Mechanisms of tumor-induced immunosuppression

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Disclosures

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Consultant: Pieris Pharmaceuticals, Kalivir, Century Therapeutics, Novasenta, BlueSphereBio
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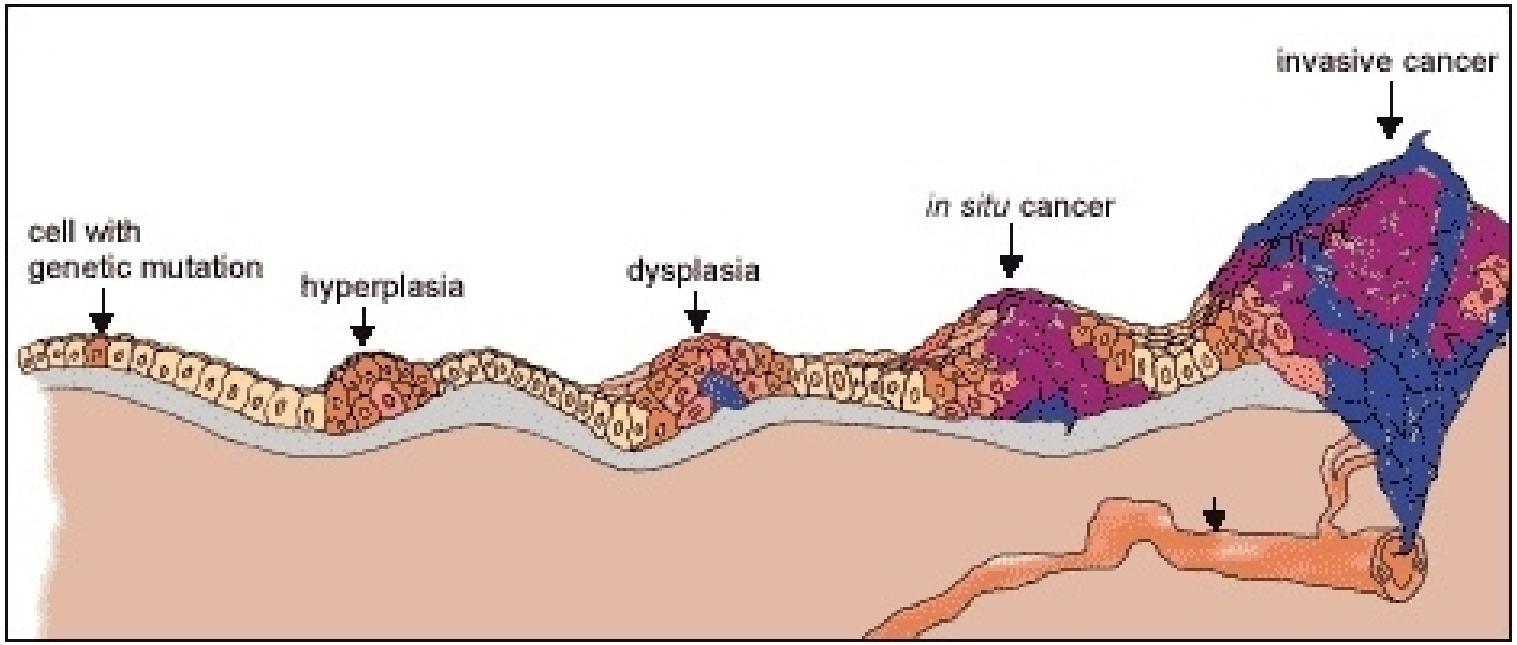
Founder and Scientific Advisor: Novasenta

Objectives

- Review tumorigenesis and how it serves as a platform for immunosuppression
- Understand the role of the immune system in surveilling the host for developing neoplasia
- Discuss cancer cell-intrinsic immunosuppressive mechanisms
- Discuss how cancer cells change their environment to be tolerogenic

Metastatic tumors do not grow overnight

- Rather, cancer represents a perfect storm, in which a few genetic lesions provide some abnormal cell growth
- This abnormal cell growth then becomes a platform for future mutation, adaptation, and unrestrained growth
- Tumor Darwinism



How do neoplastic cells begin?

- However, a few key transformations does not a cancer make
- In essence, in order to survive, cells in early genetic lesions (hyperplastic and dysplastic cells) need to become **evolution machines**
- The driving force behind this becomes **proliferation** and **mutation**
- The most successful cancer cells can break free of regulation and proliferate uncontrolled; they must continue to mutate genes in order to continue

Targeting cancer: early approaches

- Essentially, early neoplasia and transformed cells mutate essential genes, which then encode for new and different proteins
- The 1990s saw a huge rush of scientific research in identifying and cloning genes that are overexpressed in cancer, and designing drugs that might target these new proteins
- However, this proves difficult, as very few proteins are shared between individual cancers, and even then, the tumor will simply evolve away binding sites for these drugs
- These proteins essentially become **nonself**, so if we had an *in vivo* mechanism to differentiate self from nonself, we'd be set, right?

The immune system certainly sees cancer as it develops

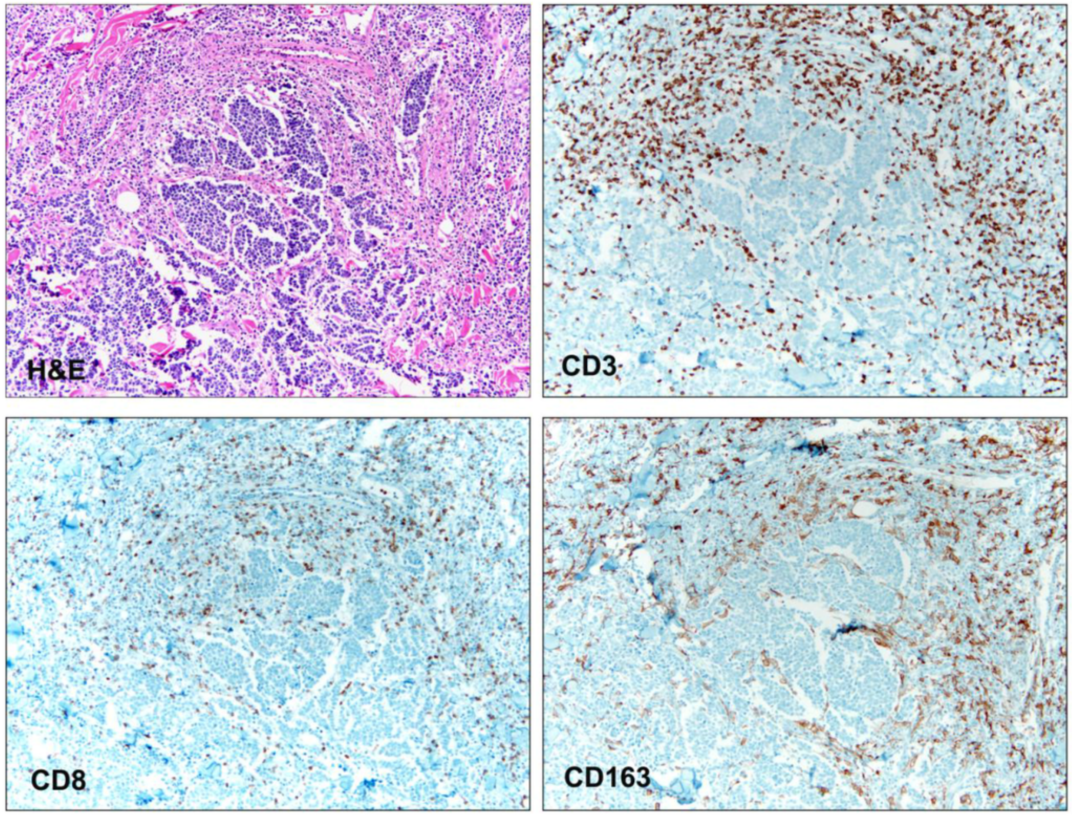
Evidence

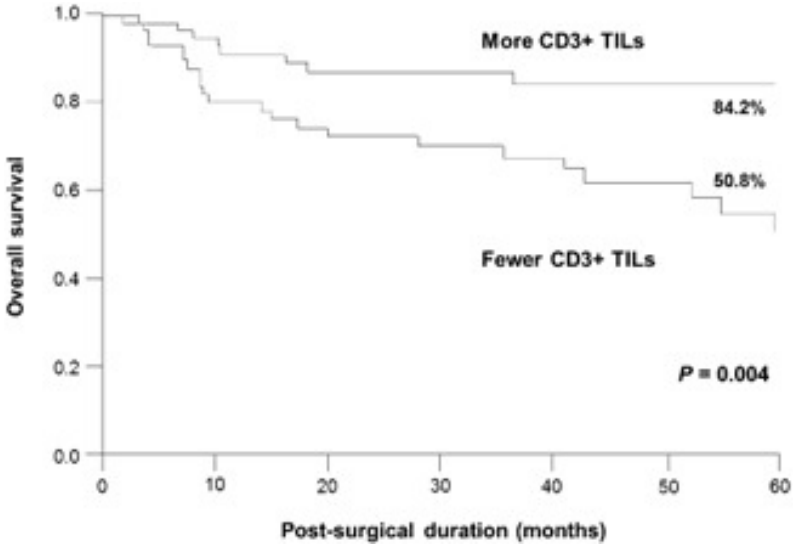
- Histopathologic observations: lymphocytic infiltrate in tumors occurs, and generally correlates with better prognosis
- Clinical: immunodeficient individuals have increased incidence of some types of cancer
- Experimental: animals retain immunologic memory to tumors

