How tumours escape the immune response

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Immune system plays a dual role in cancer

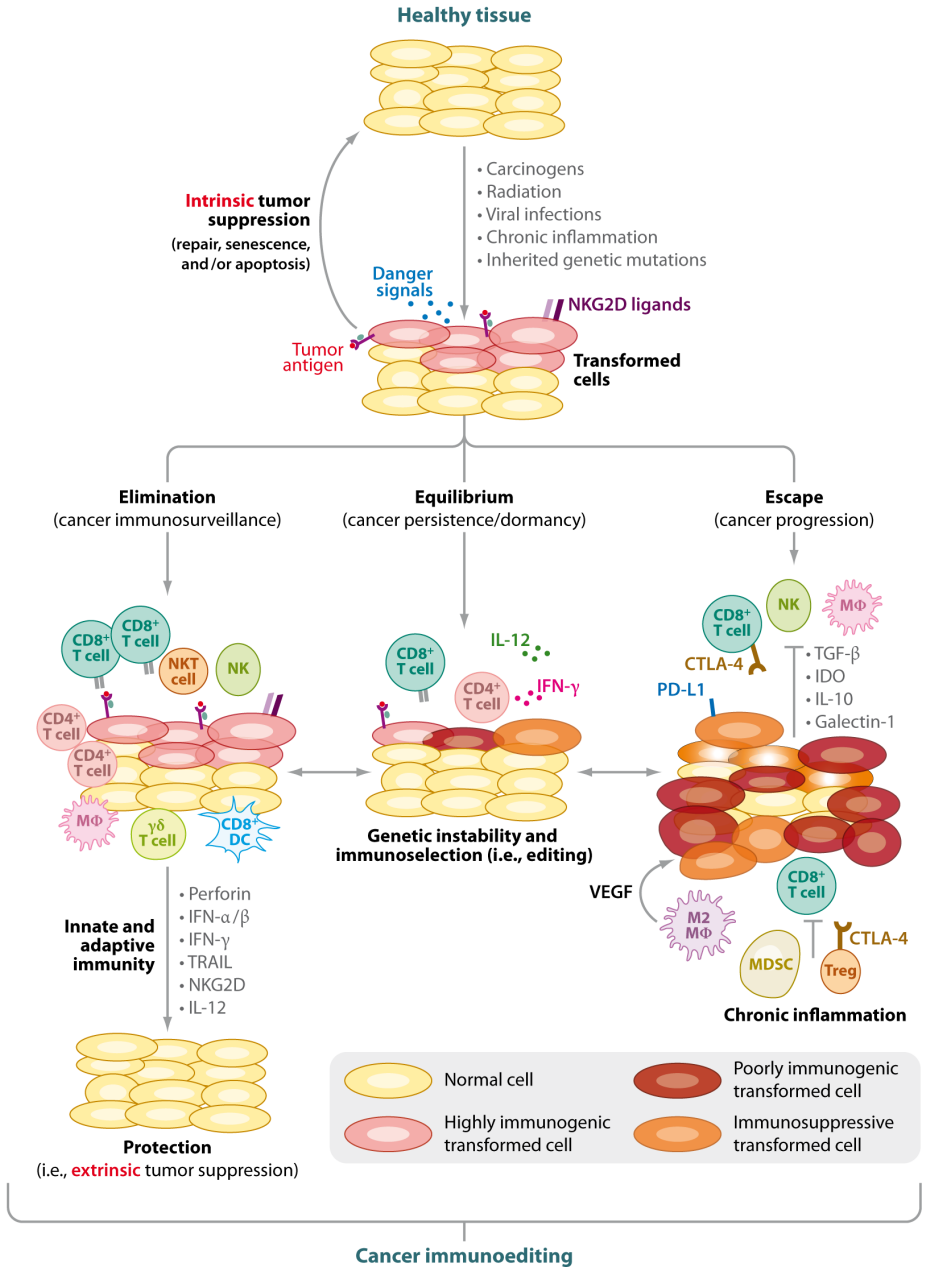
- Suppress tumour growth
  - By destroying cancer cells
  - By inhibiting their outgrowth
- Promote tumour progression
  - By selecting tumour cells that are more fit to survive in an immuno-competent host
  - By establishing tolerogenic tumour microenvironment

Cancer Immunoediting

- A continual process during tumorigenesis where the immune system both protects against tumor development and promotes their outgrowth
- Proceed sequentially through three distinct phases
- Elimination (cancer immunosurveillance)
- Equilibrium (cancer persistence or dormancy)
- Escape (cancer progression)

3E theory

- Elimination (cancer immunosurveillance)
  - modern view of cancer immunosurveillance where the immune system destroys transformed cells
- Equilibrium (cancer persistence or dormancy)
  - immune-mediated tumor dormancy
- Escape (cancer progression)
  - transformed cells acquire adaptations allowing them to grow unhindered by the immune system



Vesely MD, et al. 2011.
Annu. Rev. Immunol. 29:235–71

Why Immune system fails to clear the cancer cells

- Intrinsic immune failure
- Extrinsic immune evasion (development of immunosuppressive strategies by tumour cells)

Intrinsic immune failure

- Tumour-specific T cells might be absent from the immune repertoire.
  - *Most tumour-associated antigens (TAAs) are self-proteins*
  - *TAA-reactive T cells are deleted in the thymus*
  - *Only a low affinity TAA-specific T cells allow to mature*
- T cells fail to proliferate and persist in response to tumours.
  - *TAAs might not be cross-presented by host APCs in a form that is sufficiently antigenic for T cells.*
- Tumour-reactive immune cells do not localize to the tumours.
  - *The tumour might not be regarded as a threat to the body, so inflammatory mechanisms that are normally associated with infection might not be initiated.*
  - *Tumour-infiltrated lymphocytes could be inactivated in the tumour*
- TAA-reactive T and B cells are subjected to peripheral tolerance mechanisms.
  - *Depletion, ignorance, inactivation and regulation*

Extrinsic immune evasion (I)

- Tumour cells are poor APC.
  - *They express a low level of peptide/MHC complexes and co-stimulatory molecules, resulting in a poor T cell recognition.*

- Defects in antigen presentation.
  - *Absence of MHC class I expression*
  - *Defects in the antigen processing machinery*

- Cross-presentation of TAAs by host APCs leads to T cell tolerance
  - *TAAs released from tumour cells can be cross-presented to T cells by host APCs. This could result in T cell anergy.*

- Development of antigen loss variants.
  - *by increased frequency of mutations, genetic deletion and immune selection process can result in escape from T cell recognition*
  - *Cancer cells no longer express the TAA will escape destruction by CTLs and grow progressively.*

Extrinsic immune evasion (II)

- Secretion of immunosuppressive factors by tumour cells.
  - *Tumour cells or stromal elements can produce TGFb, IL10, and vascular endothelial growth factor which can inhibit immune cells or bias the effector type produced (such as Th1 or Th2 cells).*

- Downregulation of death-receptor pathways by tumour cells
  - *Death receptors such as CD95 and TRAIL receptors or their downstream signalling molecules can be mutated or lost completely.*

- Establishment of tolerogenic tumour microenvironment
  - *Cross-talk with other tumour-infiltrated lymphocytes and stromal cells*
  - *This local tolerogenic tumour microenvironment is composed of many cell types and factors including regulatory T cells and tolerogenic DC. As a result of this, the entry of tumour-specific T cells into the tumour tissue is impaired.*

Key players in tumour microenvironment

- Regulatory T cells
- TGFb
- Myeloid-derived suppressor cells (MDSC)
- IDO
- Inhibitory B7 molecules

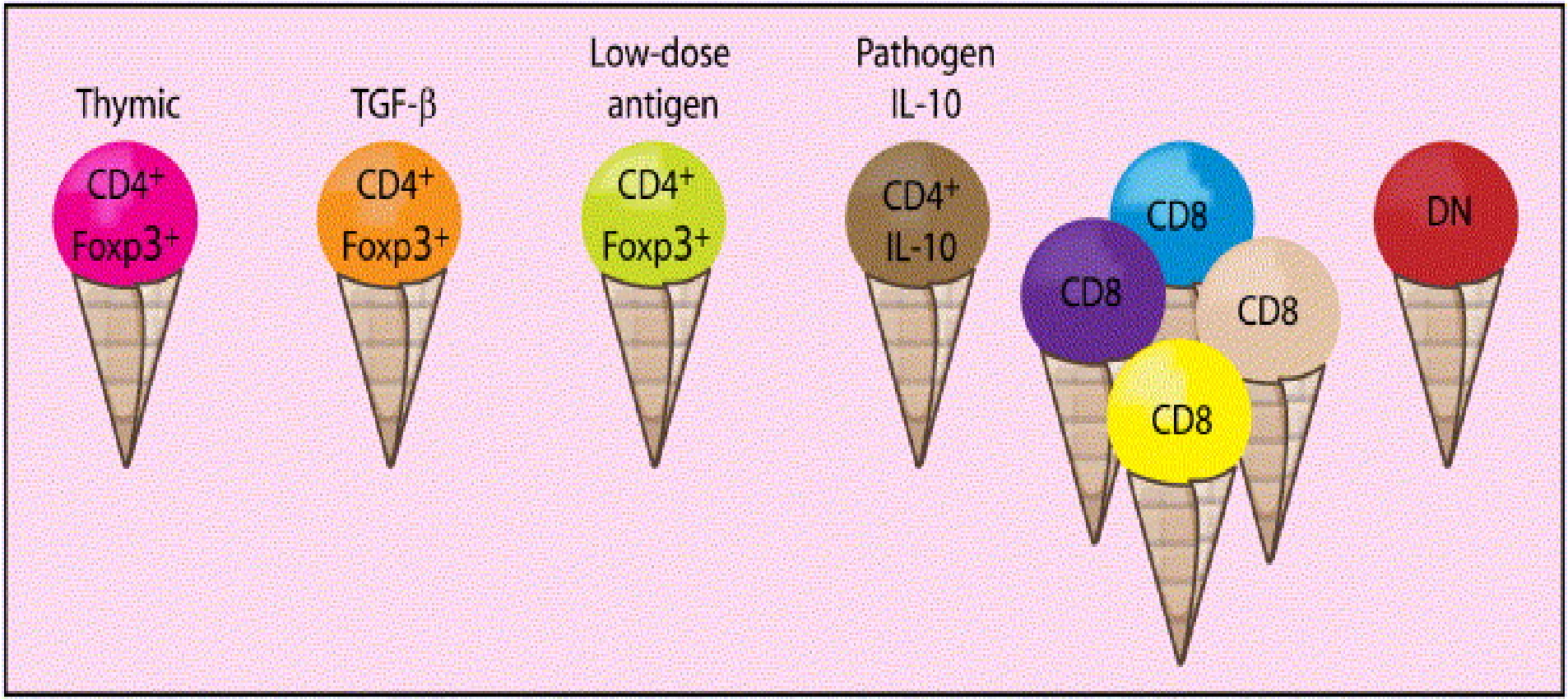
Natural and adaptive regulatory T cells

Table 1 | **A comparison of natural and adaptive regulatory T cells**

Feature	Natural T_{Reg} cells	Adaptive T_{Reg} cells
Site of induction	Thymus	Periphery
CD28–CD80/CD86 dependent	Yes	No
IL-2 dependent	Yes	Yes
CD25 expression	Yes (high)	Variable
Specificity	Self-antigens in thymus	Tissue-specific antigens and foreign antigens
Mechanism of effector-cell suppression	T-cell–T-cell/APC contact, cytokine independent	T-cell–T-cell/APC contact, cytokine dependent

APC, antigen-presenting cell; IL-2, interleukin-2; T_{Reg} cell, regulatory T cell.

