrophil | Eosinophil | Mast cell | DC | Antitumour NK or T cell | Tumour-promoting T cell

Engblom, *et al., Nat Rev Cancer*
16:447–462 (2016)

Nature Reviews | Cancer

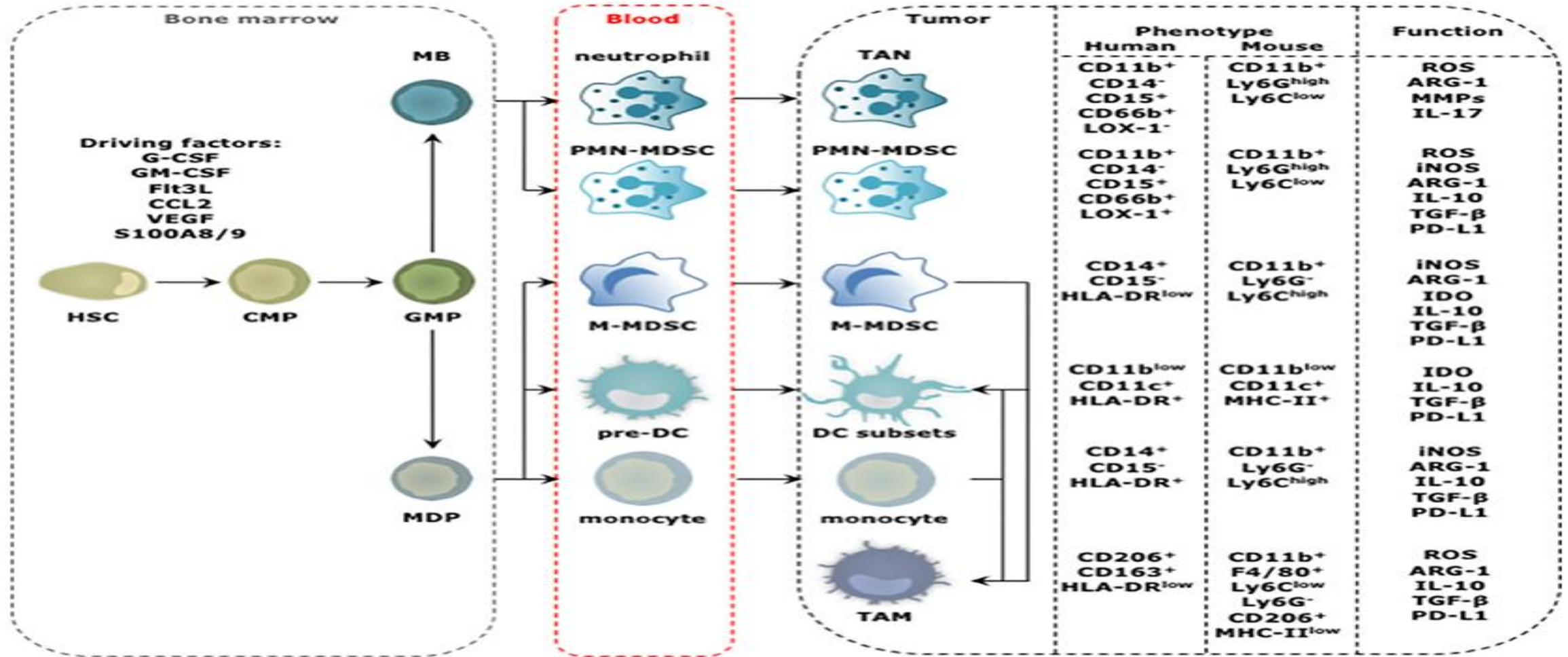# The tumor microenvironment alters myeloid cell development
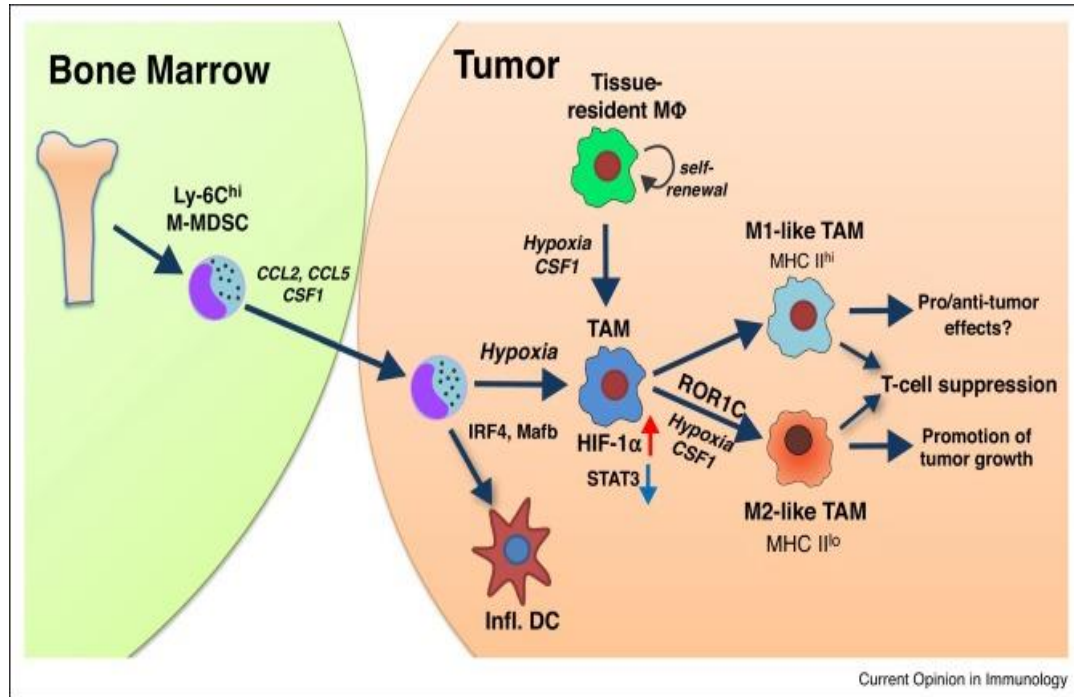
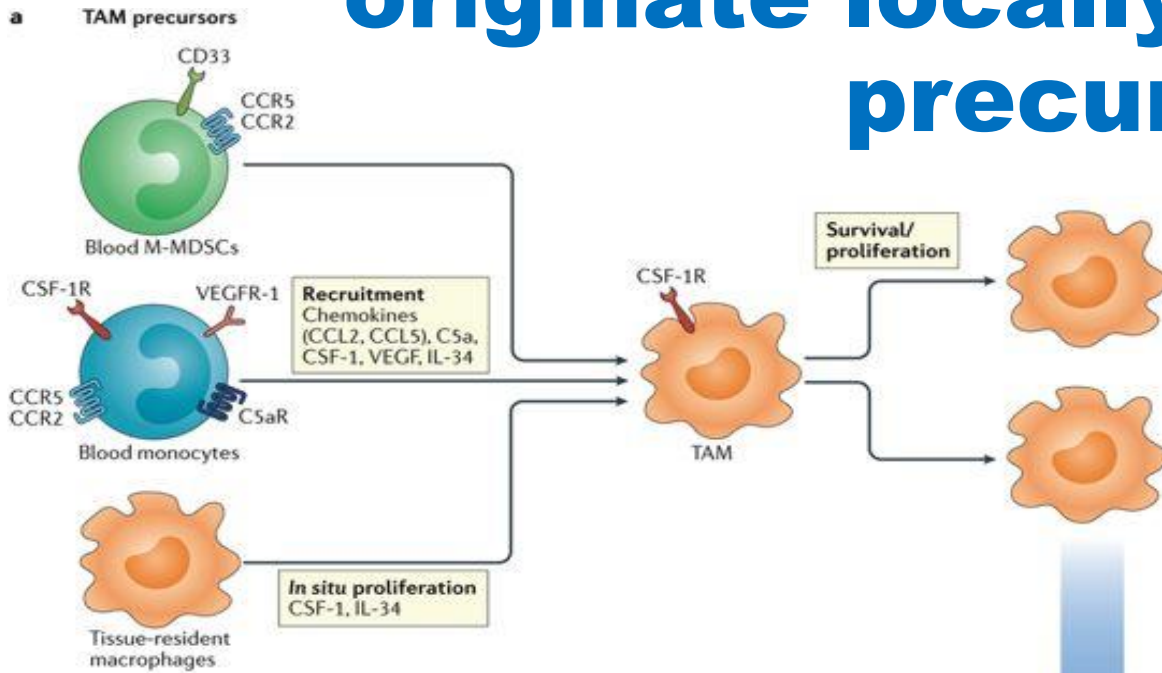Tcyganov, E., *et al., Curr Opin Immunol* 51:76-82 2018
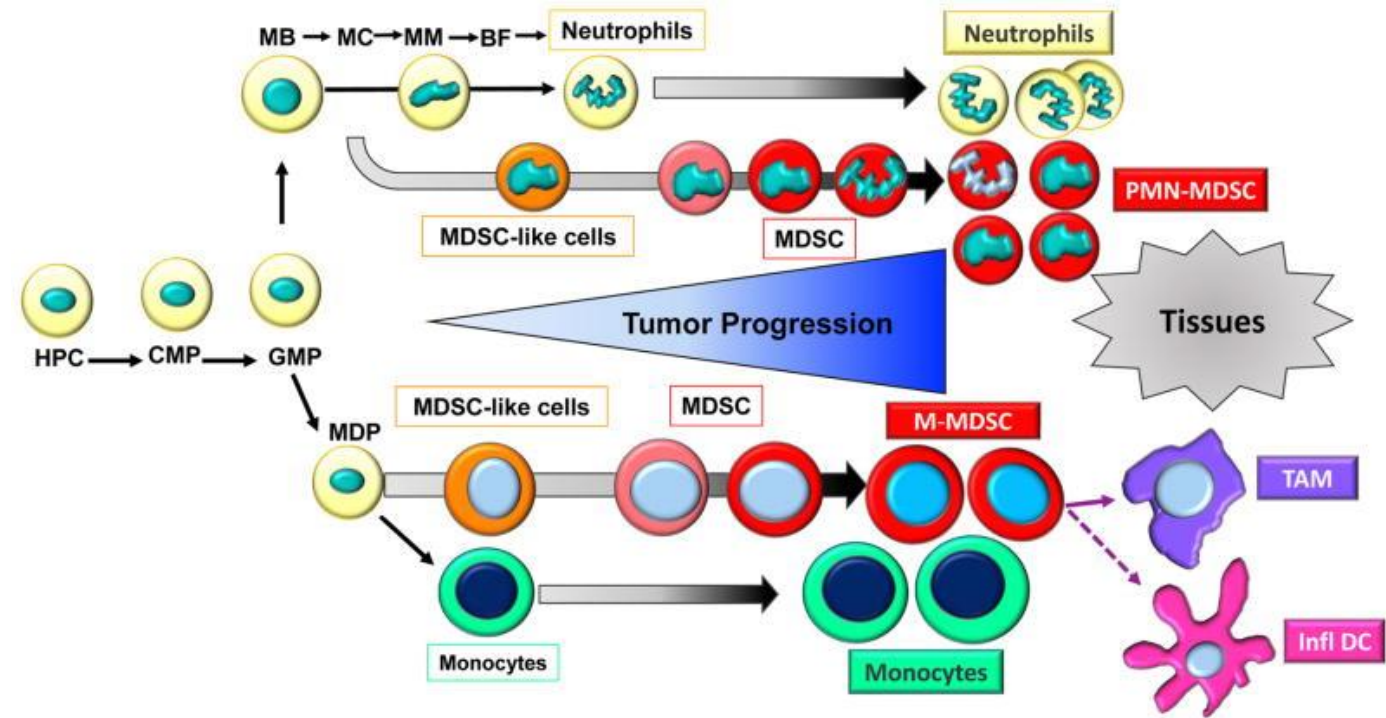
Veglia, F., *et al., Nat Immunol* 19:108-119 2018

