Restraining the immune system

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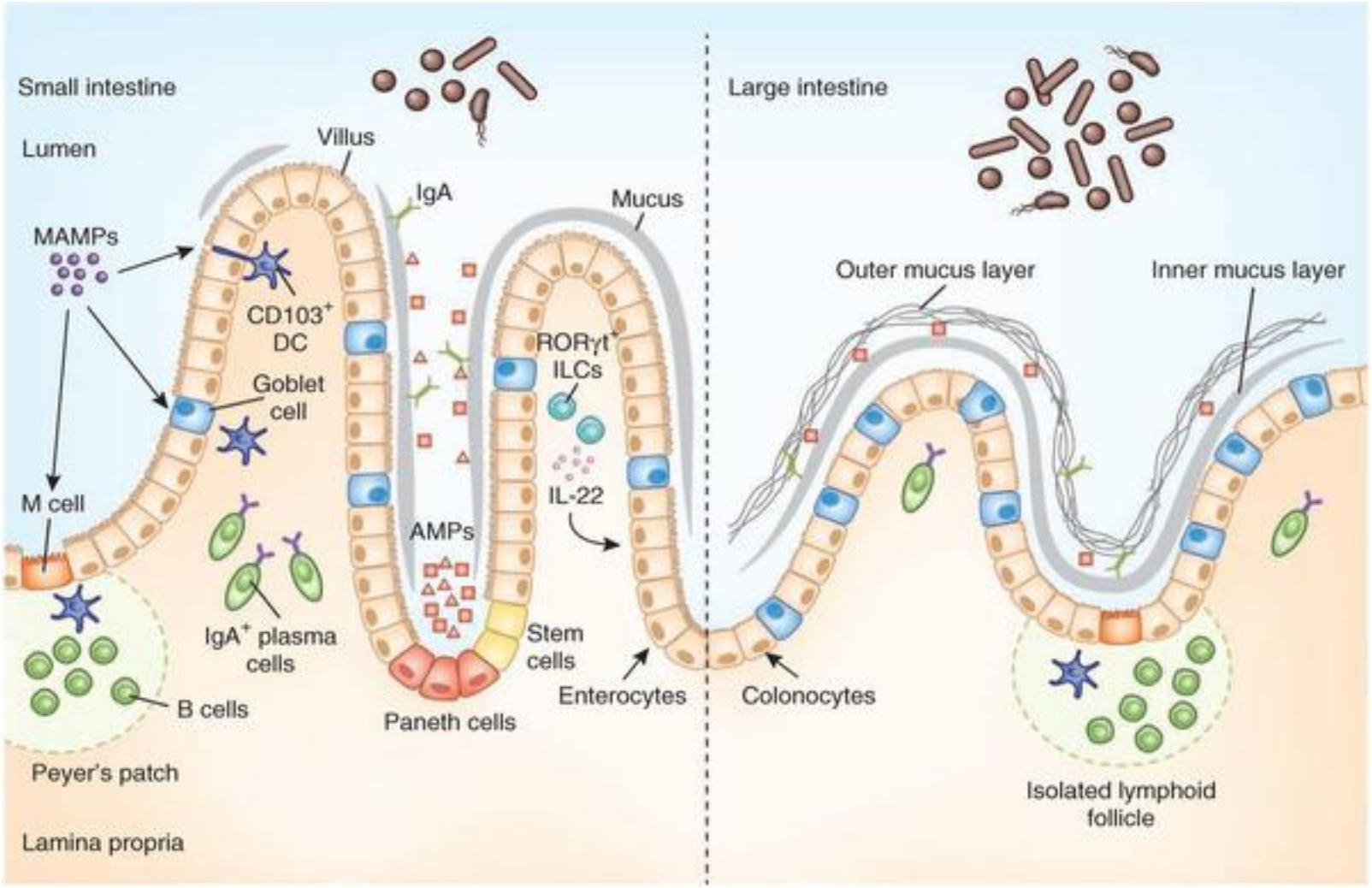
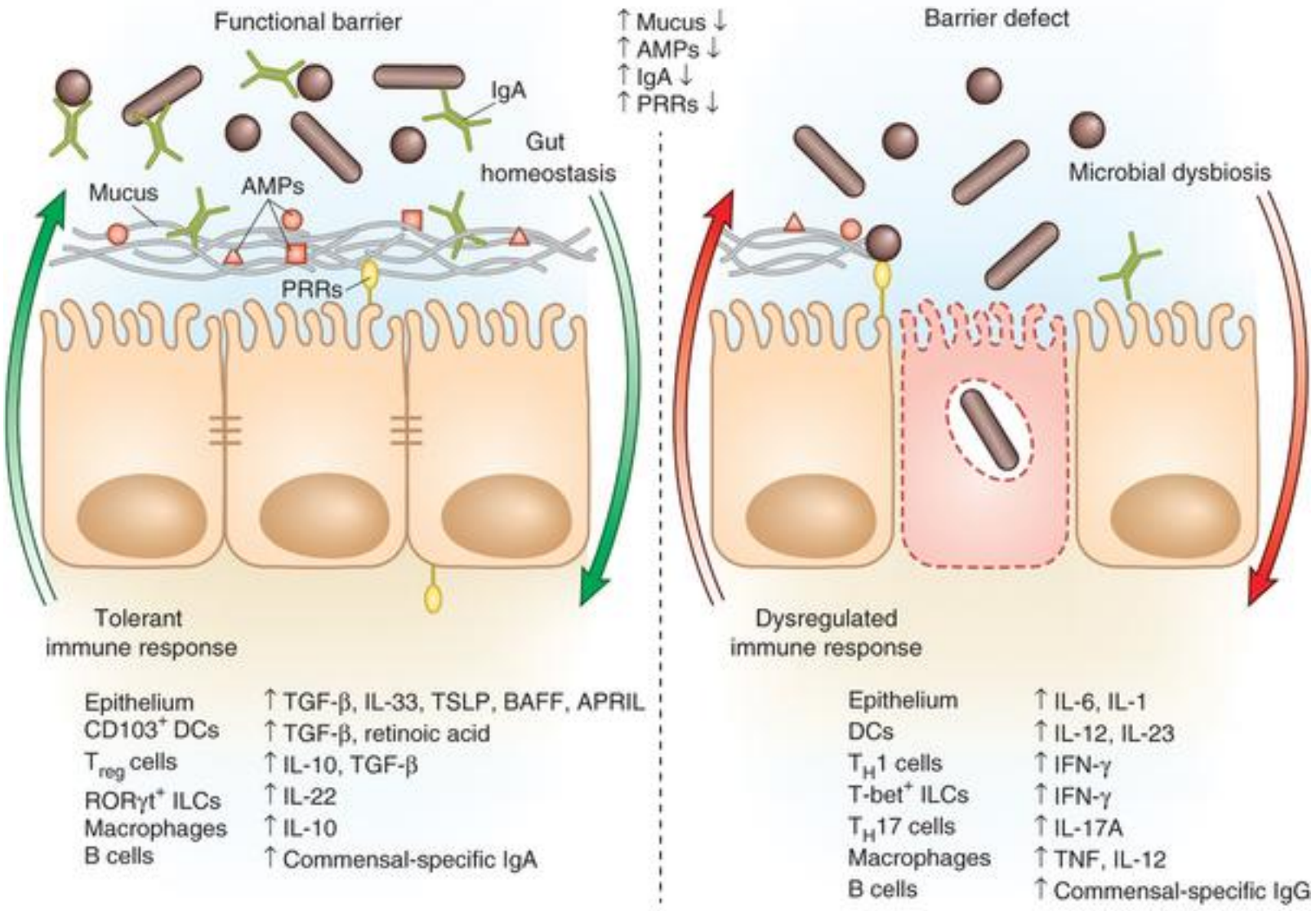
Intestines and commensal bacteria



