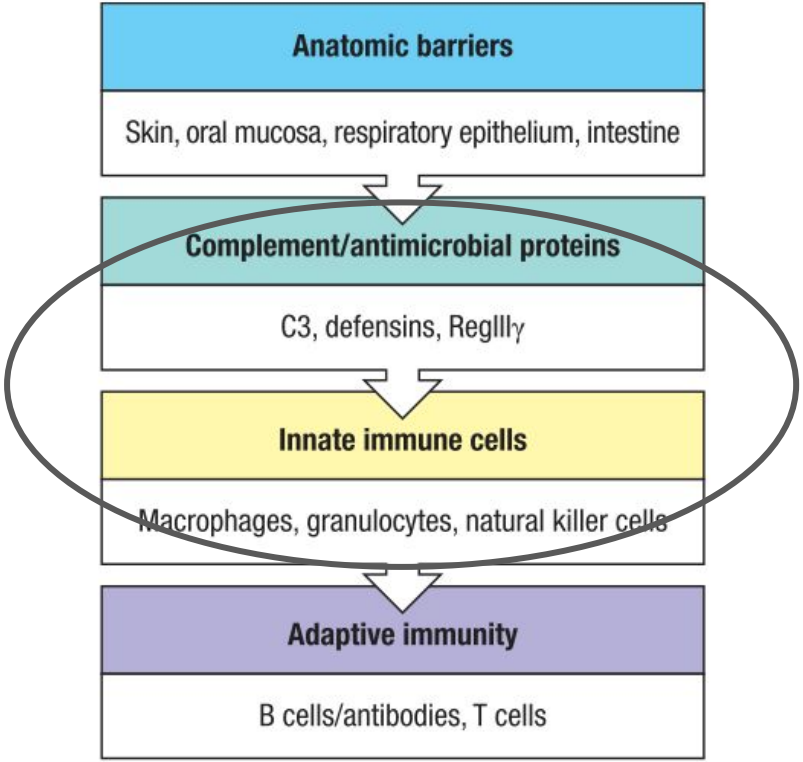
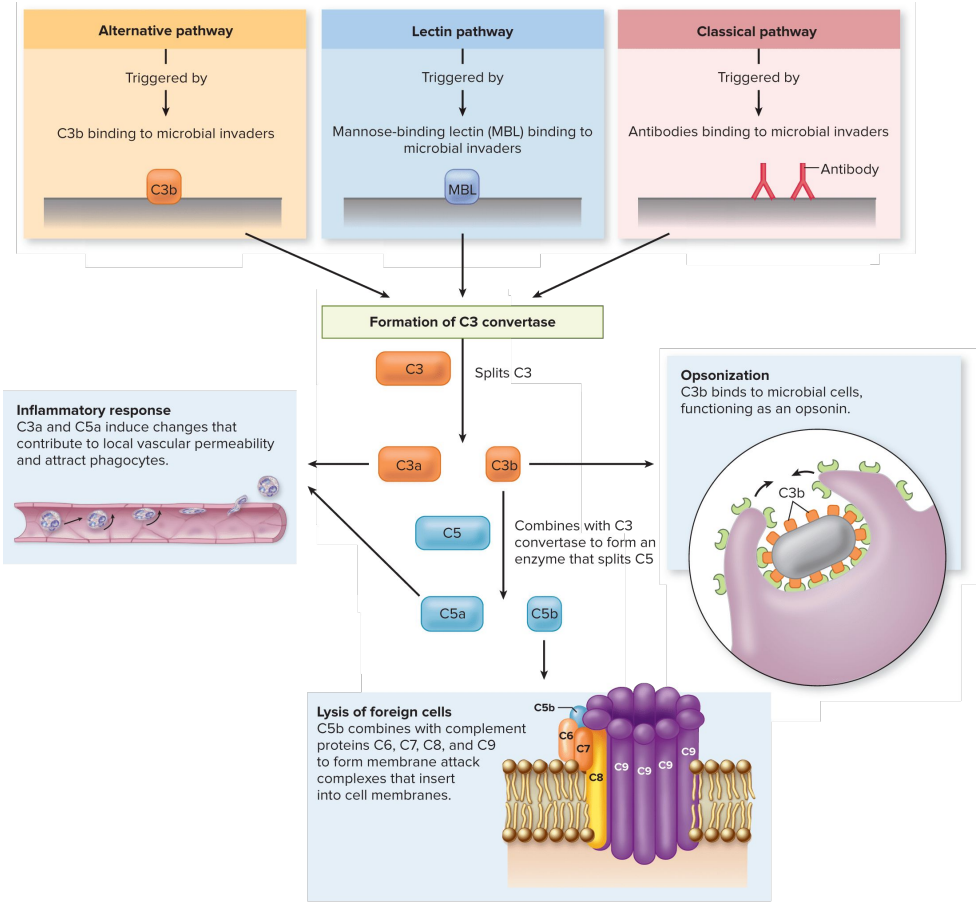
Машинное обучение в иммунологии и медицине

Клетки иммунной системы. Взаимодействие между врожденным и приобретенным иммунитетом