Multiple Flavors of T Regulatory Cells

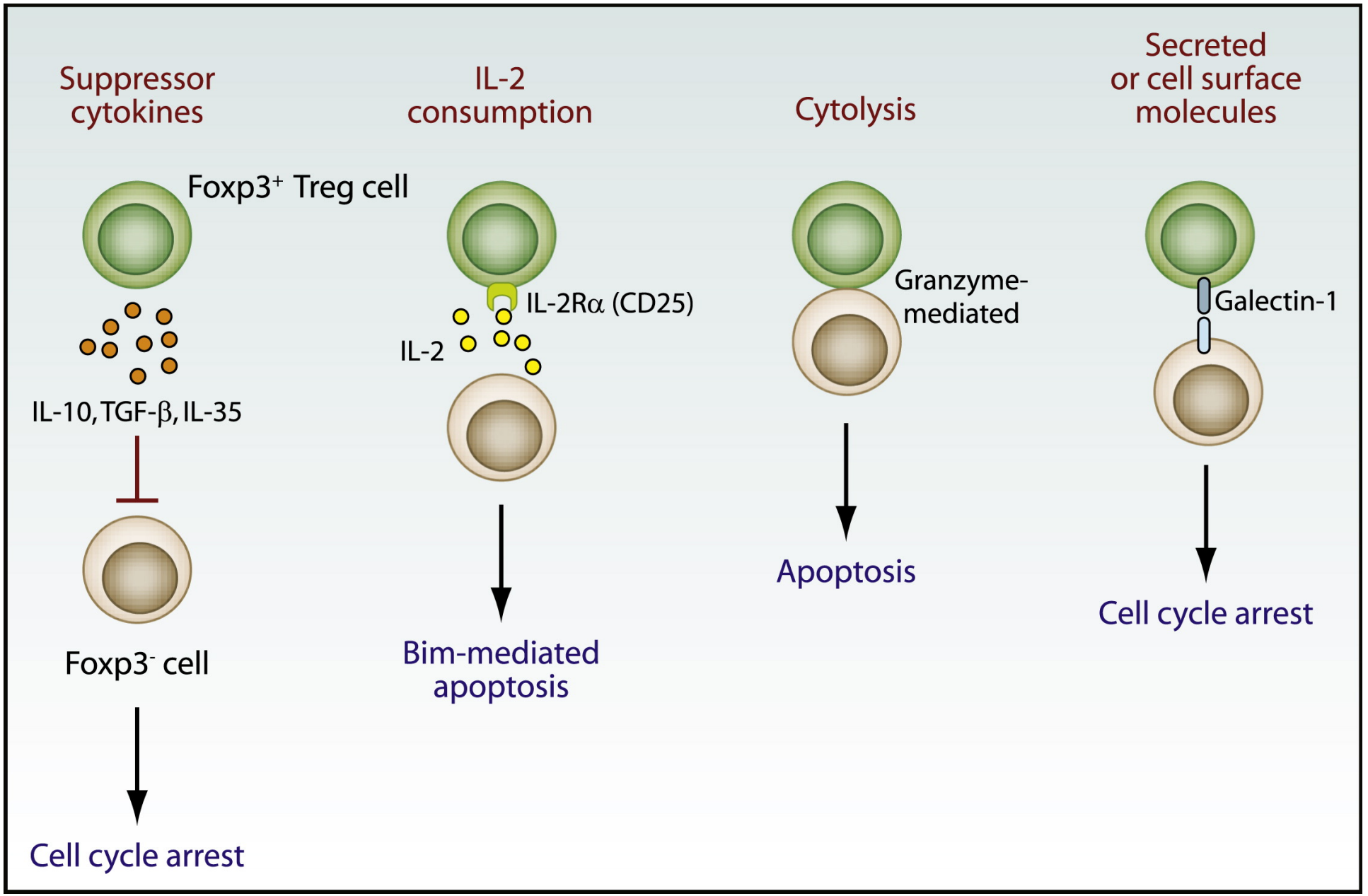


Shevach EM. From vanilla to 28 flavors: multiple varieties of T regulatory cells. Immunity. 2006 Aug;25(2):195-201.

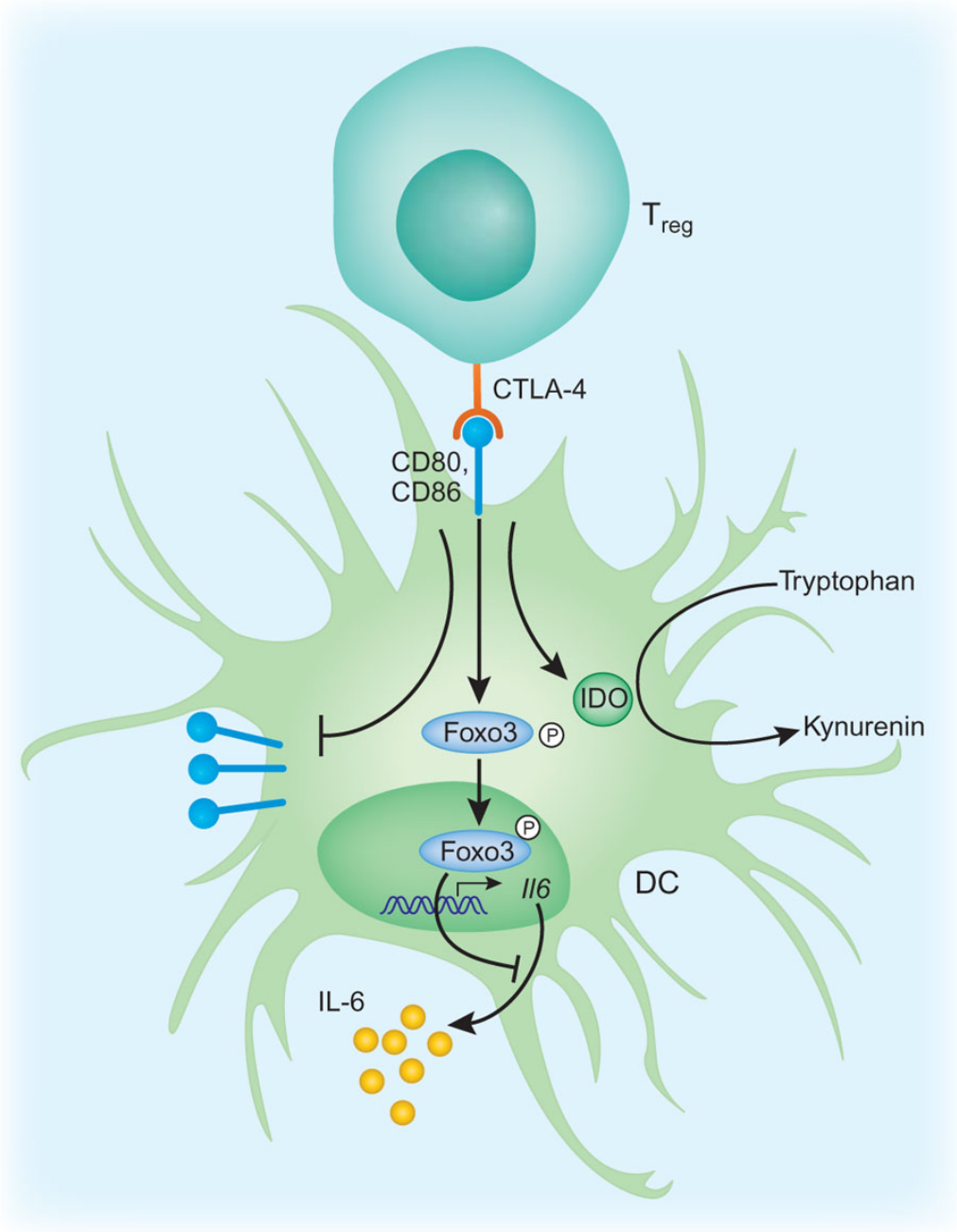
Cellular Targets of Foxp3^{+} Tregs

- CD4^{+}, CD8^{+} T cells
- Dendritic cells
- B cells
- Macrophages
- Osteoblasts
- Mast cells
- NK cells
- NK T cells

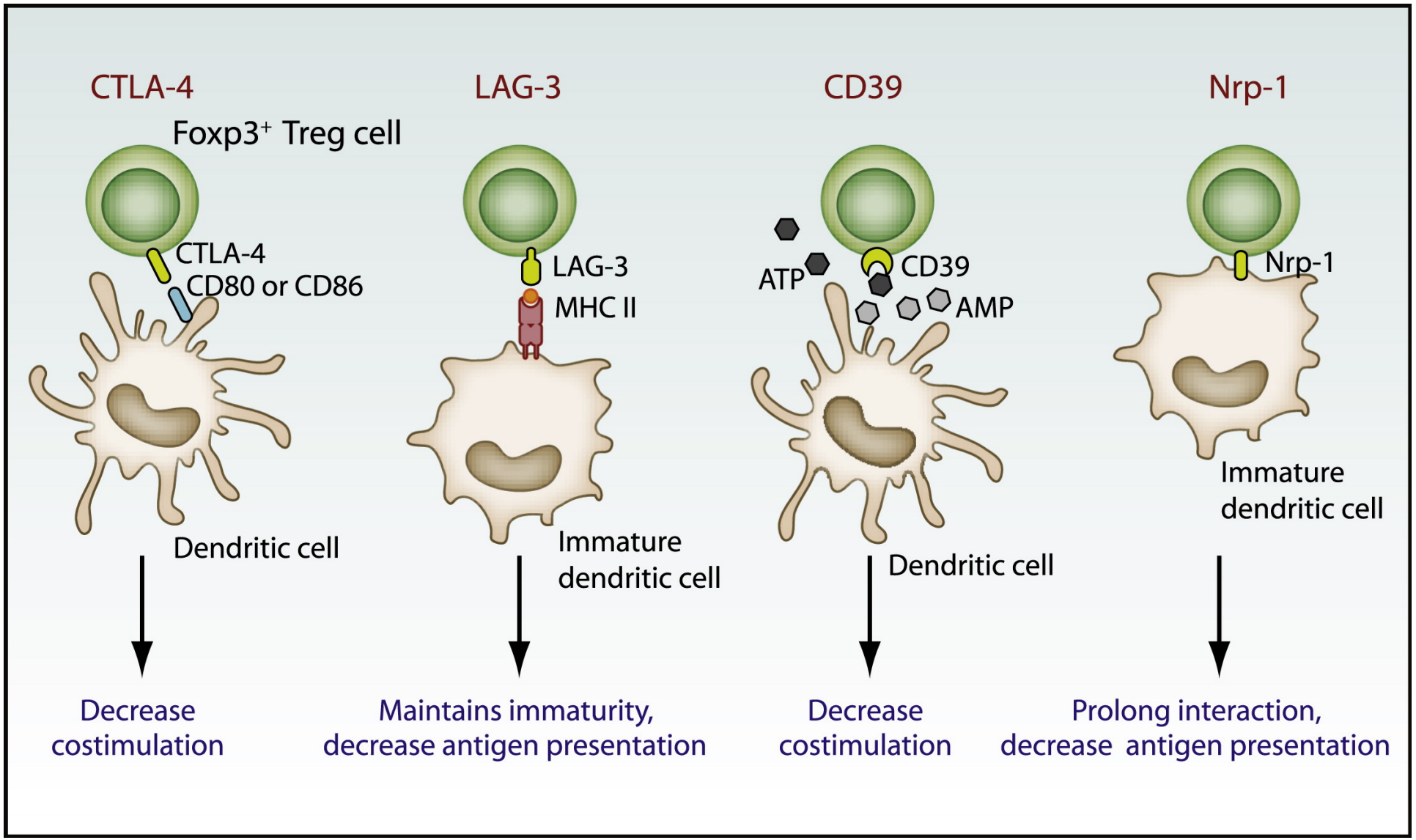
Potential Suppressor-Effector Mechanisms Utilized by Tregs