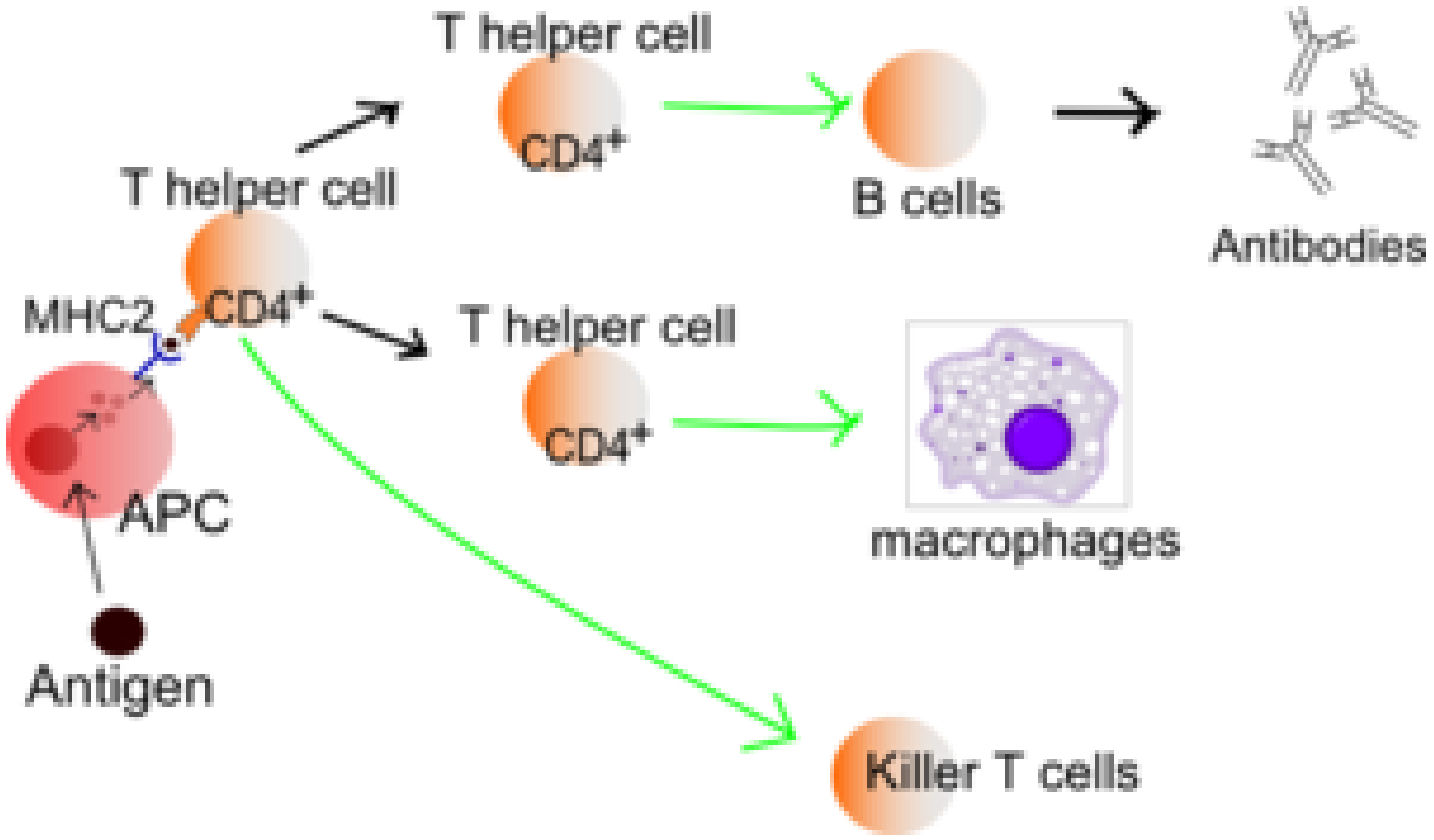
Brown E et al., *Nature Immunology*, 2013