Tumor-associated myeloid cells have diverse differentiation fates and functions

Tumor associated macrophages (TAM) originate locally or from migrating precursor cells
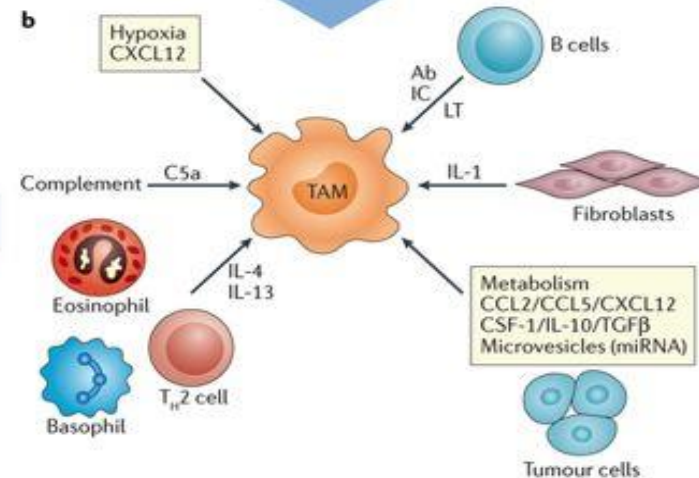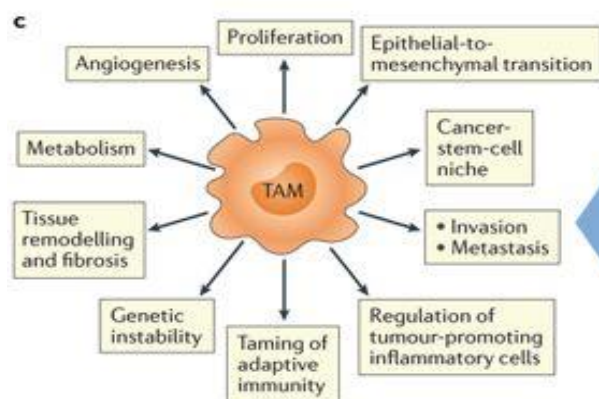

Mantovani, *et al.,*
Nat Rev Clin Onc 14: 399–416 (2017)

CD68 is a good, generic TAM marker

Macrophages/myeloid cells are often the predominant tumor-infiltrating immune cell
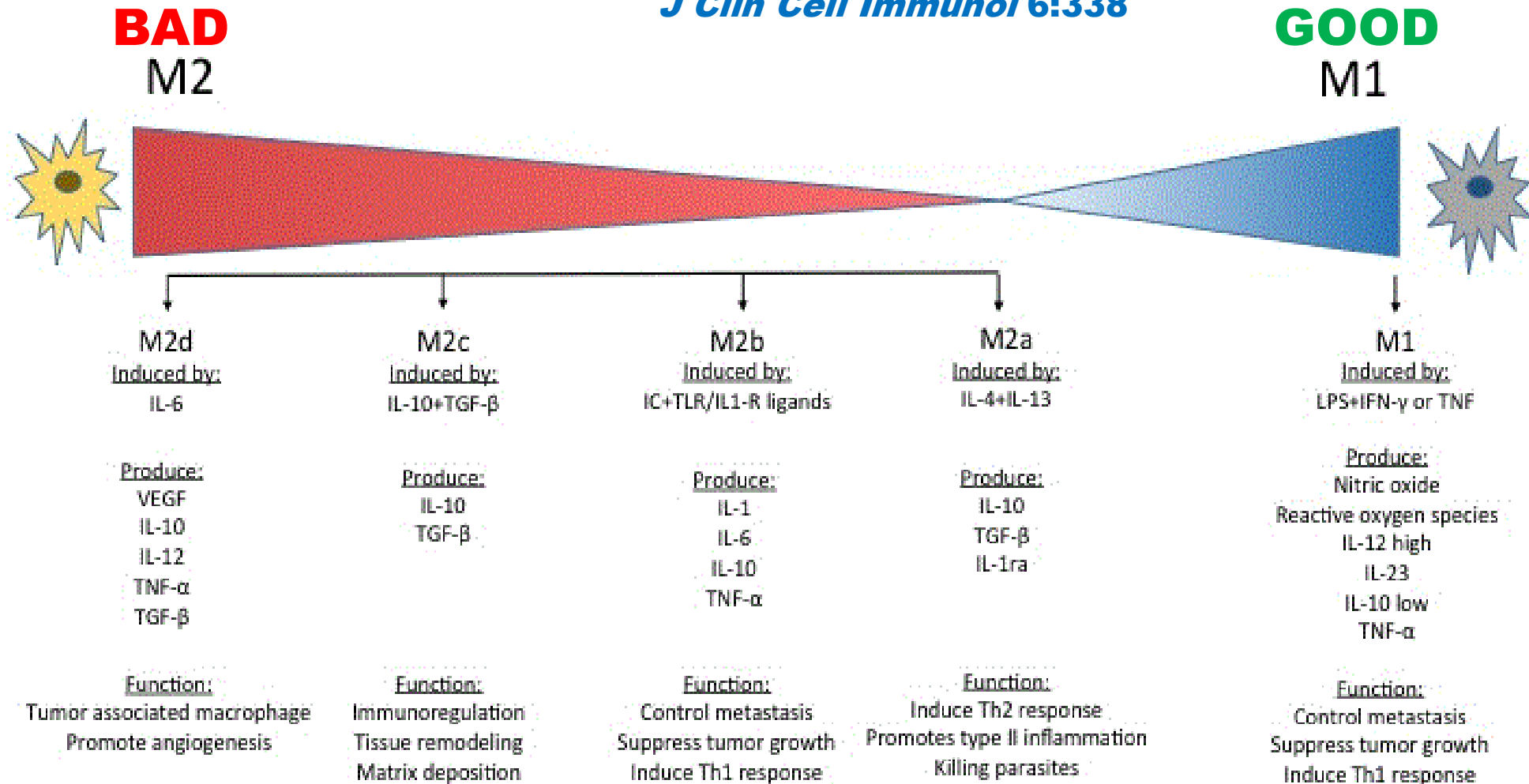
Keep that in mind in TIL work

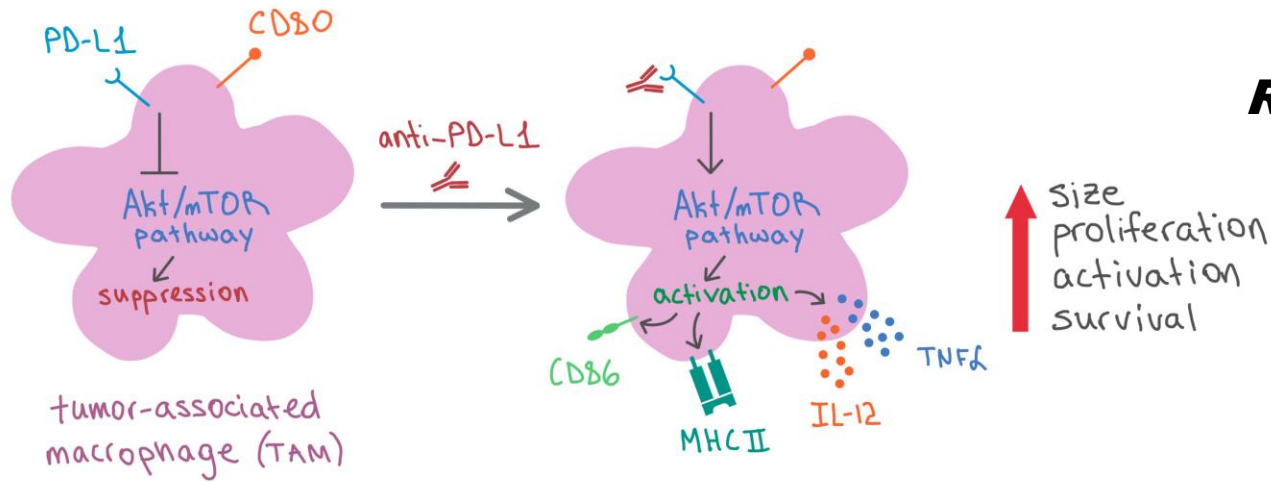Local MDSC differentiation can be a major source of TAM

Tumor associated macrophages (TAM) are plastic across a functional spectrum

Weagel E, *et al.,* (2015)
J Clin Cell Immunol 6:338

BAD M2 — **GOOD** M1

M2d	M2c	M2b	M2a	M1
Induced by: IL-6	Induced by: IL-10+TGF-β	Induced by: IC+TLR/IL1-R ligands	Induced by: IL-4+IL-13	Induced by: LPS+IFN-γ or TNF
Produce: VEGF, IL-10, IL-12, TNF-α, TGF-β	Produce: IL-10, TGF-β	Produce: IL-1, IL-6, IL-10, TNF-α	Produce: IL-10, TGF-β, IL-1ra	Produce: Nitric oxide, Reactive oxygen species, IL-12 high, IL-23, IL-10 low, TNF-α
Function: Tumor associated macrophage, Promote angiogenesis	Function: Immunoregulation, Tissue remodeling, Matrix deposition	Function: Control metastasis, Suppress tumor growth, Induce Th1 response	Function: Induce Th2 response, Promotes type II inflammation, Killing parasites	Function: Control metastasis, Suppress tumor growth, Induce Th1 response

# PD-L1 and PD-1 on TAM promote their anti-tumor activities

PD-L1: Hartley, G. P., *et al. Cancer Immunol Res* 6, 1260-1273 (2018). TAM PD-L1 promotes TAM proliferation

PD-1: Gordon, S., *et al., Nature* 495-499 (2017). TAM PD-1 inhibits TAM phagocytosis and promotes tumor growth