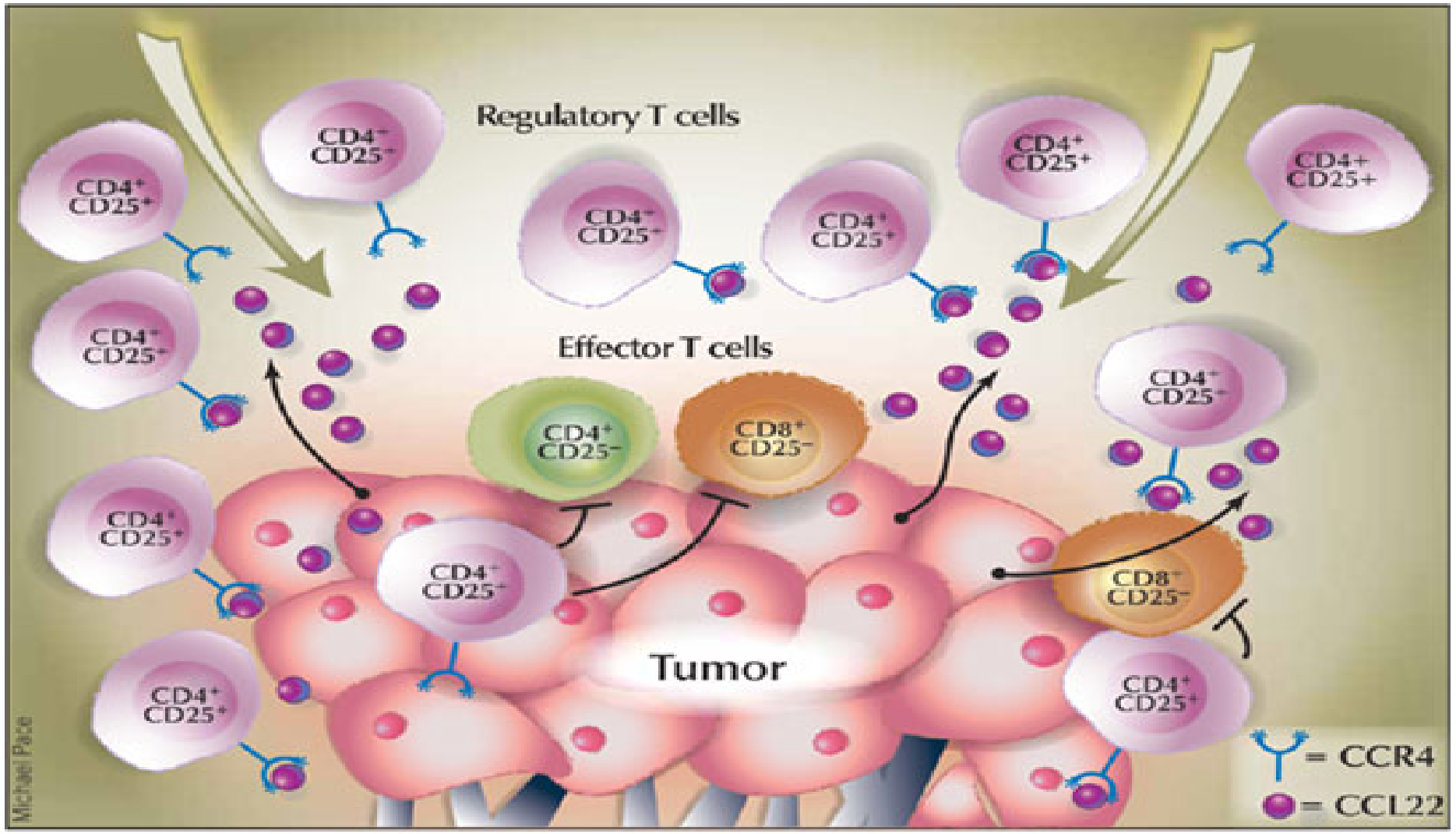
CTLA-4 may be a core mechanism through which Tregs control APC function.



Major Mechanisms by which Treg Cells Can Suppress the Function of APC

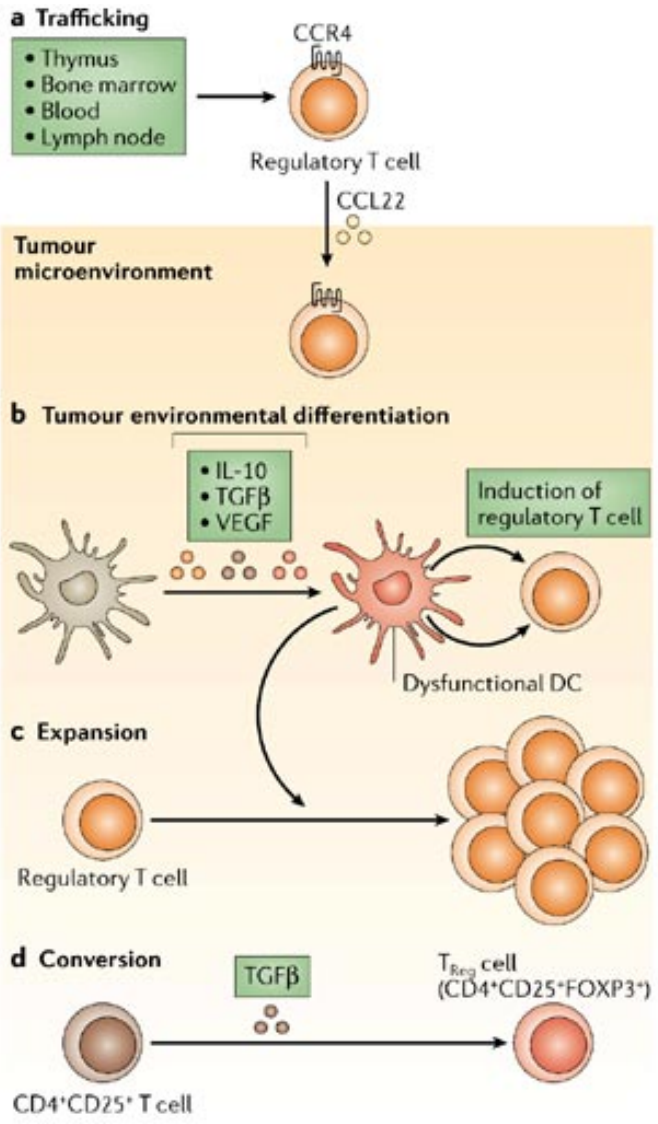


Fatal attraction: tumors beckon regulatory T cells

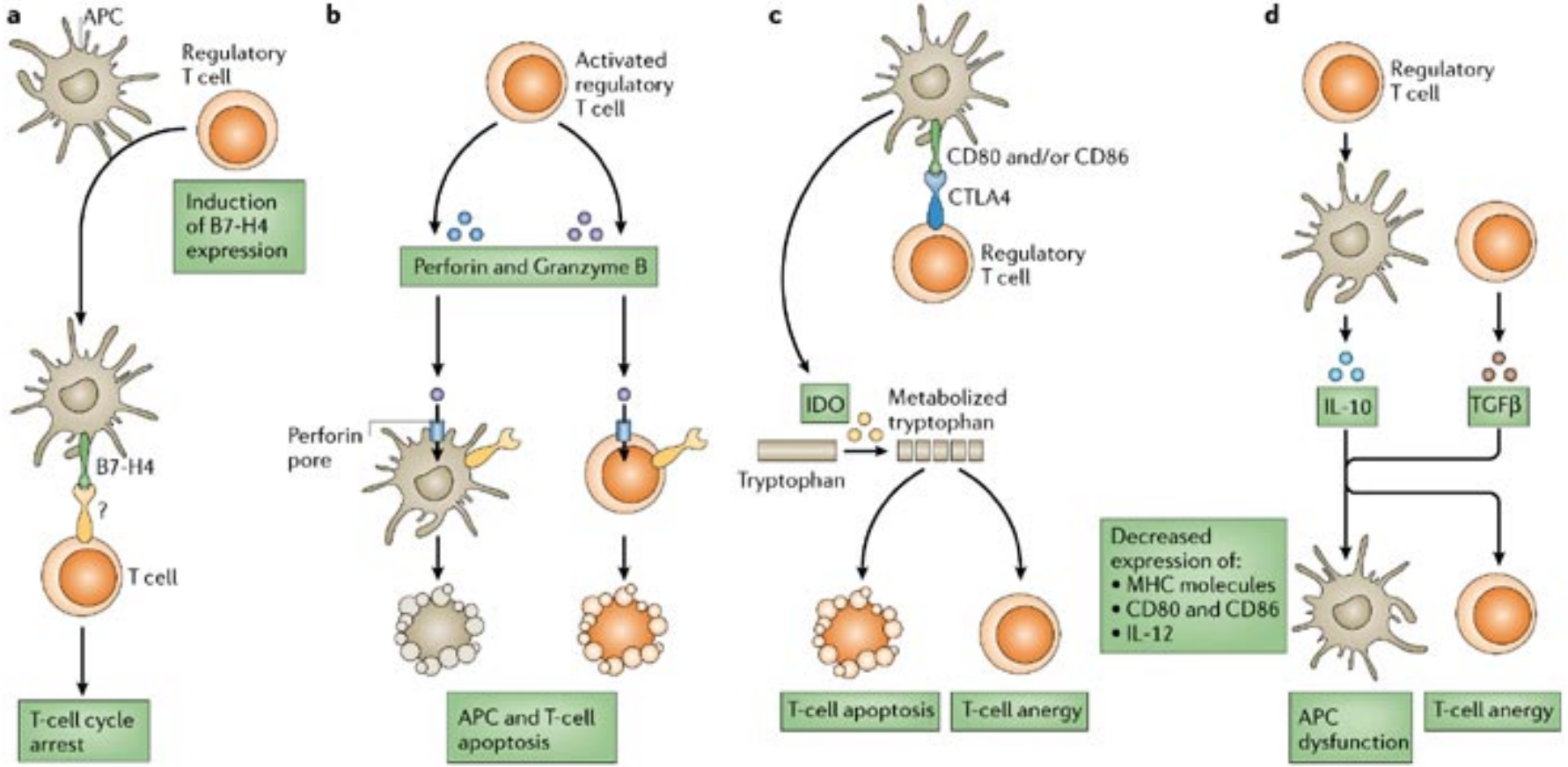


Shevach EM. Nat Med. 2004 Sep;10(9):900-1

Tregs in the tumour microenvironment



Possible suppressive mechanisms of Tregs in tumour microenvironment.



