Inflammation and cardiovascular disease

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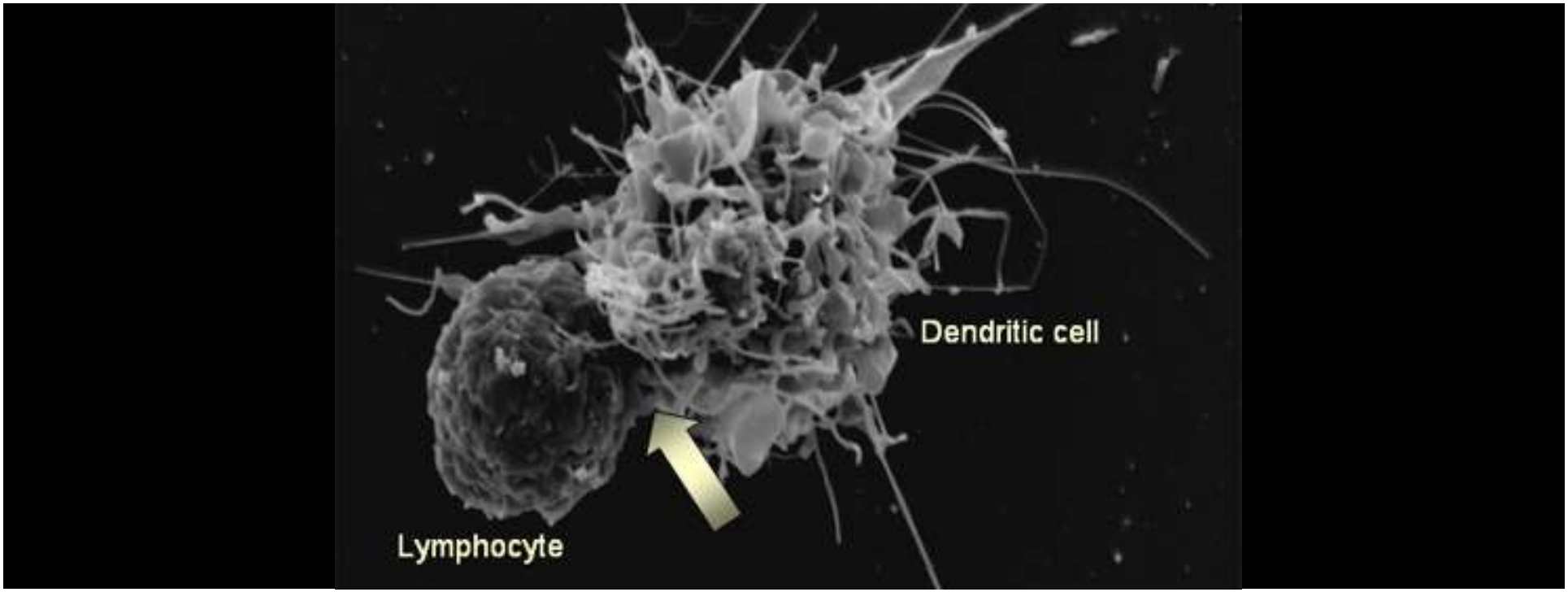
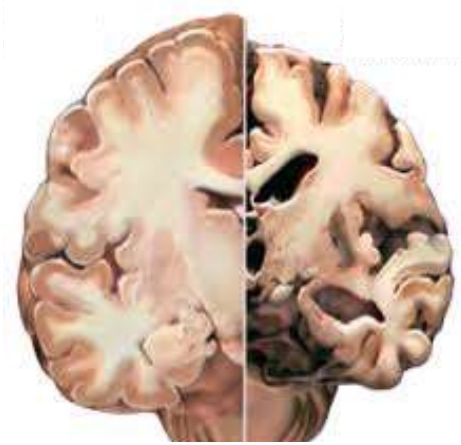
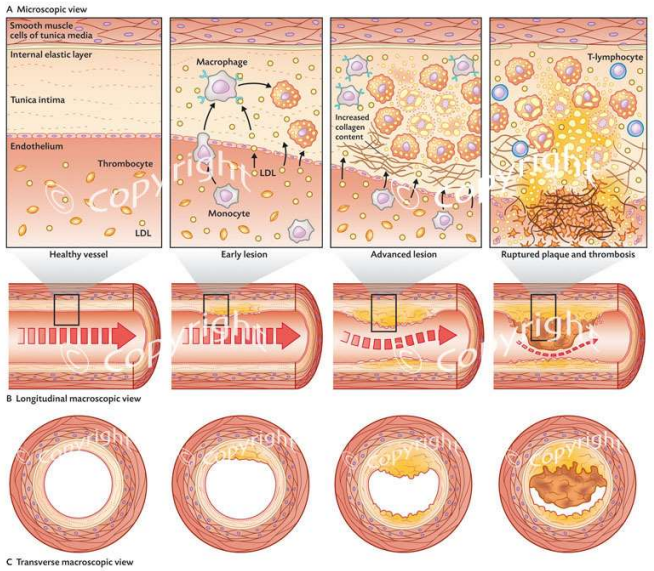