Conclusion

- Immune responses against tumors inhibit progression
- The immune system protects against some tumors
- Tumor immunity is a feature of adaptive immunity

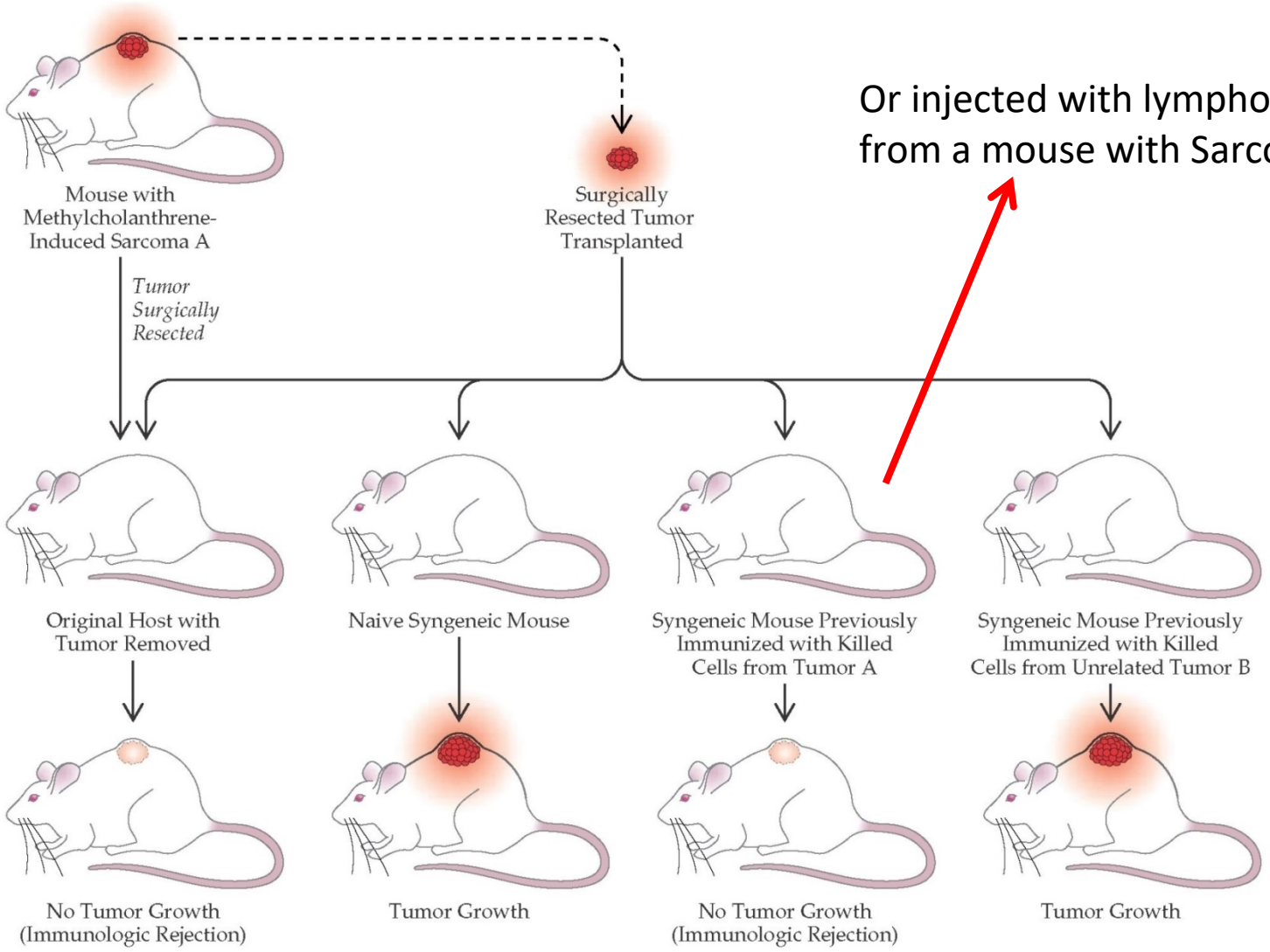
Immune cells can infiltrate tumors





Immunosuppression can promote some cancers

- **Transplant patients and individuals with primary immunodeficiencies**
  - Non-Hodgkin's lymphoma
  - Melanomas
  - Lung, colon, lung, bladder, kidney cancer can arise with greater prevalance in those receiving immunosuppression after transplants
- **AIDS (secondary immunodeficiency)**
  - Kaposi's sarcoma (traditionally a cancer of the aged)



Or injected with lymphocytes from a mouse with Sarcoma A

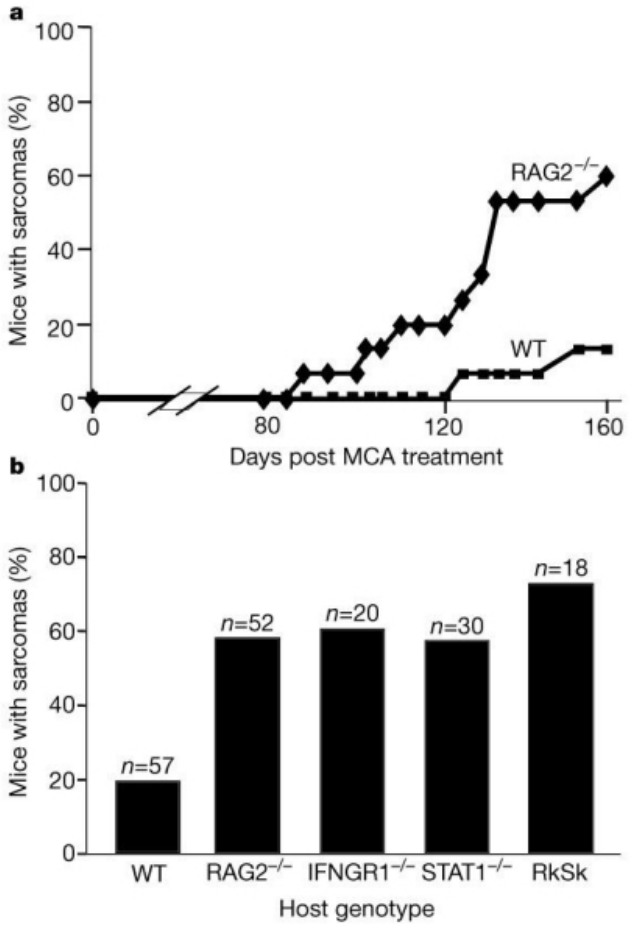
Thus, tumor immunity exists.. but how does it work?

Immunosurveillance

- 1908 – Paul Ehrlich hypothesizes that ‘the immune system could repress an overwhelming frequency of carcinomas’
- 1957 – Burnet and Thomas formalize the theory
  - Developing cancers, by virtue of mutation, present ‘neoantigens’ which can be detected by the immune system
  - Thus, the immune system constantly surveils the host for developing hyperplasia
  - Clinically apparent cancer represents a failure of the immune response to detect these antigens