Key players in tumour microenvironment

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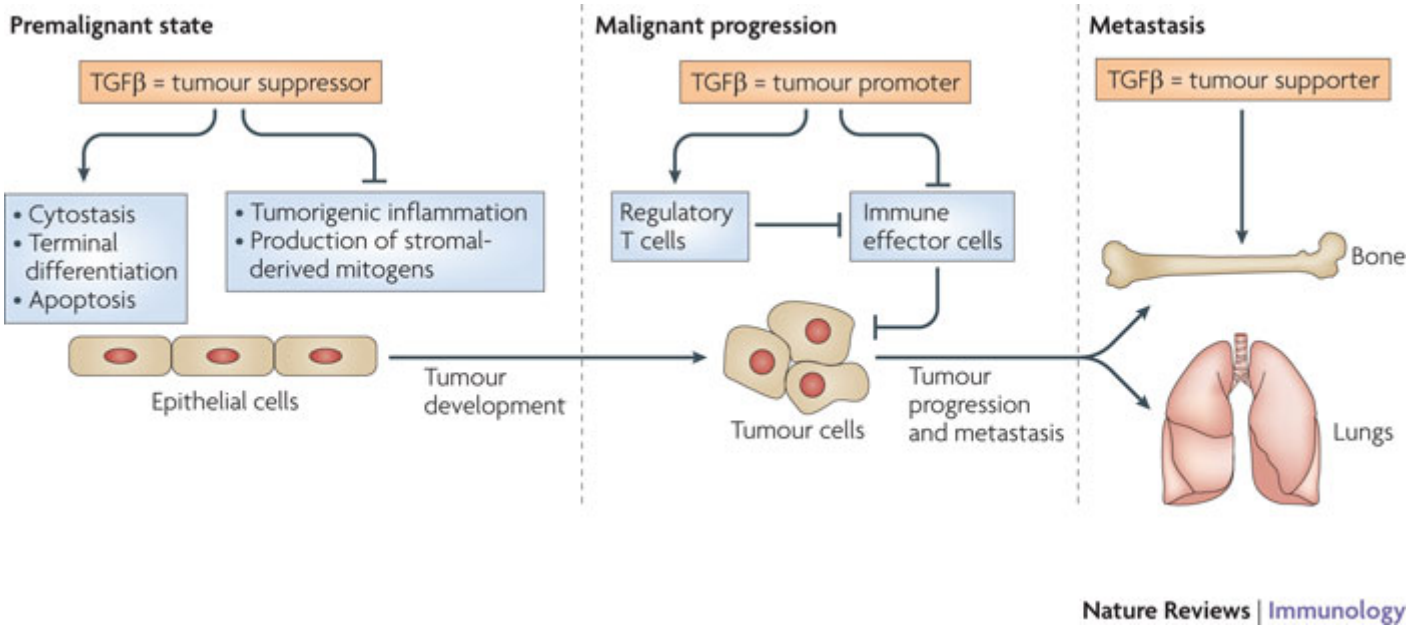
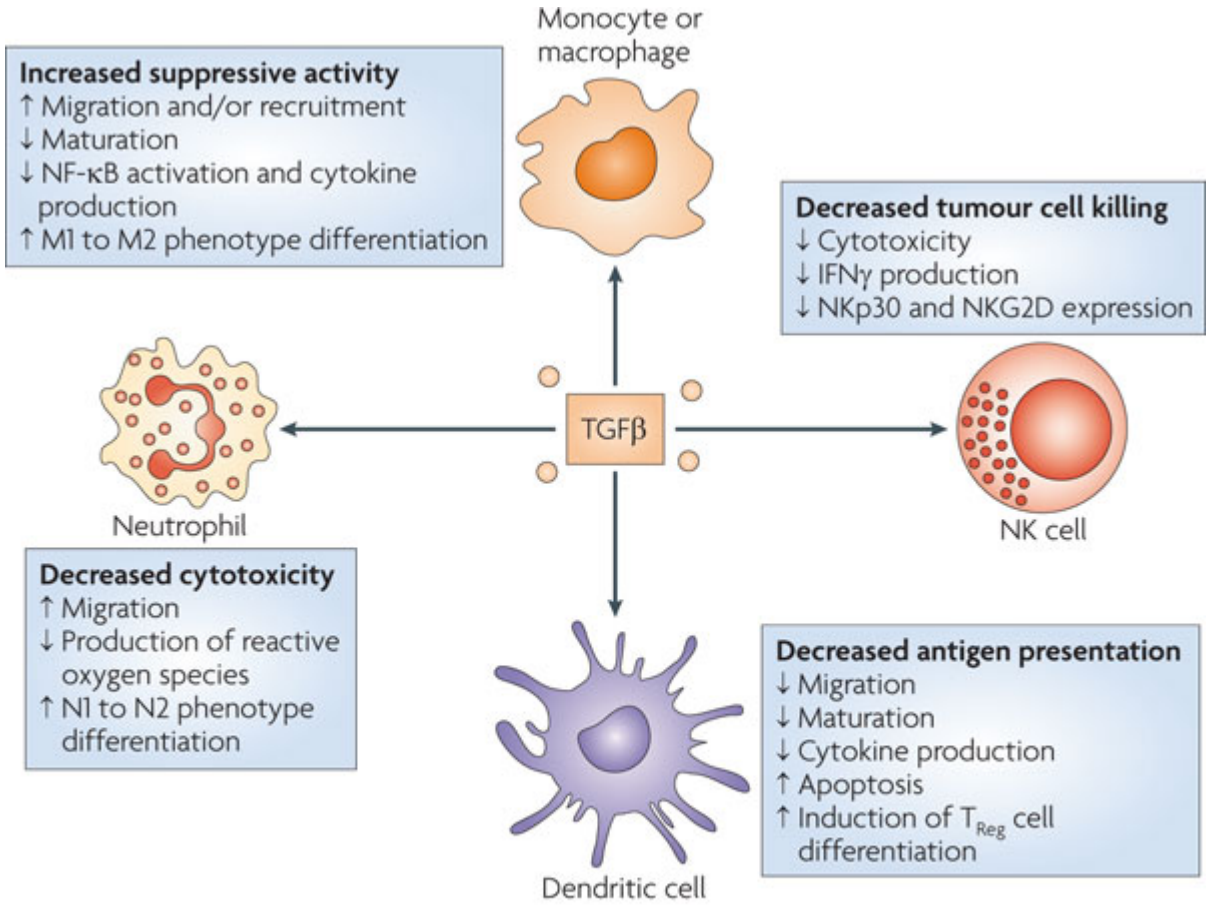
- TGFb
- Myeloid-derived suppressor cells (MDSC)
- IDO
- Inhibitory B7 molecules

The yin and yang of TGFb in tumour development, maintenance and metastasis formation



Effects of TGFb on innate immune cells



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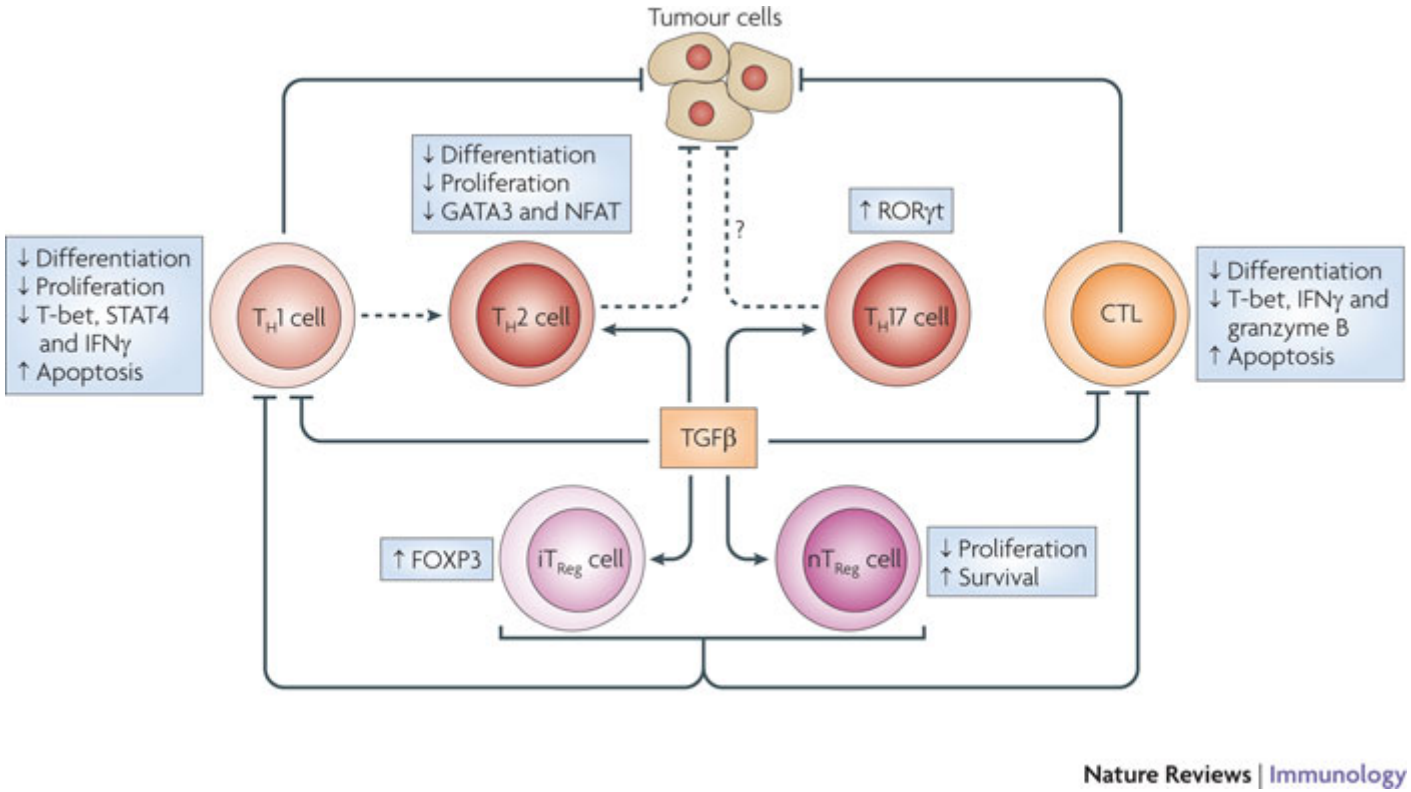
Effects of TGFb on effector T cells



