Primer on Dendritic Cells in Cancer

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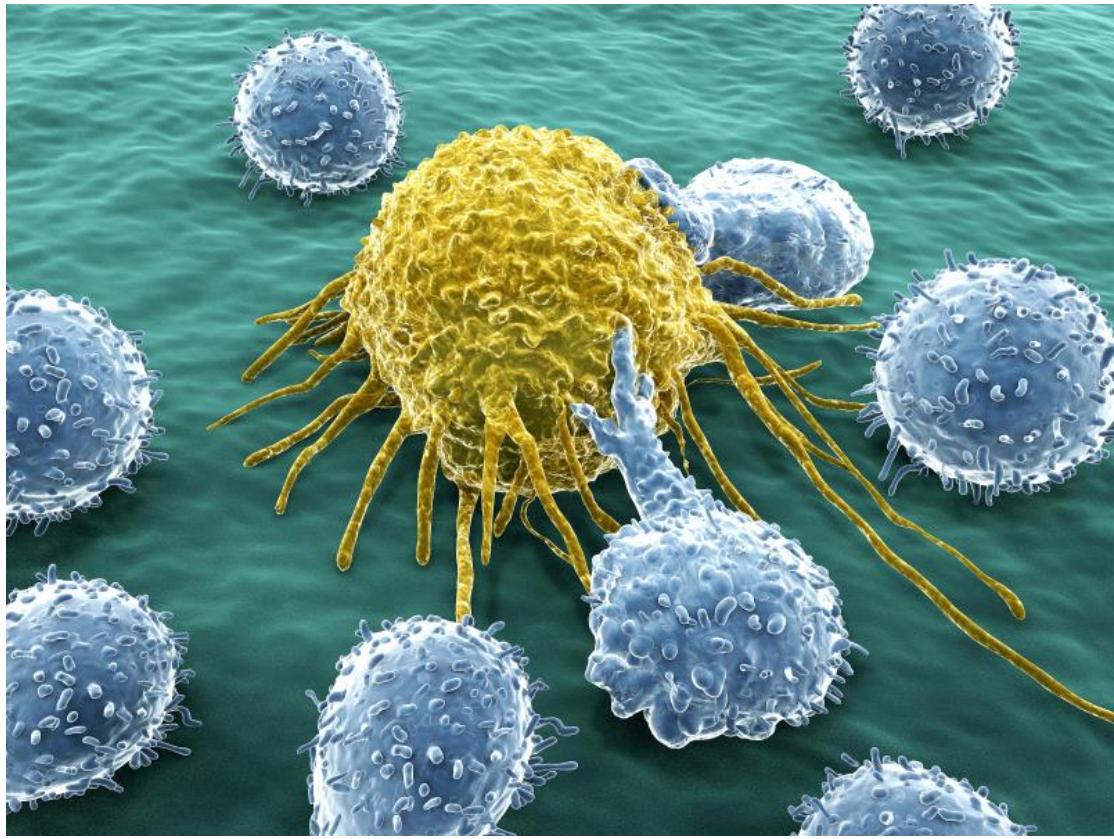
Disclosures

Consultant for Xencor, Agenus, Dr. Reddy, Cogen

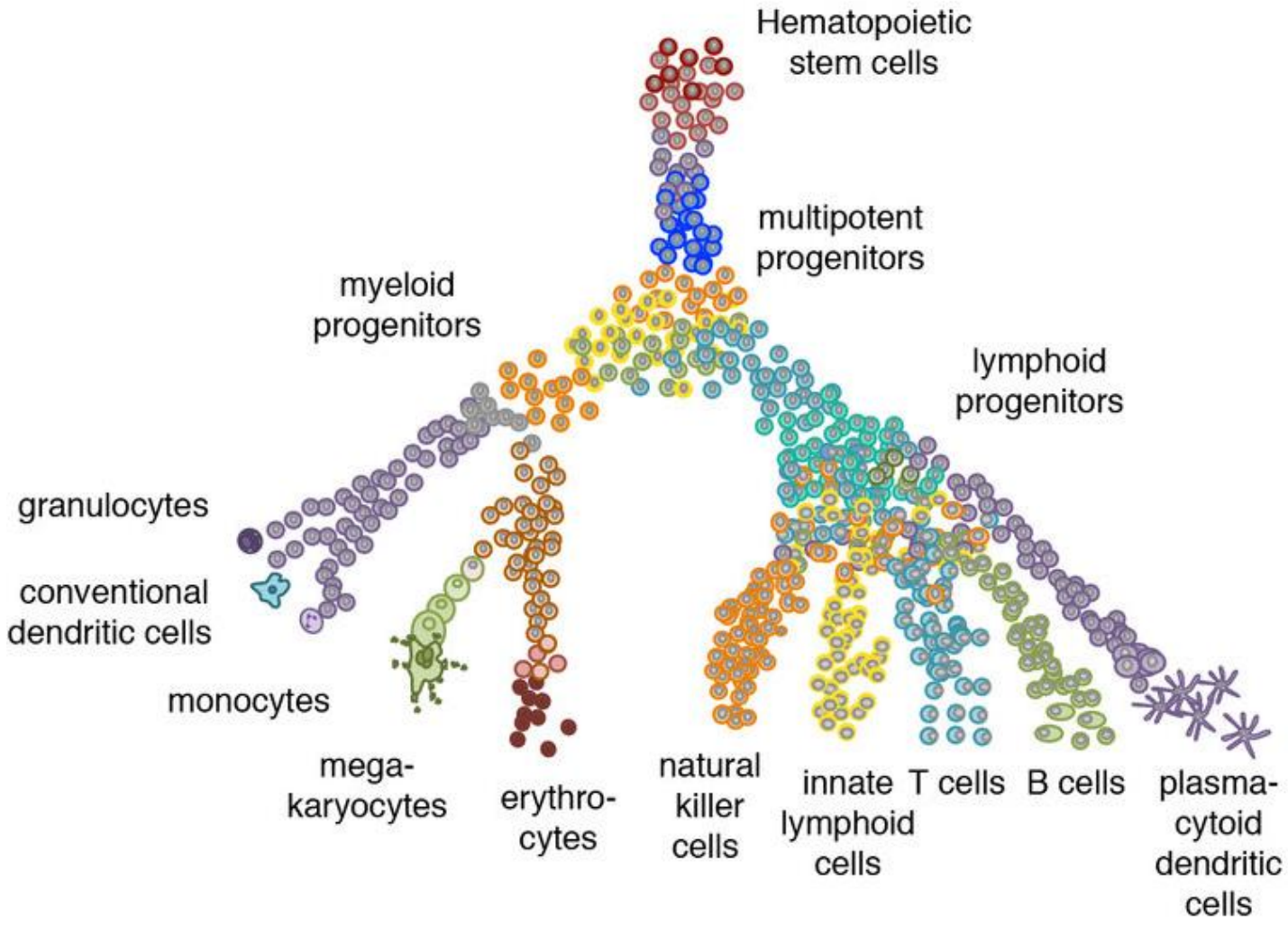
Overview

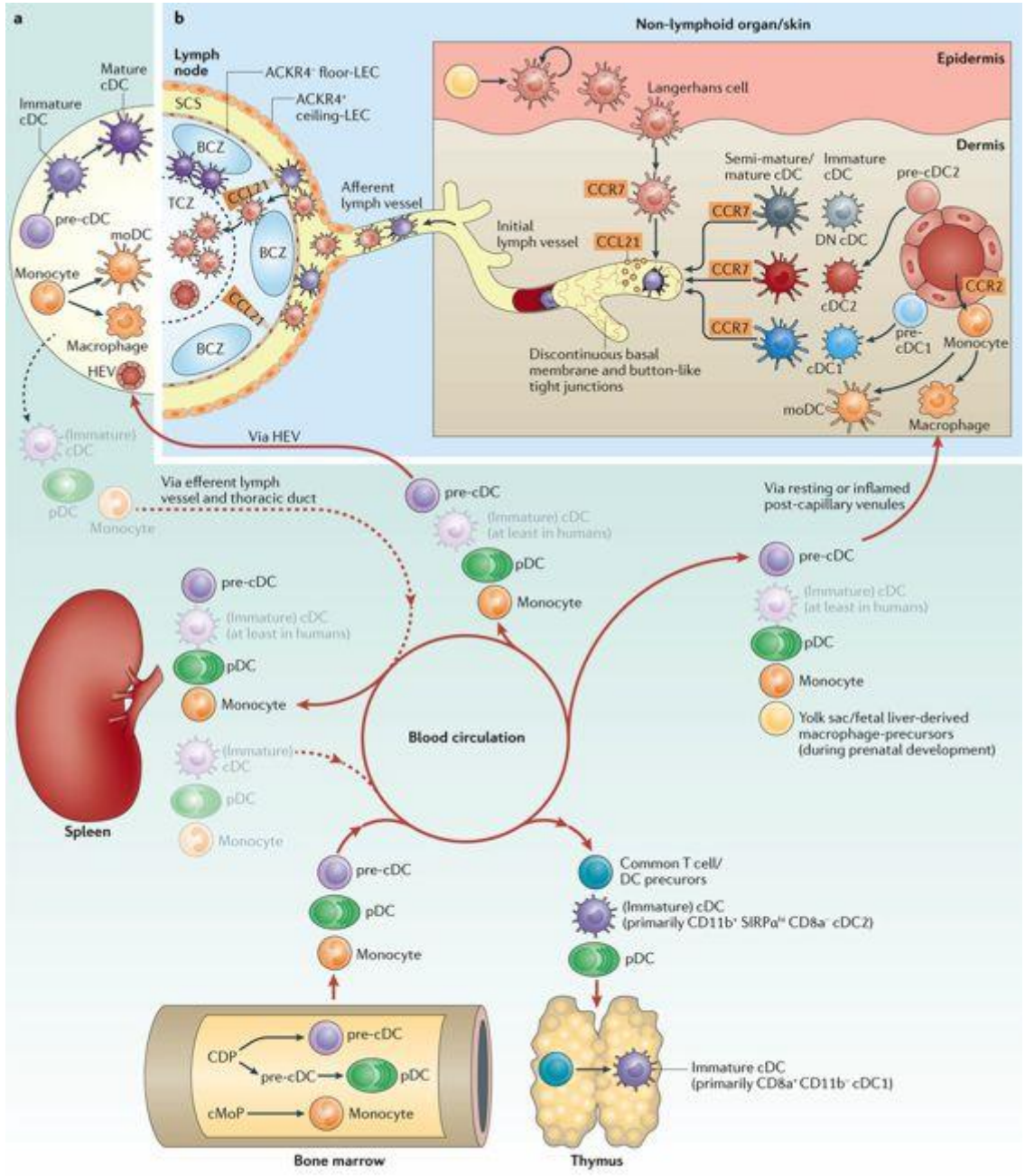
- Normal DC subsets and differentiation
- DC subsets in cancer
- Tumor microenvironment factors
- Tumor DC defects
- Will not cover DC immunotherapy