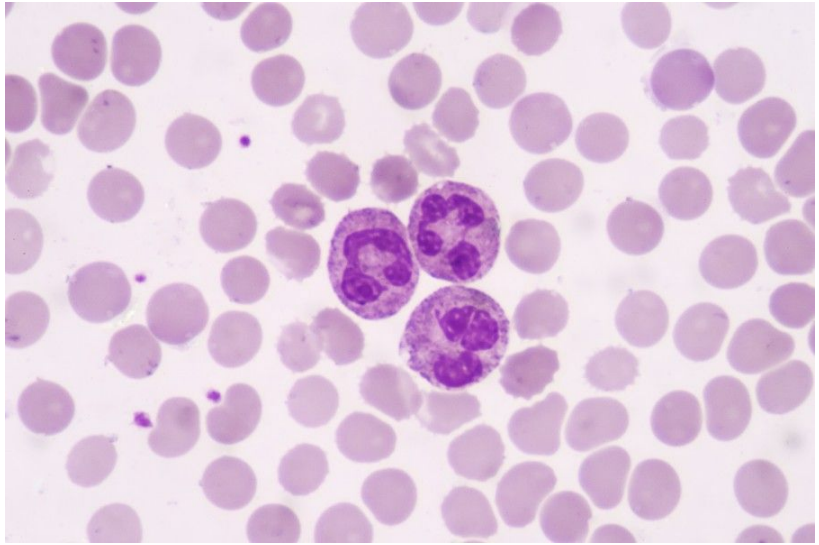
Ступени защиты организма



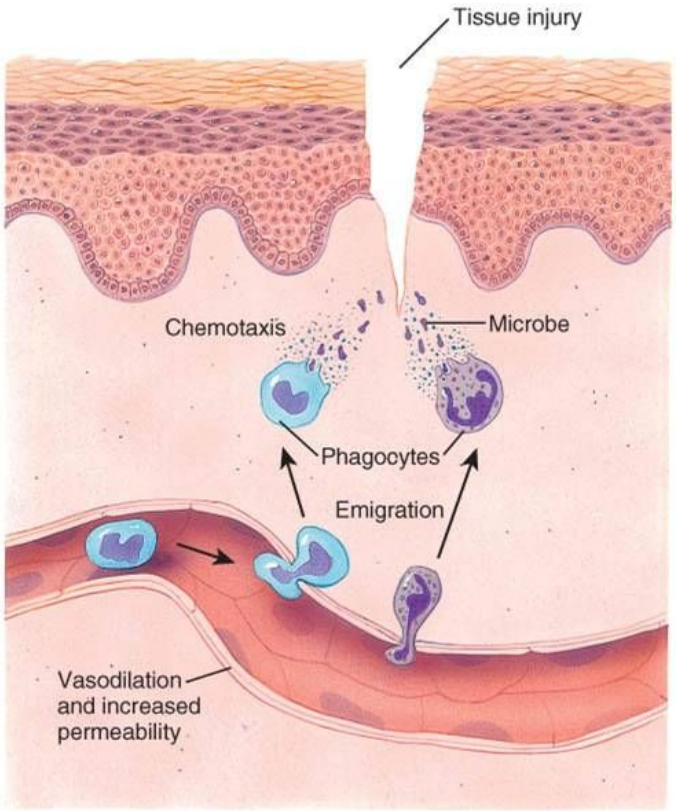
Система комплемента



Нейтрофилы

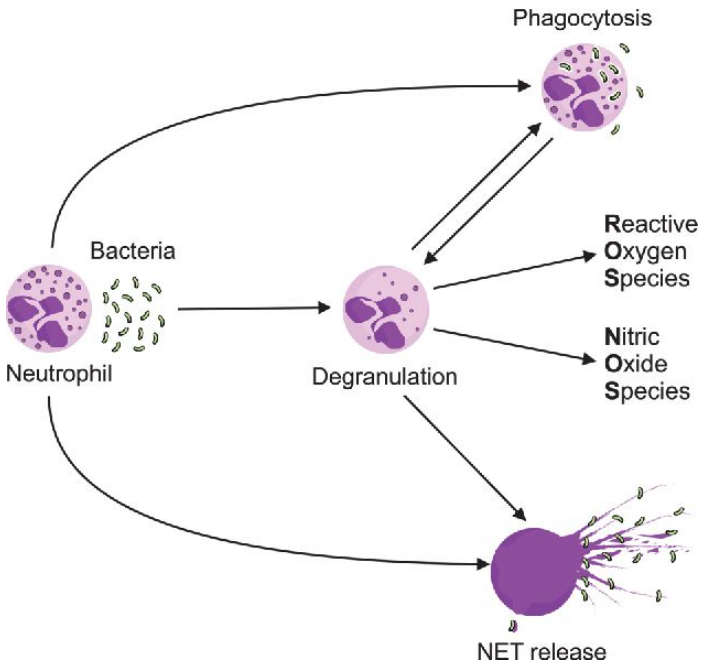


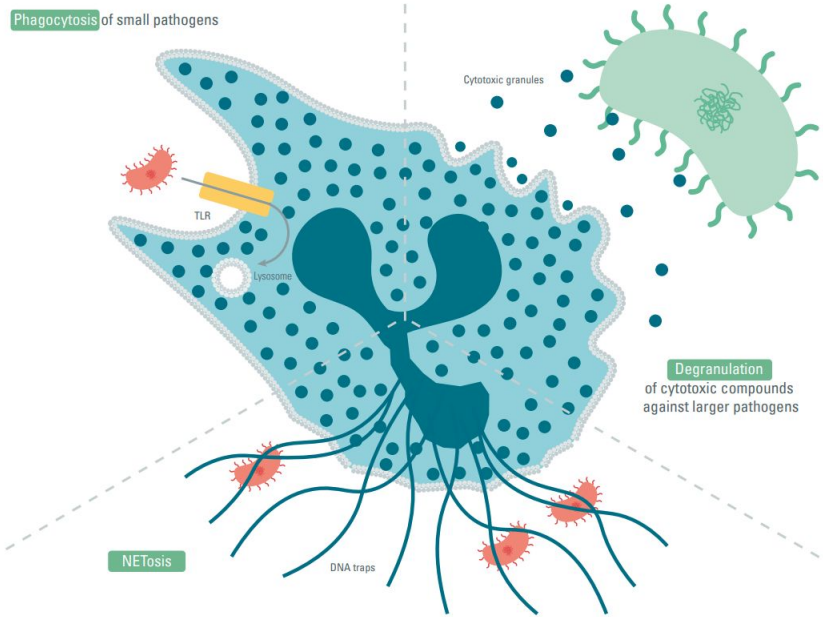
Ключевые аттрактанты: IL-8, TNFα, C5a, LTB4



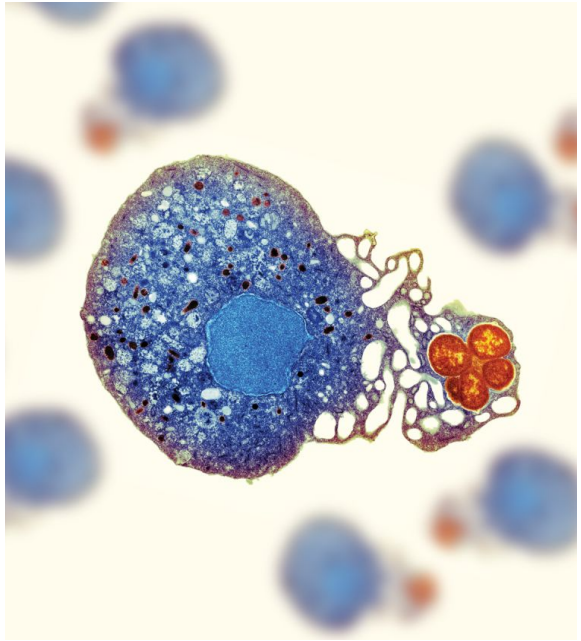
Phagocytes migrate from blood to site of tissue injury

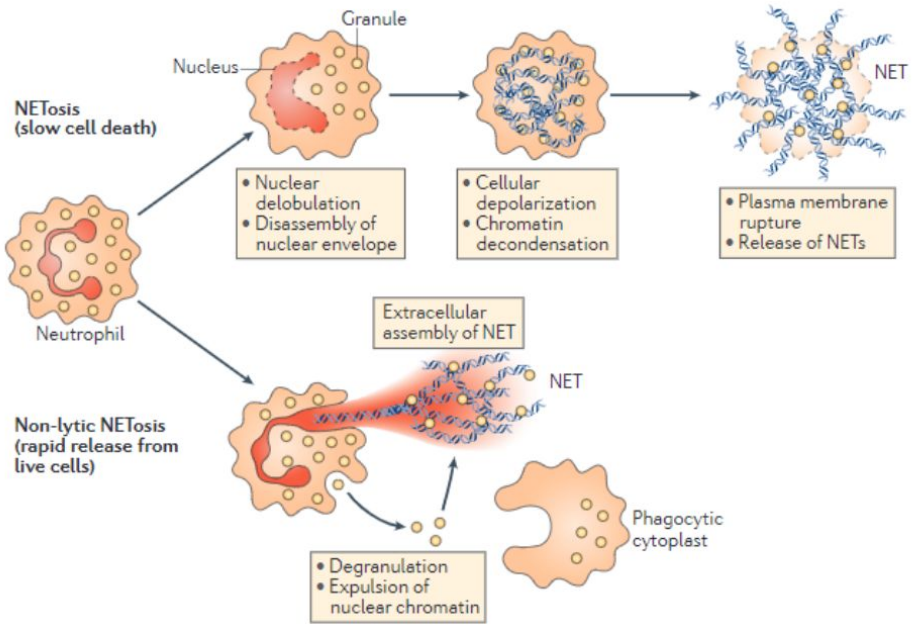
Нейтрофил должен решить, как он поступит





NETosis




Granule
Nucleus
NETosis
(slow cell death)
NET
• Nuclear delobulation
• Disassembly of nuclear envelope
• Cellular depolarization
• Chromatin decondensation
• Plasma membrane rupture
• Release of NETs
Neutrophil
Extracellular assembly of NET
NET
Non-lytic NETosis
(rapid release from live cells)
Phagocytic cytoplast
• Degranulation
• Expulsion of nuclear chromatin