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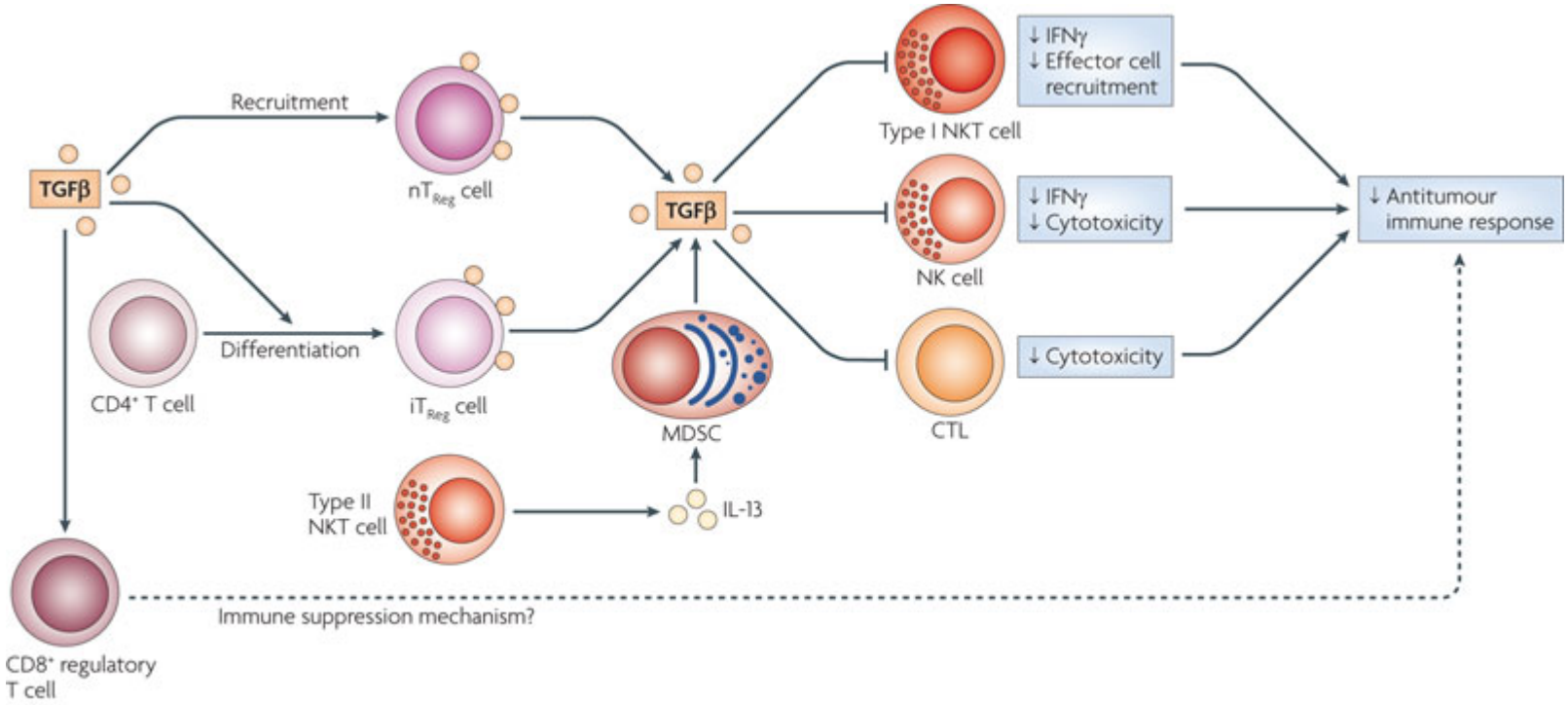
Effects of TGFb on regulatory T cells



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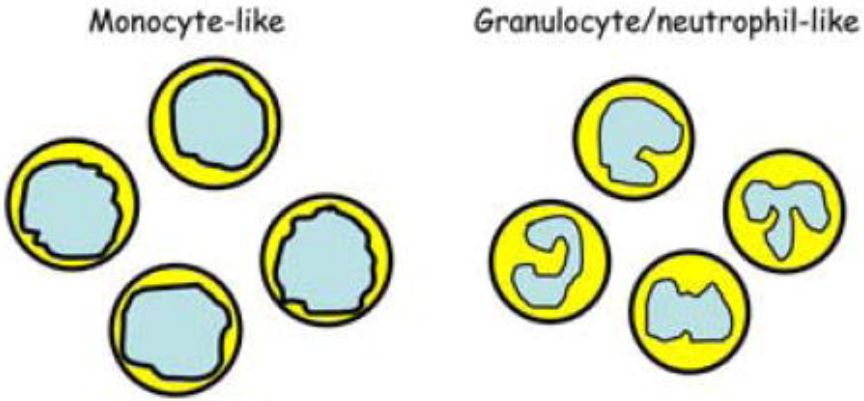
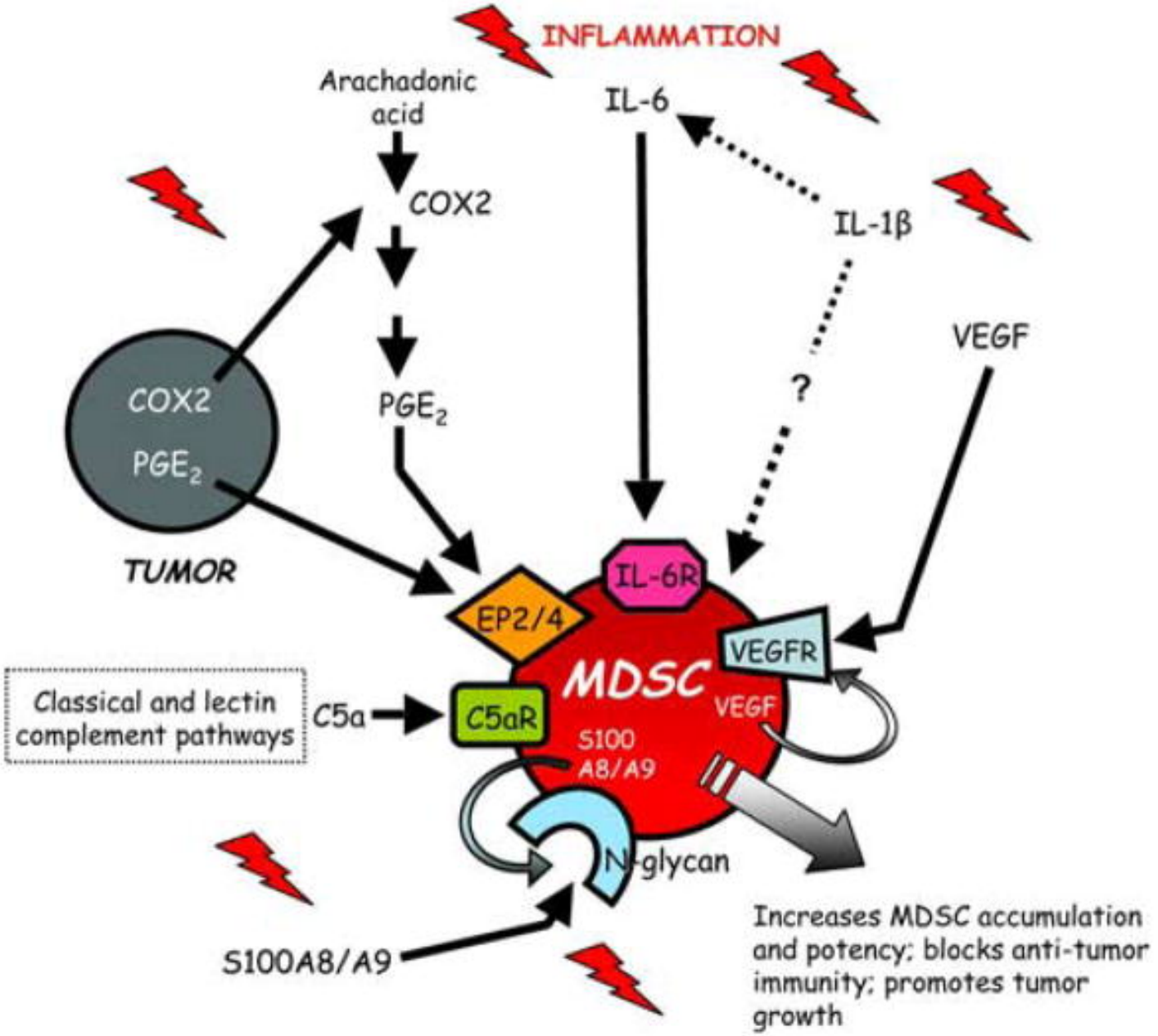
Comparison of Mouse and human MDSC