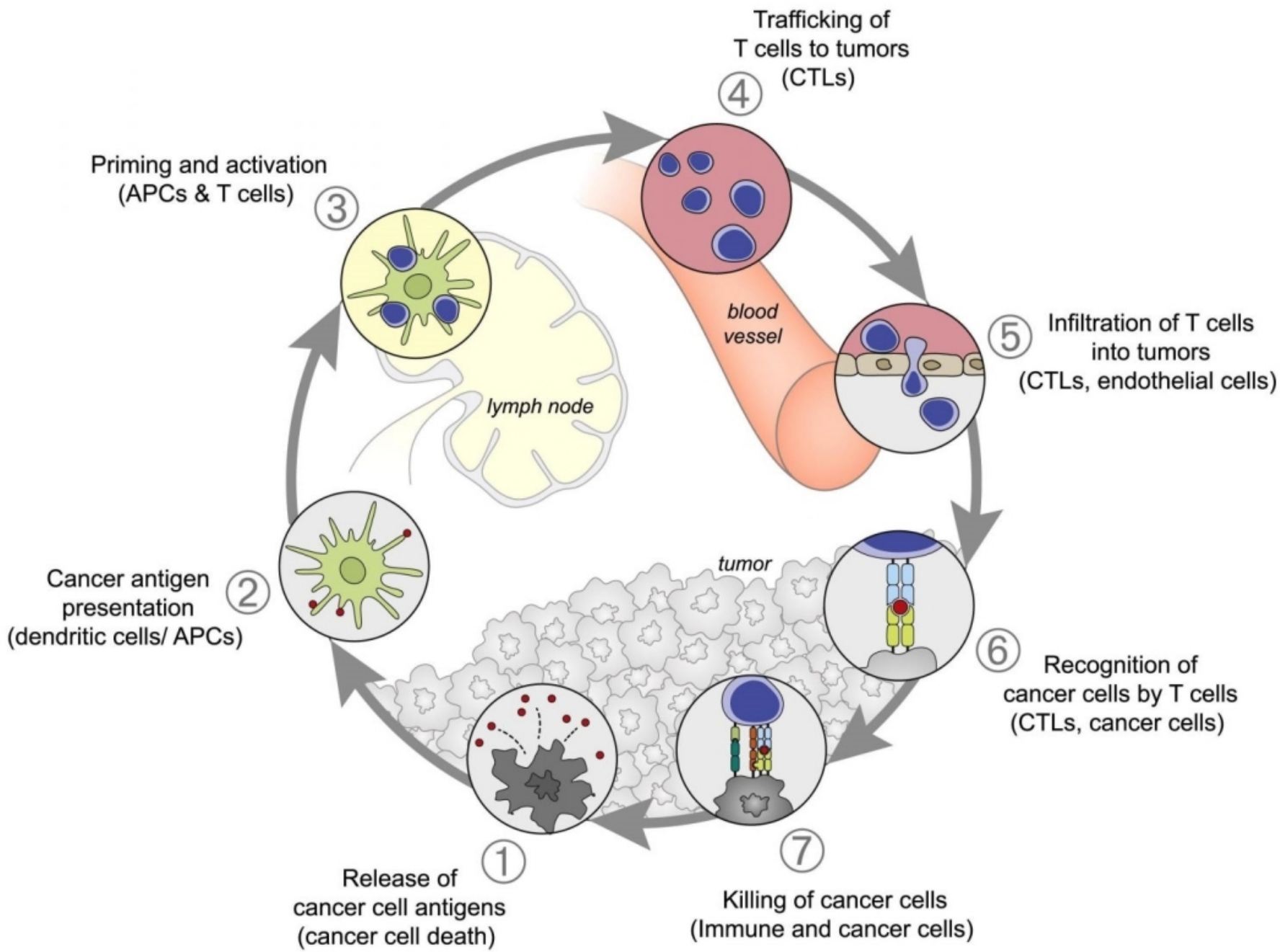
Genetic evidence for immunosurveillance

- RAG$^{-/-}$ (no B or T cells) mice get gastric cancers, increased susceptibility to chemically induced cancers
- Perforin$^{-/-}$ get lymphoma
- Defects in IFNg promote general increases in spontaneous tumors, highly susceptible to chemically induced cancers



Clinical evidence for immunosurveillance

- Occult cancers: transplant recipients under immunosuppression can develop cancers from the donor organ
- Older individuals have increased risks of cancer (immune system activity declines with age)
- In some individuals, spontaneous regression of cancers can occur!

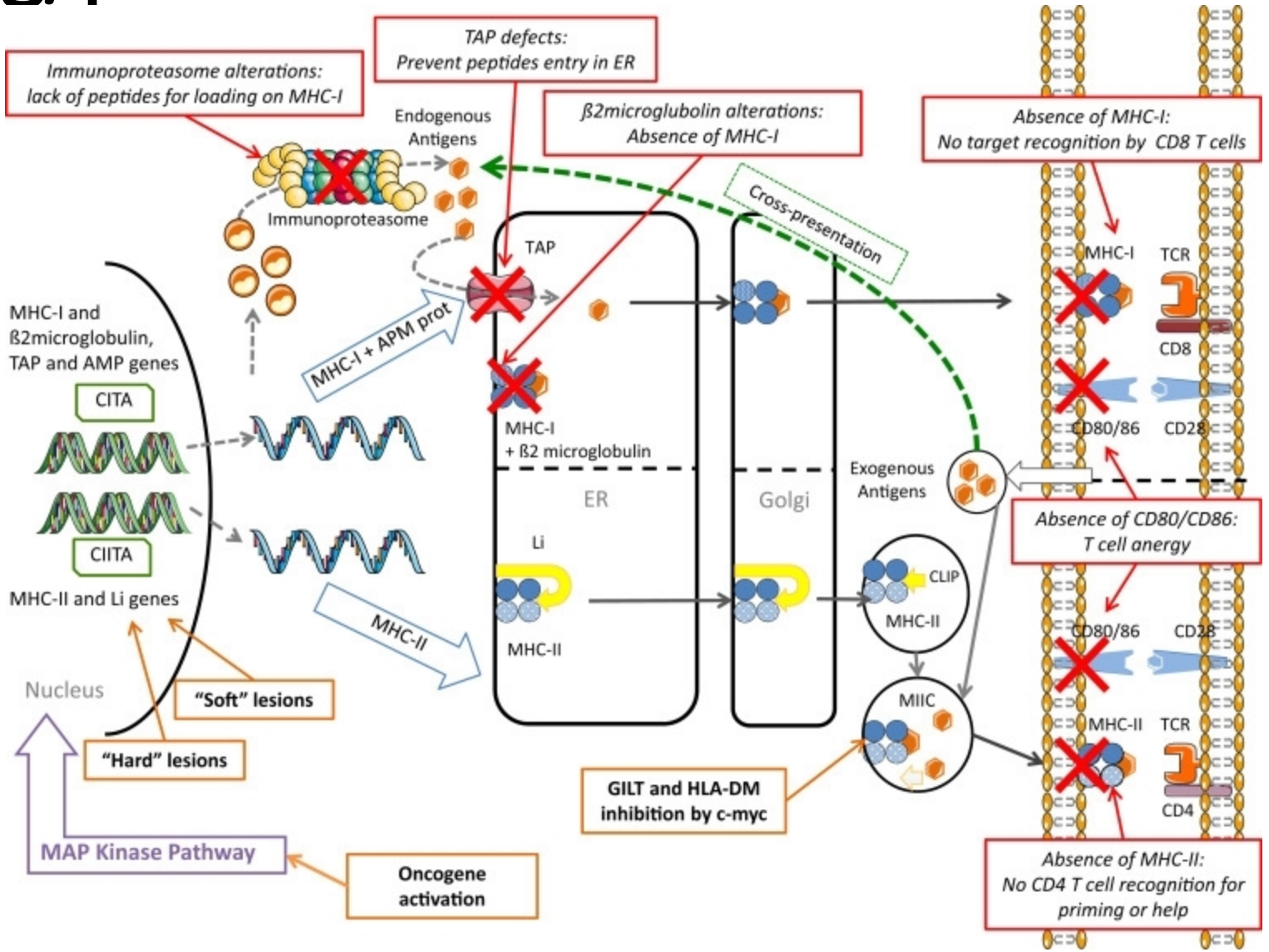


From Chen and Mellman 2013, Immunity 39(1):1-10

Going rogue: evading immune surveillance

- Despite all of the immune surveillance and tumor reactivity of the cellular players in immunity, humans still get cancer
- This is likely due to time; a subclinical cancerous lesion likely has years, even decades of trial and error to acquire beneficial adaptations
- We will first talk about cancer-cell intrinsic mechanisms, which may occur early in tumorigenesis
- Several of these are relatively common in anti-tumor immunity
  - Loss of antigen processing/presentation
  - Antigen loss
  - Lack of immunogenic cell death
  - Upregulation of inhibitory ligands

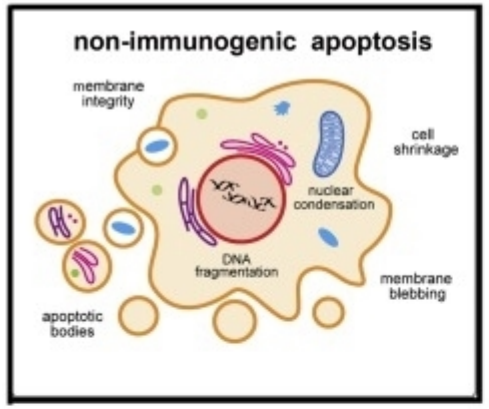
Common adaptations in MHC processing/presentation



Antigen loss variants

- Many times, what the immune system ‘sees’ is a passenger mutation, some random protein that was mutated in a way that it became detectable to a T cell, but that plays no beneficial role in the tumor cell’s biology
- In other words, the mutated gene that the immune system is detecting may be dispensable
- Strong immune stimulation may simply provide a selective pressure to downregulate or mutate the neoantigen