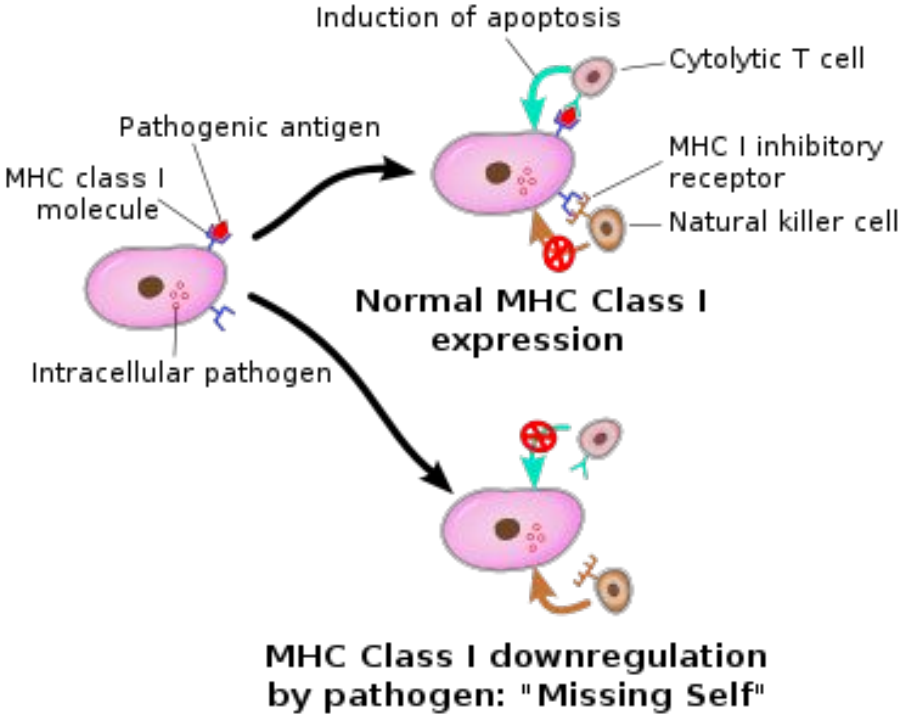
NK клетки

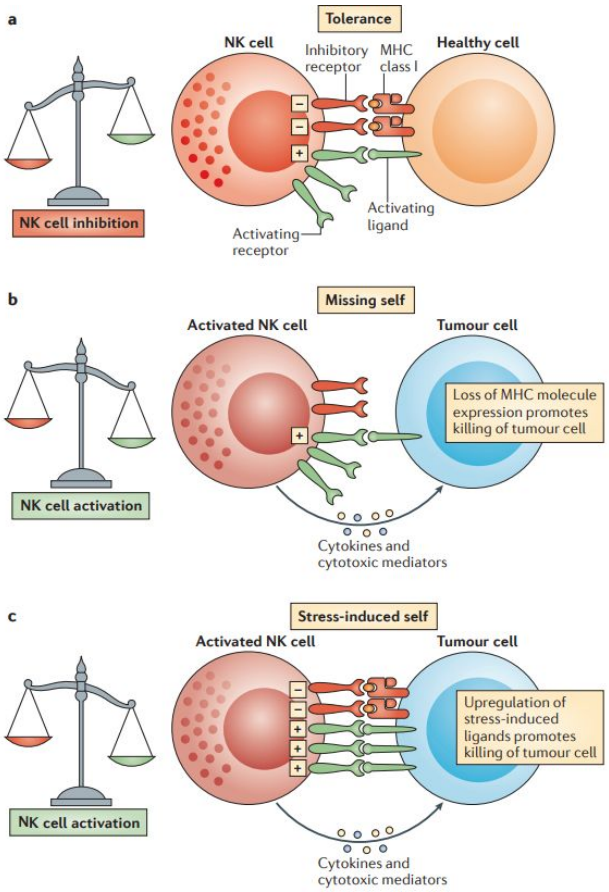
Не фагоцитируют, не принимают непосредственного участия в уничтожении патогенов

Уничтожают **клетки организма** (зараженные, раковые и тд) за счет цитотоксичности (как CD8 T клетки)

В отличие от цитотоксических CD8 T клеток, рецепторы NK клеток не являются специфическими

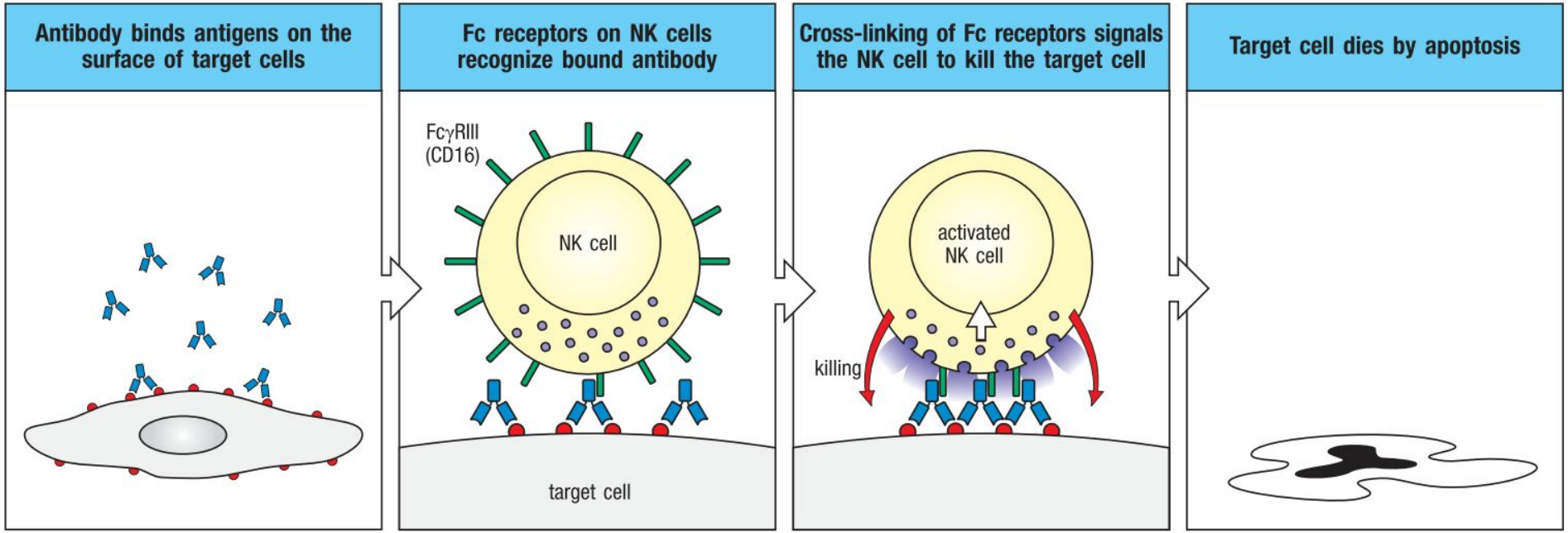
NK клетки



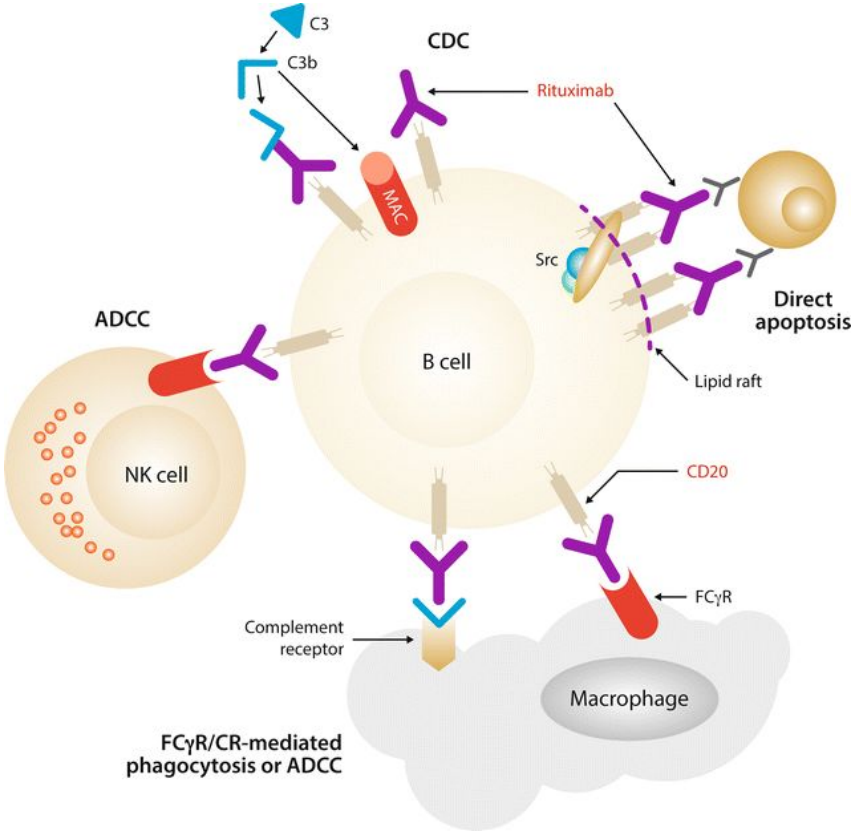


Кто-то должен убить, или NK или CD8 T клетка

Антителозависимая клеточно-опосредованная цитотоксичность (ADCC)



Ритуксимаб



Анти-CD20 моноклональные антитела для терапии неходжкинских лимфом

Макрофаги

Предшественниками макрофагов являются **моноциты**, моноциты могут становиться макрофагами в тканях, резервуар моноцитов - **селезенка**

Существуют **резидентные** макрофаги (клетки Купфера, микроглиоциты, остеокласты…), которые могут жить годами, их задача избавляться от останков мертвых клеток

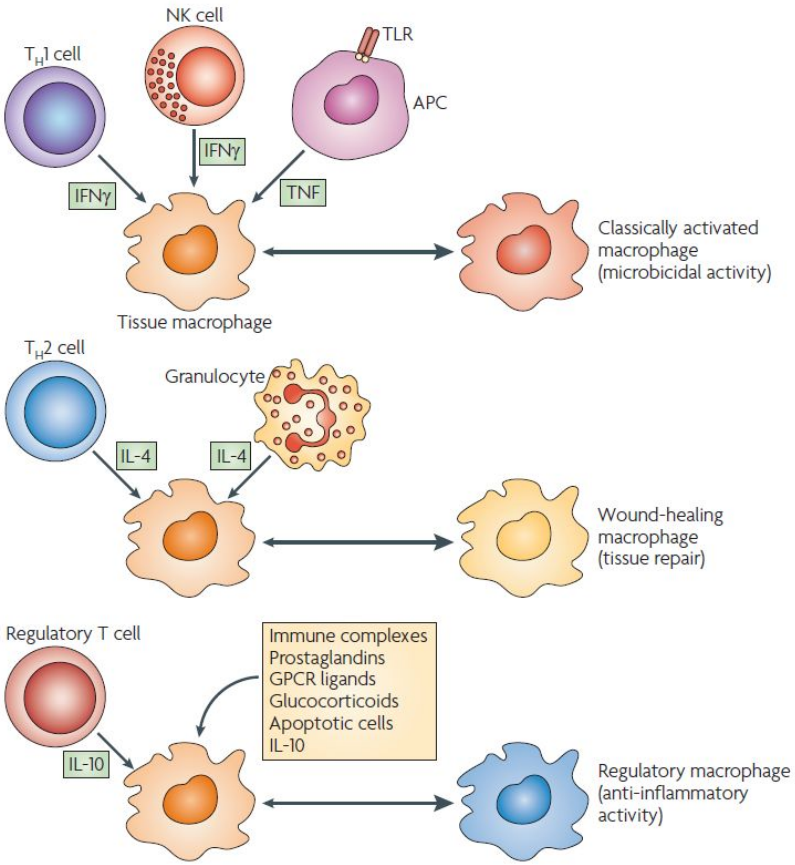
Являются **фагоцитами**, уничтожают вирусы, бактерии, грибы за счет фагоцитоза и секреции антимикробных пептидов