When things go wrong!



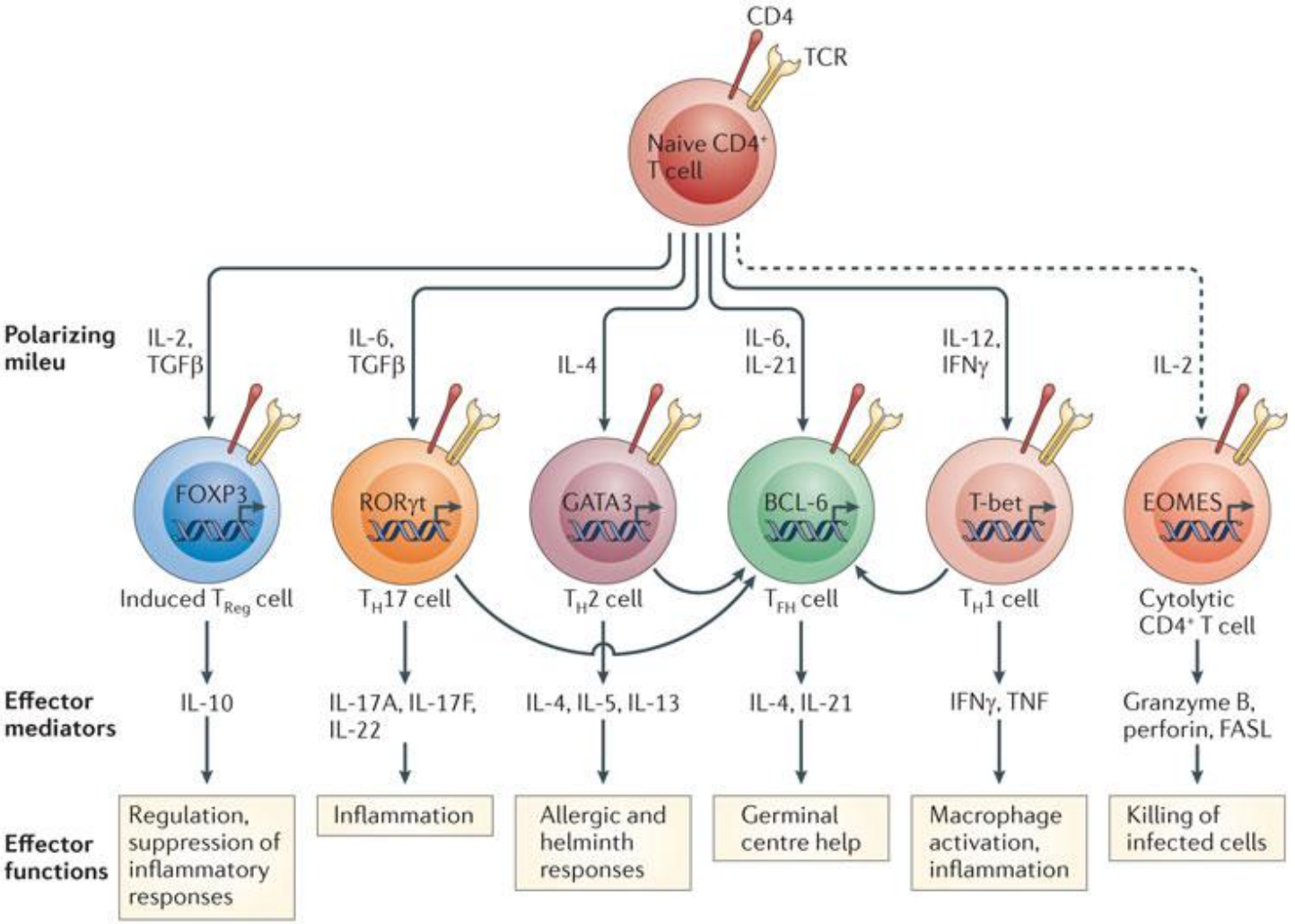
Brown E et al., *Nature Immunology*, 2013

Immune activation, then what?



Ending the immune activation or else?

Th (CD4 cells)