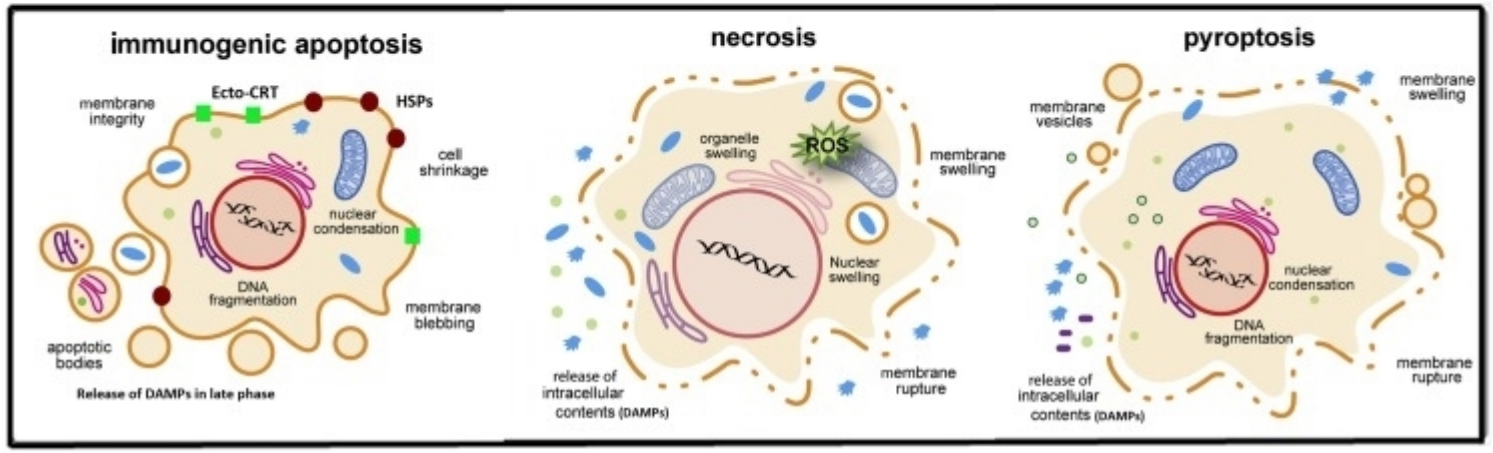
Cancer cells don’t even die the right way



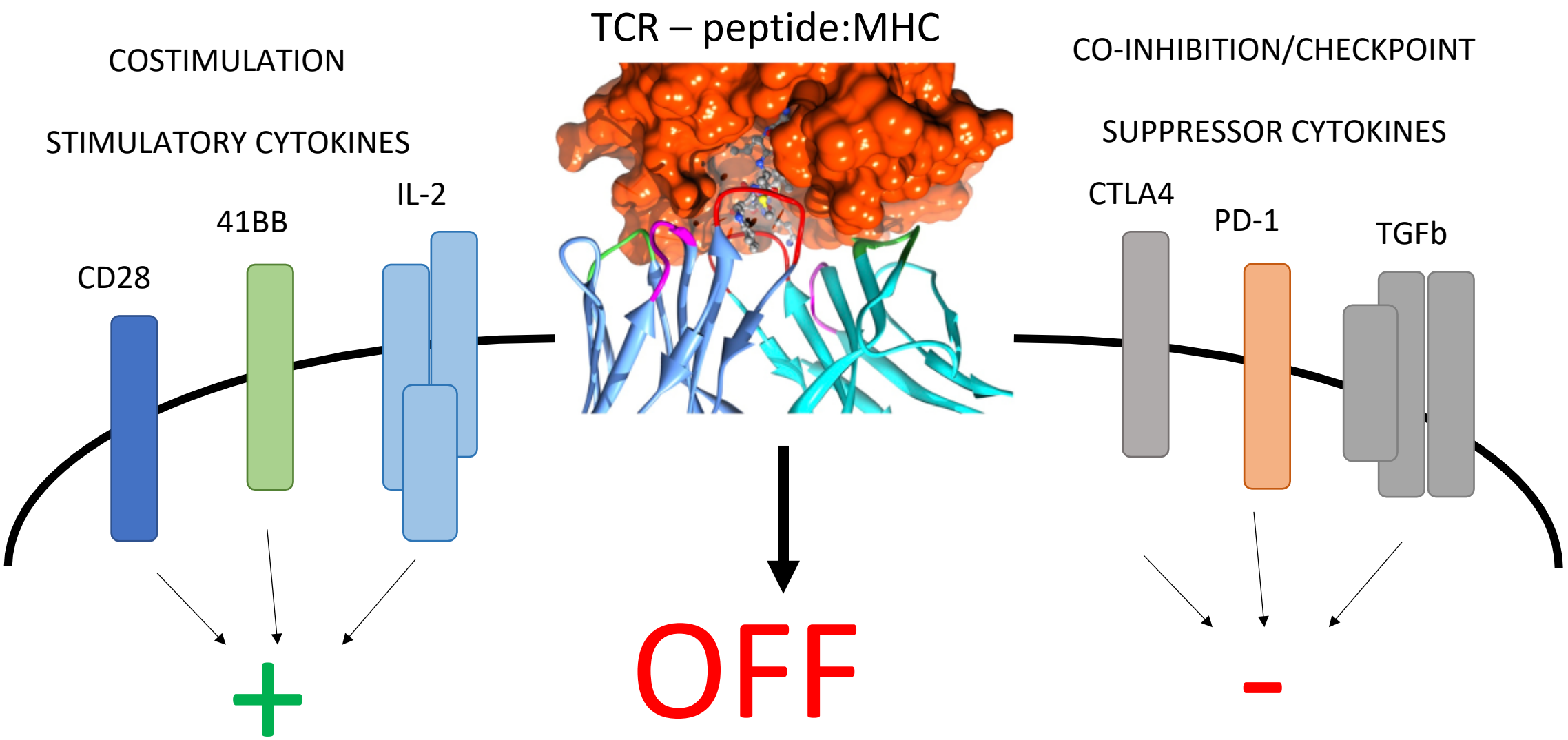
Non-immunogenic cell death mode

- Another way cancer cells avoid detection is to apoptose in ways that avoid immune detection
- Indeed some ways to boost immune-based therapies are to induce more immunogenic forms of cell death

Immunogenic cell death modes



Some brief background in basic immunology

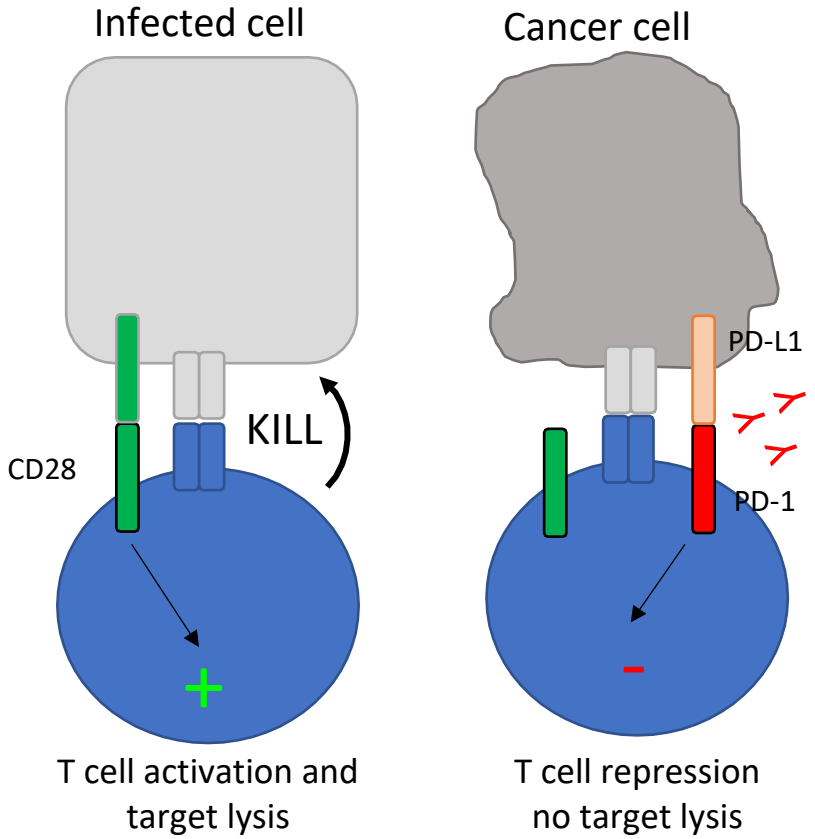


Costimulation and co-inhibition

- T cells gain a sense of context of the antigen through the cell surface ligations that take place with the target
- The 1990s-2000s saw a wave of a new study of immunoregulation, delineating these cell surface receptors, their ligands, the signaling pathways downstream, and the transcriptional programs promoted by these axis
- While an oversimplification, costimulation is essentially the ‘net sum’ of costimulatory and co-inhibitory signals; the T cell interprets these signals and makes immediate functional decisions, but also makes long-term fate decisions based on these interactions

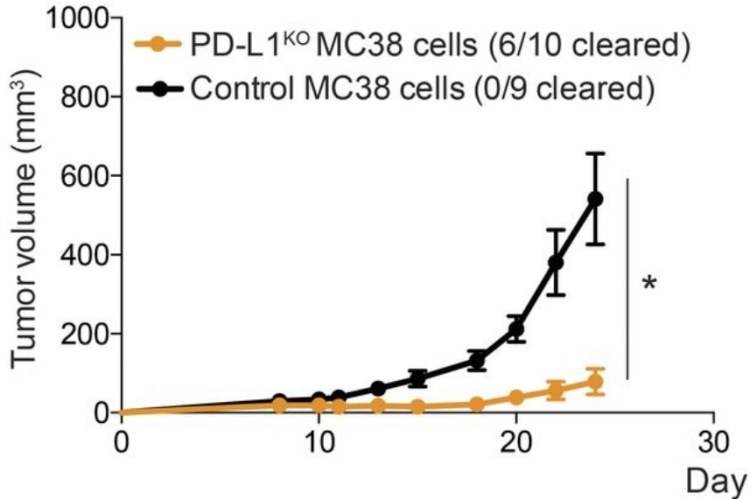
A molecular shield: upregulation of inhibitory ligands