Убирают последствия первой волны нейтрофилов (останки нейтрофилов и всего, что они уничтожили)

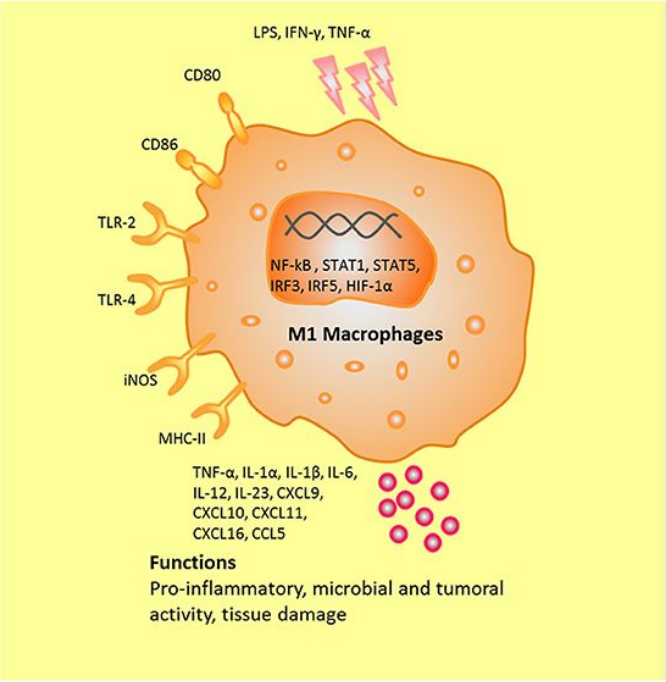
Доставляют антигены в лимфатические узлы, осуществляют антигенпрезентацию

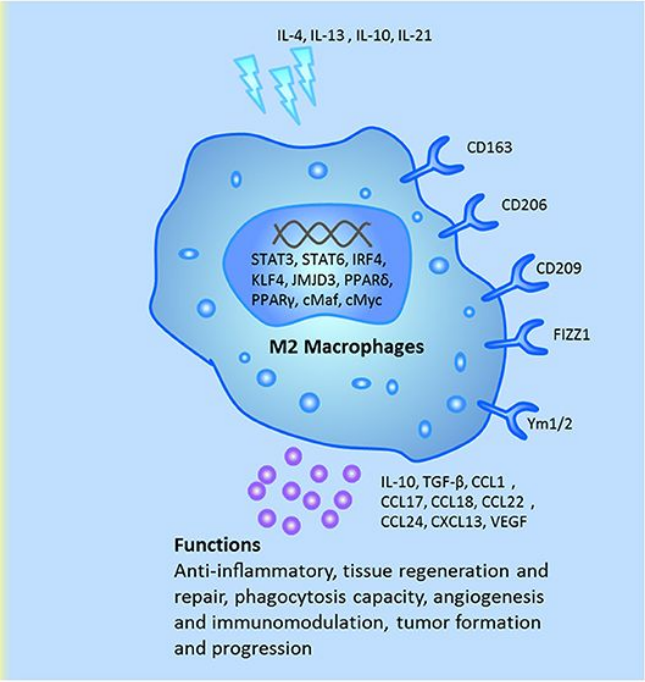
Имеют Fc рецепторы, распознают и уничтожают опсонизированные антигены

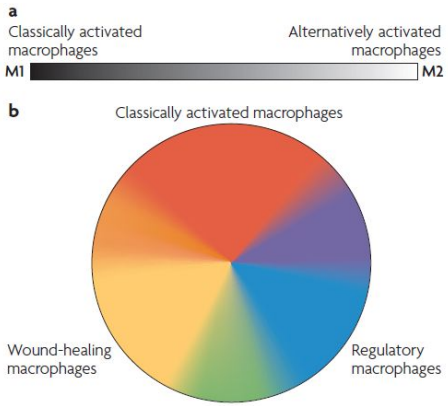
Цитокины могут менять поведение макрофагов



Макрофаги M1 и M2



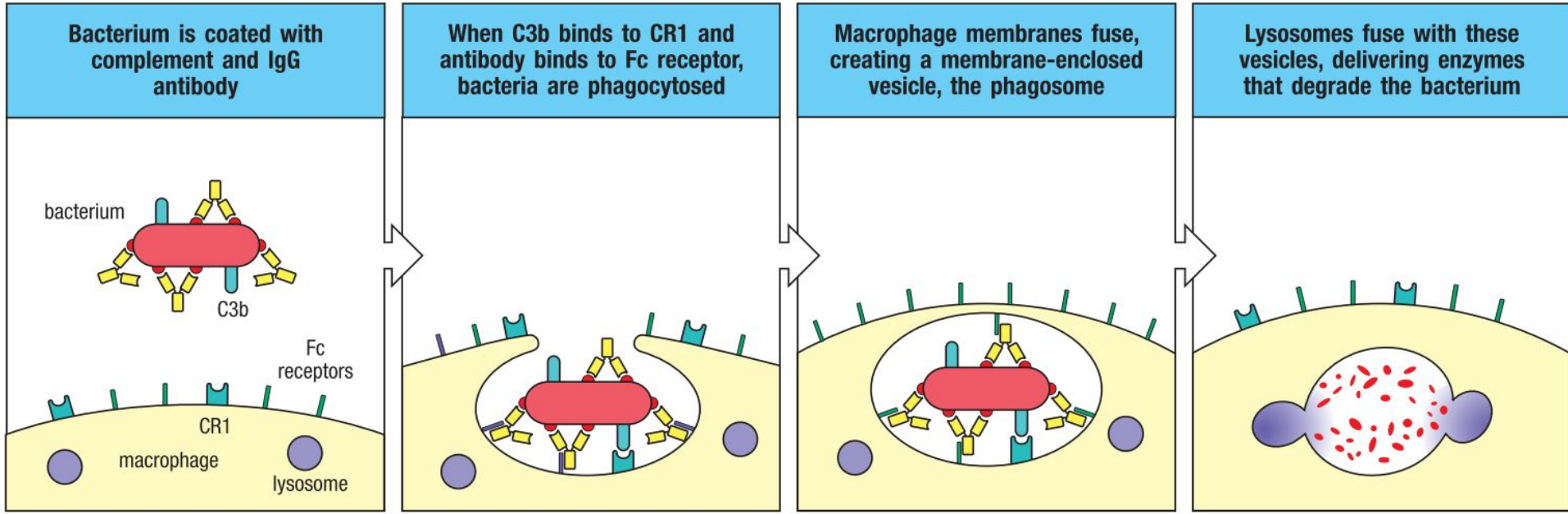




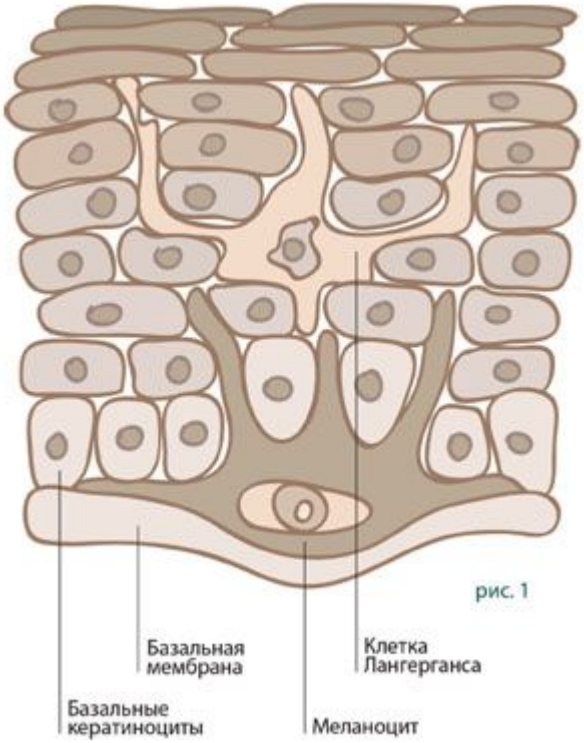
Про-воспалительные
Активируются IFN-gamma
Секретируют IL12 => стимулируют Th1 T клетки, CD8 клетки