TAM take anti-PD-1 from T cells
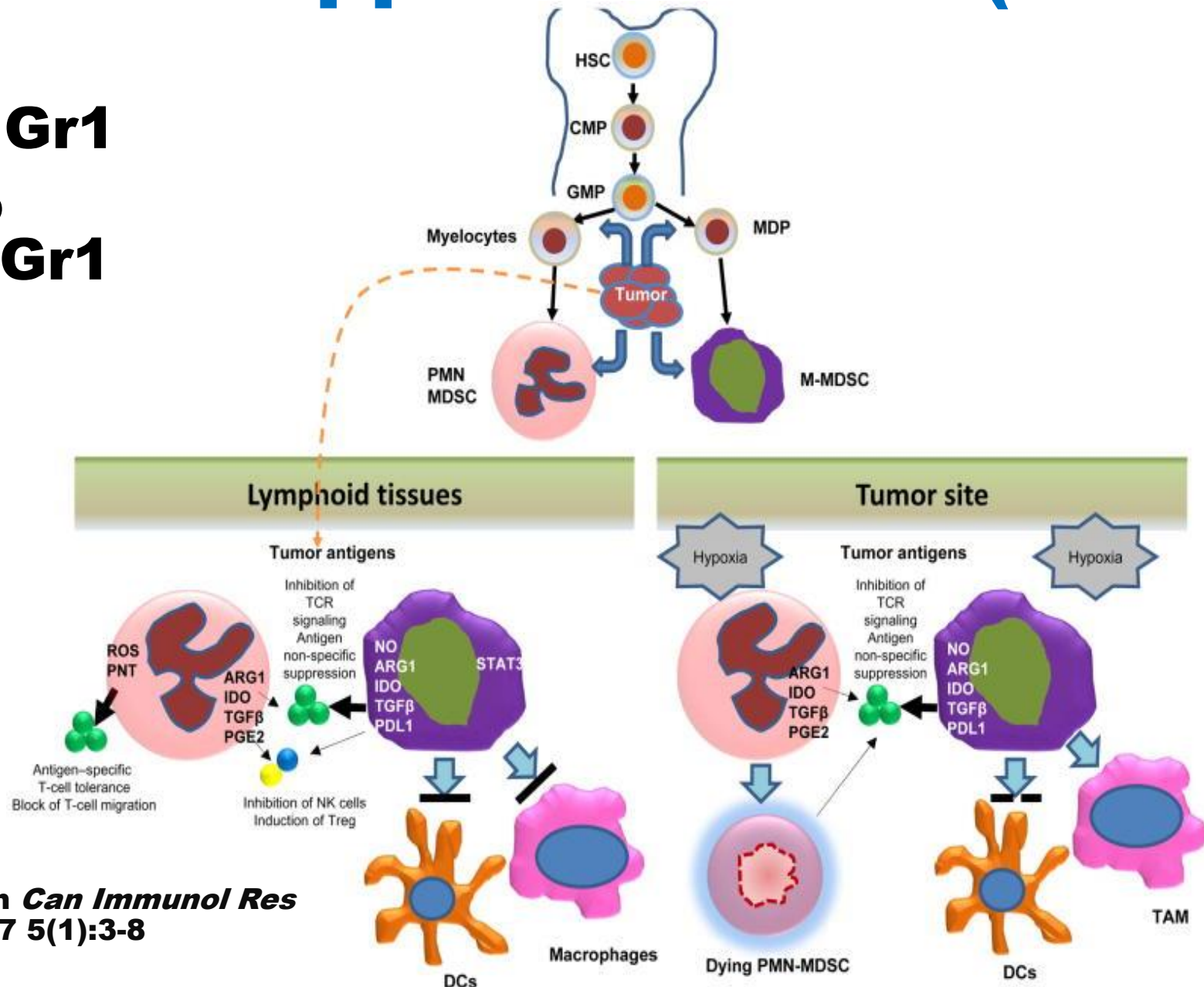Arlauckas SP, *Sci Transl Med* (2017) 9(389):eaal3604.10.1126/scitranslmed.aal3604

Paclitaxel promotes M2 to M1
Wanderley, C. W. *et al. Cancer Res* 78, 5891-5900, (2018)
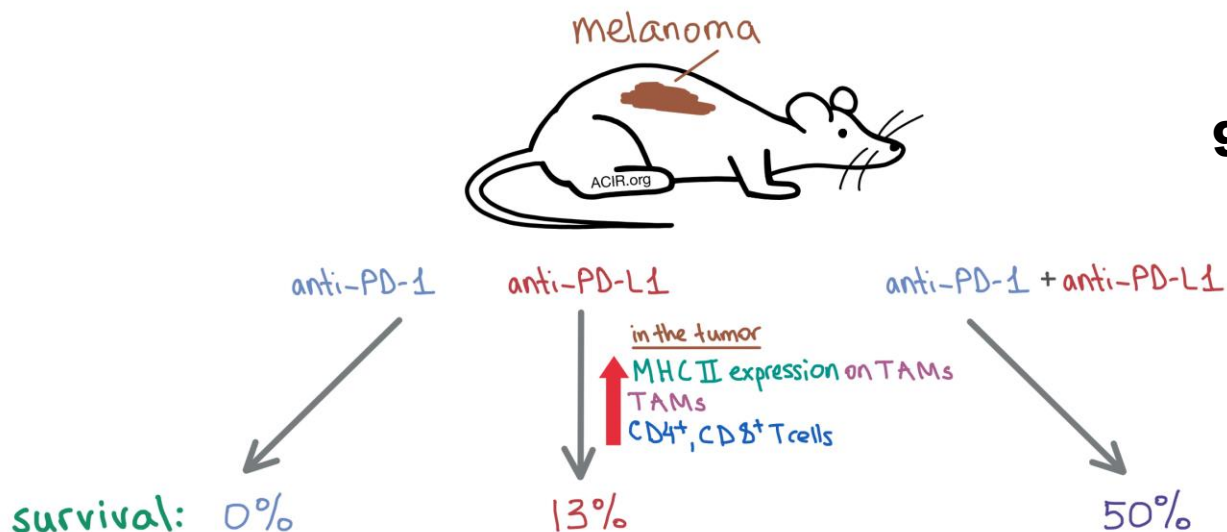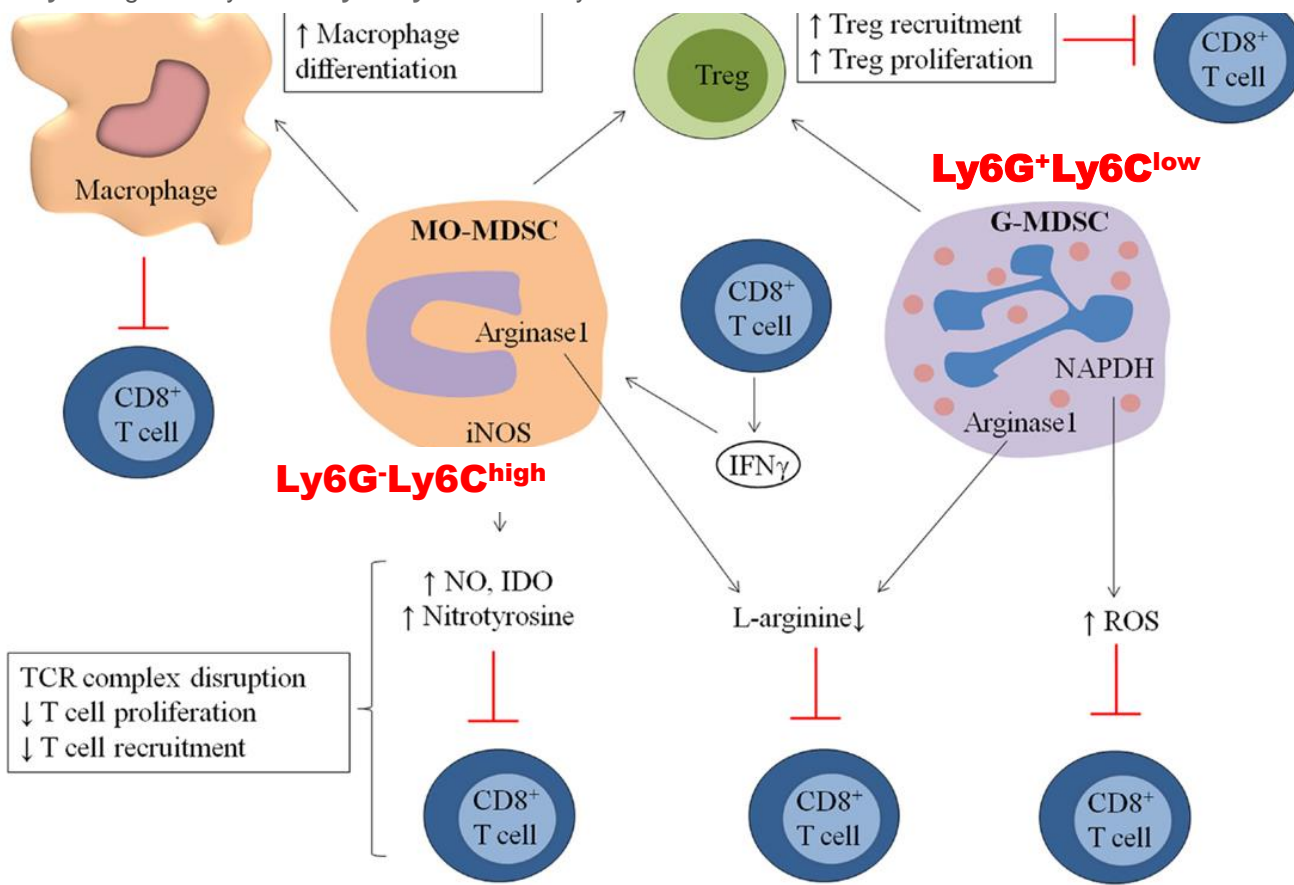
Myeloid derived suppressor cells (MDSC)

- **Express CD11b, Gr1**
- **Neutrophils also express CD11b, Gr1**

Another great review: Veglia, F., *et al., Nat Immunol* 19:108-119 2018

**D. Gabrilovich** *Can Immunol Res* 2017 5(1):3-8

Ly6G+Ly6Clow granulocytic and Ly6G-Ly6Chigh monocytic

↑ Macrophage differentiation

↑ Treg recruitment
↑ Treg proliferation

Macrophage

MO-MDSC

Ly6G⁺Ly6C^low

G-MDSC

Arginase1

NAPDH

CD8⁺ T cell

Ly6G⁻Ly6C^high

iNOS

Arginase1

IFNγ

↑ NO, IDO
↑ Nitrotyrosine

L-arginine↓

↑ ROS

TCR complex disruption
↓ T cell proliferation
↓ T cell recruitment

CD8⁺ T cell

CD8⁺ T cell

CD8⁺ T cell

B

HSC

CMP

GM-CSF, VEGF,
IL-6, IL1β

M-MDSC

G-MDSC

Survival/proliferation
S100A9
Bcl-xL
Cyclin D1
MYC
Survivin
Adiponectin
Galectin-Tim3

MDSC types: monocytic (can express PD-L1) and granulocytic (predominant in most cancers)

K. De Veirman, *et al. Front. Oncol.*, 2014
**https://doi.org/10.3389/fonc.2014.00349**
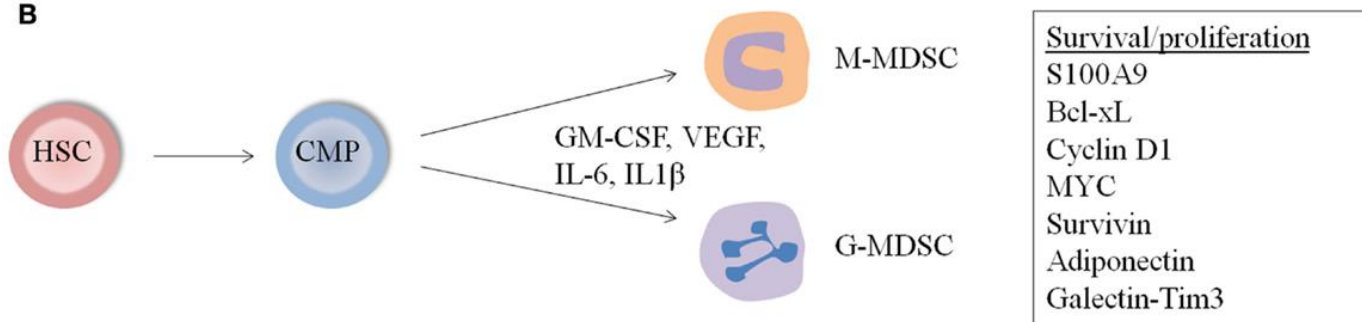
- MDSC inhibit anti-tumor immunity and impede immunotherapy in mouse cancer models

- Correlational data show MDSC affect humans as well, but direct evidence lacking thus far

- Debated if G-MDSC are really neutrophils

Tumor associated neutrophils (TAN)

- Data on the phenotype and function of TAN is limited. Human data mostly from early stage disease. Most data are from mice.