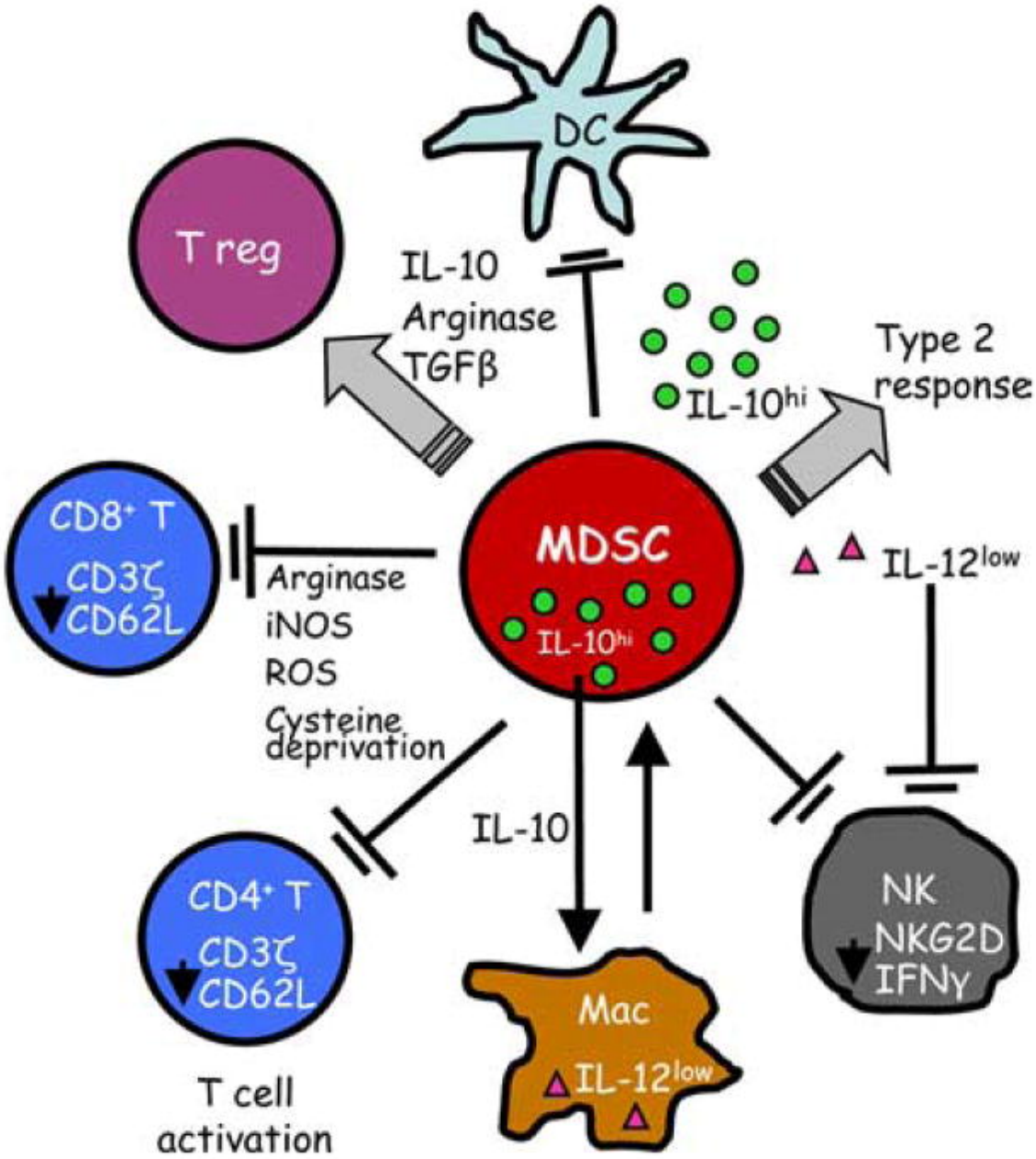


	MOUSE MDSC	HUMAN MDSC
Common plasma membrane markers:	Gr1, CD11b	CD33, CD11b, CD15, CD14 negative MHC class II negative
Plasma membrane markers found on *some* MDSC:	CD80, F4/80, IL-4Ra CD115, Ly6C, Ly6G	CD14, HLA-DR$^{low\ or\ -}$
Intracellular markers:	Arginase, iNOS, ROS	Arginase, iNOS
Suppressive activity/mechanism:	NO, Arginase, Nitrotyrosine ROS undetectable (monocyte-like) ROS, Arginase, Nitrotyrosine NO undetectable (neutrophil-like)	NO, Arginase Nitrotyrosine

MDSC are activated by multiple proinflammatory mediators.



Cellular targets of MDSC.



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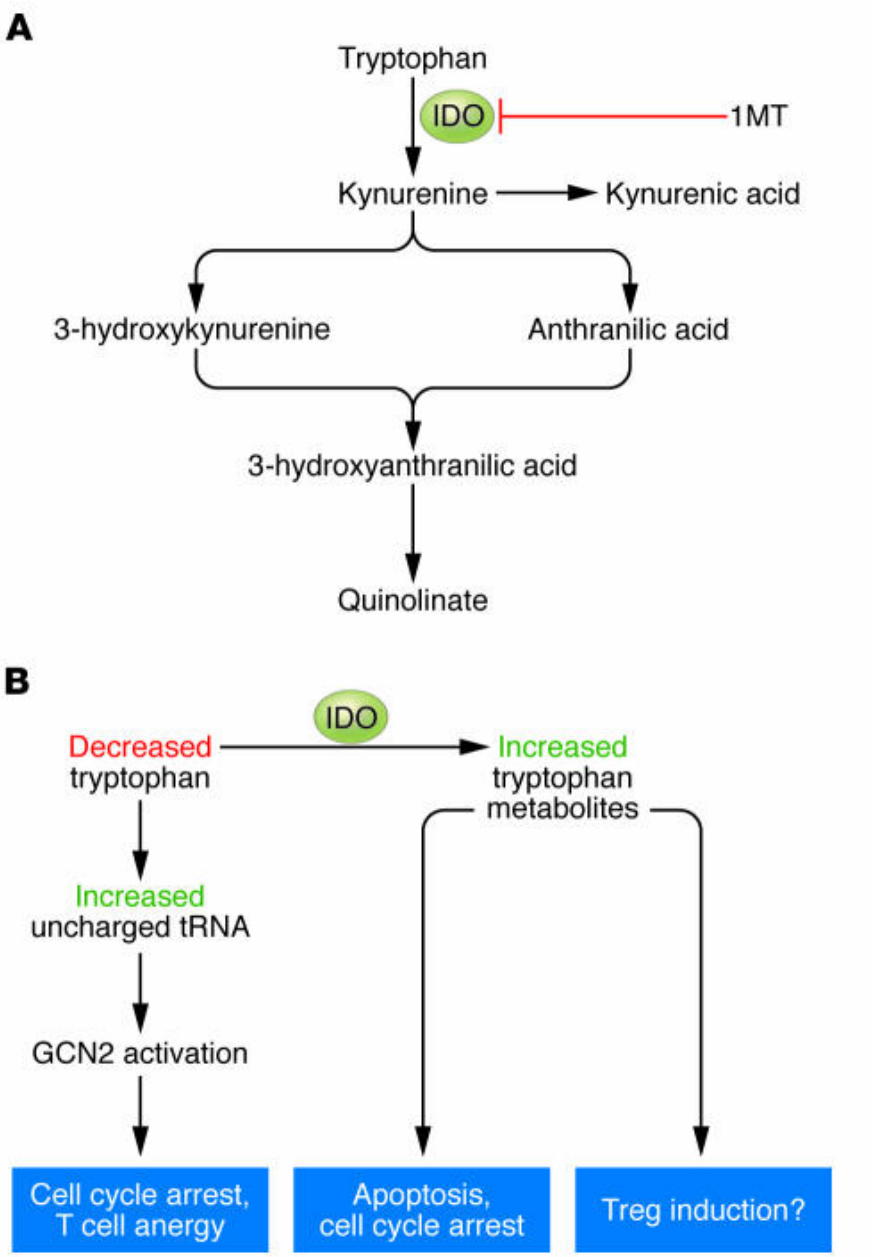
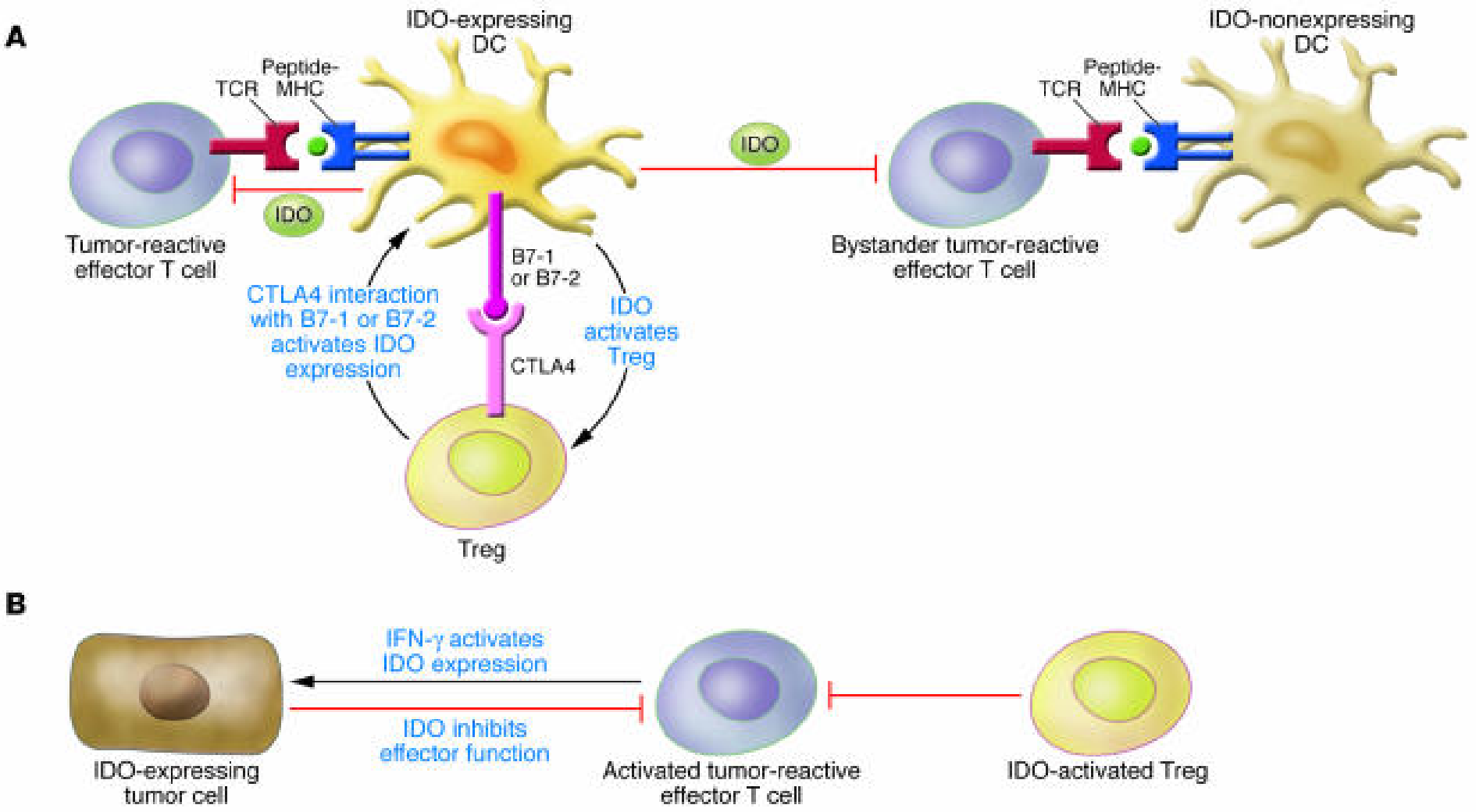
IDO and tumour immune evasion

- Indoleamine 2,3-dioxygenase (IDO) is an enzyme that degrades the essential amino acid tryptophan.
- Most mouse tumour cell lines and many fresh isolated human tumours constitutively express functionally active IDO.
- Treg cells induce plasmacytoid DC (pDC) to express IDO via CTLA4-B7 interactions
- IDO-expressing pDC inhibit T cell proliferation and induce T cell anergy
- IDO-expressing cells produce kynurenines (the main products of tryptophan catabolism by IDO) which are able to induce apoptosis of activated T and B cells.

Molecular mechanisms of IDO-induced immunosuppression.