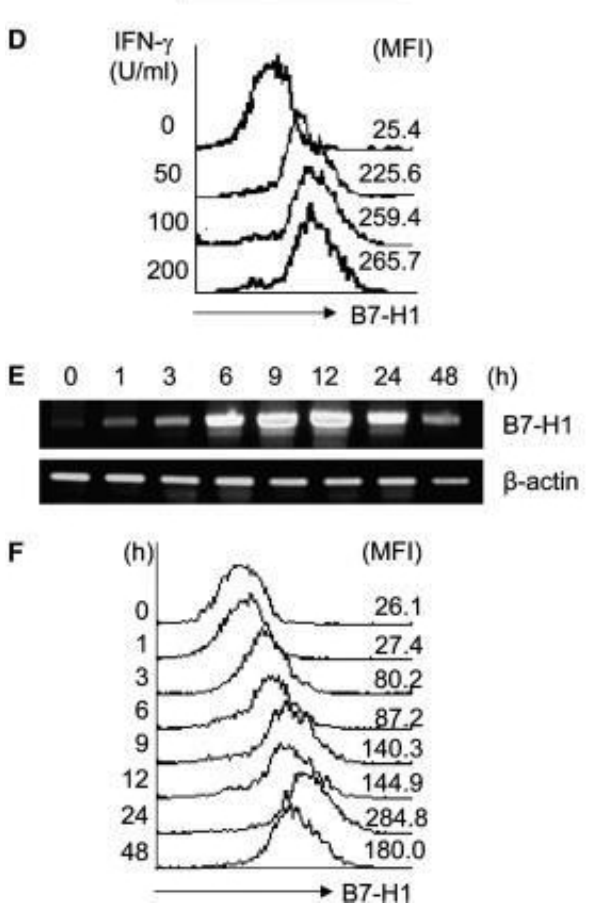
- Generally, the ligands for a T cell's costimulatory and co-inhibitory receptors are present on antigen presenting cells and on infected target cells
- However, tumor have learned to upregulate the ligands for co-inhibitory molecules
- The first and most prolific of these discovered was B7-H1, or PD-L1
- PD-L1 is one of two ligands for the programmed death 1 (PD-1) co-inhibitory molecule
- While PD-L2 is expressed by antigen presenting cells, mostly, PD-L1 can be expressed by all manner of cells
- A common adaptation of tumor cells is to upregulate PD-L1, which ligates PD-1 and delivers a negative inhibitory signal
- It is this interaction that checkpoint blockade therapy attempts to break



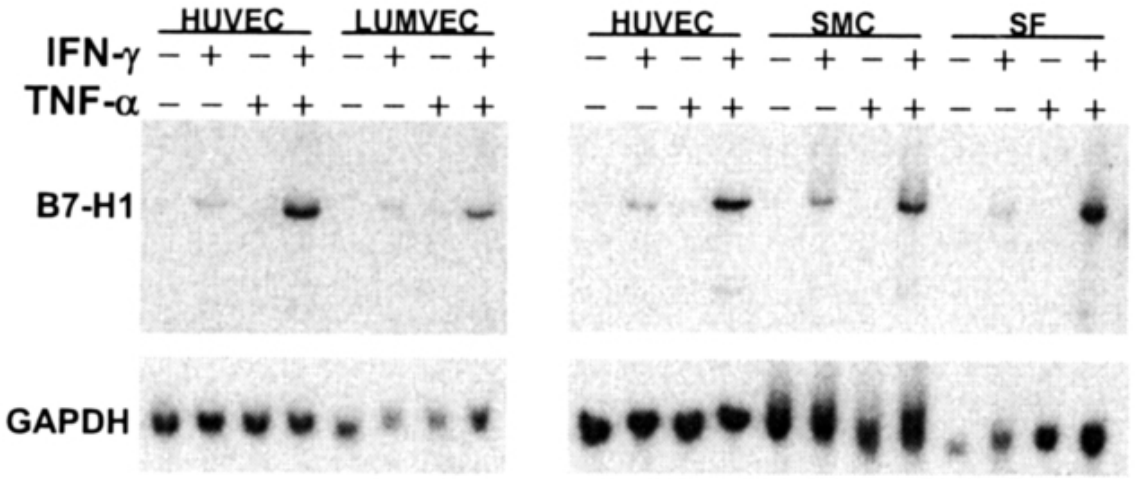
The presence of T cells promotes PD-L1 expression

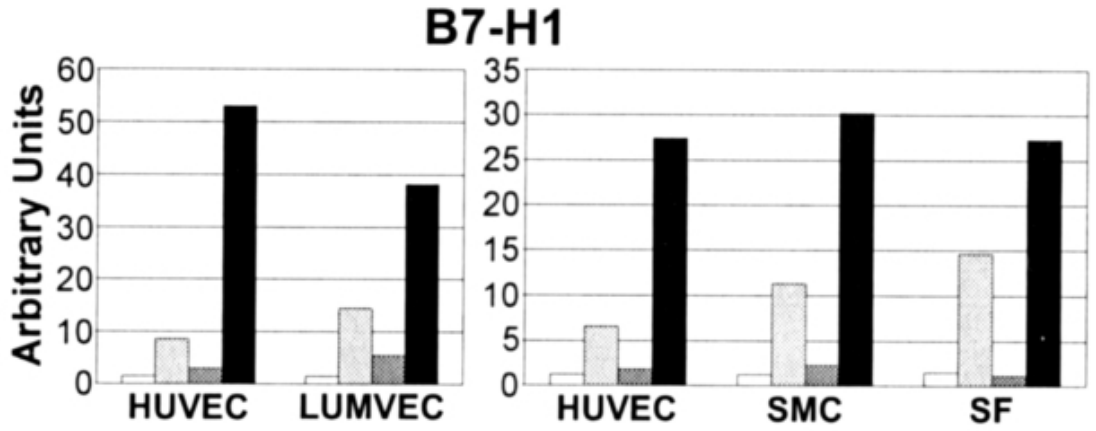
- PD-L1 deficiency on murine tumor cells results in immunologic rejection in many models
- But it is not such a straightforward story: one major way that PD-L1 is transcriptionally upregulated is through stimulation with IFN-gamma, produced by T cells
- Thus, as tumor cells are attacked by T cells, they sense the IFN-gamma and upregulate PD-L1, evading immune attack
- Other factors, like DNA damage, hypoxia, type I interferons, also can upregulate PD-L1 expression





This is not a tumor-specific thing….

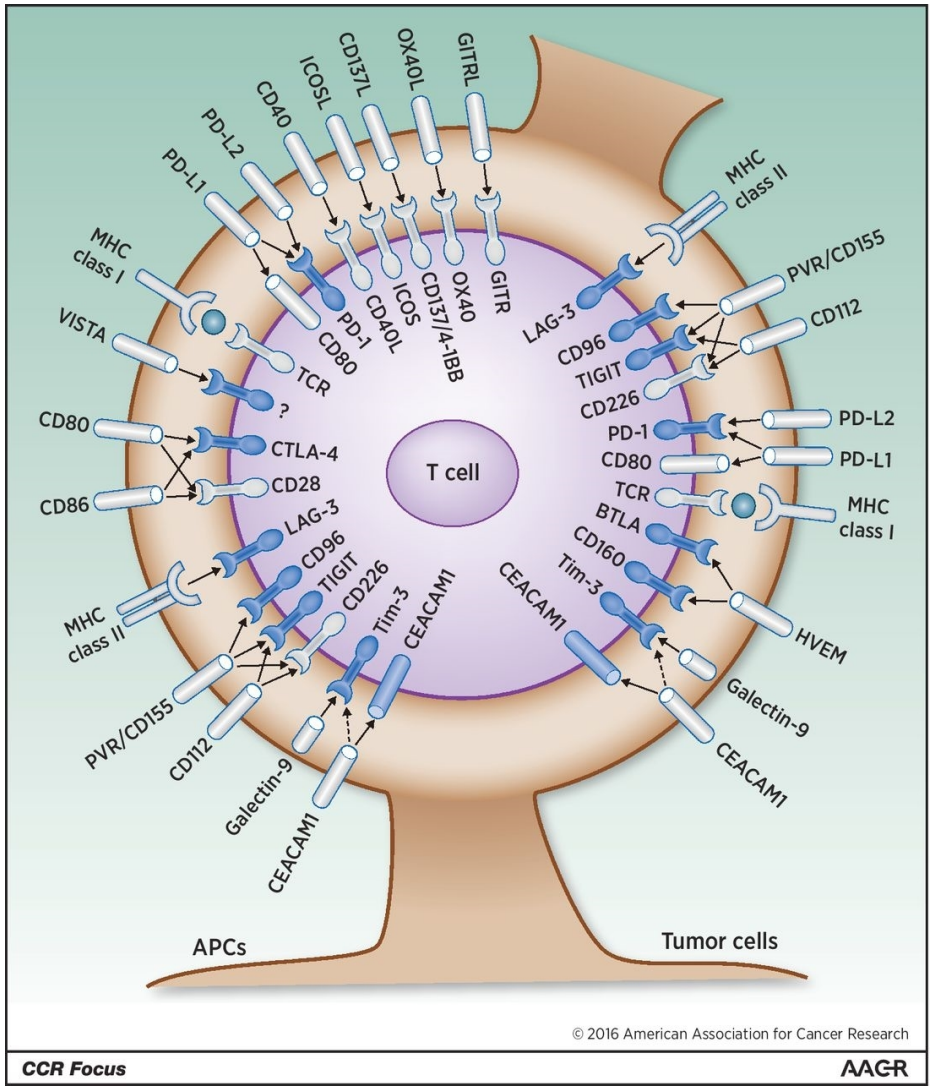




- Many normal cells that see inflammatory cytokines upregulate PD-L1/B7-H1
- Thus, PD-L1 upregulation likely evolved to prevent pathology