CD4
TCR
Naive CD4+ T cell
Polarizing mileu
IL-2, TGFβ
IL-6, TGFβ
IL-4
IL-6, IL-21
IL-12, IFNγ
IL-2
FOXP3
RORγt
GATA3
BCL-6
T-bet
EOMES
Induced T_{Reg} cell
T_H17 cell
T_H2 cell
T_{FH} cell
T_H1 cell
Cytolytic CD4+ T cell
Effector mediators
IL-10
IL-17A, IL-17F, IL-22
IL-4, IL-5, IL-13
IL-4, IL-21
IFNγ, TNF
Granzyme B, perforin, FASL
Effector functions
Regulation, suppression of inflammatory responses
Inflammation
Allergic and helminth responses
Germinal centre help
Macrophage activation, inflammation
Killing of infected cells
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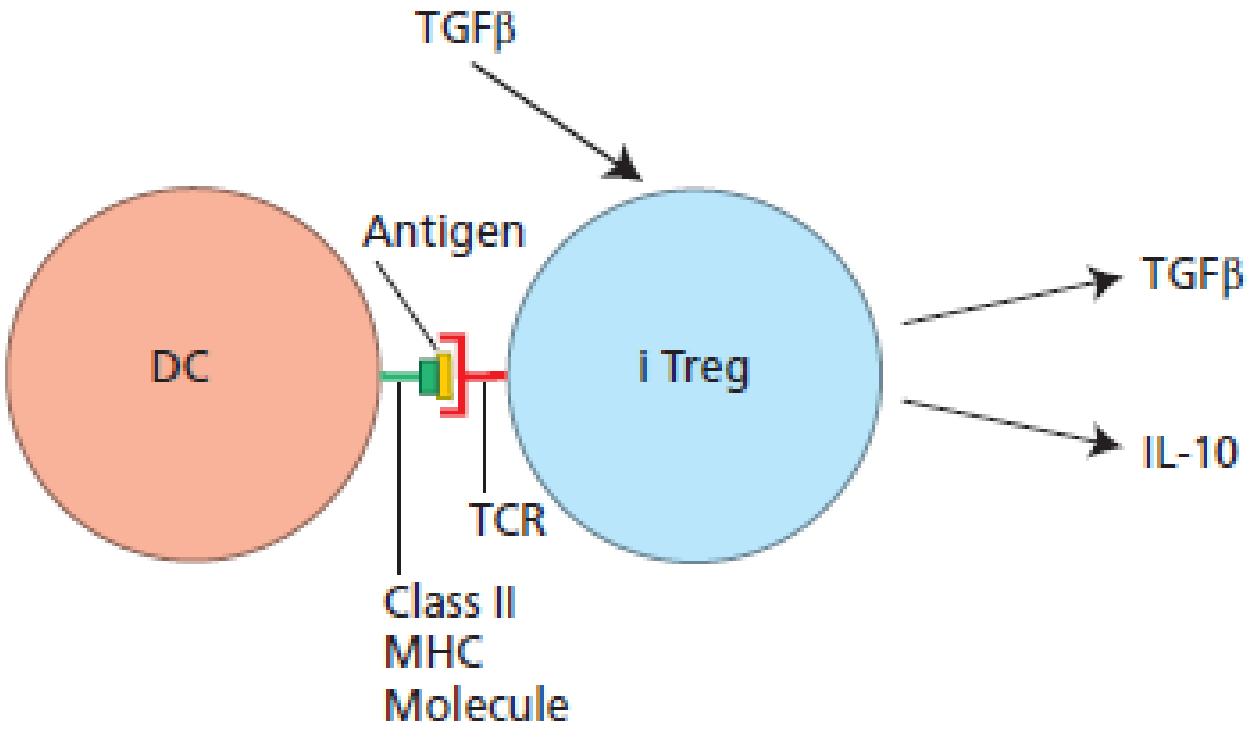
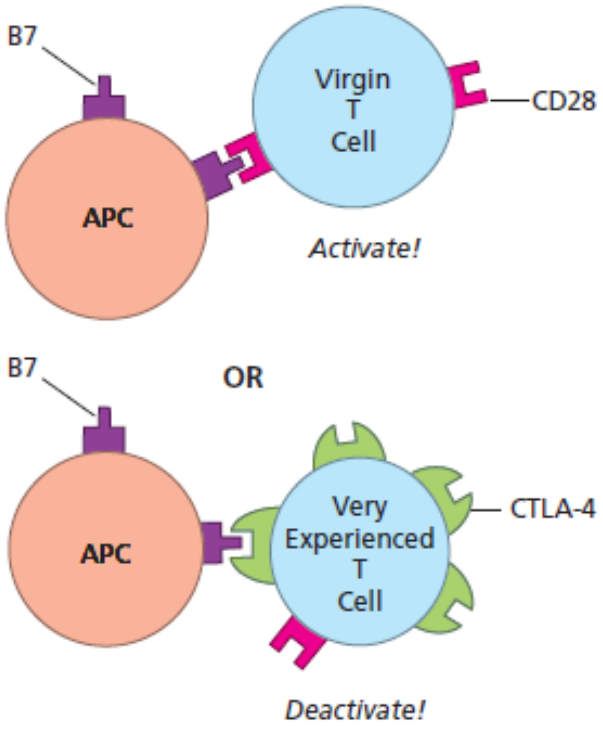
Inducible T regulatory cells (iTregs)