What do these diseases have in common?

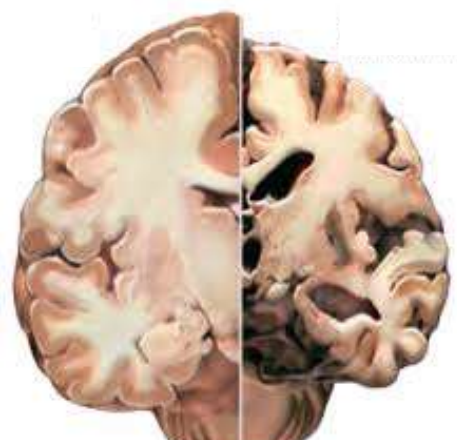


M E T S S
U E D I
I N I R
A M E E
D S L A

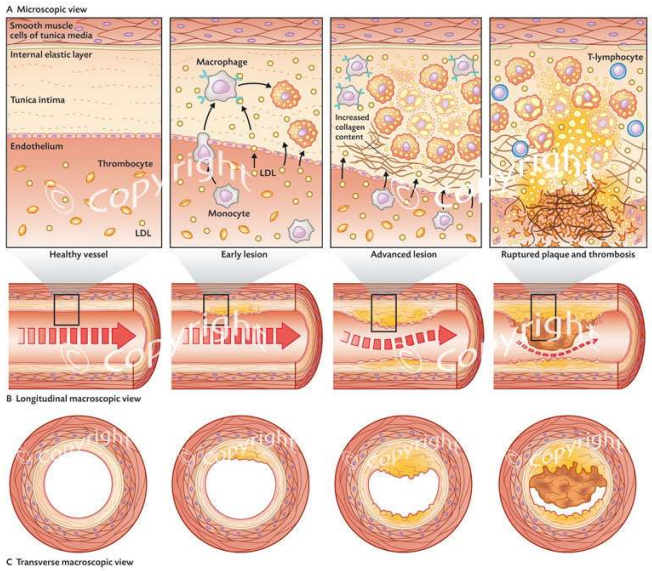


What do these diseases have in common?