Tumor cells and associated stroma can also upregulate ligands for other inhibitory receptors

- Tumor cells are not just a one-trick pony, and PD-L1 is just one of the cell surface ligations they tweak
- It is now clear that tumor cells can upregulate a variety of co-inhibitory molecule ligands, which remain the subject of much study and targeting



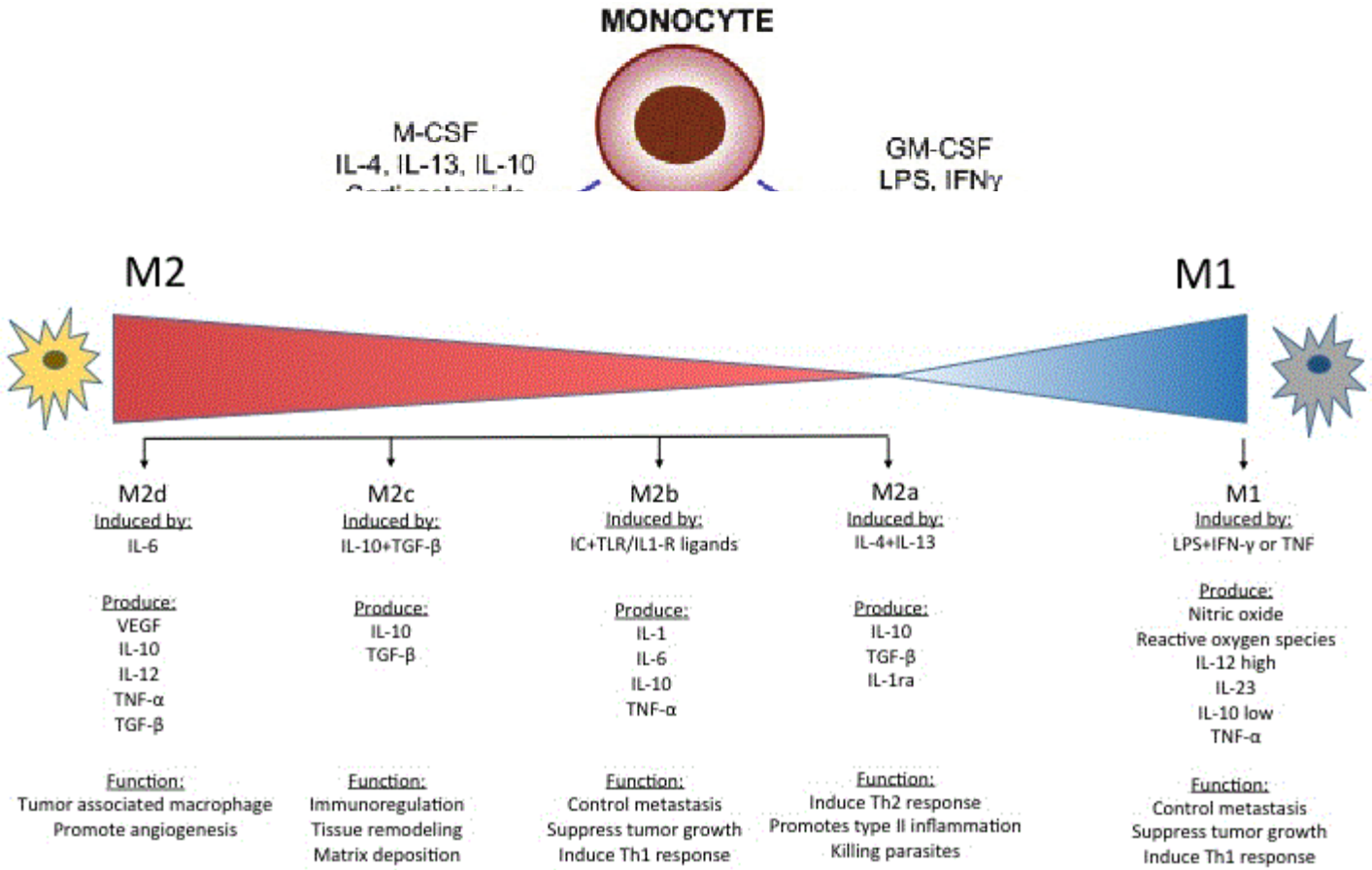
Changing T cell fate

- As mentioned previously, these costimulatory and cytokine interactions not only immediately license T cell functions, but also play vital roles in the future functions of cells
- For instance, T cells that see TCR under co-inhibitory molecule signals only may be rendered **anergic**, a hyporesponsive state that will prevent them from synthesizing cytokines even if they see a proper stimulation in the future
- Tumors can also induce T cell **exhaustion**, which is another type of hyporesponsive state that arises from persistent inflammatory stimulation (join me later for a deep dive in this topic)
- While we could easily talk about T cell dysfunctional fates for an entire hour (and we will, later!), the short story is that tumor cells not only have the machinery to turn off T cells acutely (PD-L1), but to change their differentiation such that their dysfunction persists

Recruiting the turncoats

- These types of inhibitory mechanisms are generally tumor cell-intrinsic, can be replicated *in vitro* in isolation by coculturing tumor cells and T cells, essentially (in fact, that's how most of these mechanisms were discovered!)
- However, there exists a myriad of **tumor cell extrinsic** immunosuppressive mechanisms that mostly involve recruiting inhibitory populations or changing the way that cells differentiate

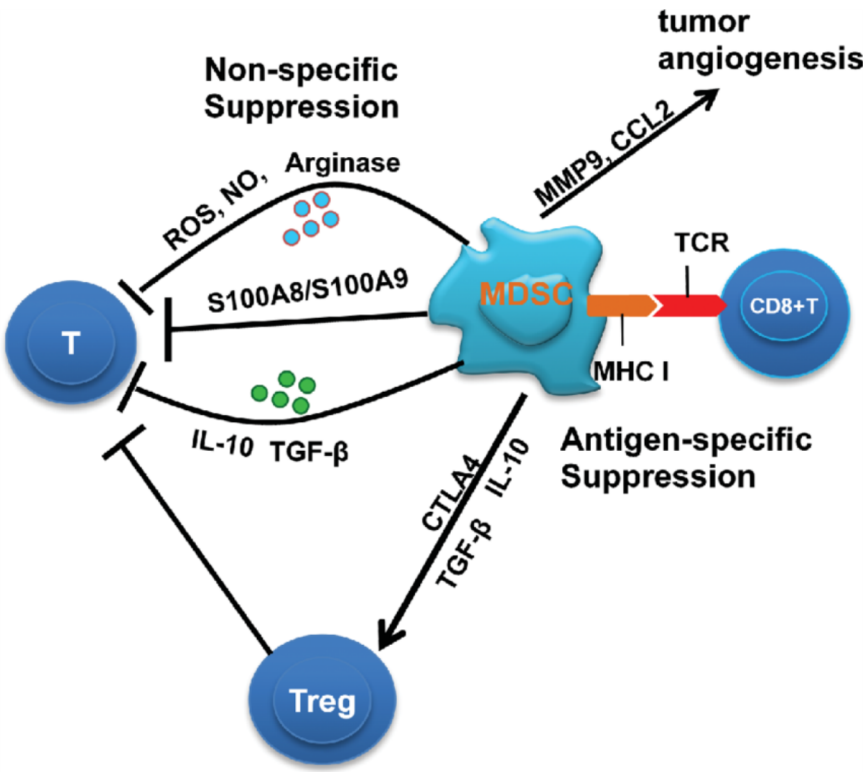
Changing APC makeup



- Productive T cell immunity requires antigen presenting cells to deliver vital costimulatory and cytokine signals
- Tumors often change their environment, which alters the APC makeup
- This is especially the case in the macrophage compartment
- It may be reprogramming or altered differentiation