Deactivating the system

As foreign antigen is eliminated, the level of activation of both the innate and adaptive systems decreases.

Binding of B7 molecules on APCs to CTLA-4 receptor on T cell, inactivates it.



Has much higher affinity to B7
Compared to CD28

CD28 vs. CTLA-4

Early in an infection, B7 binds to CD28 and acts as a co-stimulator.
Then after the battle has been raging for a while, B7 binds mainly to CTLA-4, making it harder for these T cells to be reactivated, and helping to shut down the adaptive immune response.

Other inhibitory receptors on T cells exist; example PD-1

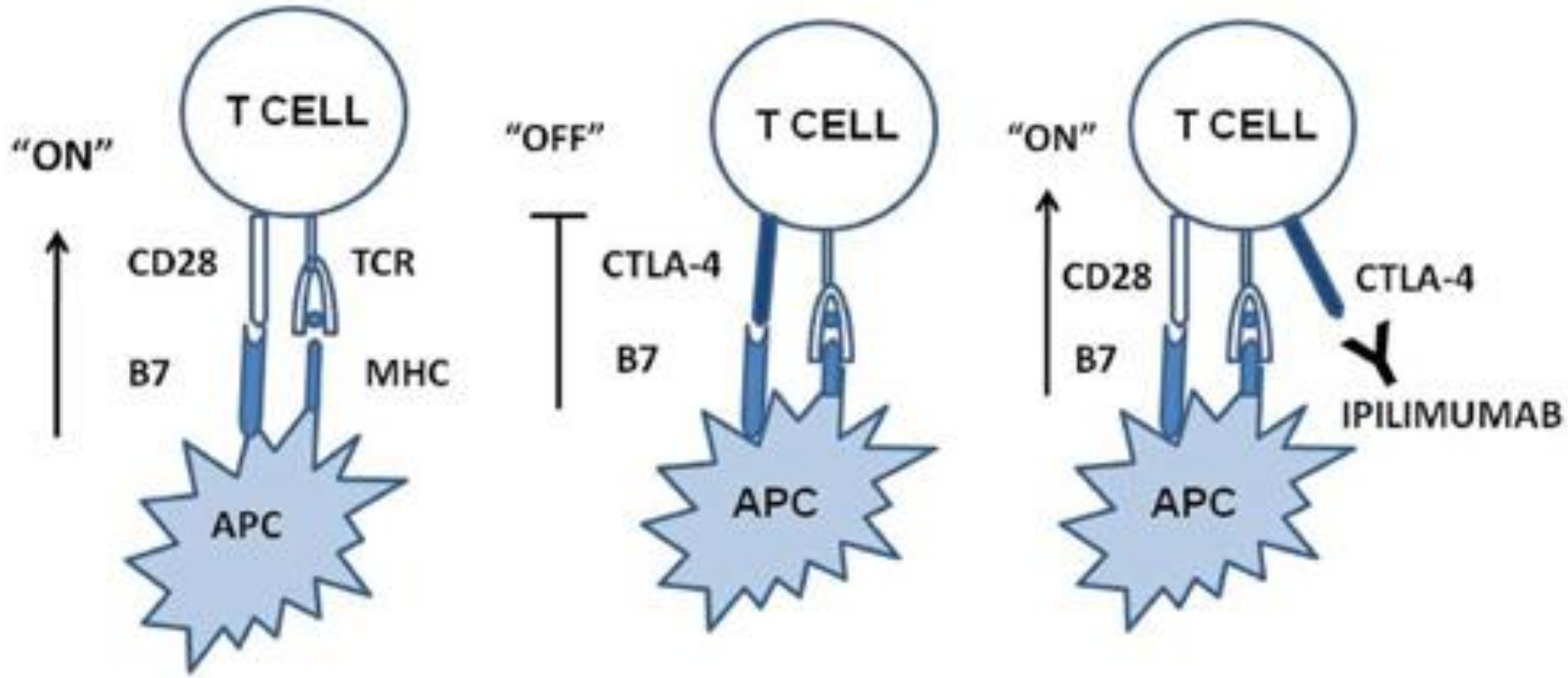
Are inhibitory receptors good or bad?