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



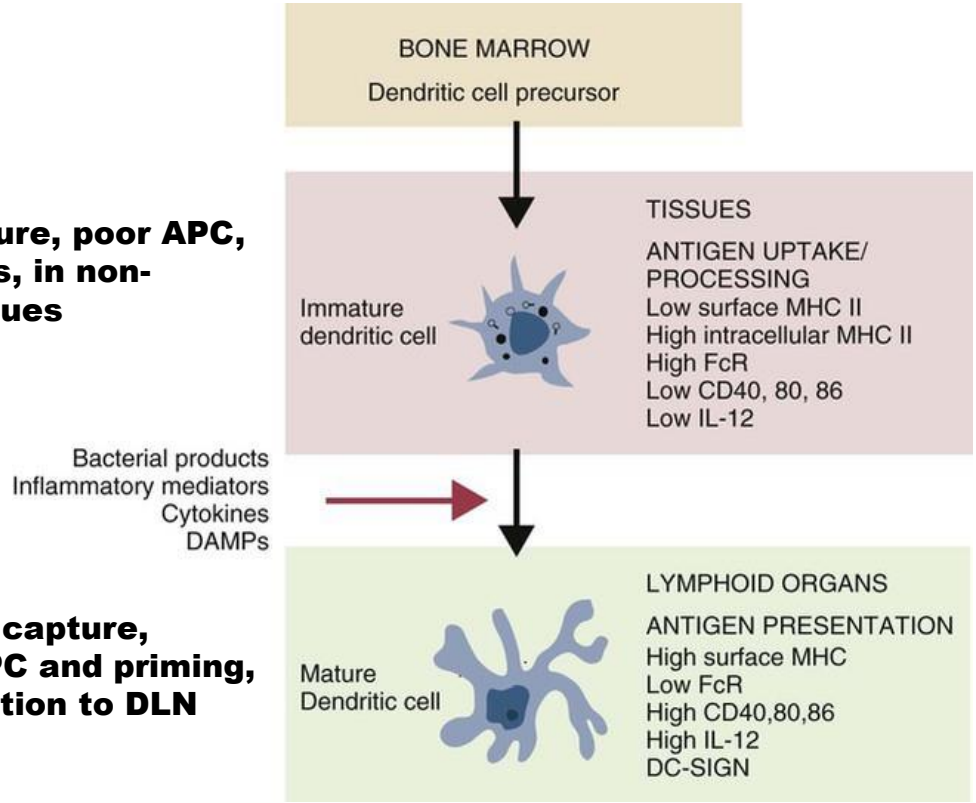


Dendritic cells are distributed basally throughout non-lymphoid and lymphoid organs and migrate homeostatically and during insults

Dendritic cell maturation

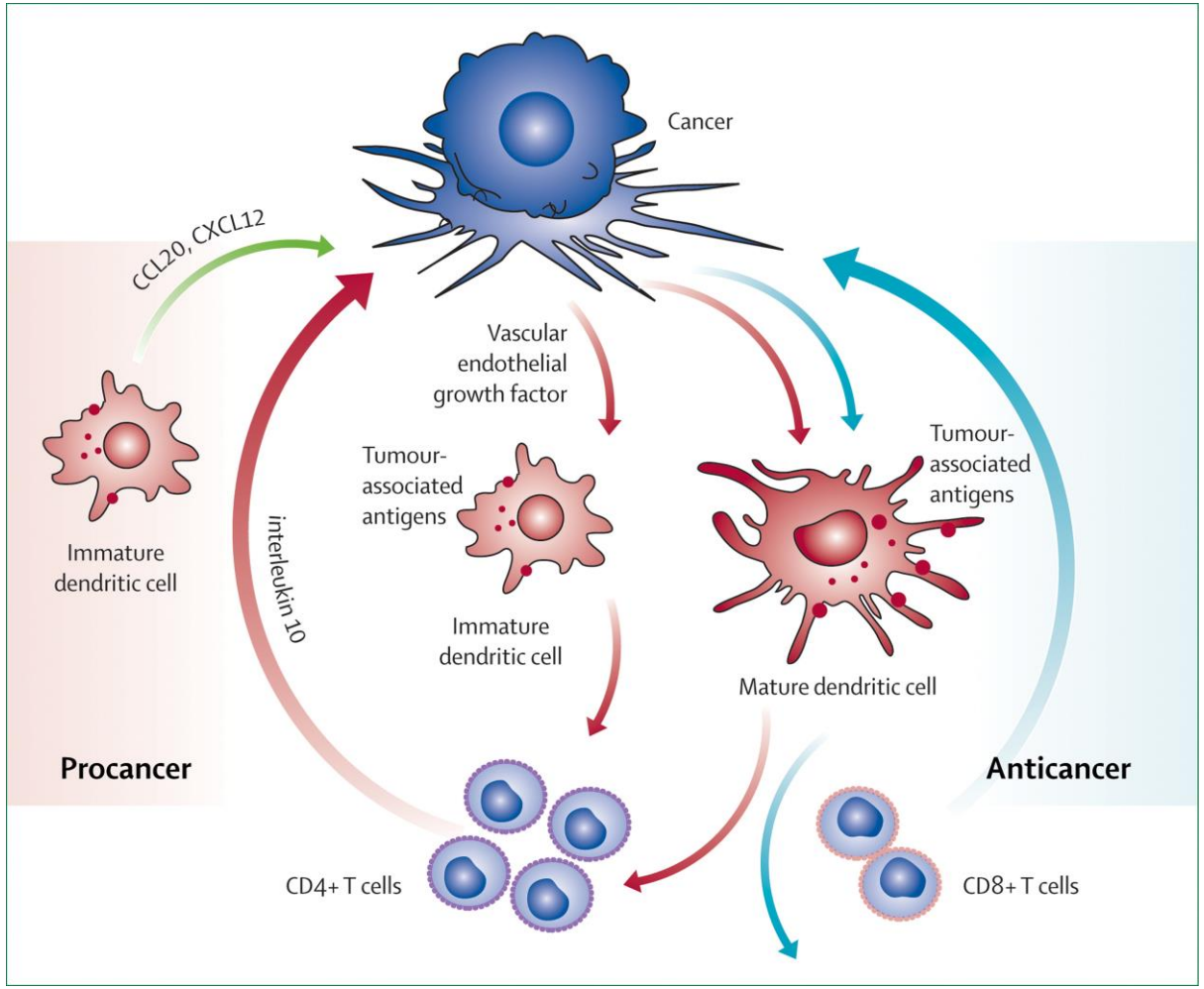
Homeostatic

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



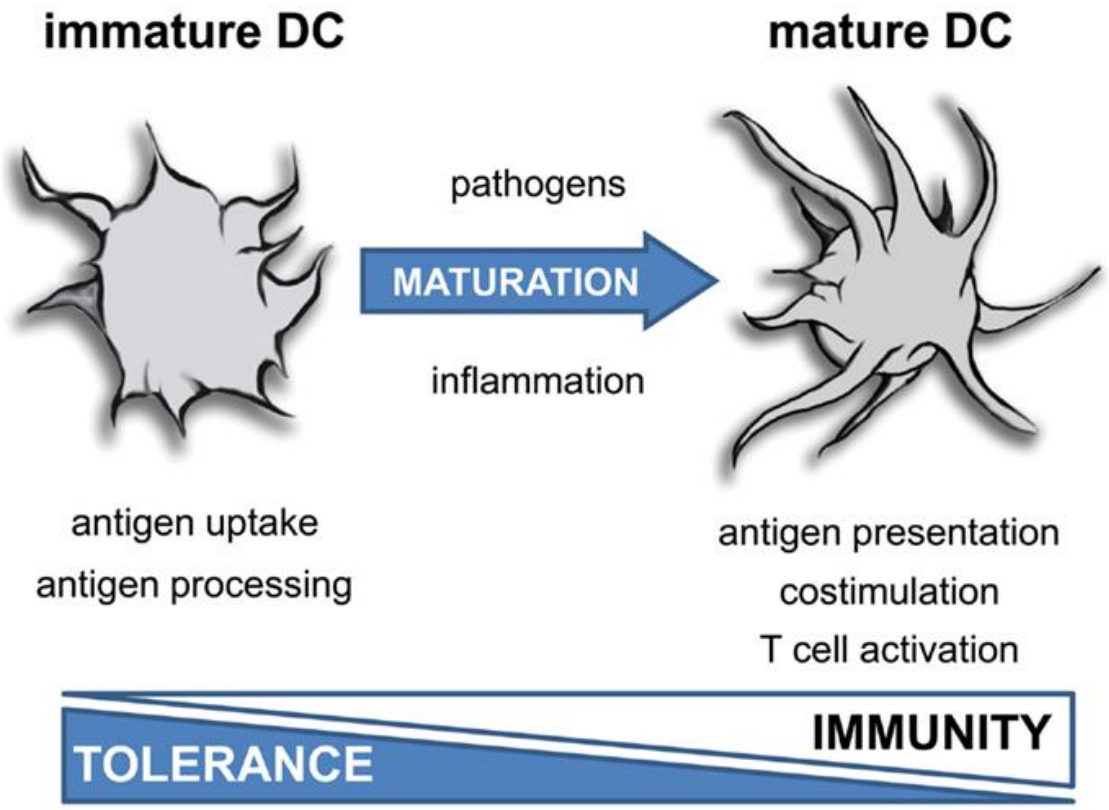
Reduced Ag capture, excellent APC and priming, CCR7, migration to DLN