apensar



IMMUNE RELATED DISEASES



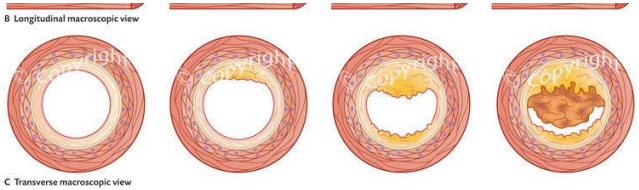
Implications

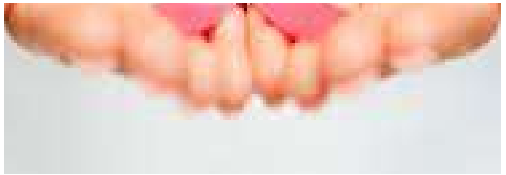
Diseases are multifactorial

- Immune system is in the basis of many diseases

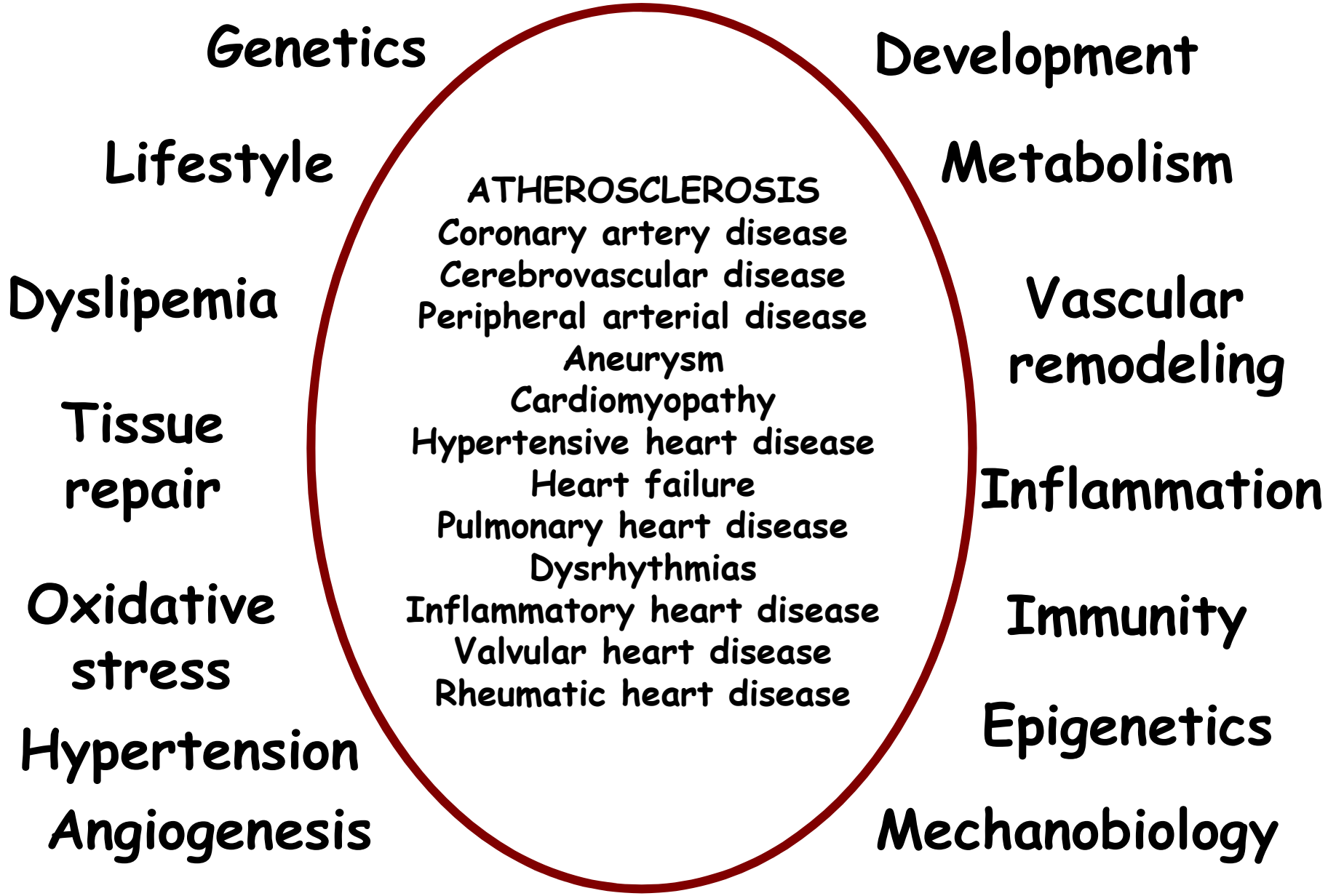
- Targeting the immune system may be potentially useful for the treatment of these diseases