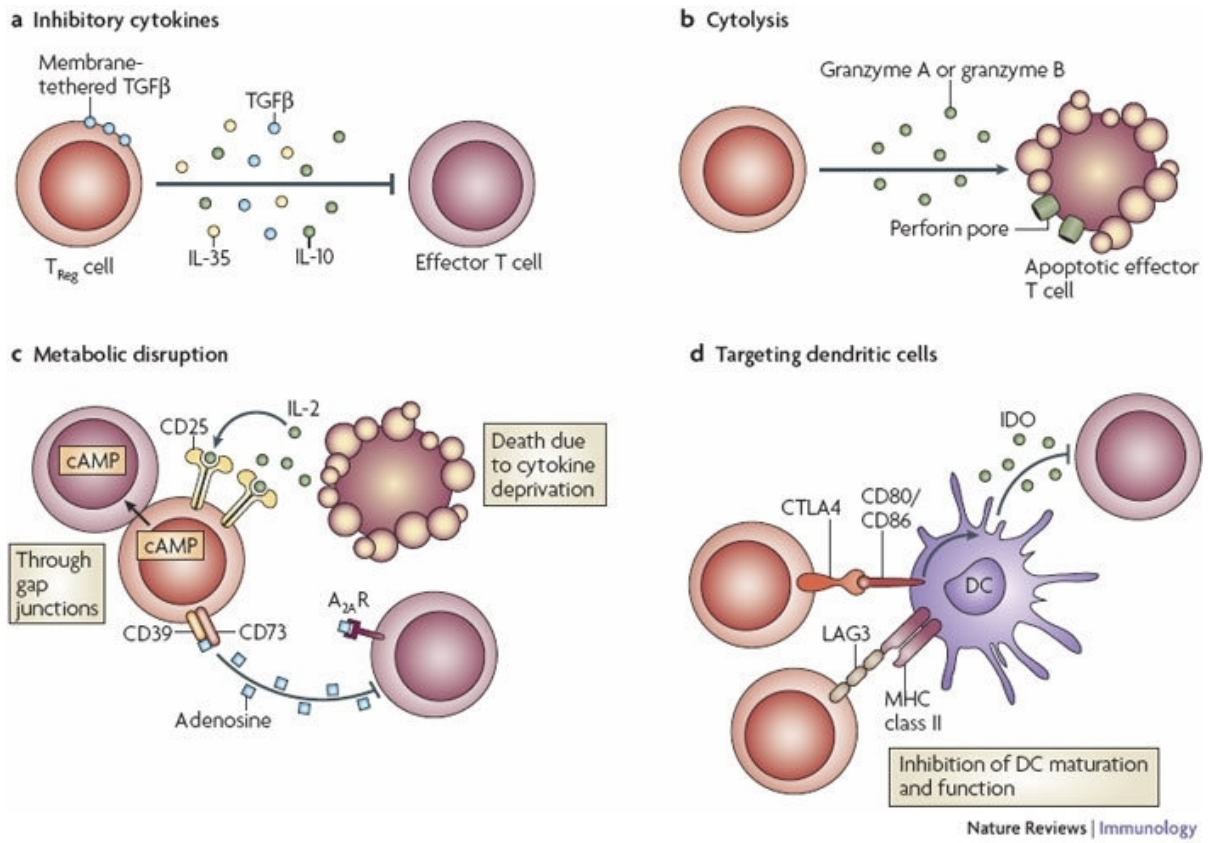
Recruitment/stabilization of MDSC

- Myeloid-derived suppressor cells (MDSC) represent a potent immunosuppressor at the tumor site
- While MDSC have a long and storied background, they are now considered a mainstay in tumor-induced immune suppression
- Tumor not only induce chemokines that help recruit MDSC, but the environment itself is conducive to MDSC generation
- MDSC suppress T cell function through a number of mechanisms

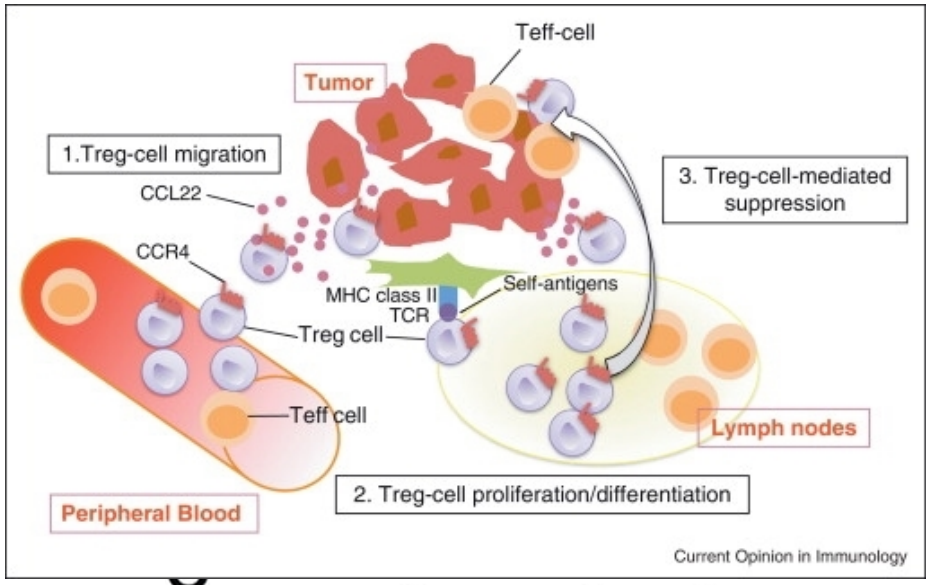


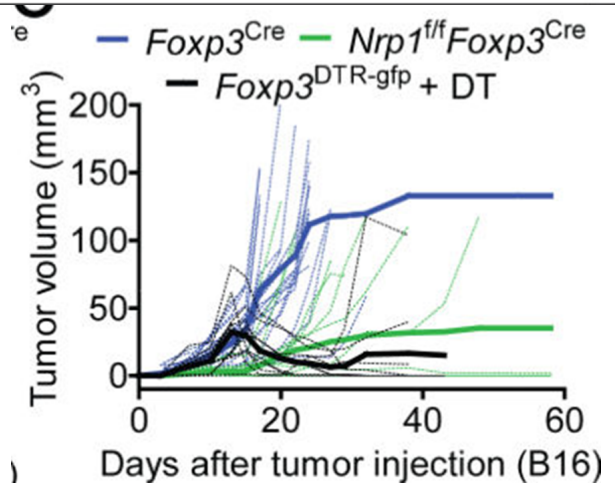
Recruitment/stabilization of regulatory T cells

- Regulatory T cells are a small subpopulation (5-10%) of $CD4^+$ T cells tasked with maintaining immune homeostasis and preventing autoimmunity
  - Marked by *Foxp3*
  - Loss of these cells results in lethal autoimmunity
- T_{reg} cells suppress antigen-specific and local immune activation through a variety of mechanisms



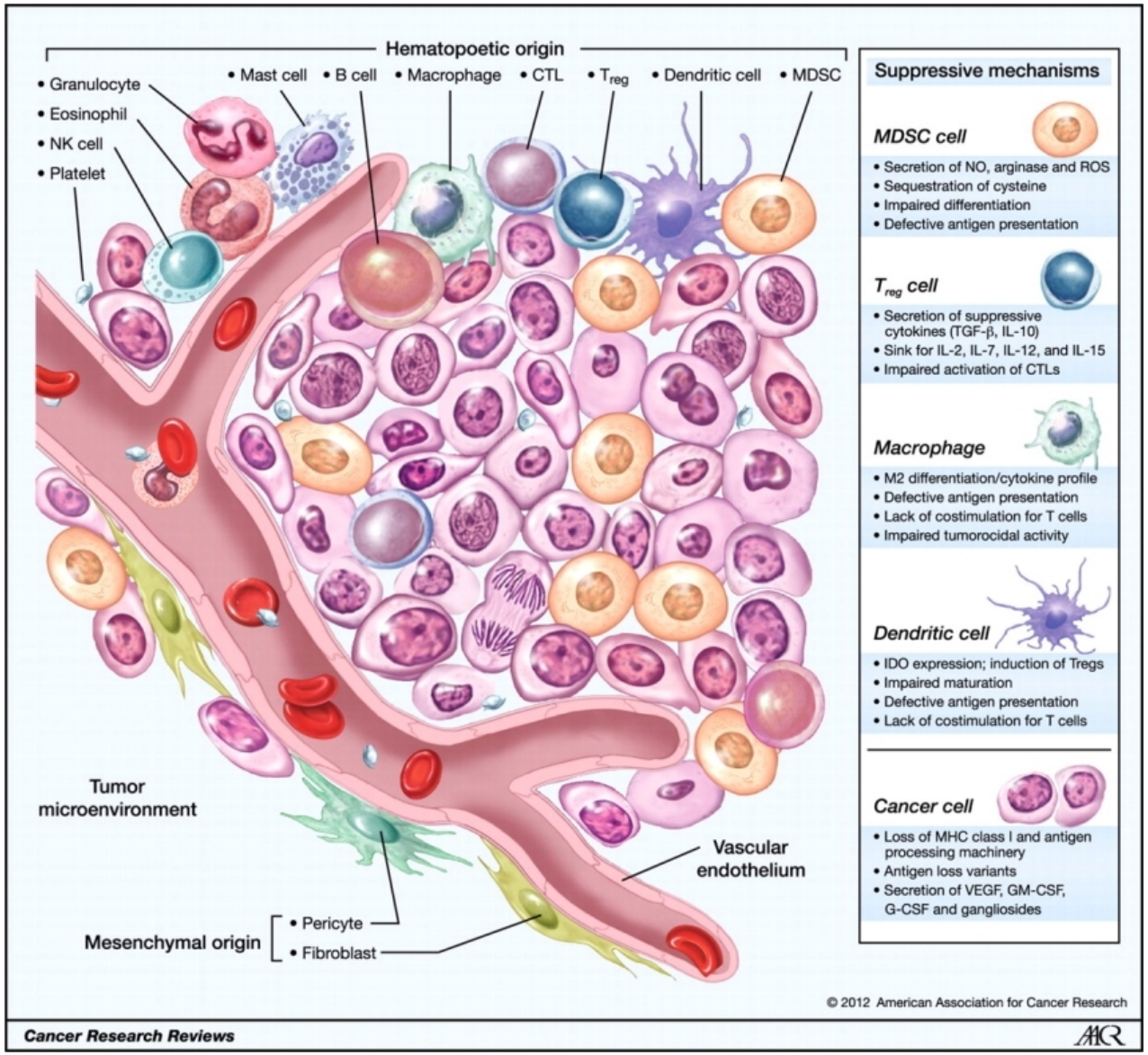
Regulatory T cells as a target in cancer