In cancer



DC instruct specific T cell differentiation that shapes immune responses:

DC maturation status has a profound effect



DC direct tolerance versus immunity based on integrating environmental factors

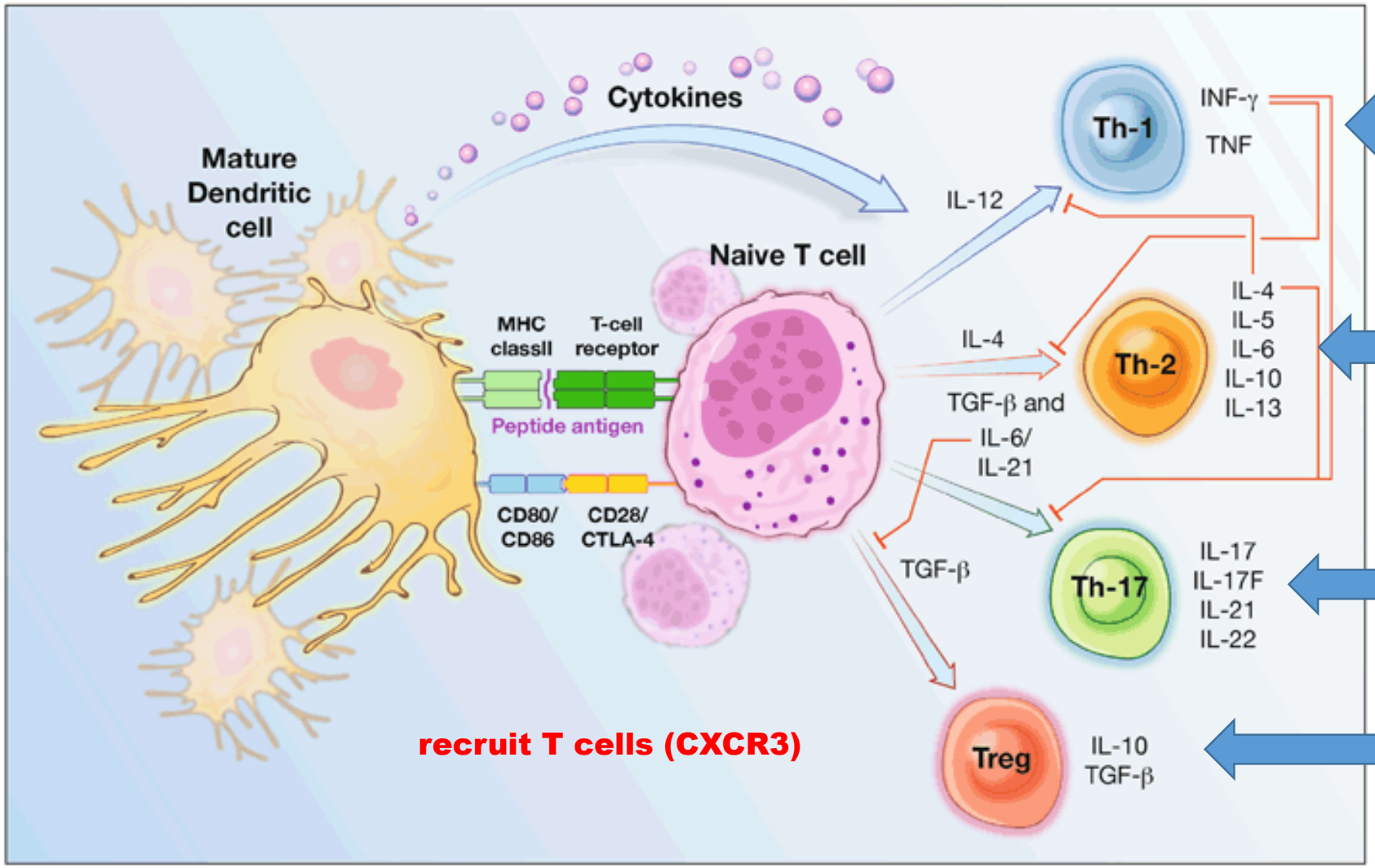
Inflammation and danger signals
induce DC maturation

- **type I IFNs**
- **inflammatory cytokines**
- **LPS and other TLR agonists**
- **Prostaglandins**
- **HMGB1, HSPs, other**