- Contribute to cancer initiation, development and progression

- Predict poor survival in many cancers

- Effects depend on intratumor location and specific markers

- Can be anti-tumor or pro-tumor

- Effects on tumor calls can be direct or indirect

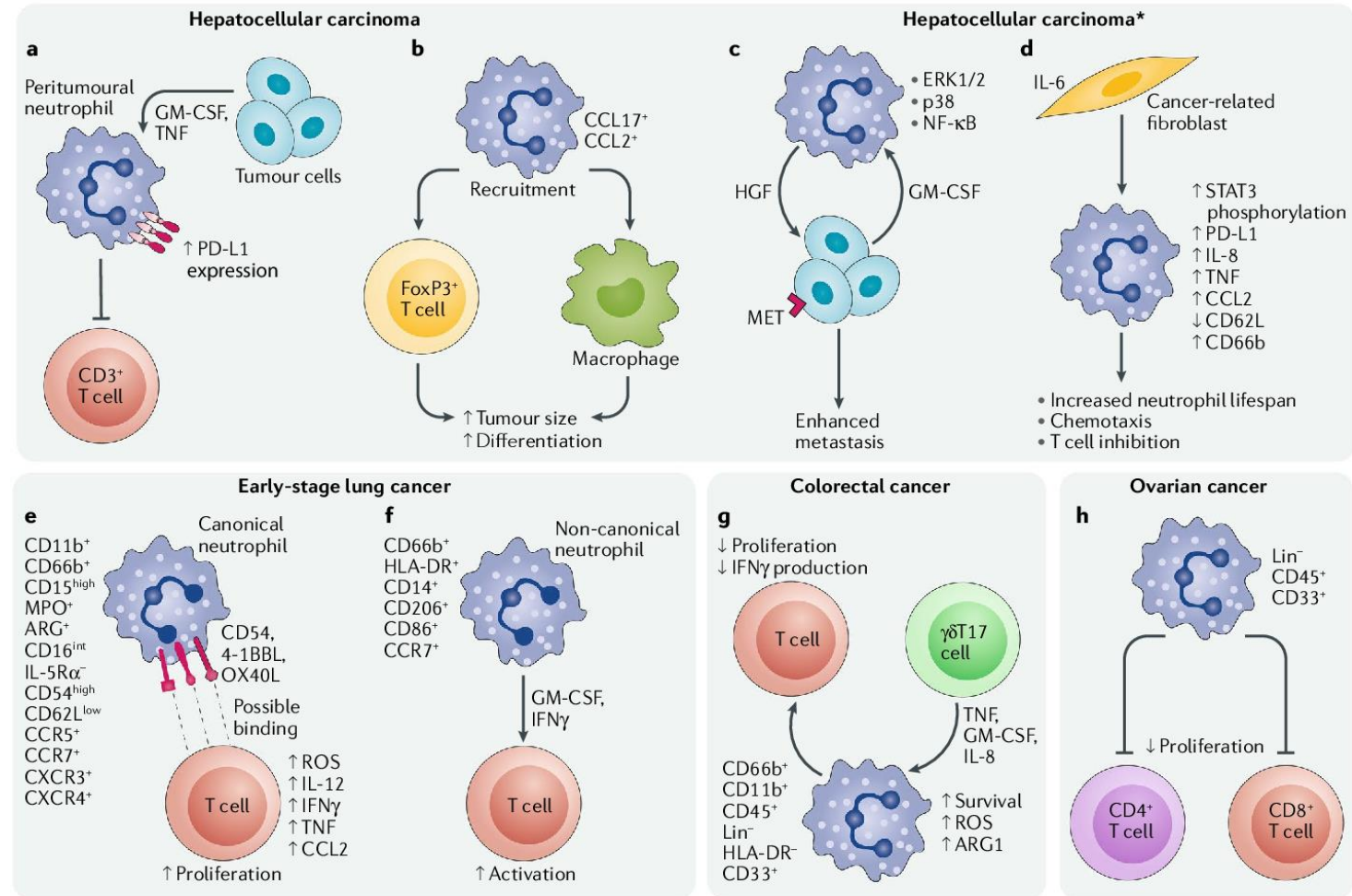- G-MDSC/PMN-MDSC are closely related to (identical with?) TAN
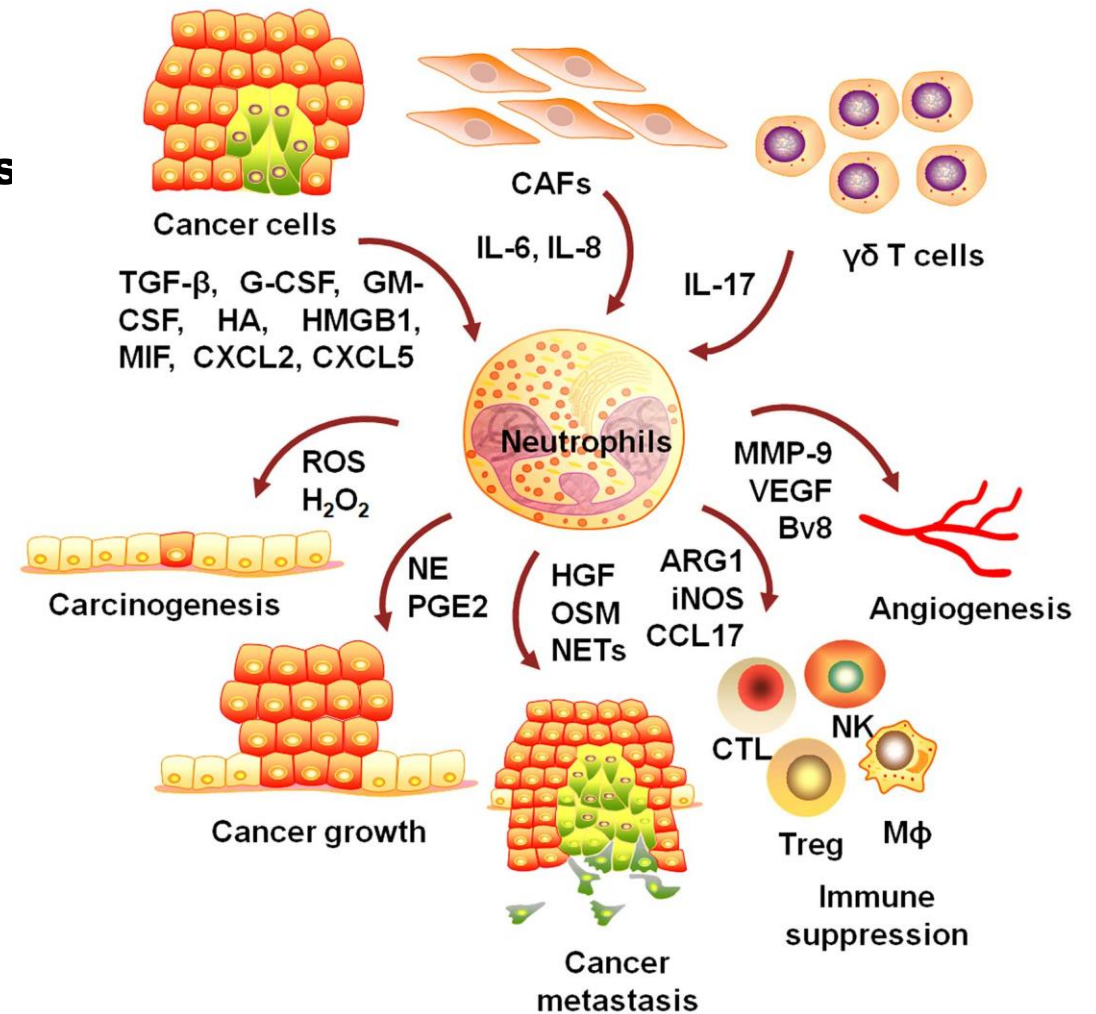
TAN classifications:
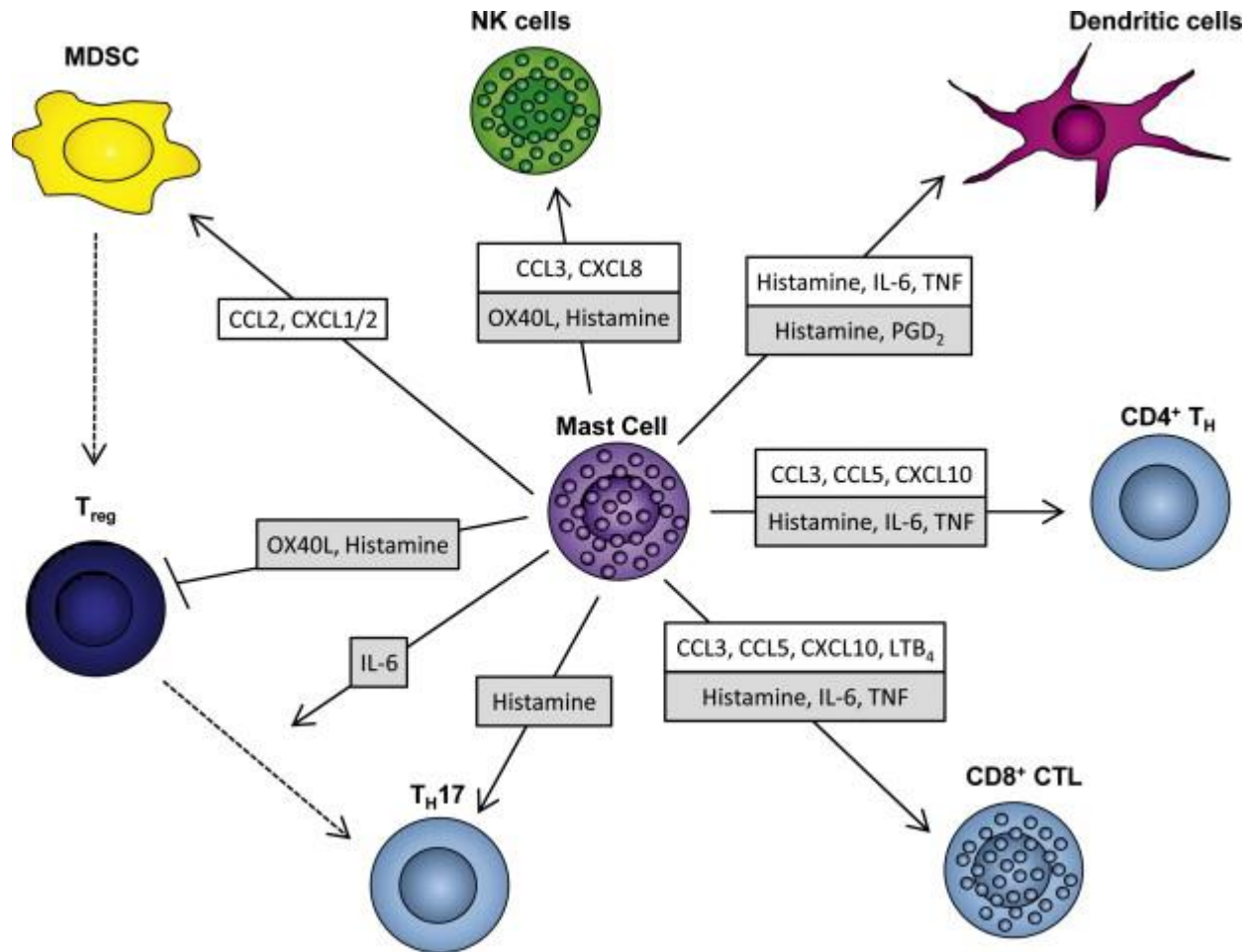## May be best to describe by tumor?
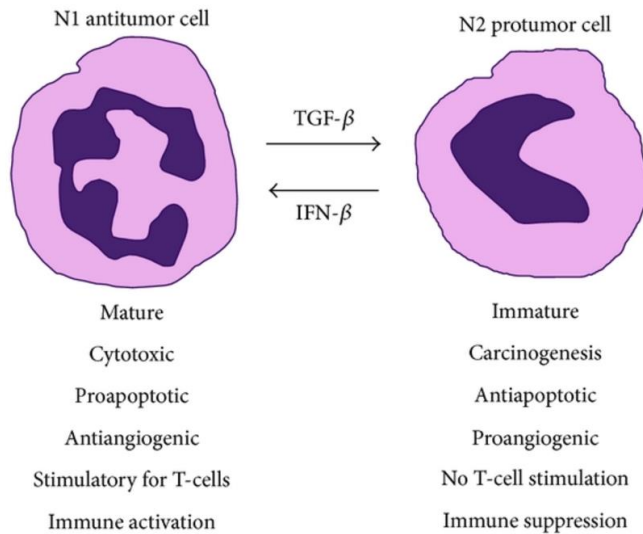
Z. Granot and J. Jablonska
Mediators Inflamm 2015; 701067