Model of the effects of IDO in tumour-draining lymph nodes and tumour tissue



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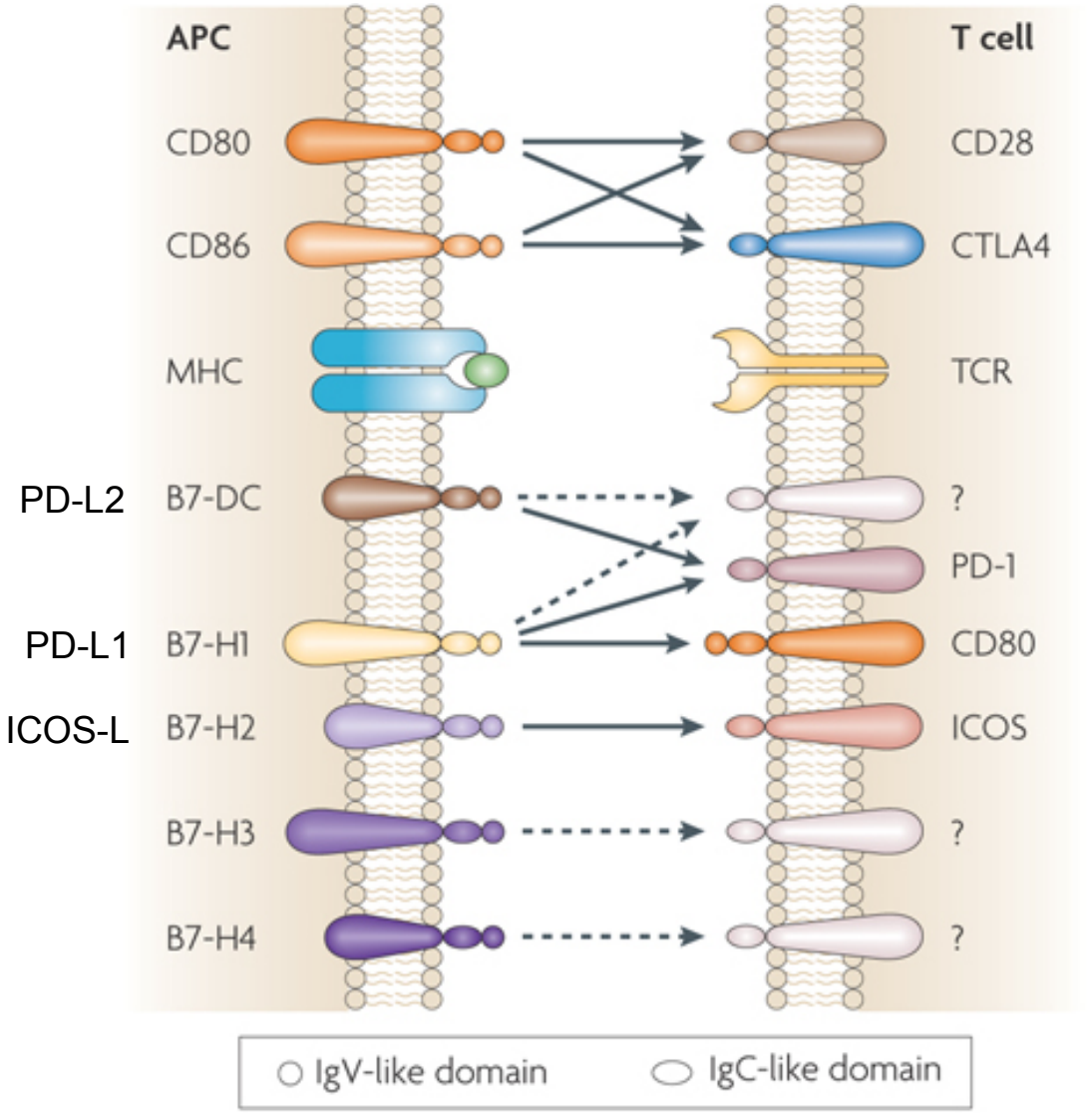
Inhibitory B7 molecules (B7-H1 and B7-H4)



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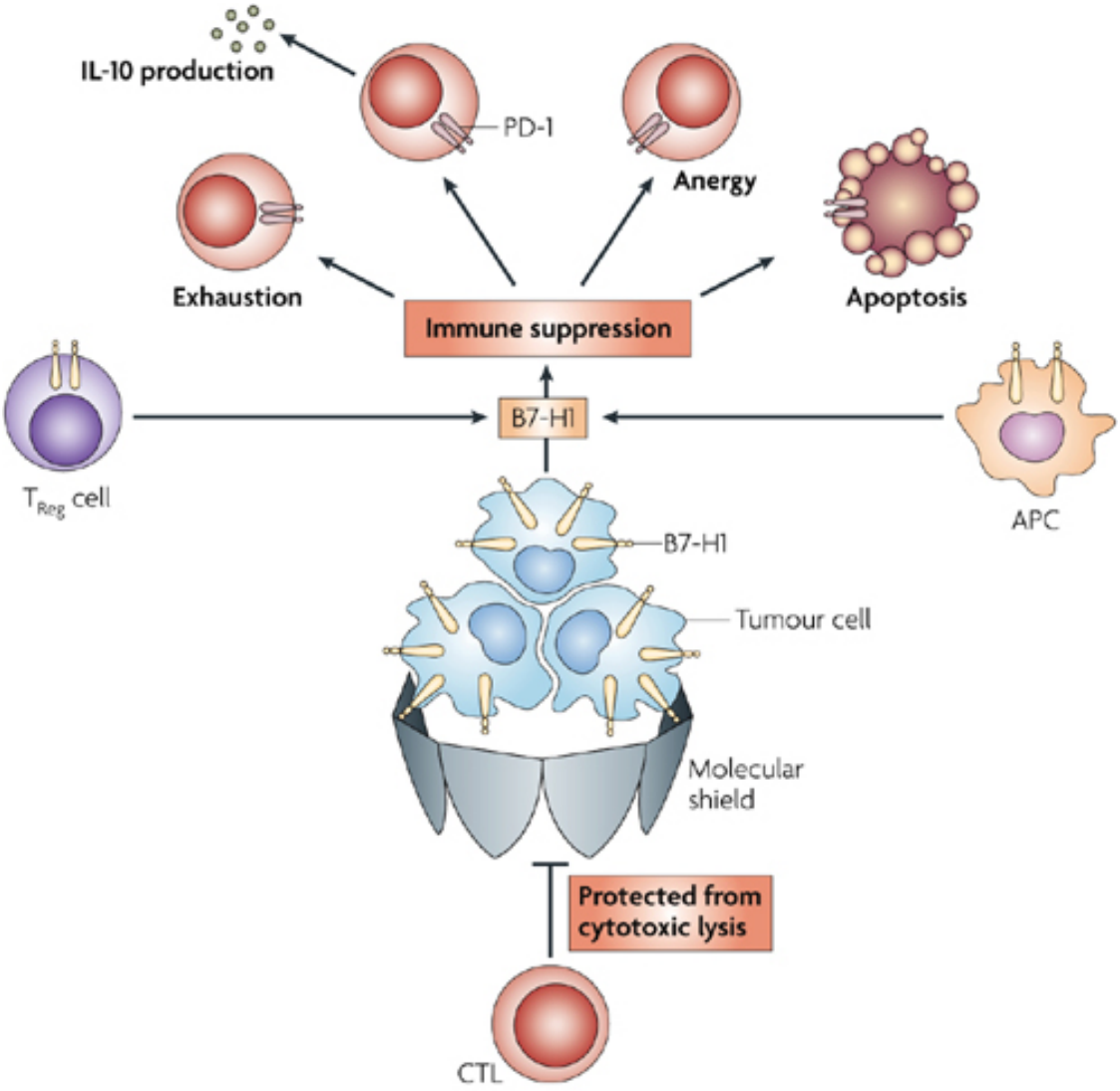
The inhibitory actions of B7-H1 in tumour immune evasion



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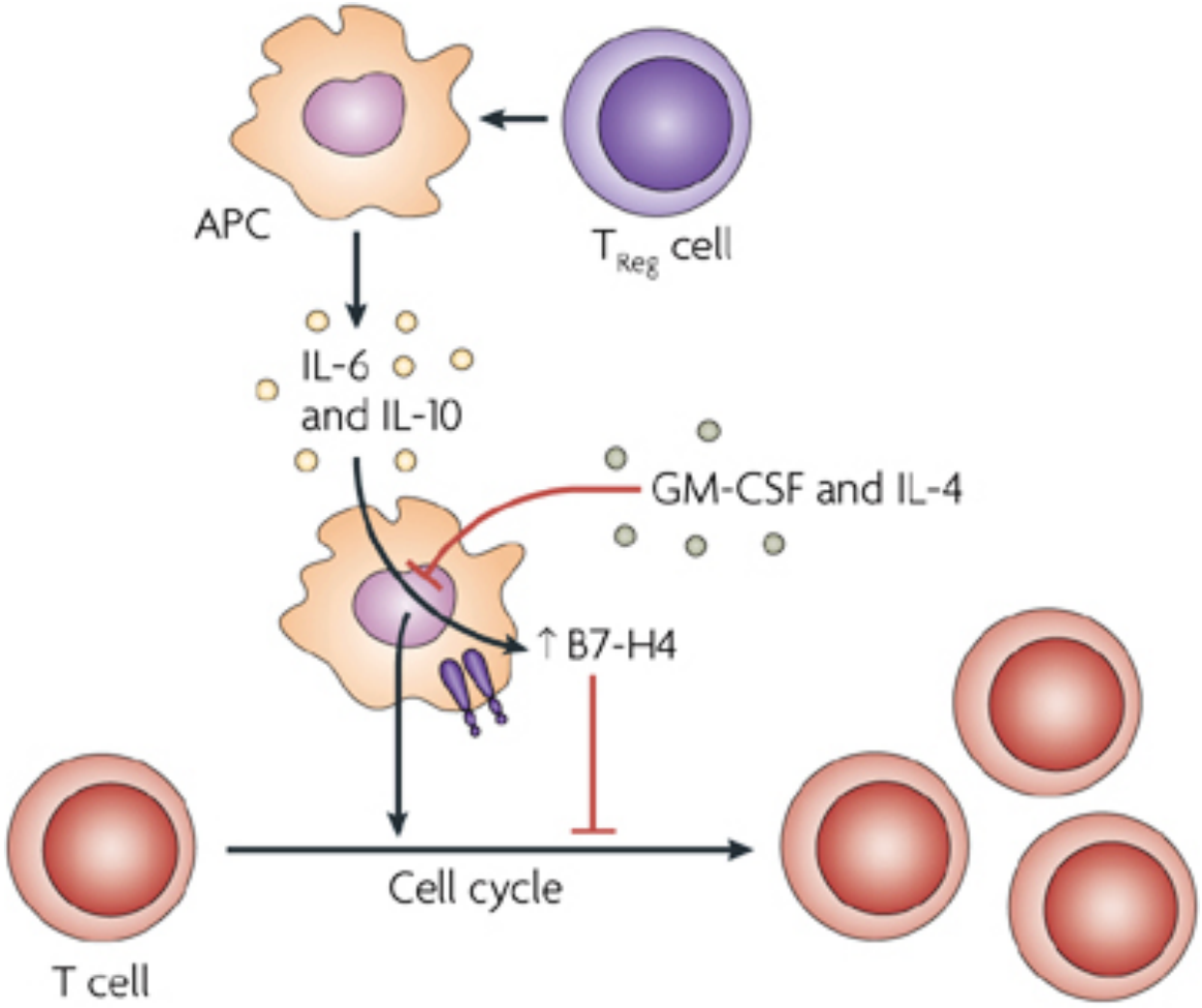
B7-H4^{+} APC (TAM) induce T cell cycle arrest