Anti-inflammatory factors
impede DC maturation

- **IL-10**
- **VEGF**
- **hypoxia, lactate, others**

DC prime T cells and help direct their differentiation



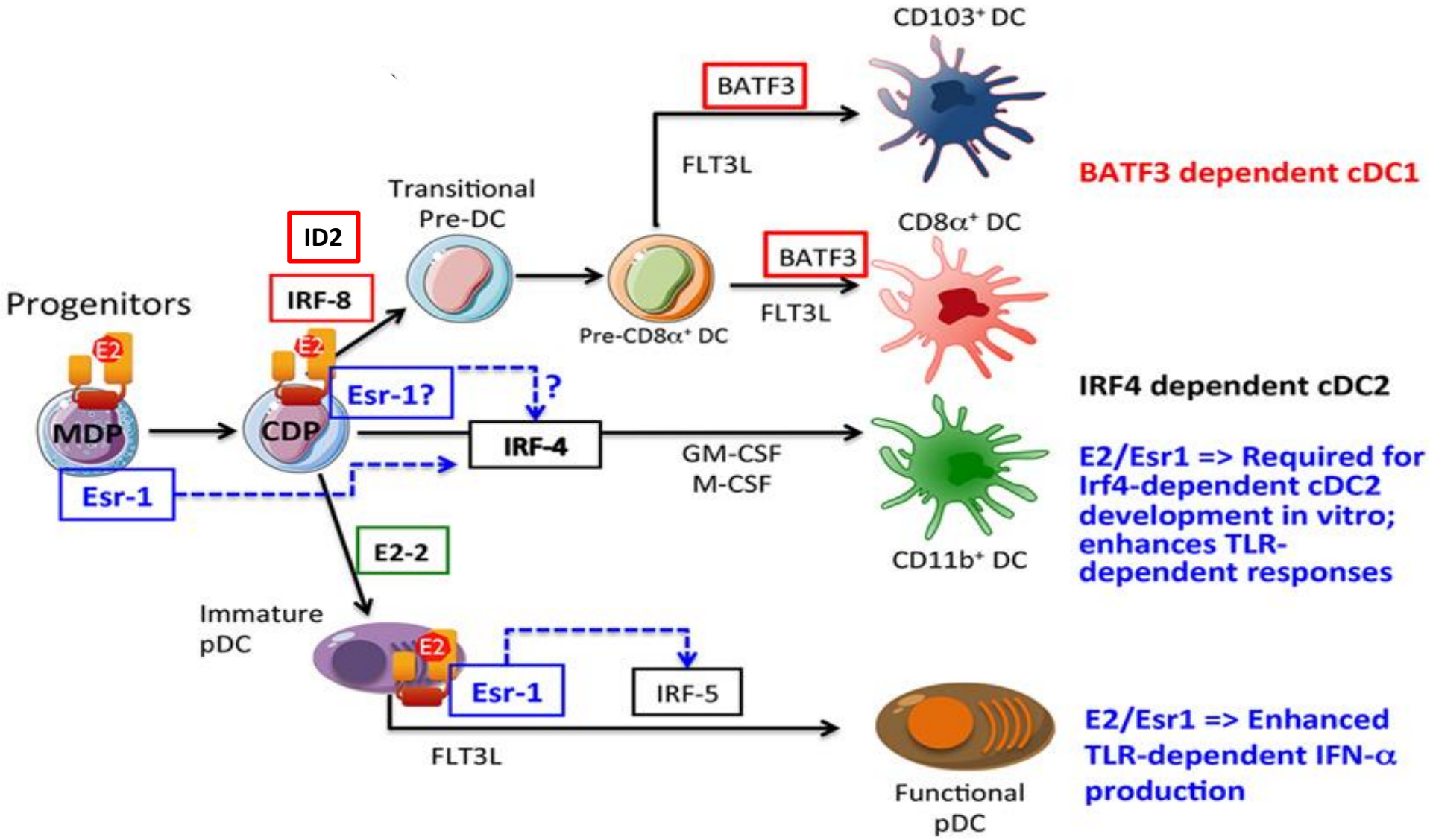
Anti-cancer

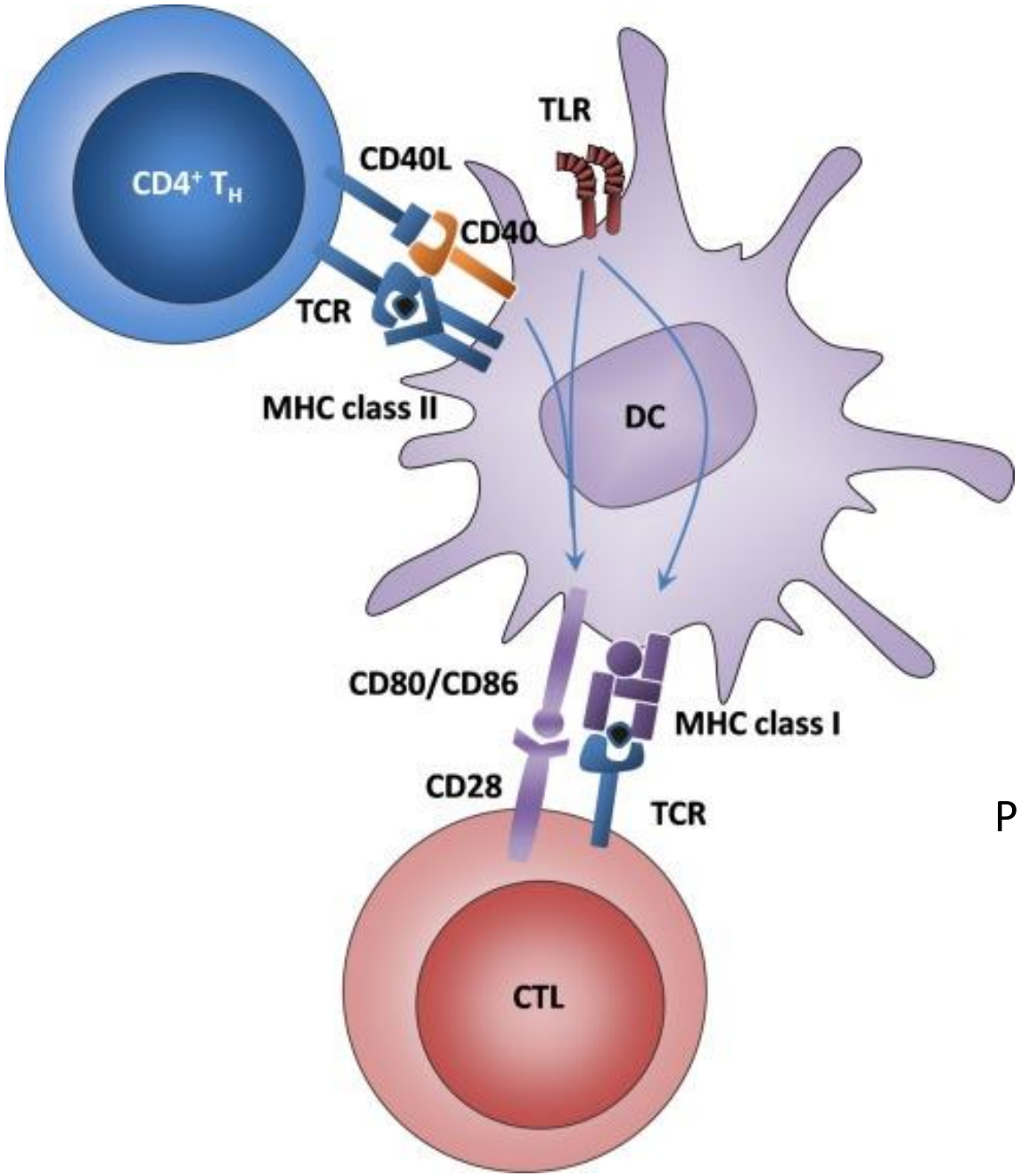
Pro-cancer

Wild card

Pro-cancer

DC subpopulations are also driven by transcription factors



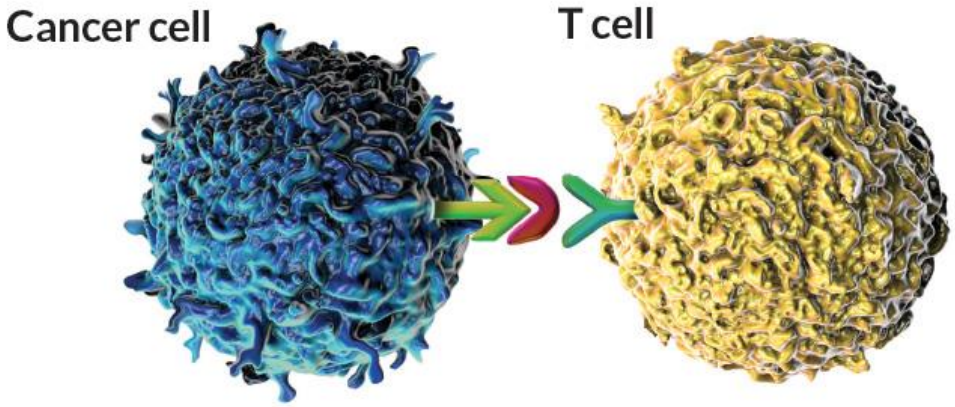


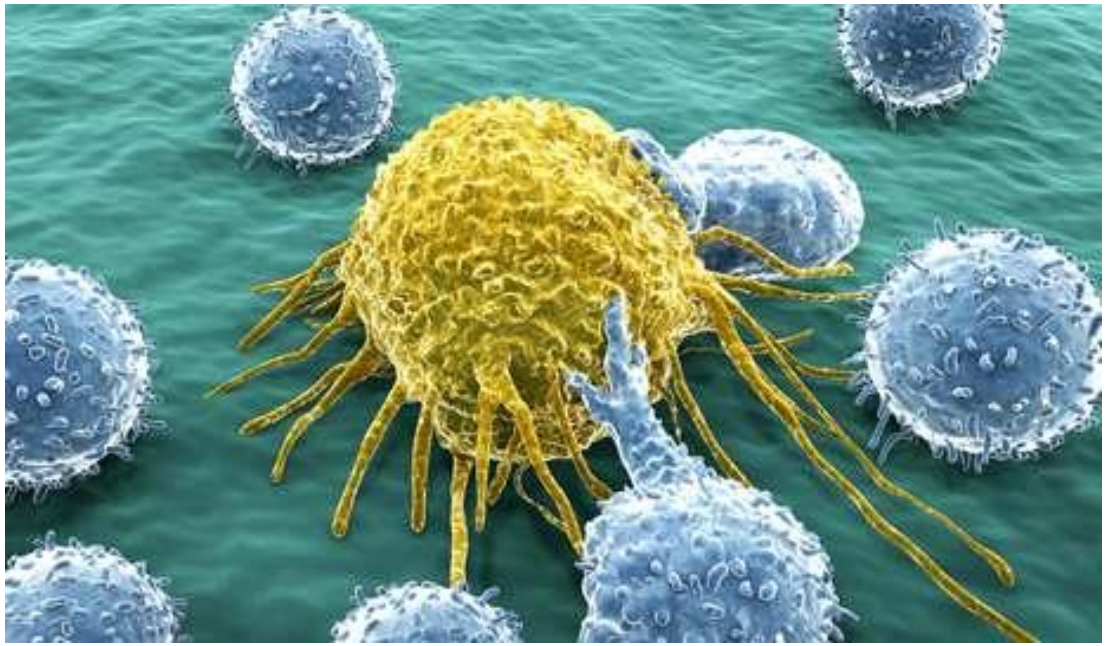
DC instruct T cell functions and get licensed from them, particularly to activate CTL

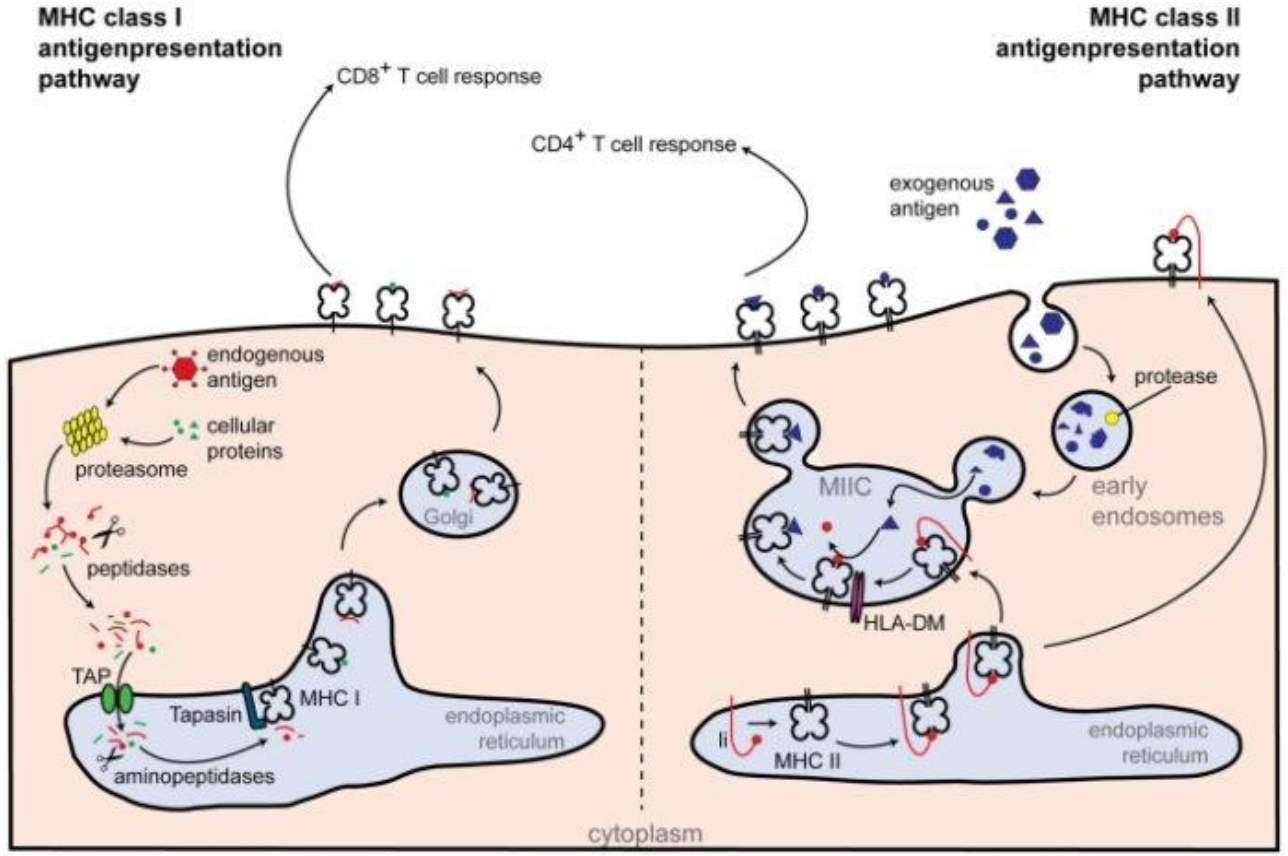
Nature 393, 474-478 1998
Nature 393 478-80 1998
Nature 393 480-483 1998