M. Shaul and Z. Fridlender
*Nat Rev Clin Oncol* 2019; 16:601

Mast cells

S. Oldford and J. Marshall. *Mol Immunol 2015*
63:2015, 113-124

Mast cells can play distinct roles in cancers

A. Komi and F. Redegeld.
*Clin Rev All & Immunol*
2019;1-13

- **c-Kit receptor tyrosine kinase inhibitors (imatinib, masitinib)**

- **tryptase inhibitors (gabexate mesylate, nafamostat mesylate)**

Wroblewski M, *et al.* (2017)
Mast cells decrease efficacy of anti-angiogenic therapy by secreting matrix-degrading granzyme B.
Nat Commun 8(1):269.
https://doi.org/10.1038/s41467-017-00327-8
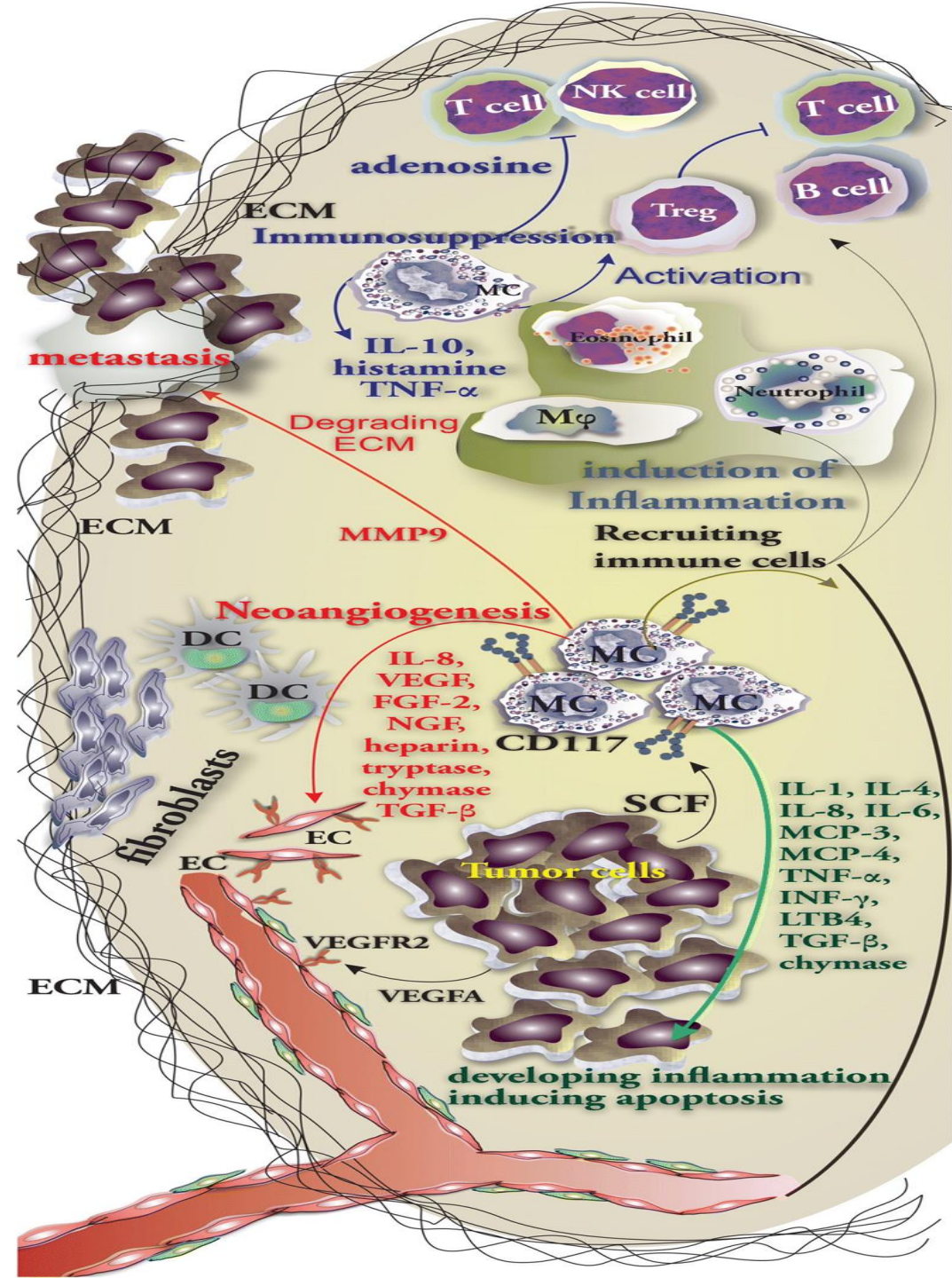
Dendritic cells: a diverse group of specialized antigen presenting cells that help instruct and orchestrate immunity

- **Immature DC** sample the environment, maintain tolerance

- **Mature DC** orchestrate immune responses
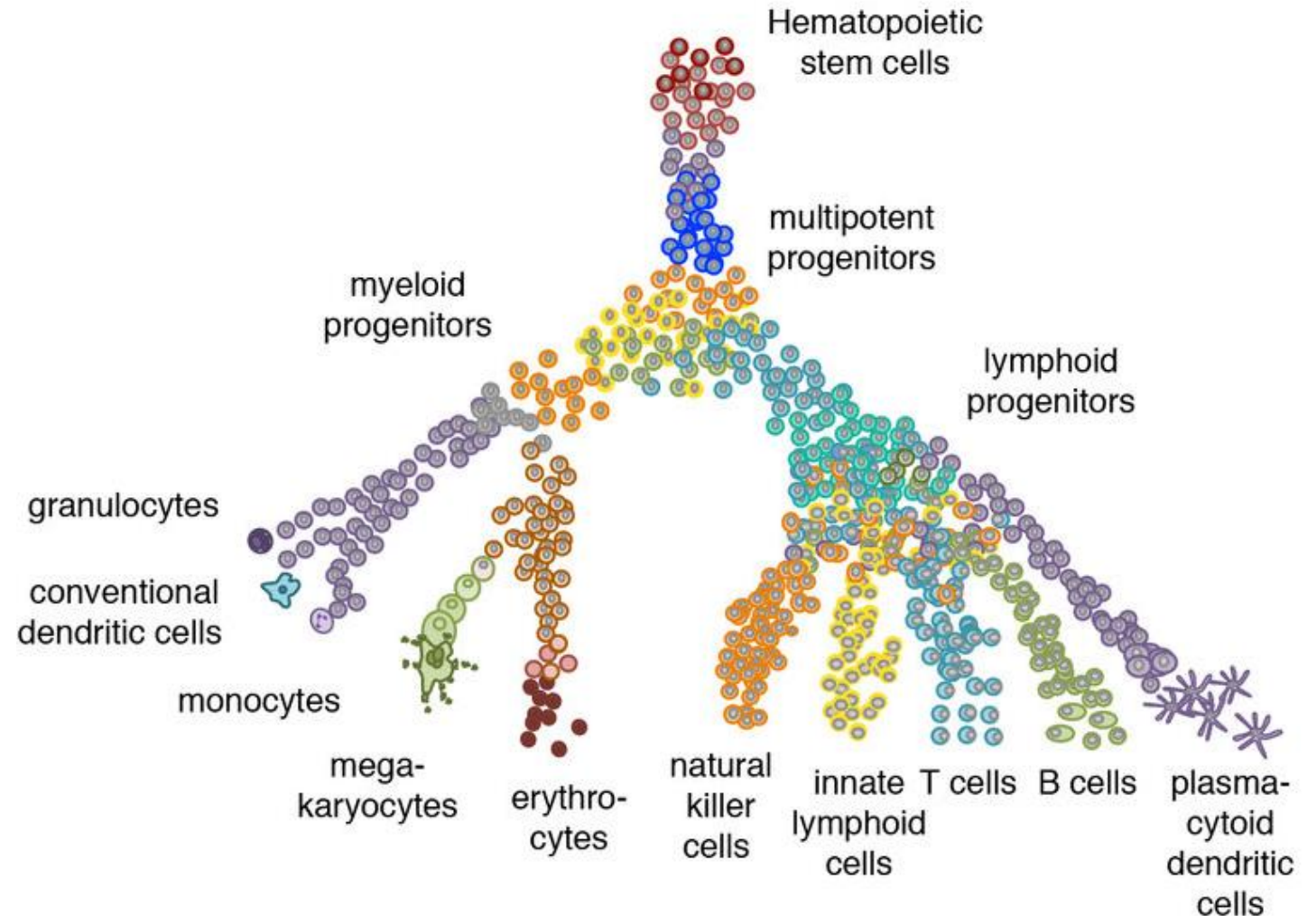
Dendritic cell maturation