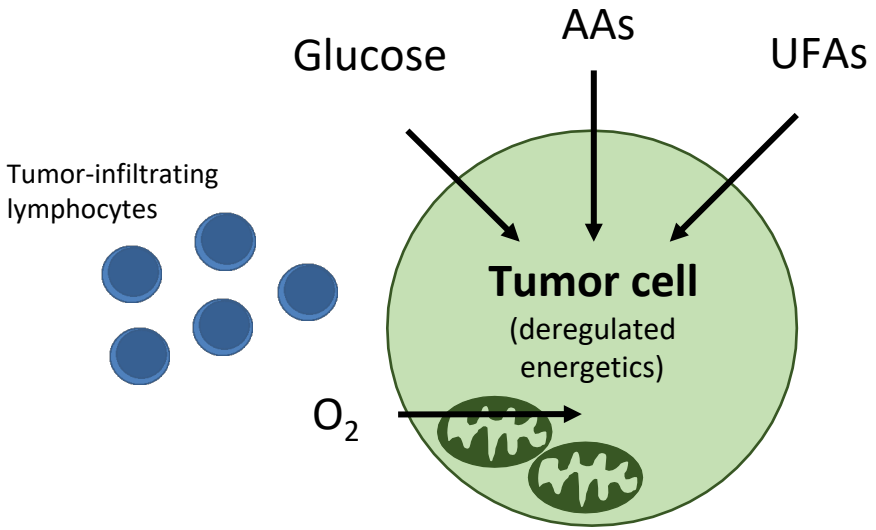


- Tumor recruit, activate, and induce the *de novo* differentiation of these cells
  - CCL19, CCL22 dependent recruitment
  - Expression of self antigens provides activation
  - TGFβ secretion can help de novo differentiation
- Many new cancer immunotherapies are aimed at targeting regulatory T cells
- However, care must be taken to not tip the balance too far, resulting in autoimmunity

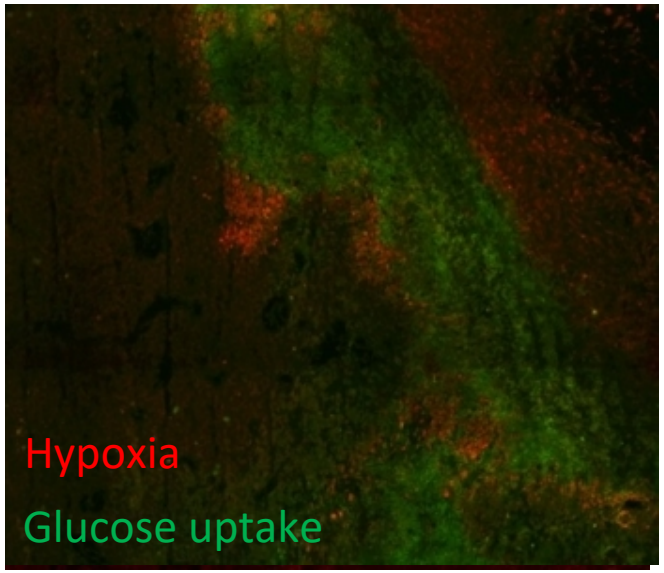
Cancer as an organ: The Tumor Microenvironment

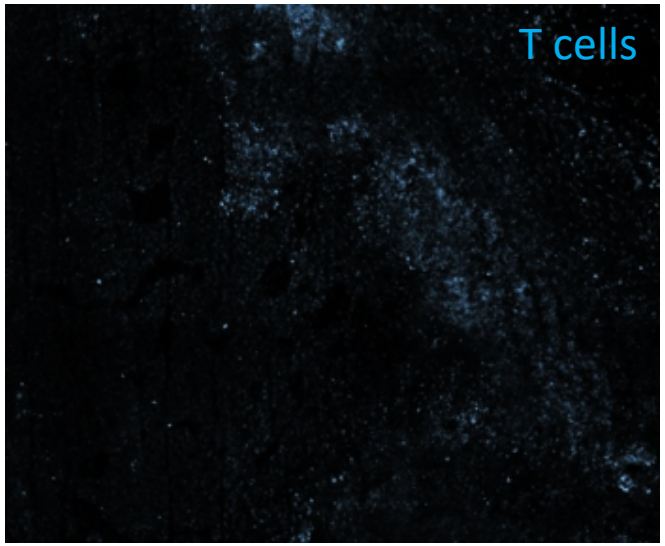


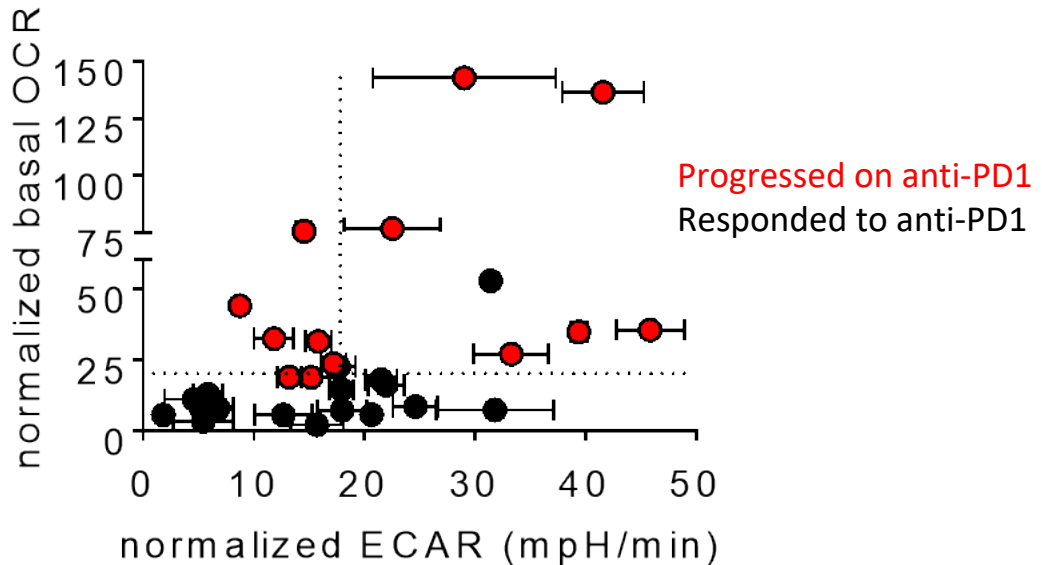
A dearth landscape: metabolic deprivation and harsh physical barriers



- As cancer cells continually proliferate, they deplete their environment of vital nutrients and oxygen
- As T cells require nutrients to thrive, this 'metabolic deprivation' is a form of immune suppression
- They also alter stromal cell populations, creating physical barriers to immune infiltration
- Indeed, patients that have 'hungrier' tumors (especially those that crave oxygen) are far less likely to respond to immunotherapy
- Our group recently reported that T_{reg} cells can utilize the byproducts of tumor metabolism, so tumors don't just 'starve' anti-tumor T cells but 'feed' regulatory populations







Conclusions

- Mutation and proliferation give cancer cells a platform to test immune evasion adaptations
- Cancer cells can possess intrinsic immunosuppressive traits like antigen presentation defects, antigen loss variants, changes in cell death programs, upregulation of inhibitory ligands, and the induction of T cell anergy and exhaustion
- Cancer cells also create an environment that promotes cell-extrinsic immunosuppression, recruiting tolerogenic populations, creating physical barriers, and metabolically depriving infiltrating immunity
- Immunotherapies like anti-PD1 only leverage **one** of these axes: combinations targeting multiple arms (hopefully in a biomarker driven way) will be key in bringing the promise of immune based therapies to all cancer patients