Priming: Martin-Fontecha, *et al. J Exp Med* **205**, 2561-2574 2008

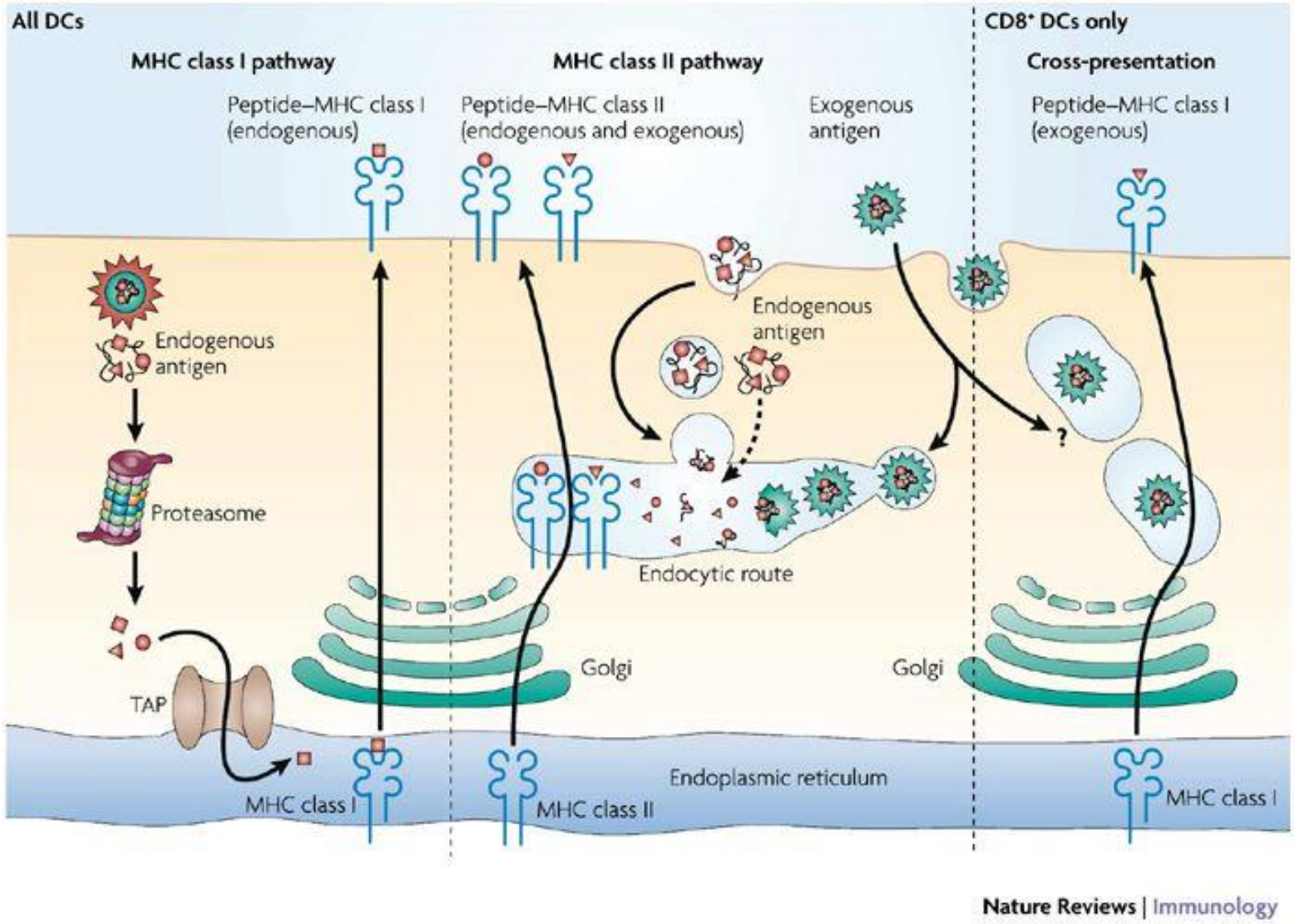
Tumor antigens are exogenous to DC







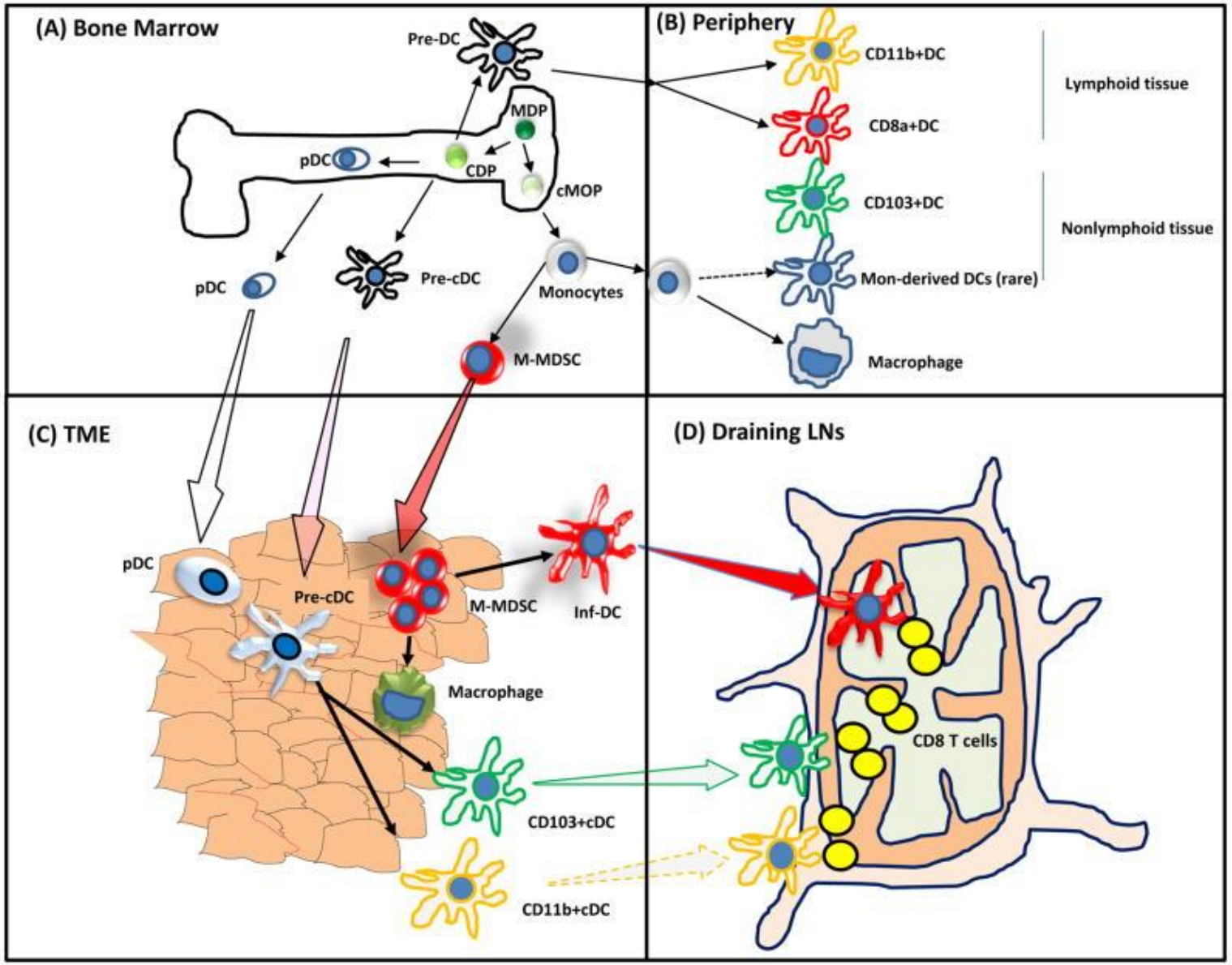
DC are excellent at antigen cross presentation and cross priming



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)