Homeostatic

In cancer

High Ag capture, poor APC, few cytokines, in non-lymphoid tissues

Reduced Ag capture, excellent APC and priming, CCR7, migration to DLN
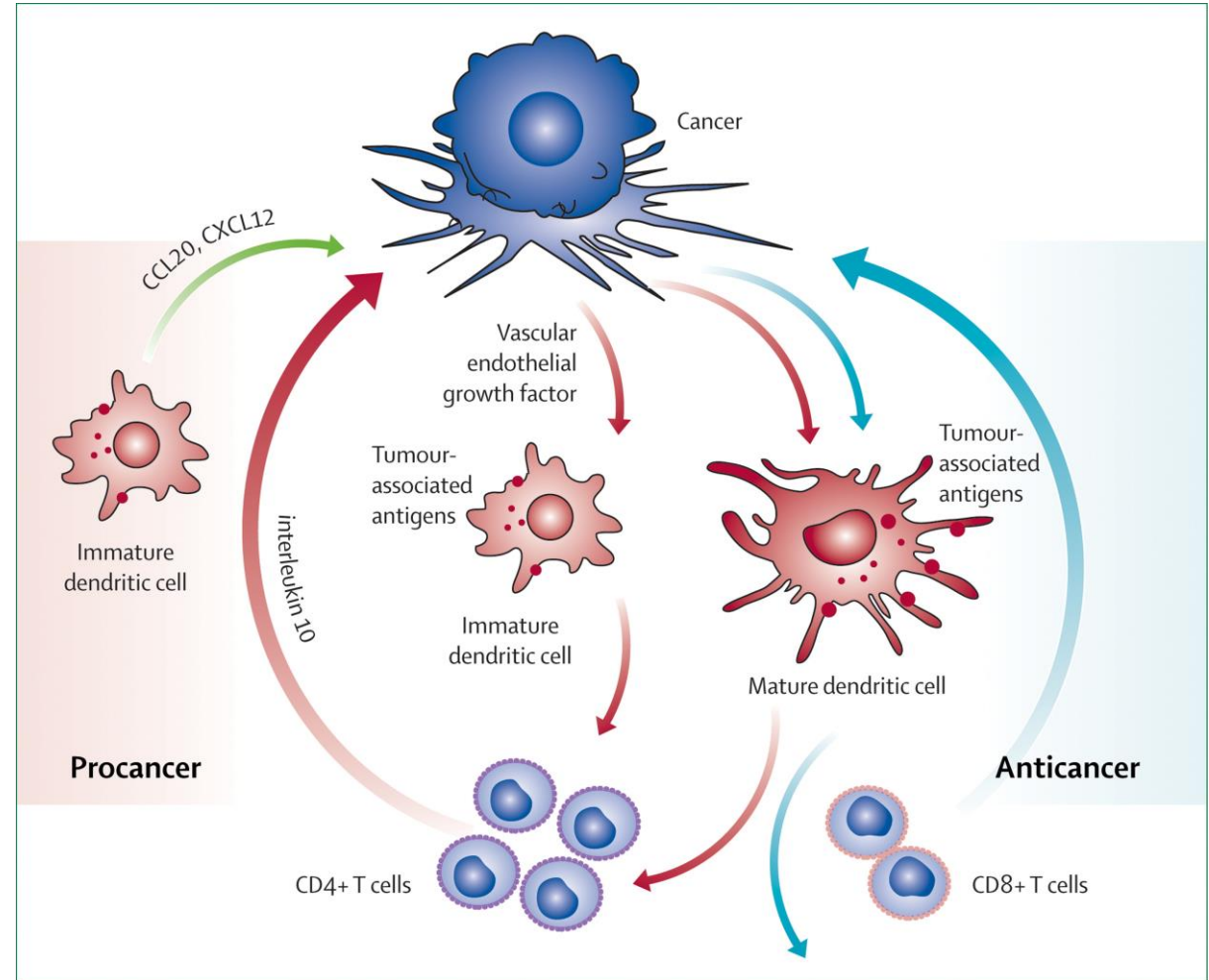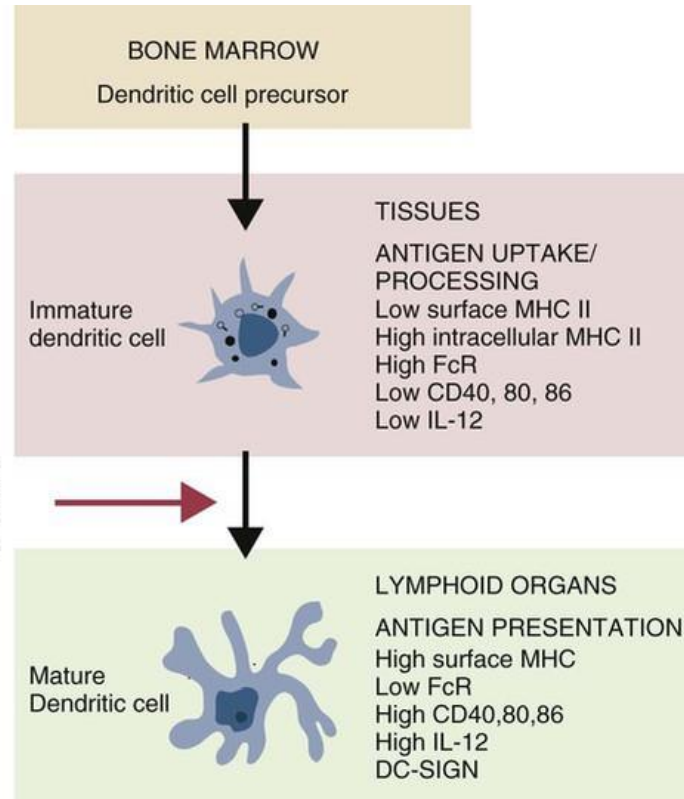
DC prime T cells and help direct their differentiation
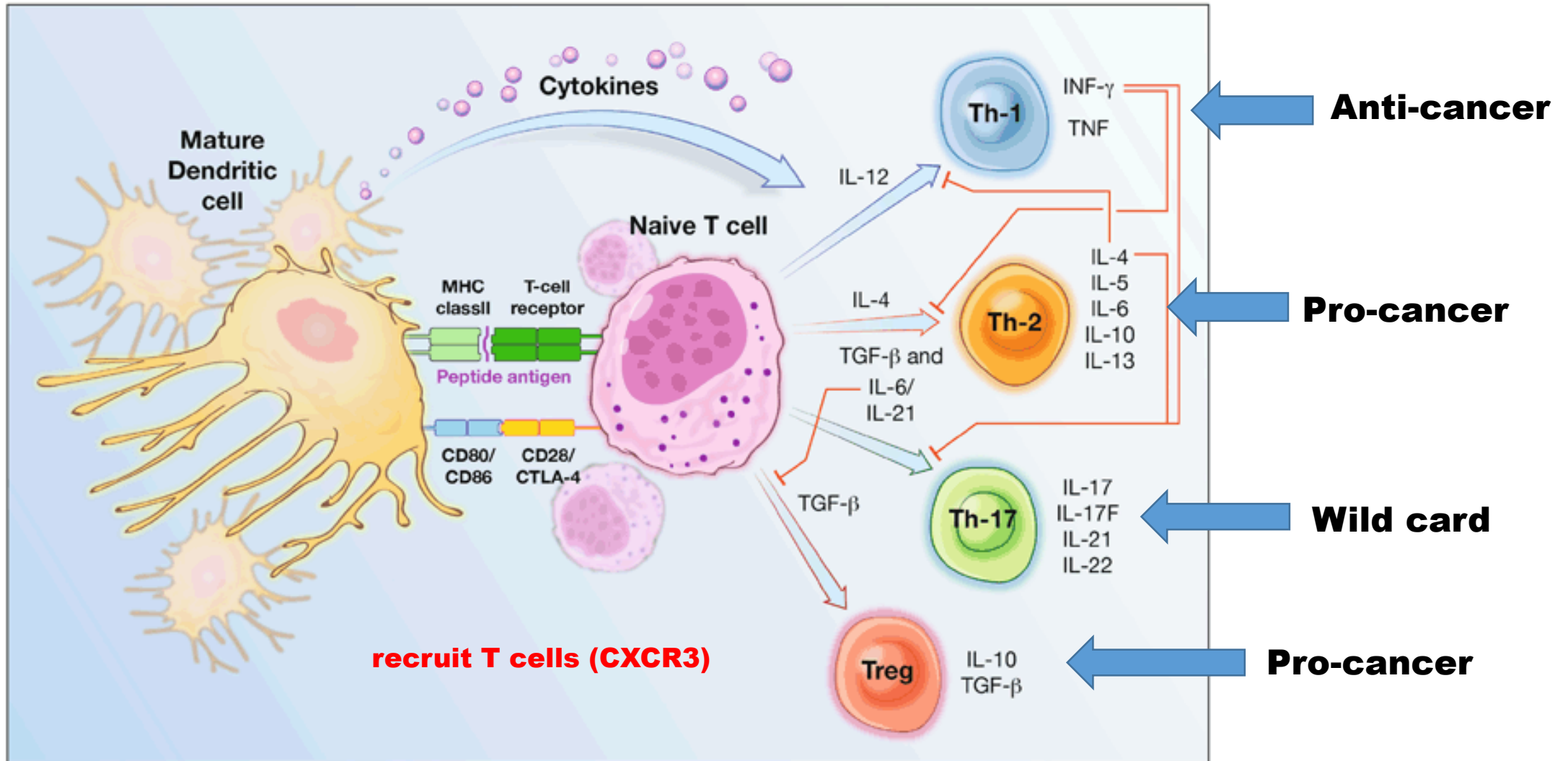
DC are excellent at antigen cross presentation and cross priming
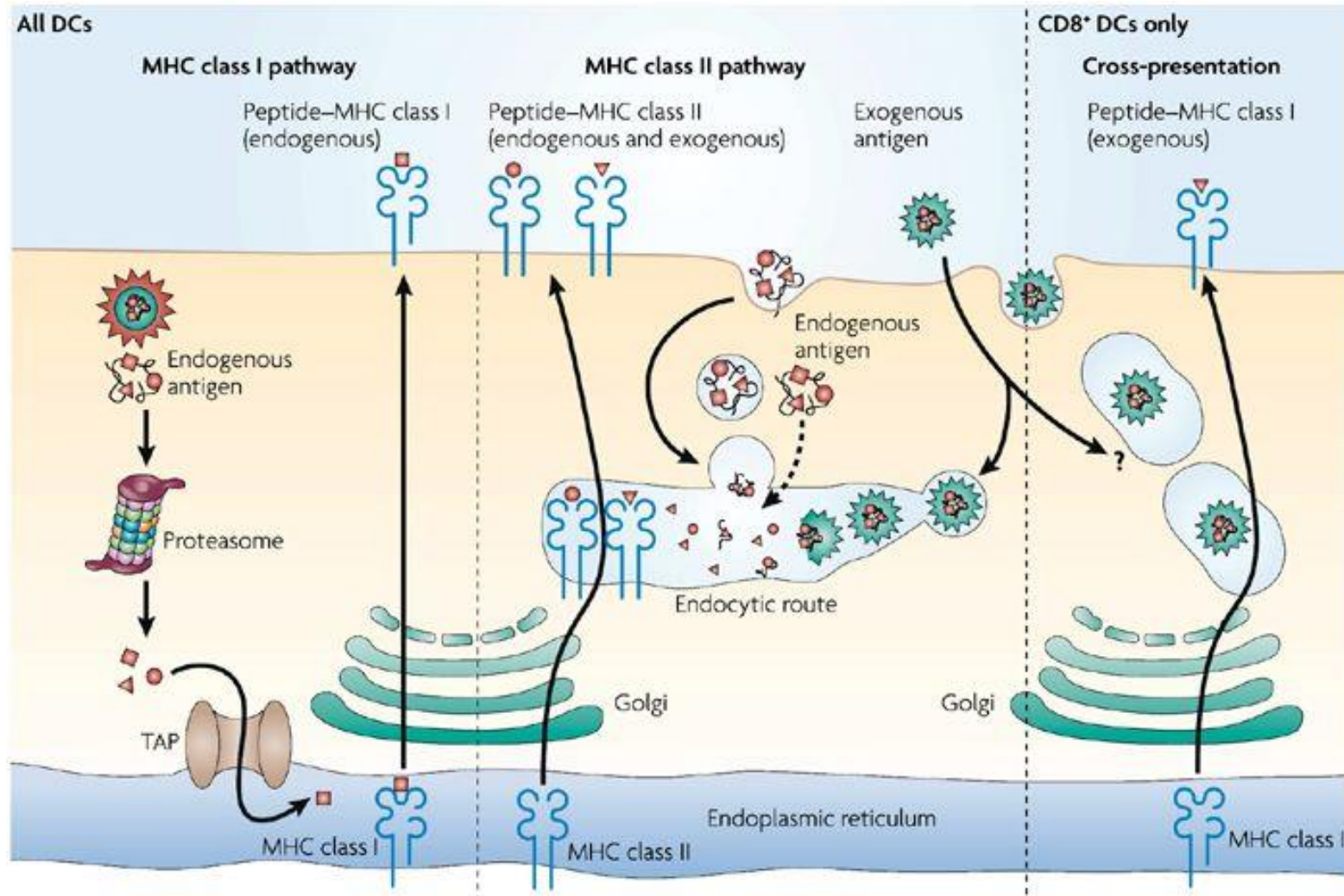
DNGR1 limits tissue damage
Del Fresno, *et al.*
Science 362, 351-356 (2018)