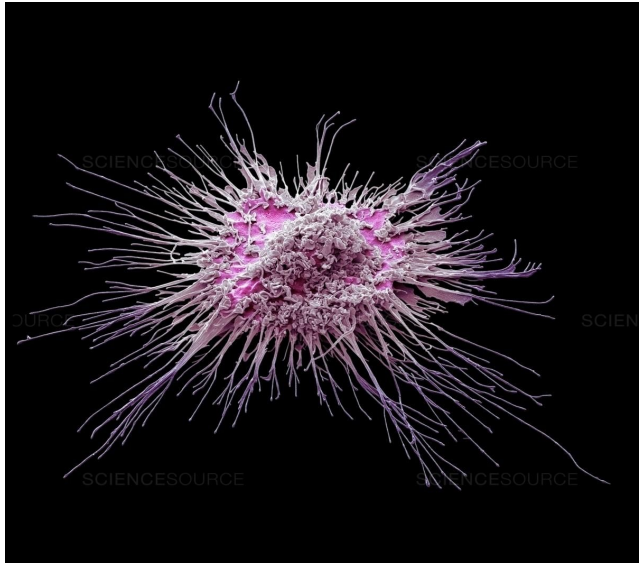
Регенерация, поддержание гомеостаза
Резидентные, количество зависит от IL4
Секретируют IL10, TGF-beta => стимулируют Treg CD4 T клетки

Удаление иммунных комплексов и опсонизированных патогенов

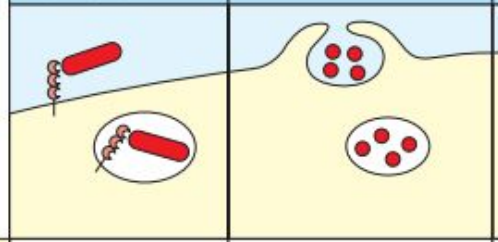
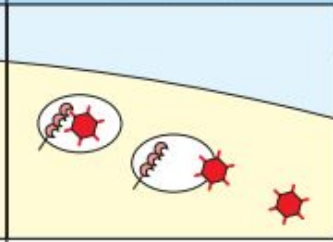
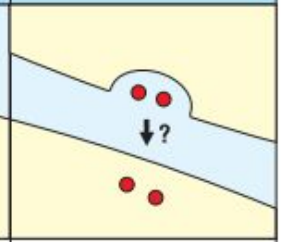


Дендритные клетки





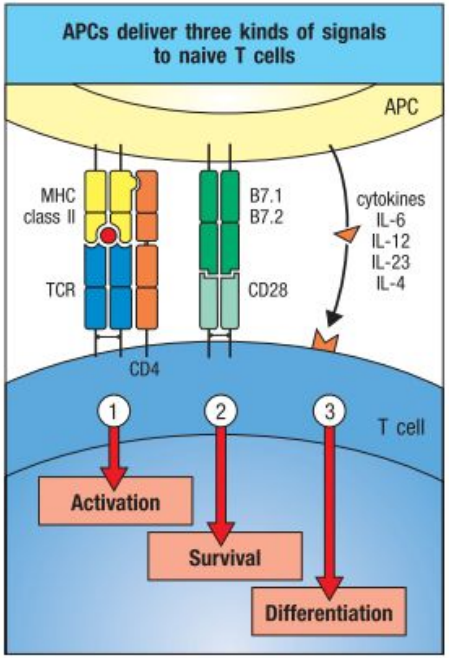
Способы захвата антигенов дендритными клетками

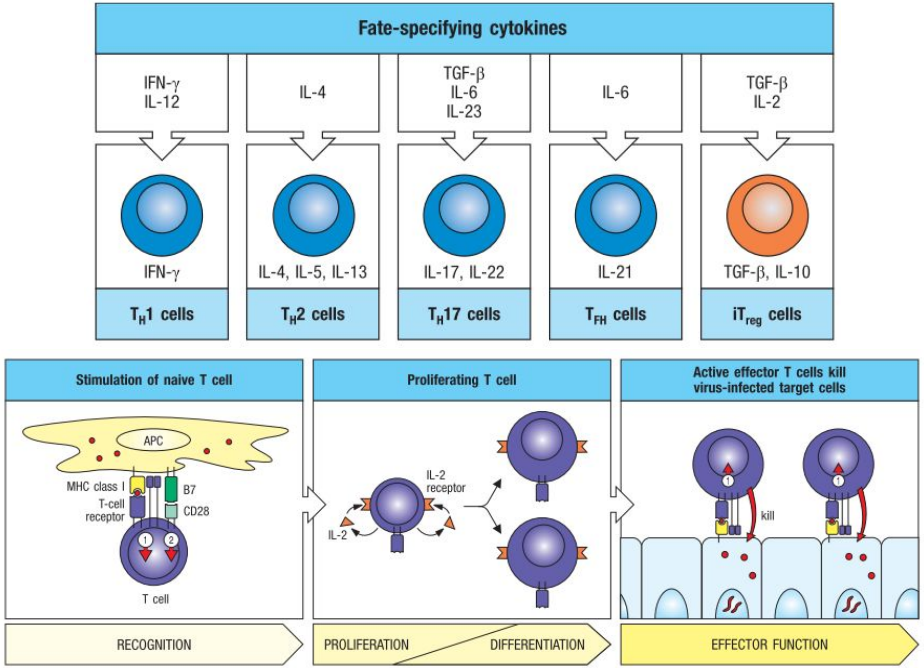
	Routes of antigen processing and presentation by dendritic cells				
	Receptor-mediated phagocytosis	Macropinocytosis	Viral infection	Cross-presentation after phagocytic or macropinocytic uptake	Transfer from incoming dendritic cell to resident dendritic cell
					
Type of pathogen presented	Extracellular bacteria	Extracellular bacteria, soluble antigens, virus particles	Viruses	Viruses	Viruses
MHC molecules loaded	MHC class II	MHC class II	MHC class I	MHC class I	MHC class I
Type of naive T cell activated	CD4 T cells	CD4 T cells	CD8 T cells	CD8 T cells	CD8 T cells

Основной путь процессинга антигенов для презентации на MHC II

Путь процессинга внеклеточных антигенов для презентации на MHC I **кросс-презентация**

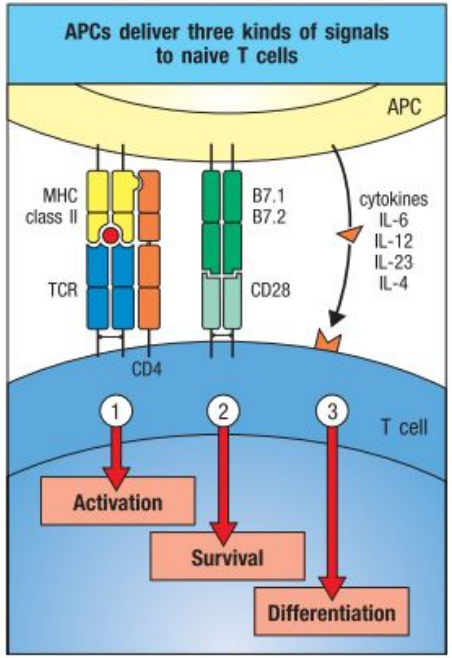
Активация и дифференцировка наивных CD4$^+$ Т клеток

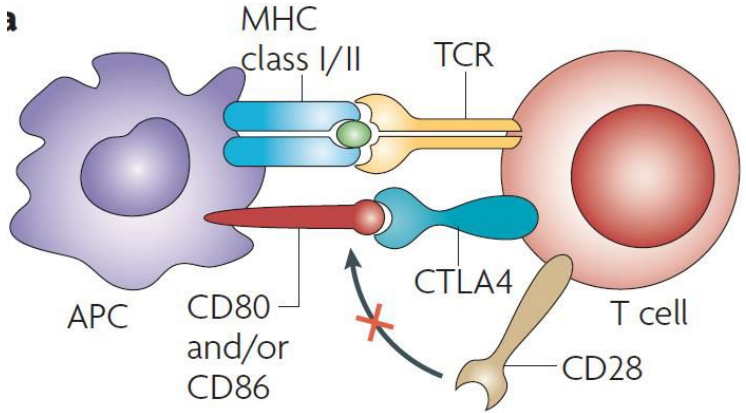




Для активации наивных CD4 Т клеток распознавание комплекса пептид:MHC II необходимо, но недостаточно