DC differentiation in cancer



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

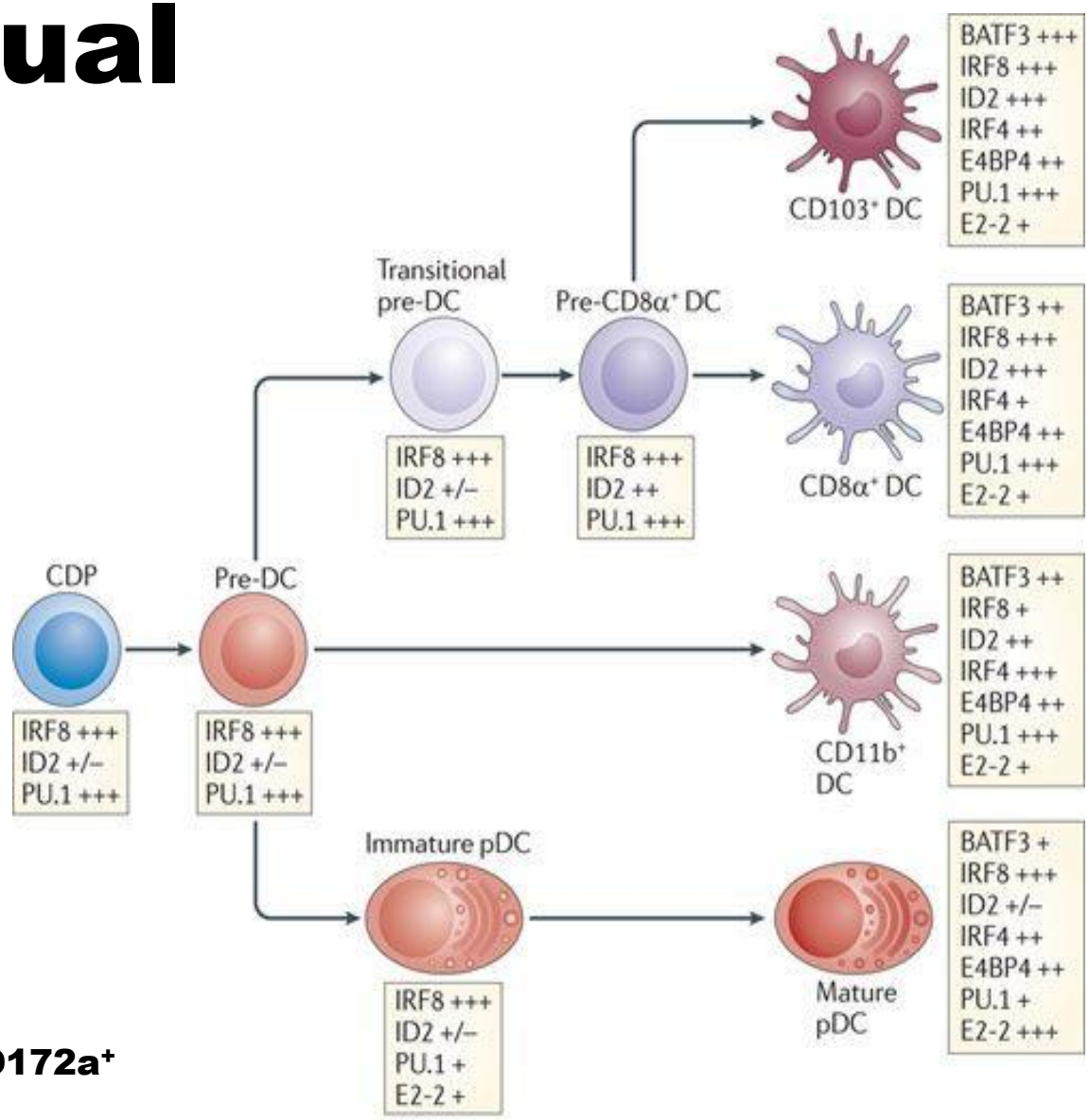
Conventional DC
It helps to be bilingual

Mouse

- Divided into $CD11b^+$ and $CD11b^-$
  - $CD11b^-$
    - $CD8a^+CD11b^-$ (lymphoid tissue)
      - $CD11c^+Clec9a/DNGR\text{-}1^+XCR1^+$
    - non-lymphoid tissue (including cancer) $CD103^+CD11b^-$
      - $CD11c^+Clec9a/DNGR\text{-}1^+XCR1^+CD103^+$
    - 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

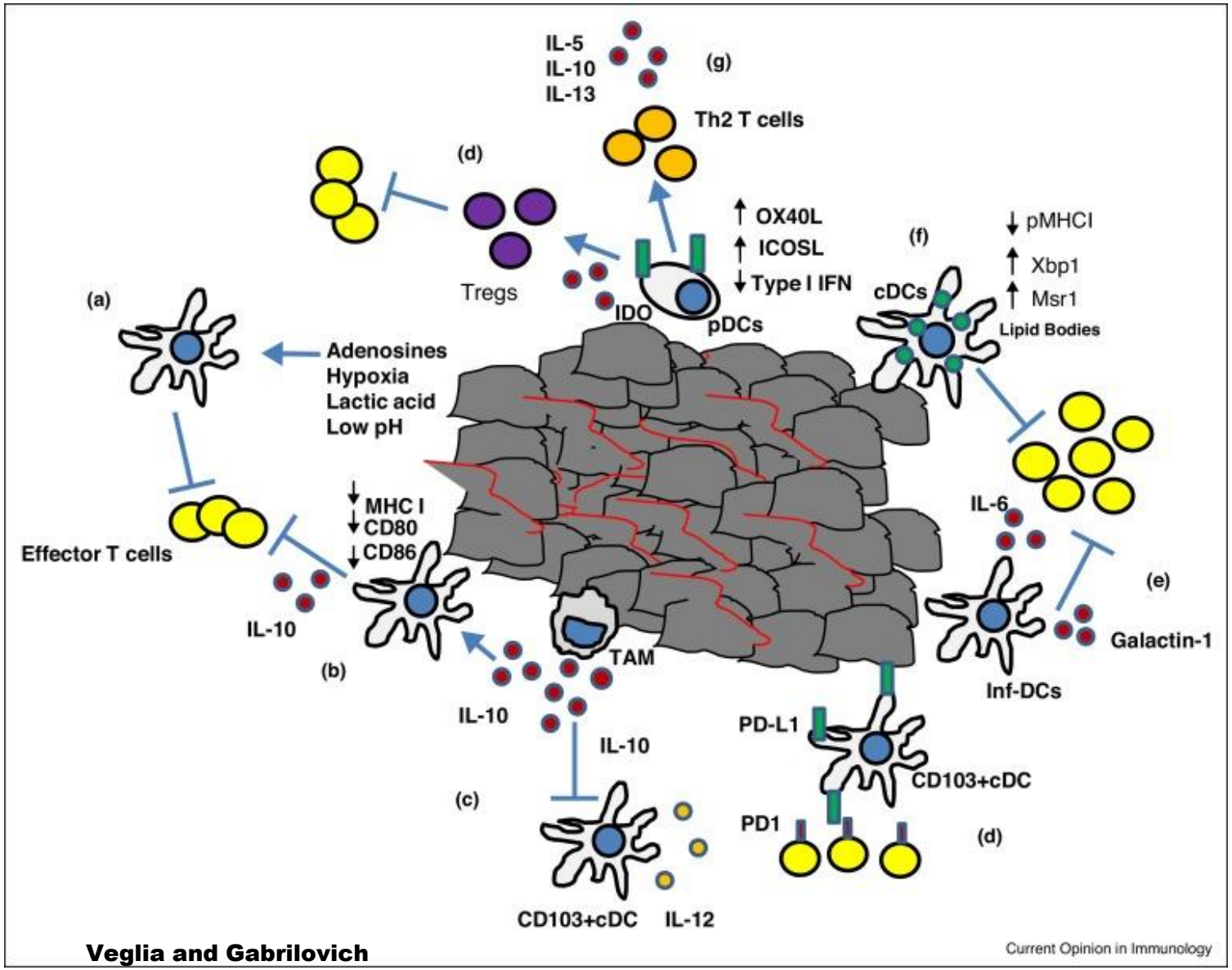
Human

- 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



Nature Reviews | Immunology

Dendritic cell dysfunction in the TME



Veglia and Gabrilovich

Curr Opin Immunol 2017;45:43-51

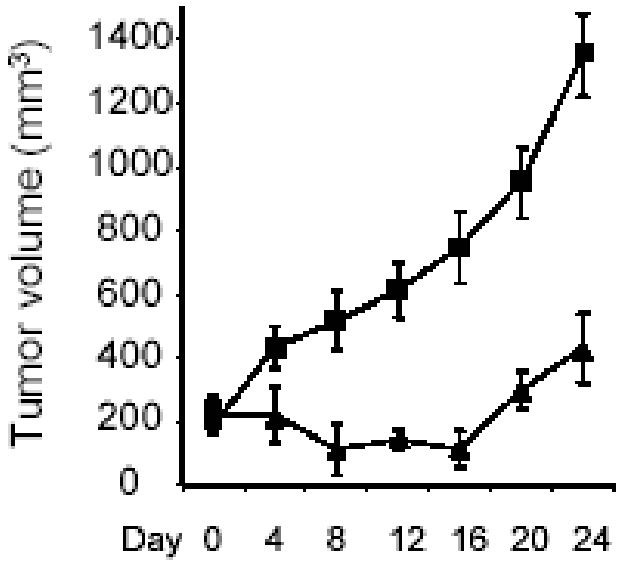
Hypoxia, adenosine, lactate, low pH, accumulation of lipids impair DCs.
IL-10 can inhibit IL-12^{+} CD103^{+}CD11b^{-} DCs.
IL-12 and anti-tumor responses restored with IL-10R. Anti-IL-10R and CpG restore tumor DC function.

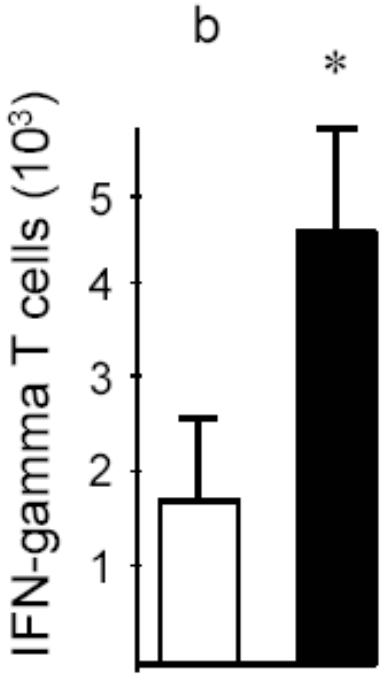
PDC are immature and make little type I IFN but can induce Treg through IDO.