Gubin, *et al. Nature* 515, 577-581 (2014)
Salmon, *et al. Immunity* 44, 924-938 (2016)

Nature Reviews | Immunology

Conventional DC:
It helps to be bilingual

Mouse

- **Divided into CD11b$^+$ and CD11b$^-$**
  - **CD11b$^-$**
    - **CD8a$^+$CD11b$^-$ (lymphoid tissue)**
      - **CD11c$^+$Clec9a/DNGR-1$^+$XCR1$^+$**
    - **non-lymphoid tissue (including cancer) CD103$^+$CD11b$^-$**
      - **CD11c$^+$Clec9a/DNGR-1$^+$XCR1$^+$CD103$^+$**
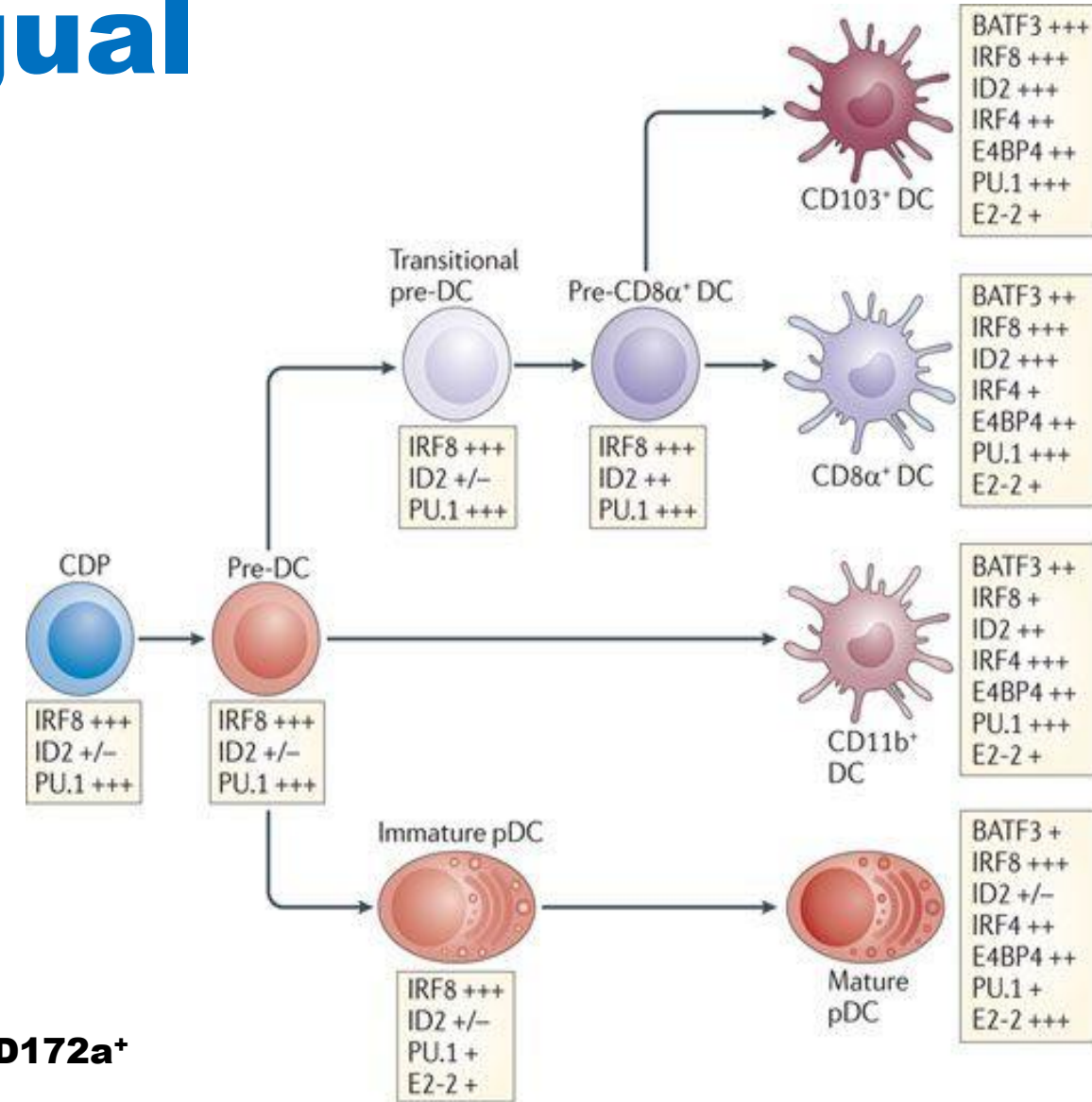   - **These are Batf3$^+$ DC and are the best at cross presenting**
- **CD11b$^+$**
  - **IRF4-dependent**
  - **CD11c$^+$CD172a$^+$**
  - **Present ag on MHC class II to CD4+ T cells**

Human

- **Divided into CD11c$^+$ and CD11c$^-$**
  - **BDCA3$^+$ similar to mouse CD103$^+$ (CD11b$^-$)**
  - **BDCA1$^+$ similar to mouse CD11b$^+$**
- **CD141/BDCA3$^+$ equivalent to Batf3$^+$ (CD11c$^+$)**
  Clec9a/DNGR1$^+$XCR1$^+$
- **Irf4-dependent DCs are CD11c$^+$CD11b$^+$CD1c/BDCA1$^+$CD172a$^+$**
- **Other rare subsets await better definitions**

CDP — IRF8 +++, ID2 +/-, PU.1 +++

Pre-DC — IRF8 +++, ID2 +/-, PU.1 +++

Transitional pre-DC — IRF8 +++, ID2 +/-, PU.1 +++

Pre-CD8α$^+$ DC — IRF8 +++, ID2 ++, PU.1 +++

CD103$^+$ DC — BATF3 +++, IRF8 +++, ID2 +++, IRF4 ++, E4BP4 ++, PU.1 +++, E2-2 +

CD8α$^+$ DC — BATF3 ++, IRF8 +++, ID2 +++, IRF4 +, E4BP4 ++, PU.1 +++, E2-2 +

CD11b$^+$ DC — BATF3 ++, IRF8 ++, ID2 ++, IRF4 +++, E4BP4 ++, PU.1 +++, E2-2 +

Immature pDC — IRF8 +++, ID2 +/-, PU.1 +, E2-2 +

Mature pDC — BATF3 +, IRF8 +++, ID2 +/-, IRF4 ++, E4BP4 ++, PU.1 +, E2-2 +++

Dendritic cell dysfunction in the TME

Veglia and Gabrilovich
Curr Opin Immunol 2017;45:43-51

Hypoxia, adenosine, lactate, low pH, accumulation of lipids impair DCs.
IL-10 can inhibit IL-12$^+$ CD103$^+$CD11b$^-$ DCs.
IL-12 and anti-tumor responses restored with IL-10R. Anti-IL-10R and CpG restore tumor DC function.

PDC are immature and make little type I IFN but can induce Treg through IDO.

B. Wylie, *et al. Cancers* 2019, *11*(4),521
https://doi.org/10.3390/cancers11040521
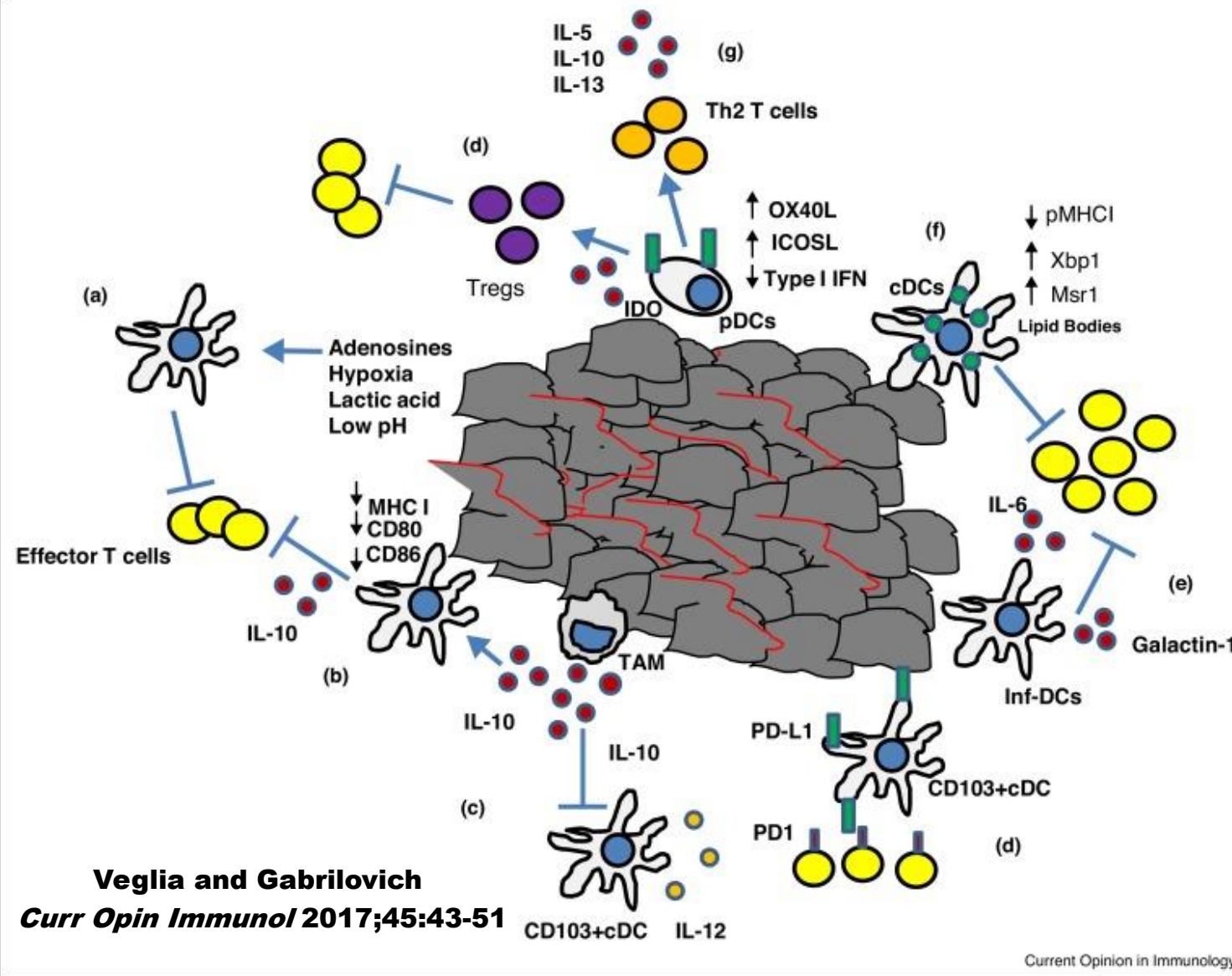
Punch Line: Much DC dysfunction appears to be from dysfunctional maturation