CTLA-4



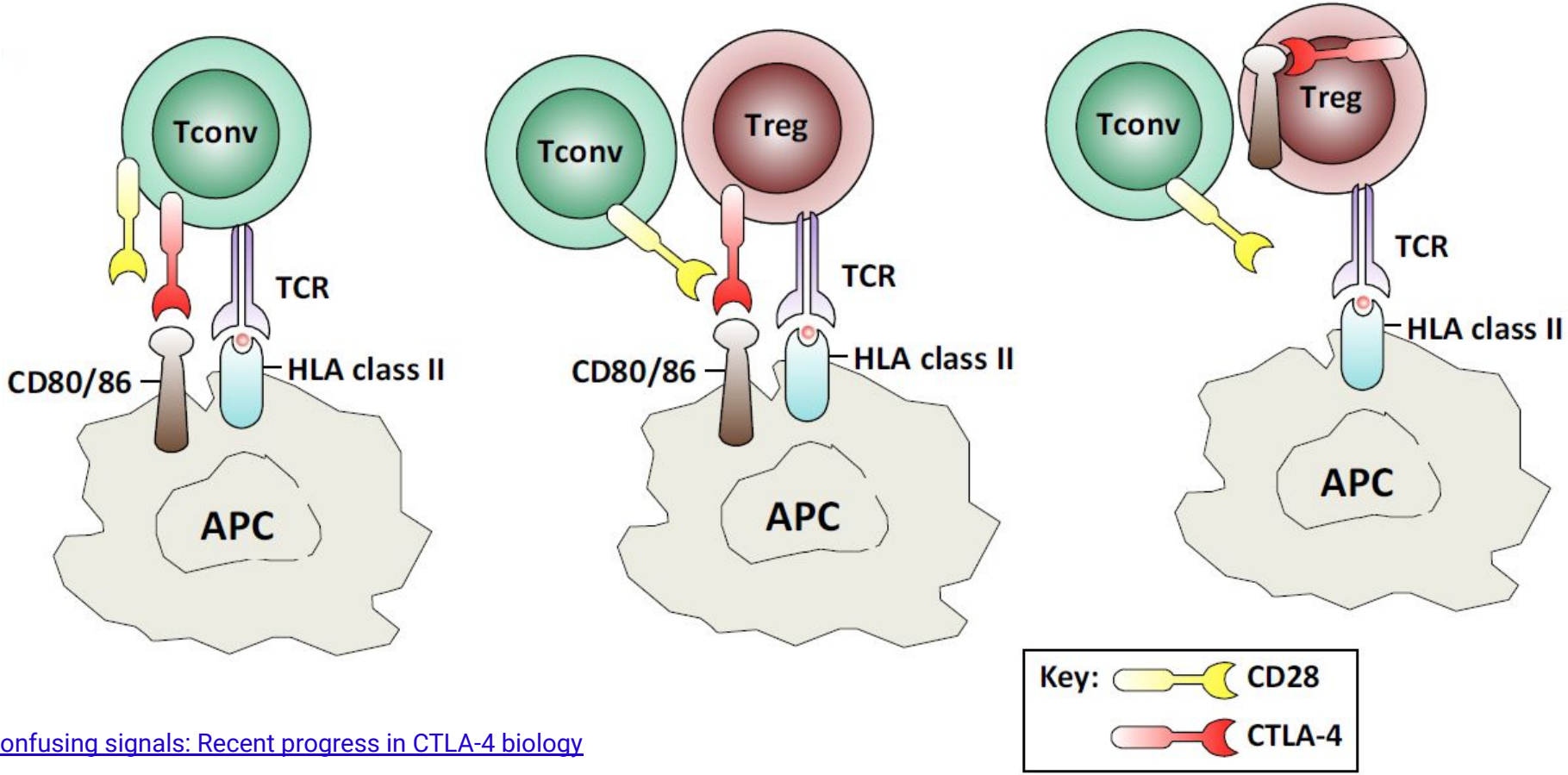


CTLA 4 ингибиторный костимуляторный рецептор

CTLA 4 не экспрессируется конститутивно, появляется после активации наивной Т клетки

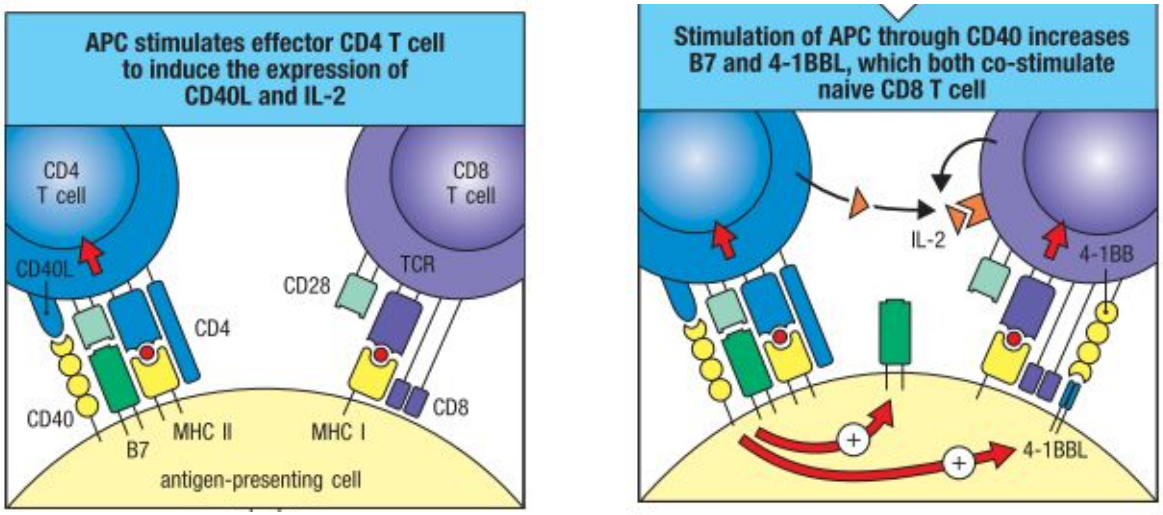
Связывается с CD80/86 (B7.1 /2)
в 100 раз сильнее чем CD28

CTLA-4



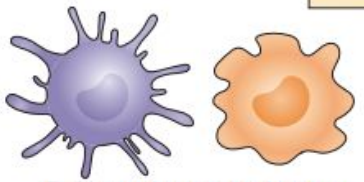
[Confusing signals: Recent progress in CTLA-4 biology]

Активация CD8$^+$ Т клеток

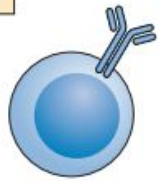


Антигенпрезентирующие клетки

Professional APCs



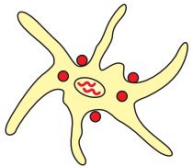
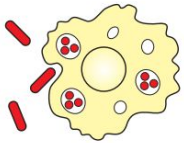
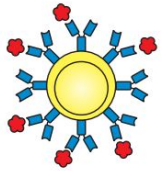
DCs and macrophages



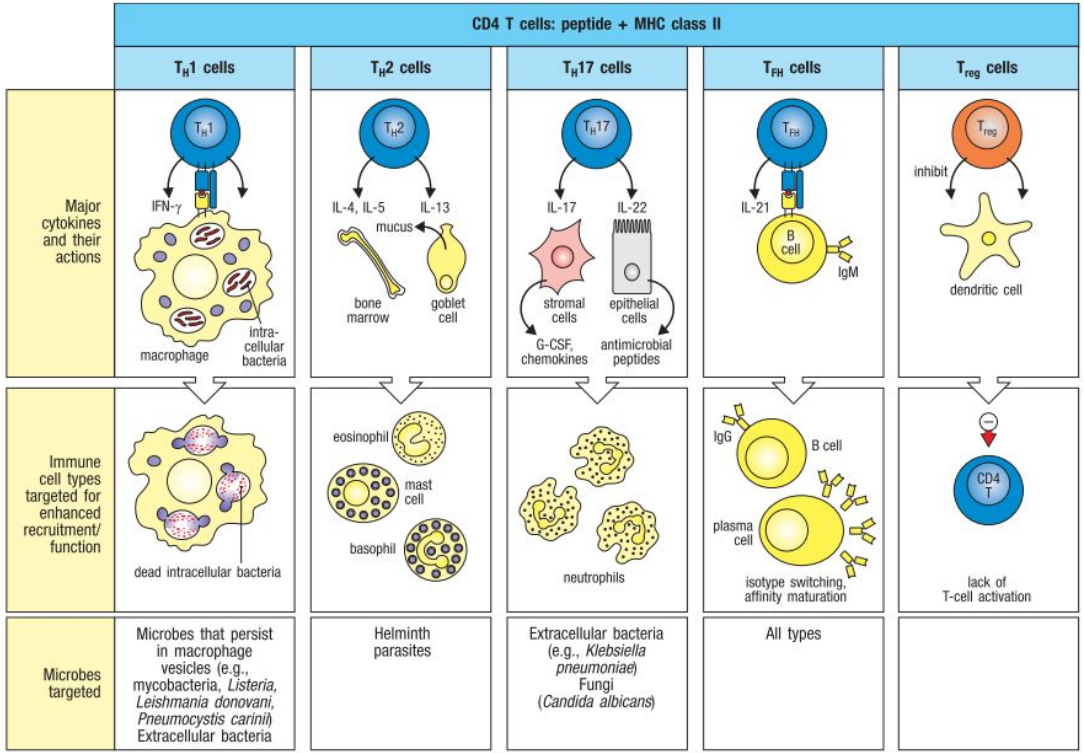
B cells

Key features
- Phagocytic
- Express receptors for apoptotic cells, DAMPs and PAMPs
- Localize to tissues
- Localize to T cell zone of lymph nodes following activation (DCs)
- Constitutively express high levels of MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