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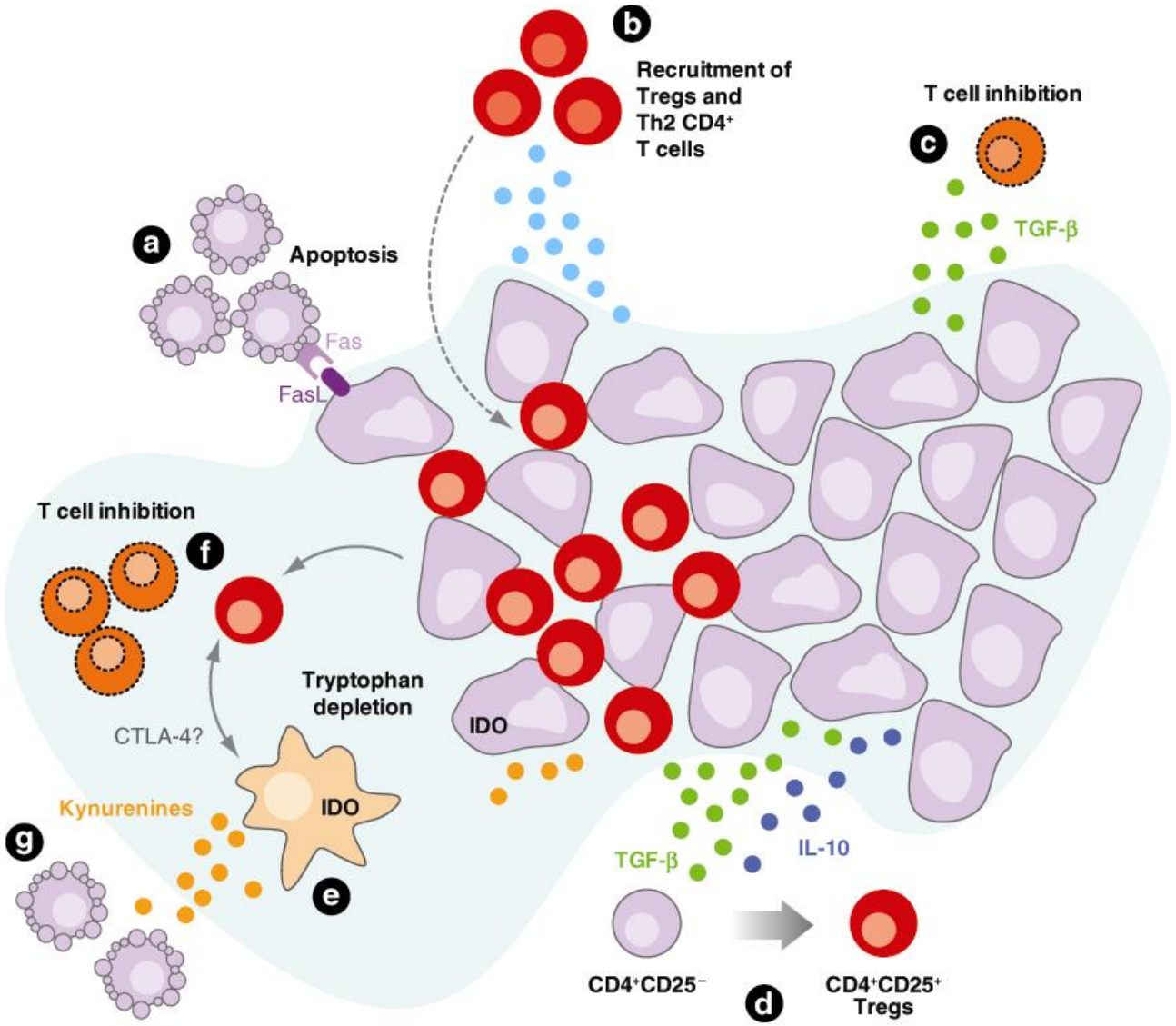
Tumor immune evasion strategies.



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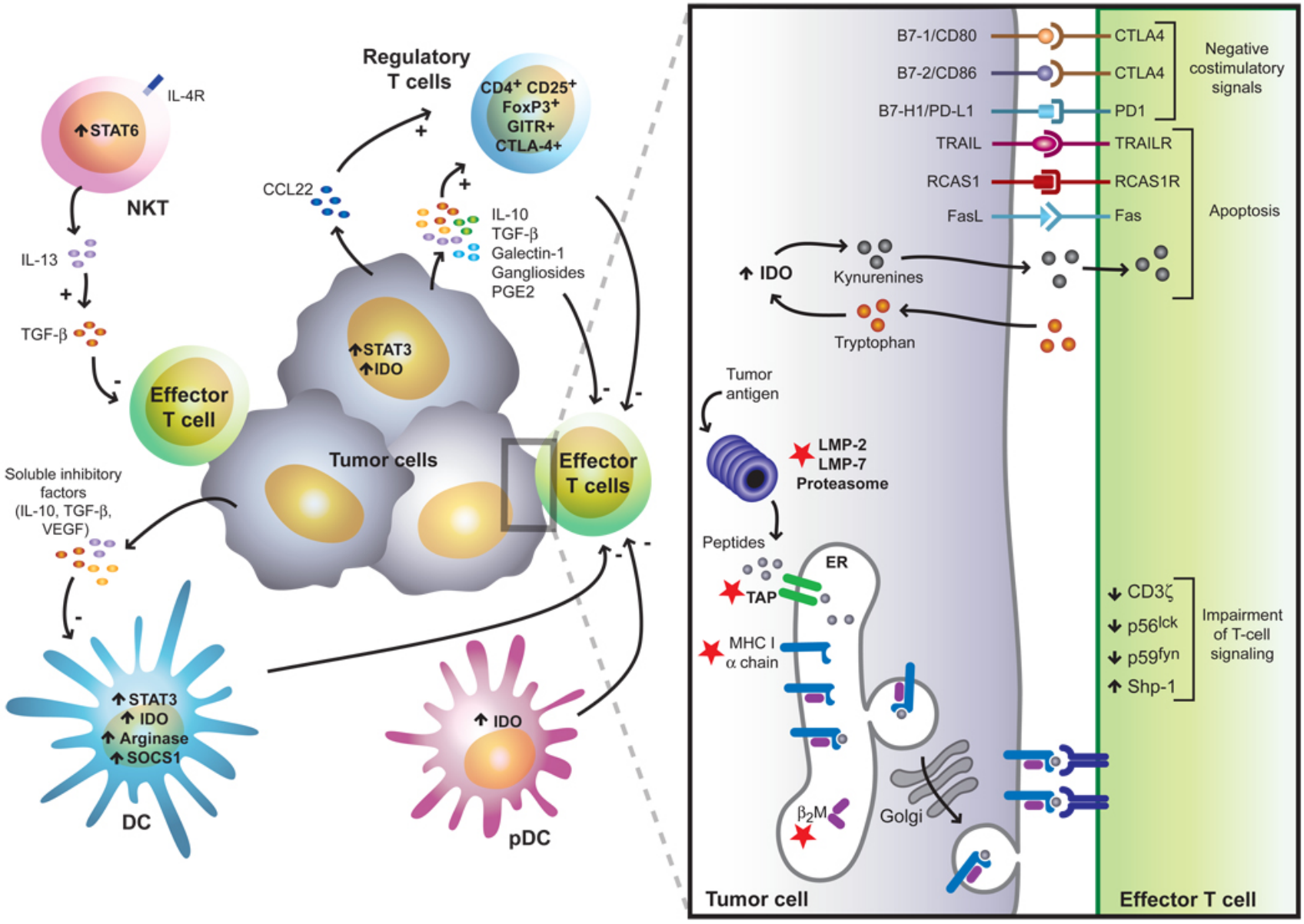
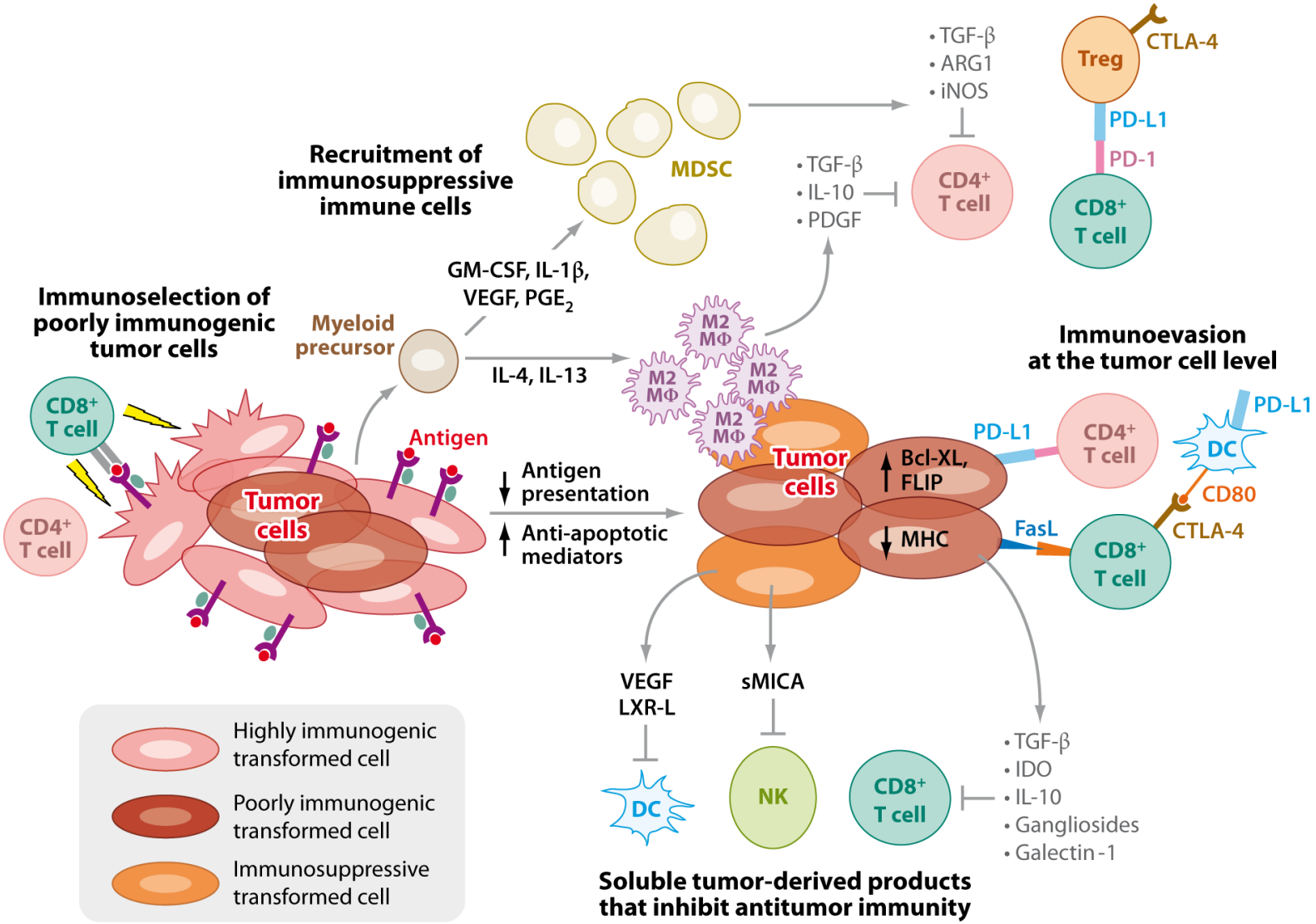
Tumor immune evasion strategies.



Tumor immune evasion strategies.



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