Monocyte-derived inflammatory DC (inf-DC)

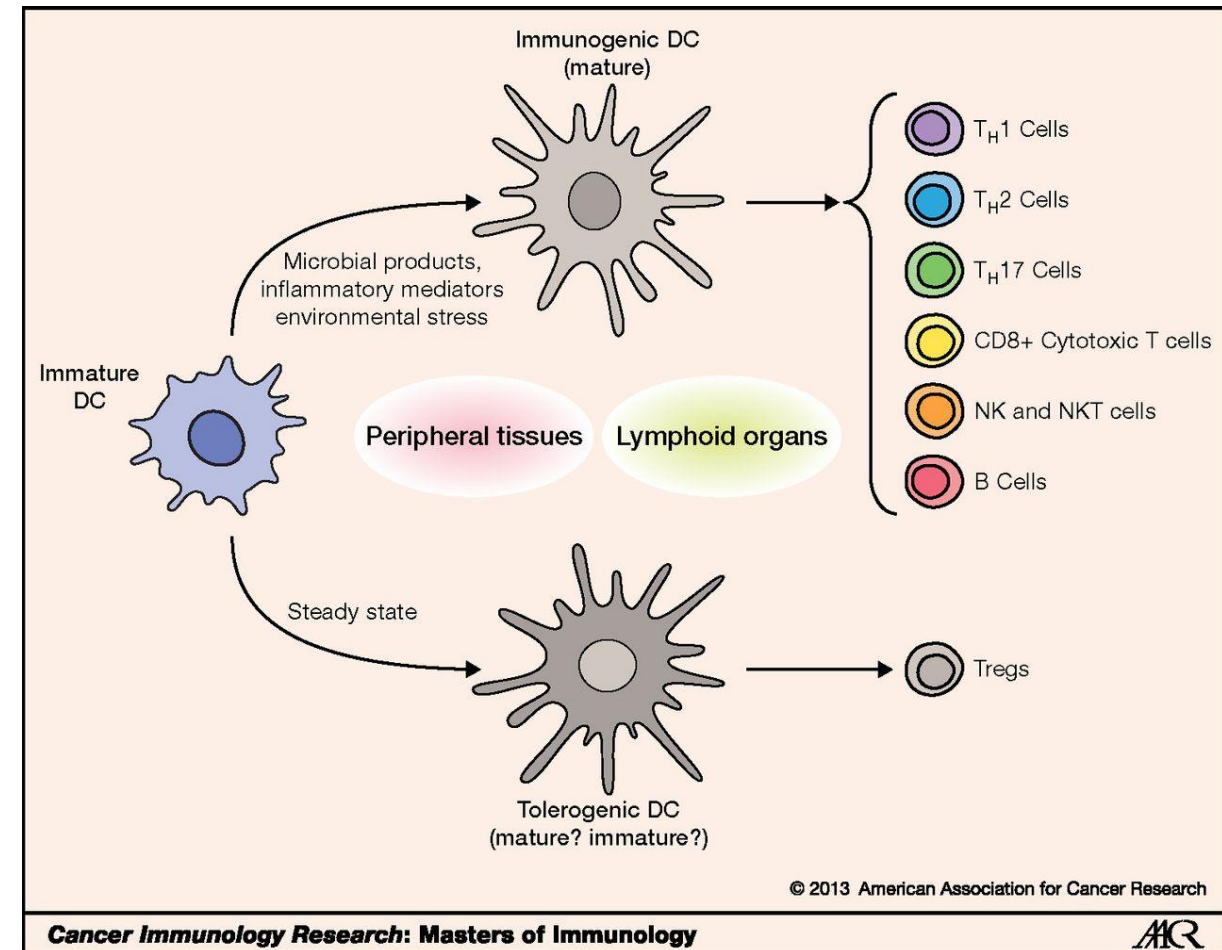- **Induced by inflammation from monocytes**
  - **Mouse**
    - From Ly6C^{hi} monocytes
    - MHC II$^+$ CD11b$^+$ CD11c$^+$ F4/80$^+$ Ly6c$^+$, and CD206$^+$, GM-CSFR$^+$ (CD115), CD107b$^+$ (Macb), FcεRI$^+$, CD64$^+$
    - Activate CD4$^+$ T cells
    - FcεR1 distinguishes inf-DC from cDC and macrophages

  - **Human**
    - Similar to mice
    - HLA-DR, CD11c, BDCA1, CD1a, FceRI, CD206, CD172a, CD14 and CD11b. Express M-CSFR and ZBTB46 like mouse inf-DC
    - Seen in human cancers. Can induce Th17 in ovarian cancer

Immunogenic DC (mature)

Immature DC

Microbial products, inflammatory mediators environmental stress

Peripheral tissues   Lymphoid organs

Steady state

Tolerogenic DC (mature? immature?)

T$_H$1 Cells
T$_H$2 Cells
T$_H$17 Cells
CD8+ Cytotoxic T cells
NK and NKT cells
B Cells

Tregs

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Cancer Immunology Research: Masters of Immunology

Strategies to mitigate myeloid cell effects in the TME

- Anti-CCL2
- Anti-VEGF or anti-VEFG plus altiratinib (MET/TIE2/VEGFR2 inhibitor) to mitigate increased compensatory pathways
- Anti-IL-8
- GM-CSF plus something to reduce compensatory mechanisms (IFNg, IFNb)
- STING agonists (plus anti-PD-L1 or anti-CCL2)
- CSF-1R inhibitors
- COX2/PGE2 inhibitors
- EGFR inhibitor (plus anti-CCL2)
- RTK inhibitors (sunitinib, sorafenib)
- Gemtuzumab ozogamicin depletes MDSC

Figure: Awad, *et al., Front. Immunol.*, 2018
https://doi.org/10.3389/fimmu.2018.01977
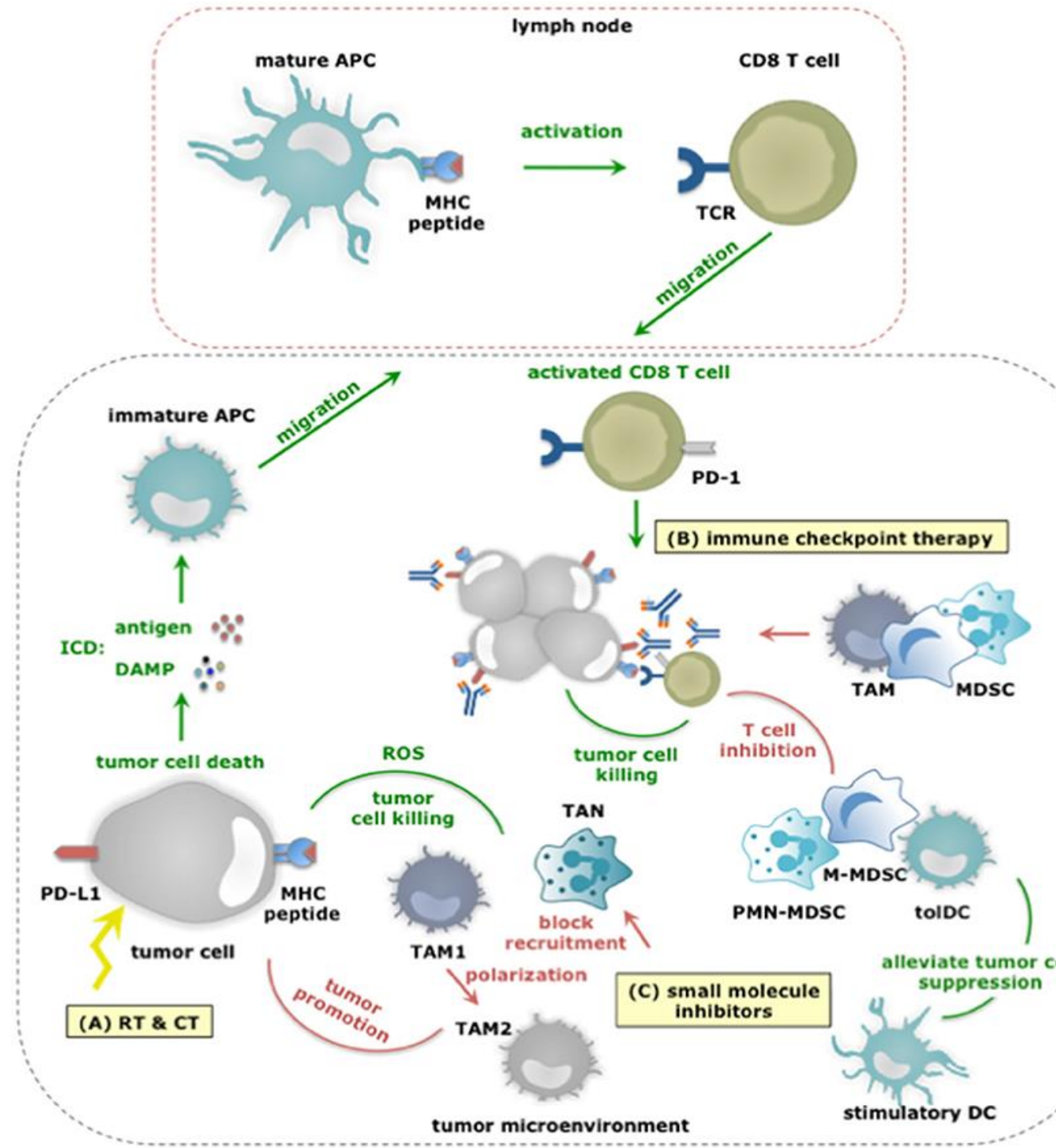
Myeloid cell review bullets

- Abundant in stroma of many tumor types
- Comprise various subsets with distinct functions
- Can mediate pro-cancer/pro-metastases
- Can inhibit anti-tumor immunity or promote it
- Tumors reprogram myeloid cells to promote cancer
- Myeloid cells have major influences on all cancer treatments (surgery, chemotherapy, radiotherapy, immunotherapy and targeted small molecules)
- Altering myeloid cell functions/numbers/co-localiations could augment treatment efficacy