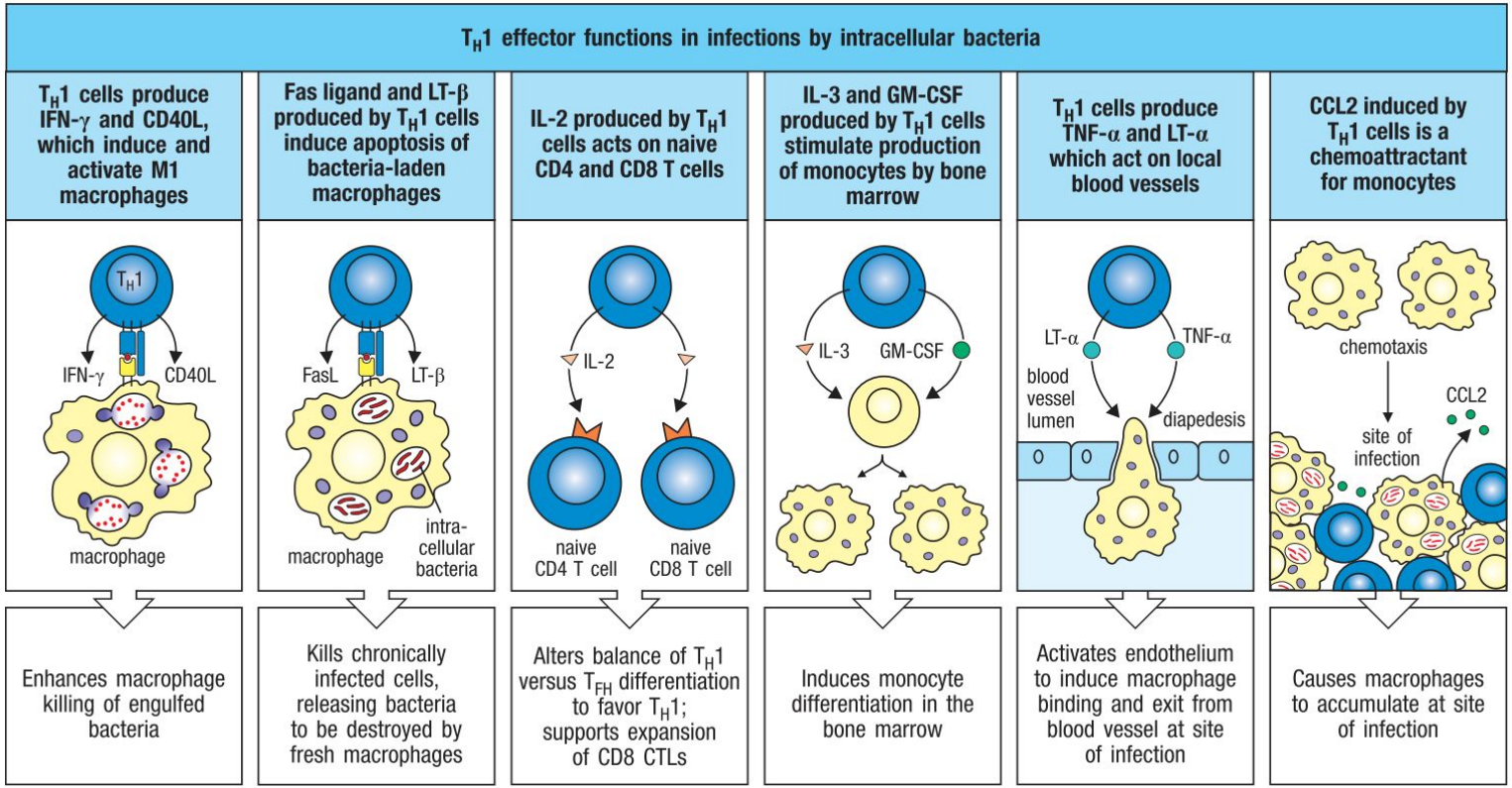
Key features
- Internalize antigens via BCRs
- Constitutively express MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells	+++ Macropinocytosis +++ Phagocytosis	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue-resident dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulation delivery	Inducible High on dendritic cells in lymphoid tissues ++++	Inducible – to +++	Inducible – to +++
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood
Effect	Results in activation of naive T cells	Results in activation of macrophages	Results in delivery of help to B cell

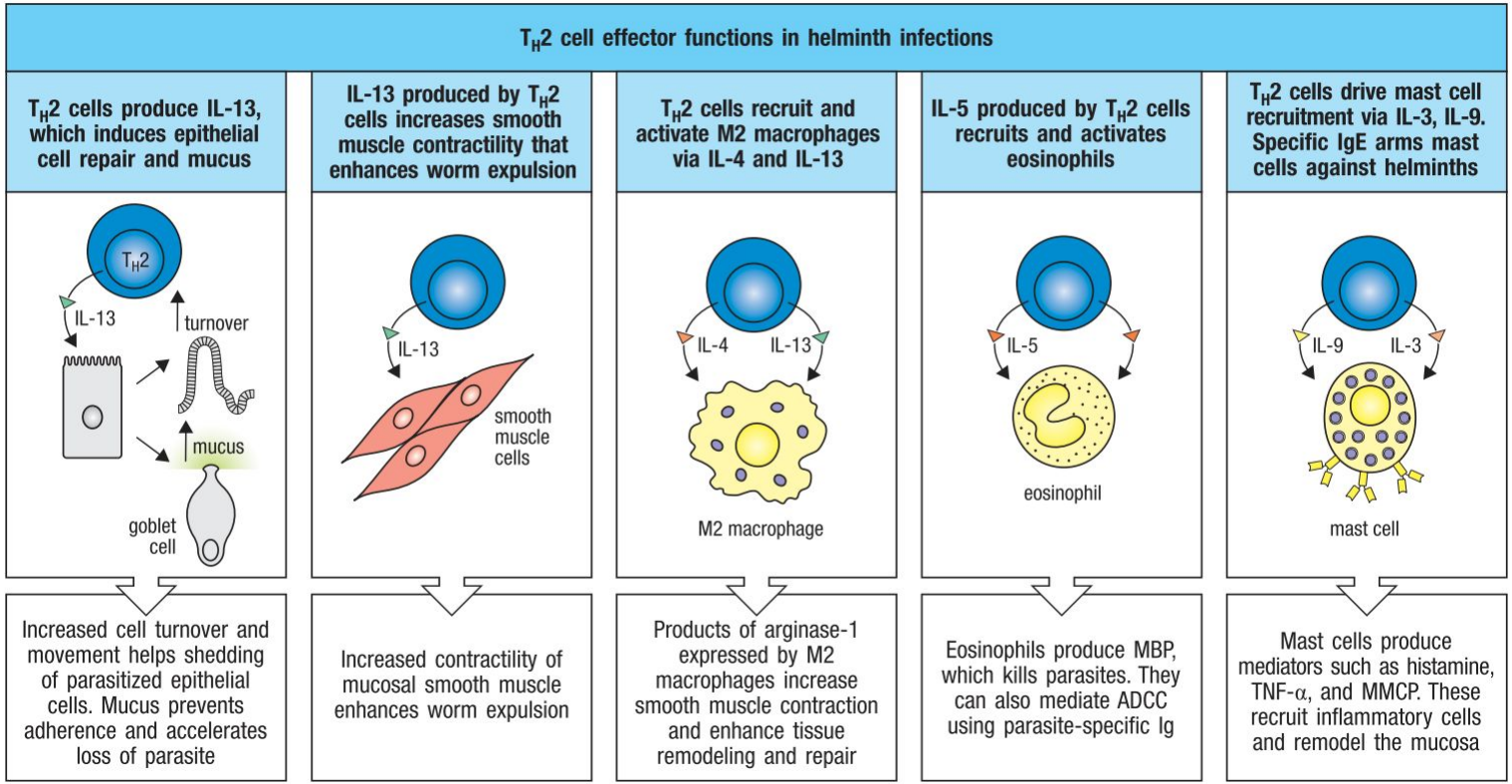
Активированные CD4$^+$ Т клетки определяют дальнейшее развитие иммунного ответа