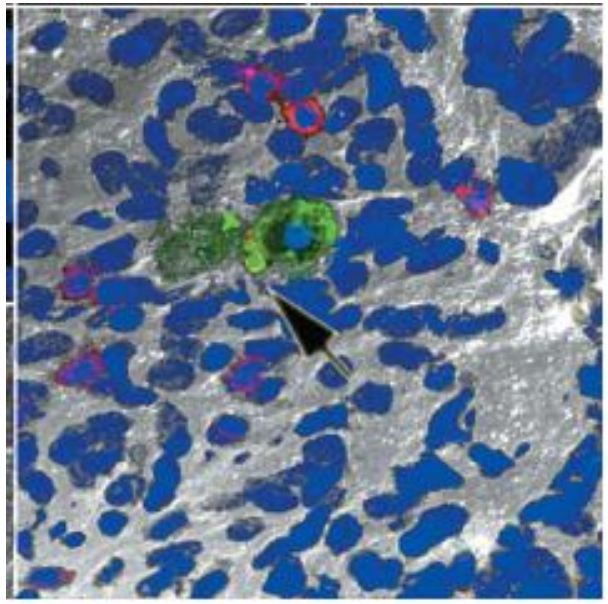
Punch Line: Much DC dysfunction appears to be from dysfunctional maturation

Tumor myeloid DC induce IL-10$^+$ T cells through PD-L1 signals

Curiel, *et al*., *Nature Medicine* 2003; 9(5):562-567



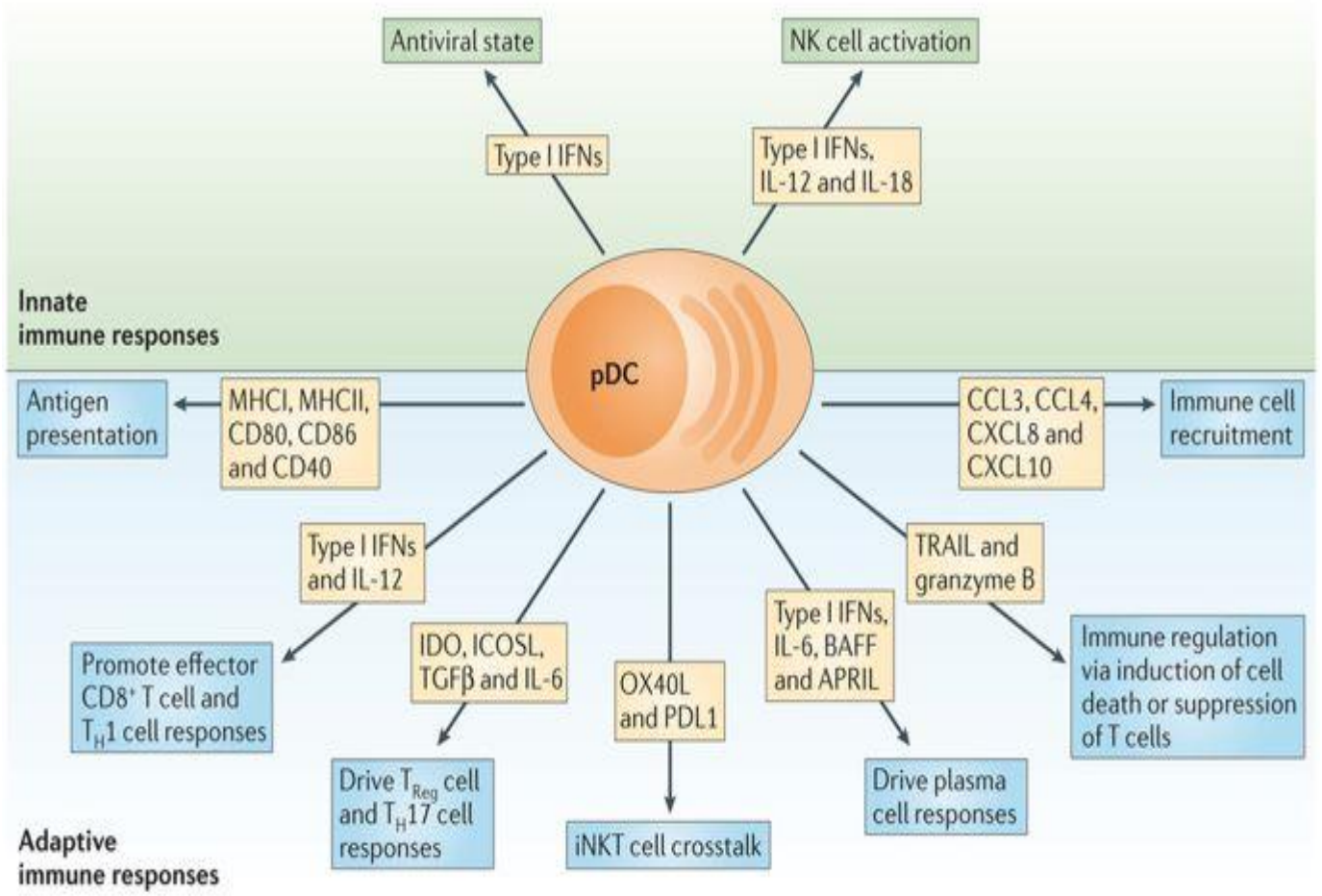




VEGF and IL-10 from the tumor induce PD-L1 expression

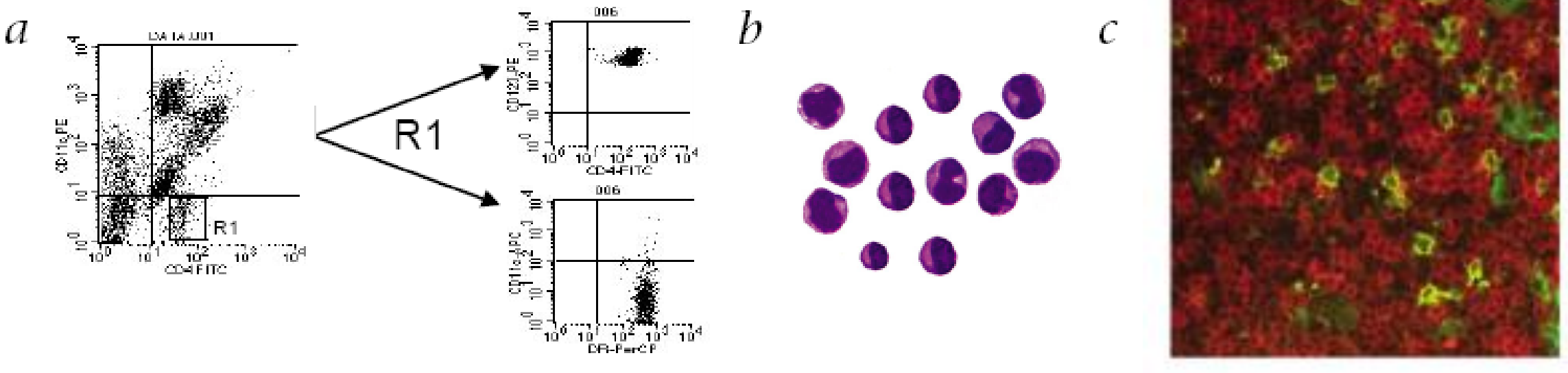
Plasmacytoid Dendritic Cells

- **Mouse**
  - Express Siglec-H, B220, Ly6c,
  - Low CD11c, variable CD8α, CD4
- **Human**
  - Express DR, CD123, CD4, PDCA-2, TLR7/9
  - TLR7/9 induces type I IFN, IL-12, IL-6, TNF-α, other pro-inflammatory factors
  - Poor APC versus cDC and can be tolerogenic

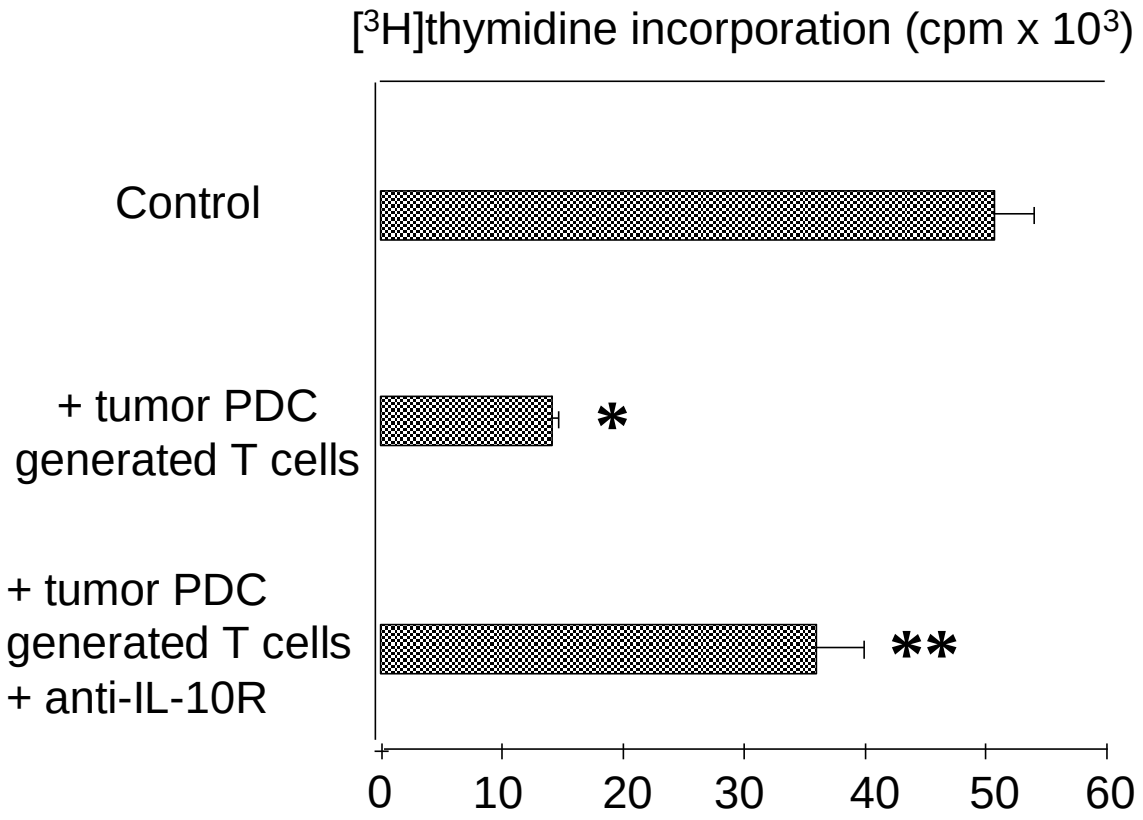


PDC are abundant in human ovarian cancer

Zou, *et al*., *Nature Medicine* 2001; 7(12):1339-1346



Tumor PDC generate IL-10$^+$ T cells (Tr1 Tregs)



Zou, et al., *Nature Medicine* 2001; 7(12):1339-1346

Mouse

- TLR-activated PDC kill B16 melanoma through TRAIL and GzB/C.
- Type I IFN activates CTL and NK cells.
- Anti-tumor in breast cancer model.