Depends!

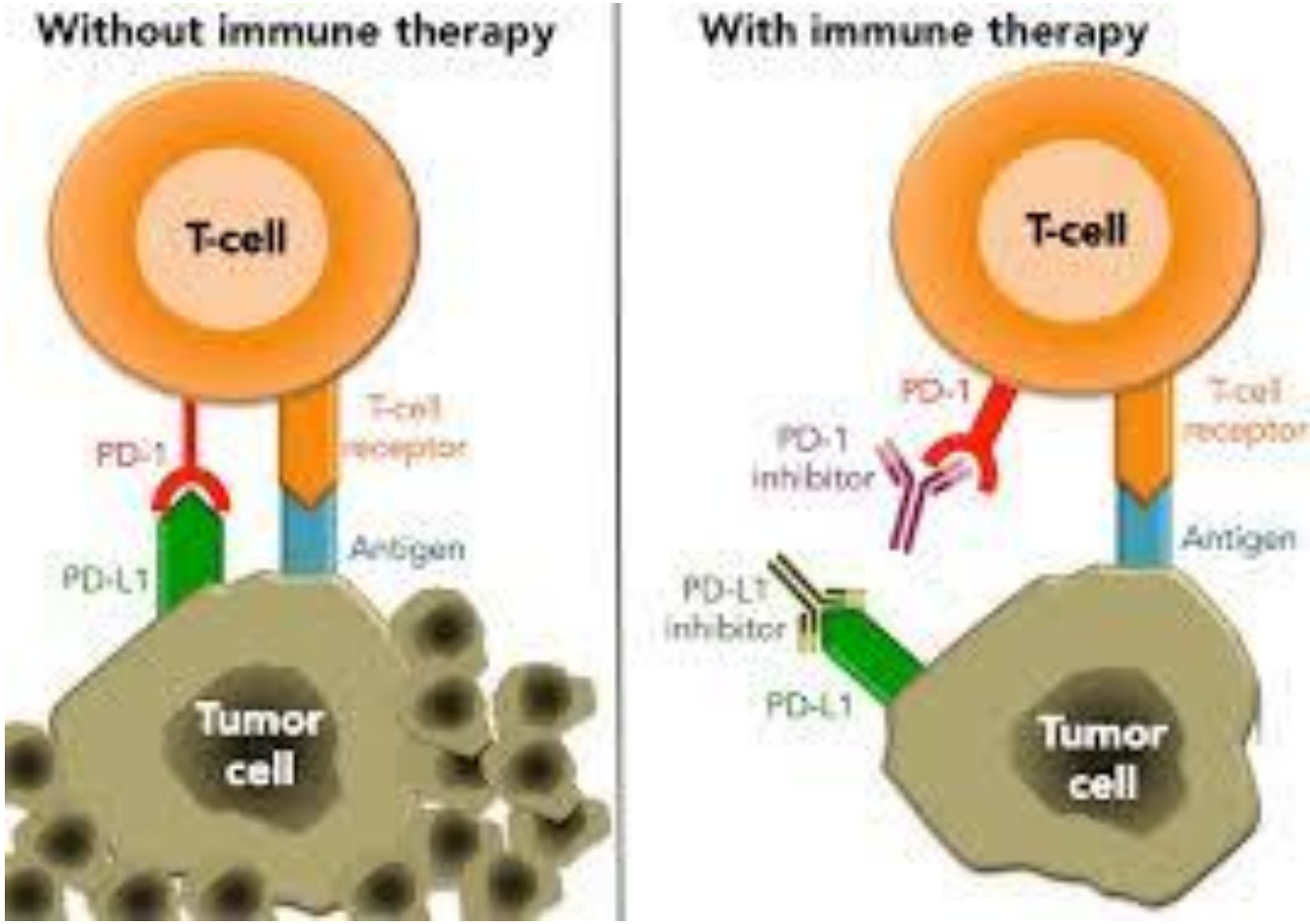
Good in ending immune response and avoiding autoimmune disease

Can be bad in Cancer control and cause treatment failure!