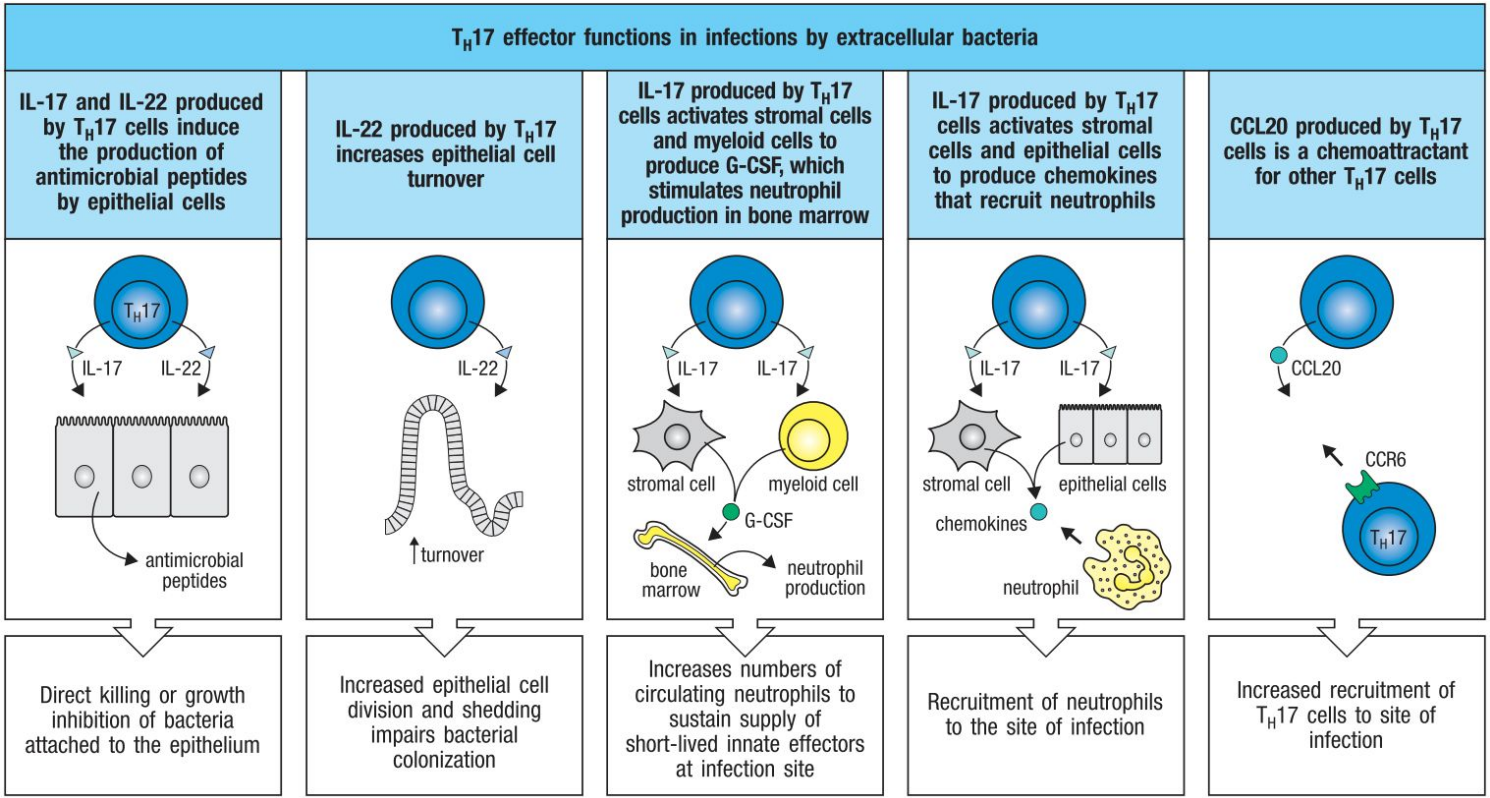
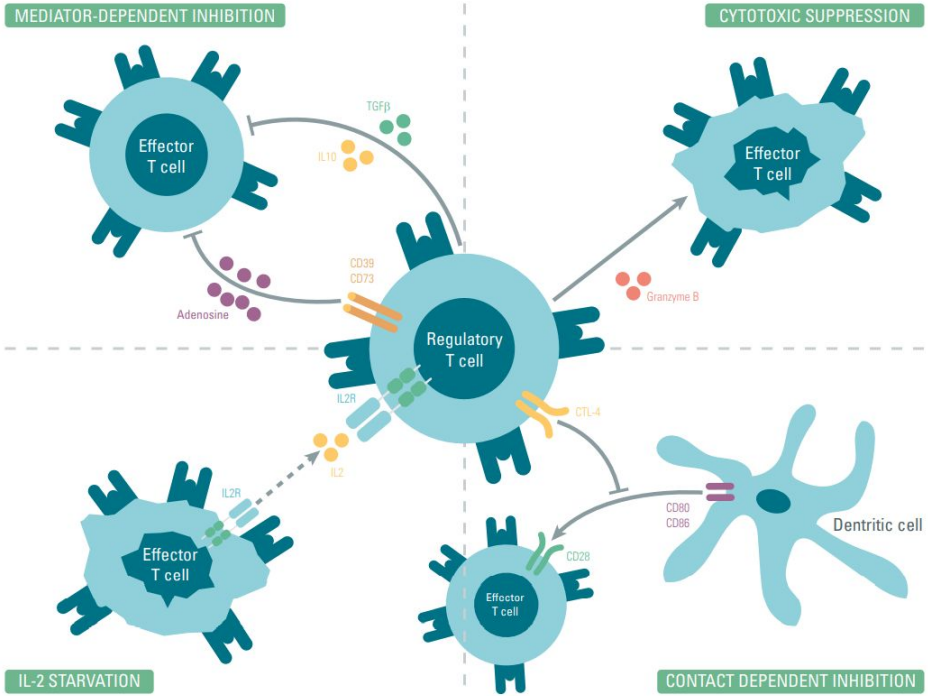
Th1 ответ


T_H1 effector functions in infections by intracellular bacteria
T_H1 cells produce IFN-γ and CD40L, which induce and activate M1 macrophages
Fas ligand and LT-β produced by T_H1 cells induce apoptosis of bacteria-laden macrophages
IL-2 produced by T_H1 cells acts on naive CD4 and CD8 T cells
IL-3 and GM-CSF produced by T_H1 cells stimulate production of monocytes by bone marrow
T_H1 cells produce TNF-α and LT-α which act on local blood vessels
CCL2 induced by T_H1 cells is a chemoattractant for monocytes
T_H1
IFN-γ
CD40L
macrophage
FasL
LT-β
macrophage
intra-cellular bacteria
IL-2
naive CD4 T cell
naive CD8 T cell
IL-3
GM-CSF
LT-α
TNF-α
blood vessel lumen
diapedesis
chemotaxis
CCL2
site of infection
Enhances macrophage killing of engulfed bacteria
Kills chronically infected cells, releasing bacteria to be destroyed by fresh macrophages
Alters balance of T_H1 versus T_{FH} differentiation to favor T_H1; supports expansion of CD8 CTLs
Induces monocyte differentiation in the bone marrow
Activates endothelium to induce macrophage binding and exit from blood vessel at site of infection
Causes macrophages to accumulate at site of infection

Th2 ответ


T_H2 cell effector functions in helminth infections
T_H2 cells produce IL-13, which induces epithelial cell repair and mucus
IL-13 produced by T_H2 cells increases smooth muscle contractility that enhances worm expulsion
T_H2 cells recruit and activate M2 macrophages via IL-4 and IL-13
IL-5 produced by T_H2 cells recruits and activates eosinophils
T_H2 cells drive mast cell recruitment via IL-3, IL-9. Specific IgE arms mast cells against helminths
T_H2
IL-13
turnover
mucus
goblet cell
IL-13
smooth muscle cells
IL-4
IL-13
M2 macrophage
IL-5
eosinophil
IL-9
IL-3
mast cell
Increased cell turnover and movement helps shedding of parasitized epithelial cells. Mucus prevents adherence and accelerates loss of parasite
Increased contractility of mucosal smooth muscle enhances worm expulsion
Products of arginase-1 expressed by M2 macrophages increase smooth muscle contraction and enhance tissue remodeling and repair
Eosinophils produce MBP, which kills parasites. They can also mediate ADCC using parasite-specific Ig
Mast cells produce mediators such as histamine, TNF-α, and MMCP. These recruit inflammatory cells and remodel the mucosa

Th17 ответ


T_H17 effector functions in infections by extracellular bacteria
IL-17 and IL-22 produced by T_H17 cells induce the production of antimicrobial peptides by epithelial cells
IL-22 produced by T_H17 increases epithelial cell turnover
IL-17 produced by T_H17 cells activates stromal cells and myeloid cells to produce G-CSF, which stimulates neutrophil production in bone marrow
IL-17 produced by T_H17 cells activates stromal cells and epithelial cells to produce chemokines that recruit neutrophils
CCL20 produced by T_H17 cells is a chemoattractant for other T_H17 cells
T_H17
IL-17
IL-22
antimicrobial peptides
IL-22
turnover
IL-17
IL-17
stromal cell
myeloid cell
G-CSF
bone marrow
neutrophil production
IL-17
IL-17
stromal cell
epithelial cells
chemokines
neutrophil
CCL20
CCR6
T_H17
Direct killing or growth inhibition of bacteria attached to the epithelium
Increased epithelial cell division and shedding impairs bacterial colonization
Increases numbers of circulating neutrophils to sustain supply of short-lived innate effectors at infection site
Recruitment of neutrophils to the site of infection
Increased recruitment of T_H17 cells to site of infection

Регуляторные Т клетки