Human

- Activated PDCs bearing tumor Ags induced Ag-specific CD4$^+$ and CD8$^+$ T cells
- PDC in ovarian, head and neck, breast and melanoma are poor prognostic.
- PDC ICOSL predicts breast cancer progression (induces IL-10$^+$ Tregs.
- OX40L+/ICOSL+ PDC associated with Th2 cytokine+ T cells (IL-5, IL-10, IL-13) in melanoma, and these PDC associated with melanoma progression

Swiecki, M. & Colonna, M. *Nat Rev Immunol* **15**, 471-485 (2015)

Monocyte-derived inflammatory DC (inf-DC)

- Induced by inflammation from monocytes

Mouse

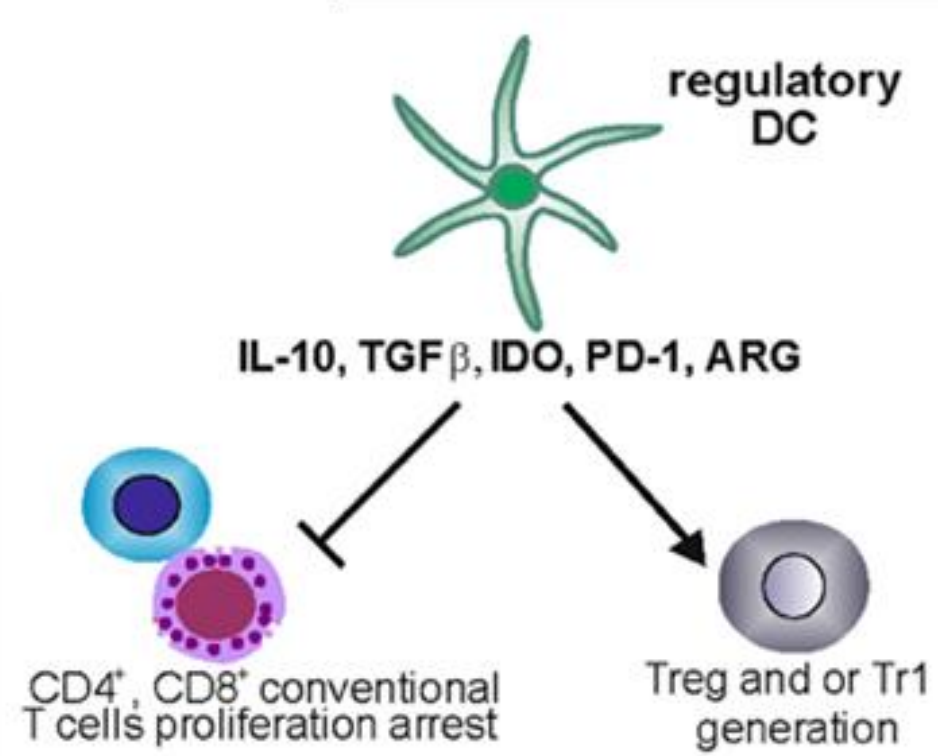
- From Ly6C^{hi} monocytes
- MHC II$^+$ CD11b$^+$ CD11c$^+$ F4/80$^+$ Ly6c$^+$, and CD206$^+$, GM-CSFR$^+$ (CD115), CD107b$^+$ (Macb), FceRI$^+$, CD64$^+$
- Activate CD4$^+$ T cells
- FcεR1 distinguishes inf-DC from cDC and macrophages

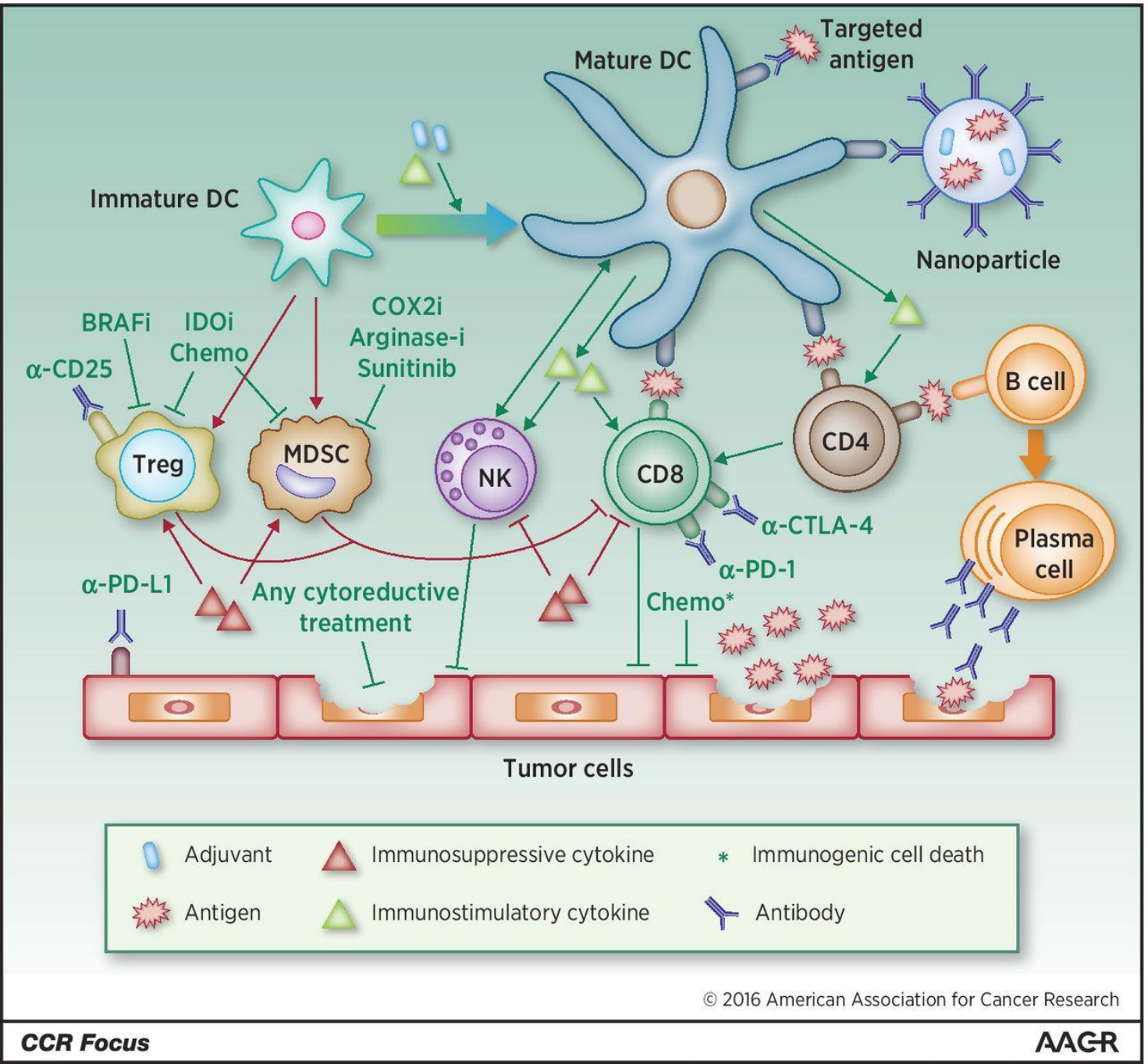
Human

- 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
- TIP-DC (Cell 2016)

Regulatory DC

- Tumors can convert DC into immunosuppressive regulatory DC
- Produce IL-6 and galectin-1
- Express CD11c, MHCII, Dngr1/Clec9, Zbt46, FCeRI, CD11b and CCR7
- Can overexpress STAT3 to inhibit DC maturation





DC in cancer immunotherapy

Obermajer, *et al. Nat Protoc* **13**, 335-357 2018

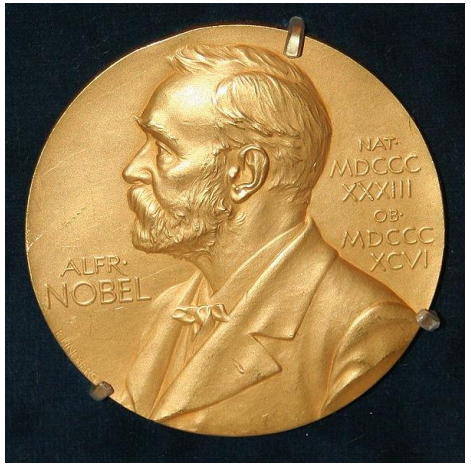
Kalinski & Talmadge. *Adv Exp Med Biol* **1036**, 1-18 2017

Summary

- **DC play various roles (stimulatory/inhibitory/regulatory) in cancers**
- **All DC subsets can participate in cancer defense or immunopathology**
- **Means to improve DC function or reduce inhibition can improve cancer immunotherapy**
- **Improved research methods still needed**

Ralph Steinman

In vivo veritas



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