CTLA-4 targeted Immunotherapy



PD-1 targetted Immunotherapy



Life is short!

Neutrophils live for few days only.

Half-life of NK cells is about a week.

Less NK= less IFN-γ= less Mφ activation

DCs live for about a week after arriving to lymph node.

Less APC activity= less Th and B cell activity

Plasma cells die after about 5 days.

Antibodies have a short life too (IgG half-life is longest= 3 weeks)

Immune response can end relatively fast and invader-specific antibodies drop fast

Exhaustion

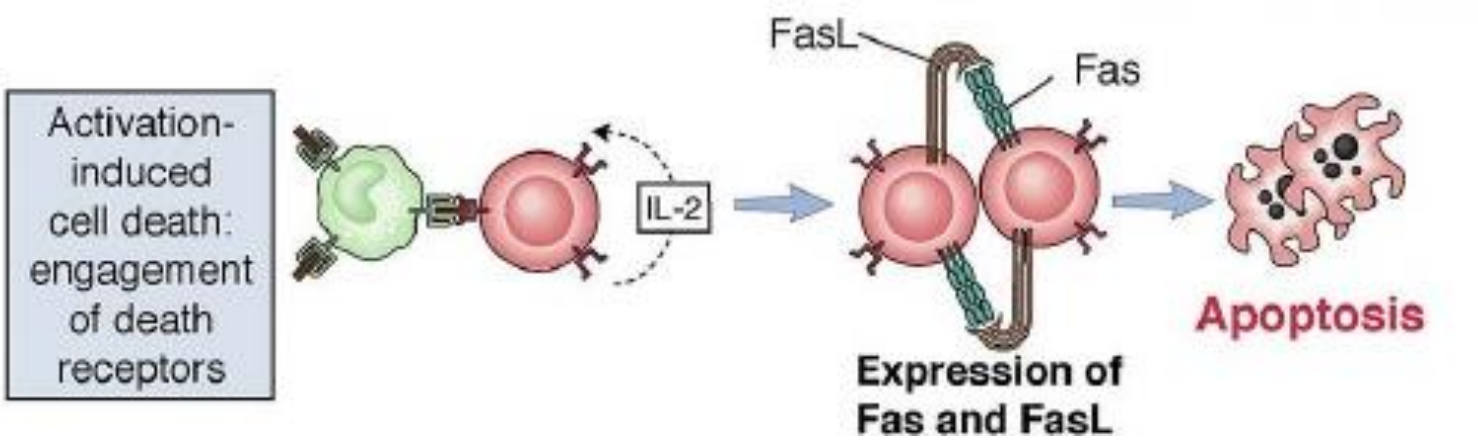
Although DCs, NK, and plasma cells have a short life, T cells don't, They actually live long. How do we get rid of the big number of activated T cells??

Activation-Induced Cell death (AICD)

Activated T cells are sensitive to FasL-Fas Interactions, so they can help each other commit suicide.

AICD eliminates T cells which have been repeatedly activated, and makes room for new T cells that can protect us from the next microbes which might try to harm us.

Activation-Induced Cell Death (AICD)



Summary

The immune system uses several tolerogenic mechanisms to avoid unnecessary stimulation of the immune system. Ex: T-regs

Disappearance of foreign antigen upon end of infection is the first step to end an immune response

The short life of many immune components help end an immune response quickly
ex: Neutrophils, NK cells, and plasma cells

The presence of negative immune regulators help inactivate T cells
ex: CTLA-4 and PD-1

Exhaustion and killing by AICD helps eliminate repetitively activated T cells

All of the above help reset the system to be ready for the next attack!

?Any question