- A diversity of models available to test biological questions

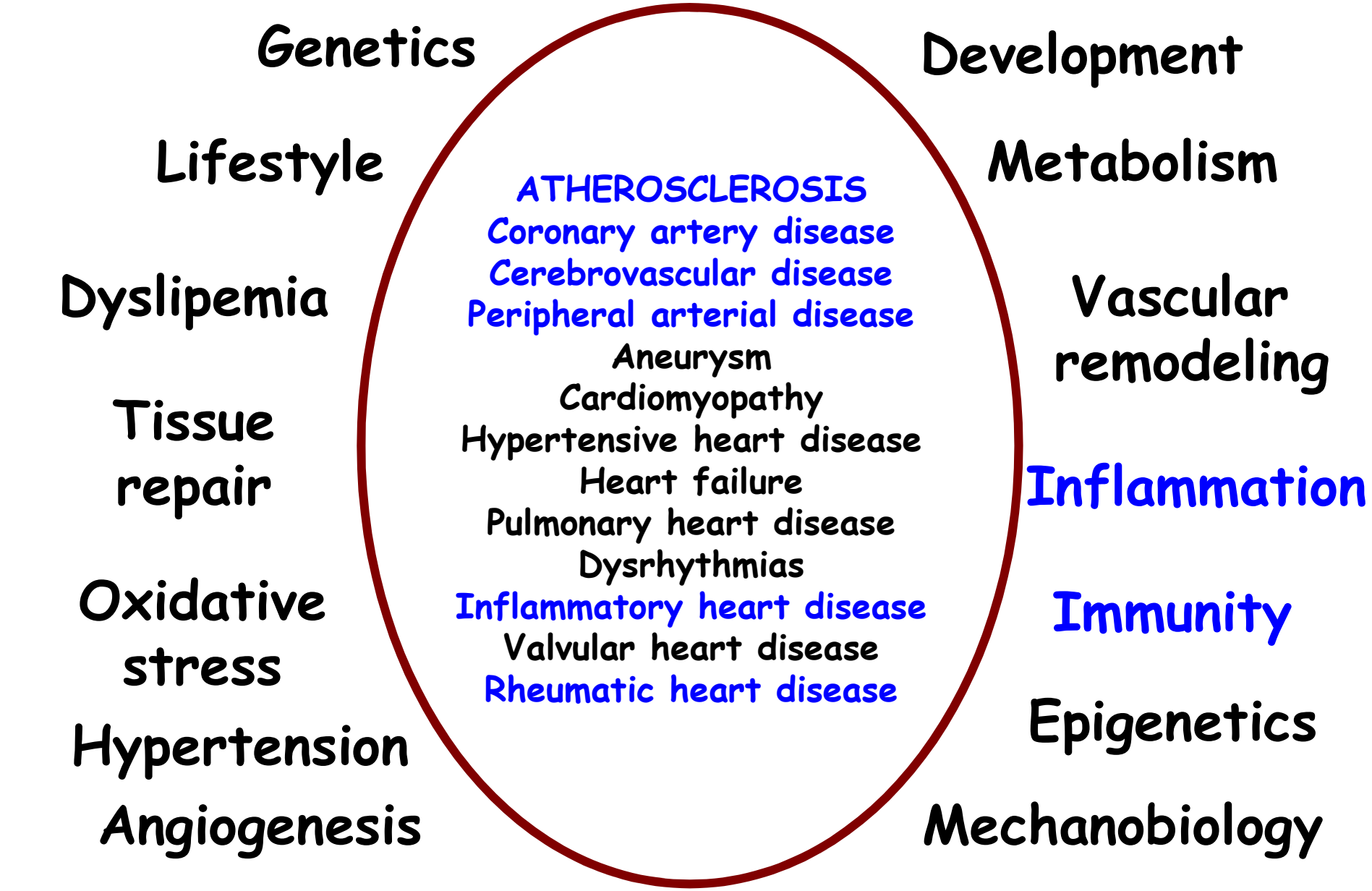




Cardiovascular diseases are multifactorial



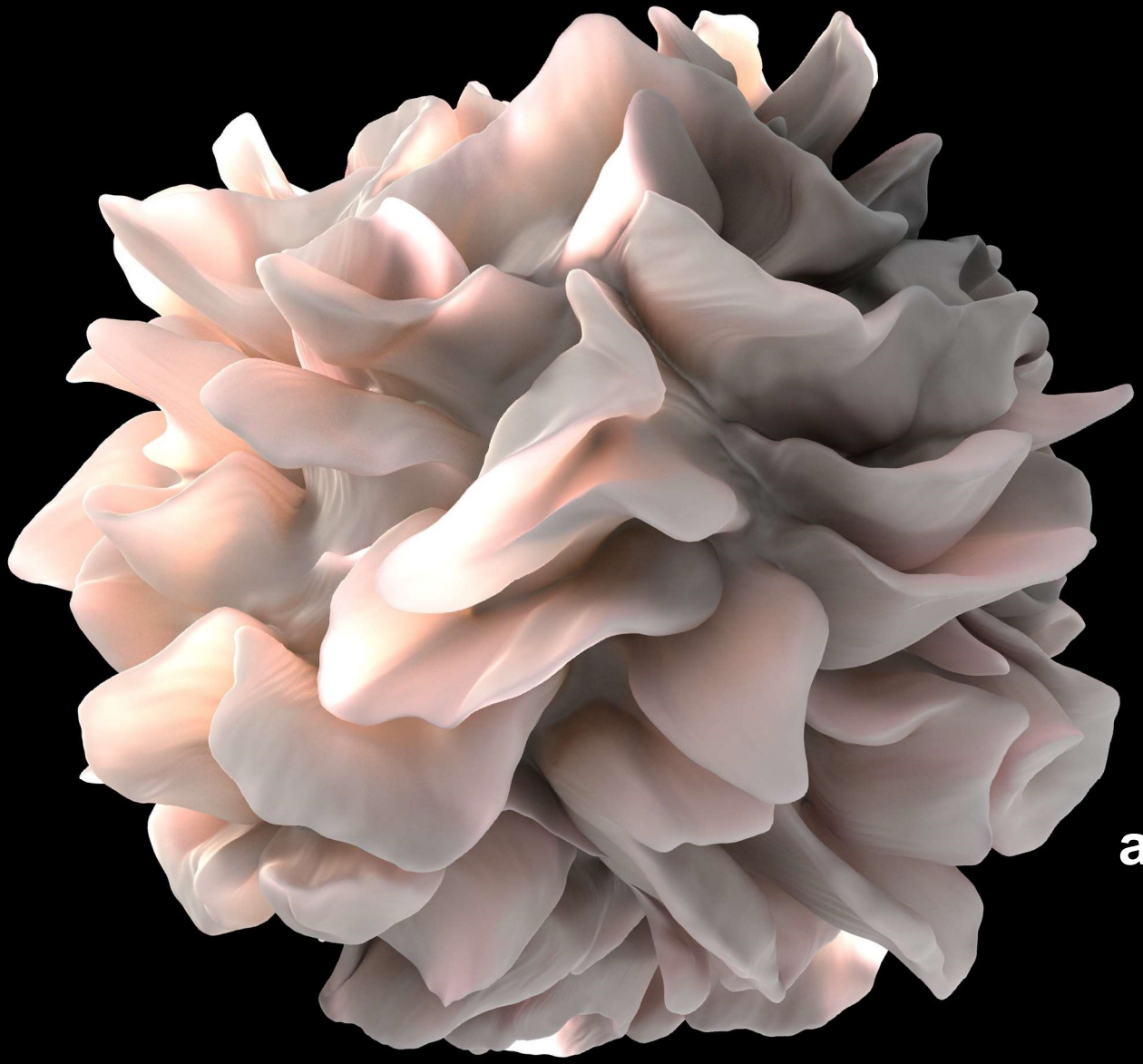
Cardiovascular diseases are multifactorial



Immunity and Inflammation

	Inflammation	Immunity
Infectious	Innate response to infection	Adaptive response to infection
Non-infectious	Chronic inflammation	Autoimmunity

Which cells control immunity and inflammation?



Dendritic cells and macrophages

Source: Donny Bliss, National Library of Medicine

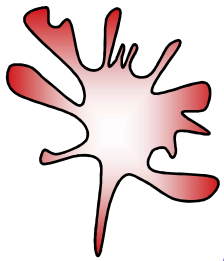
Dendritic cells & macrophages: at the basis of immunity and inflammation

TRIGGER (sterile or microbial)

Inflammation

Dendritic cells

Macrophages



Innate immunity

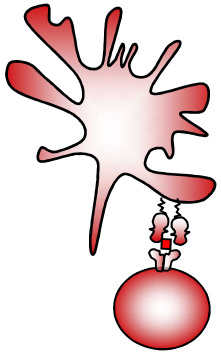
Proinflammatory cytokines

Monocytes Macrophages granulocytes

Innate lymphoid cells NK cells

Immunity

Foreign antigen or neoantigen



Dendritic cells

Adaptive immunity

T cells

NKT cells CD8 (CTL)

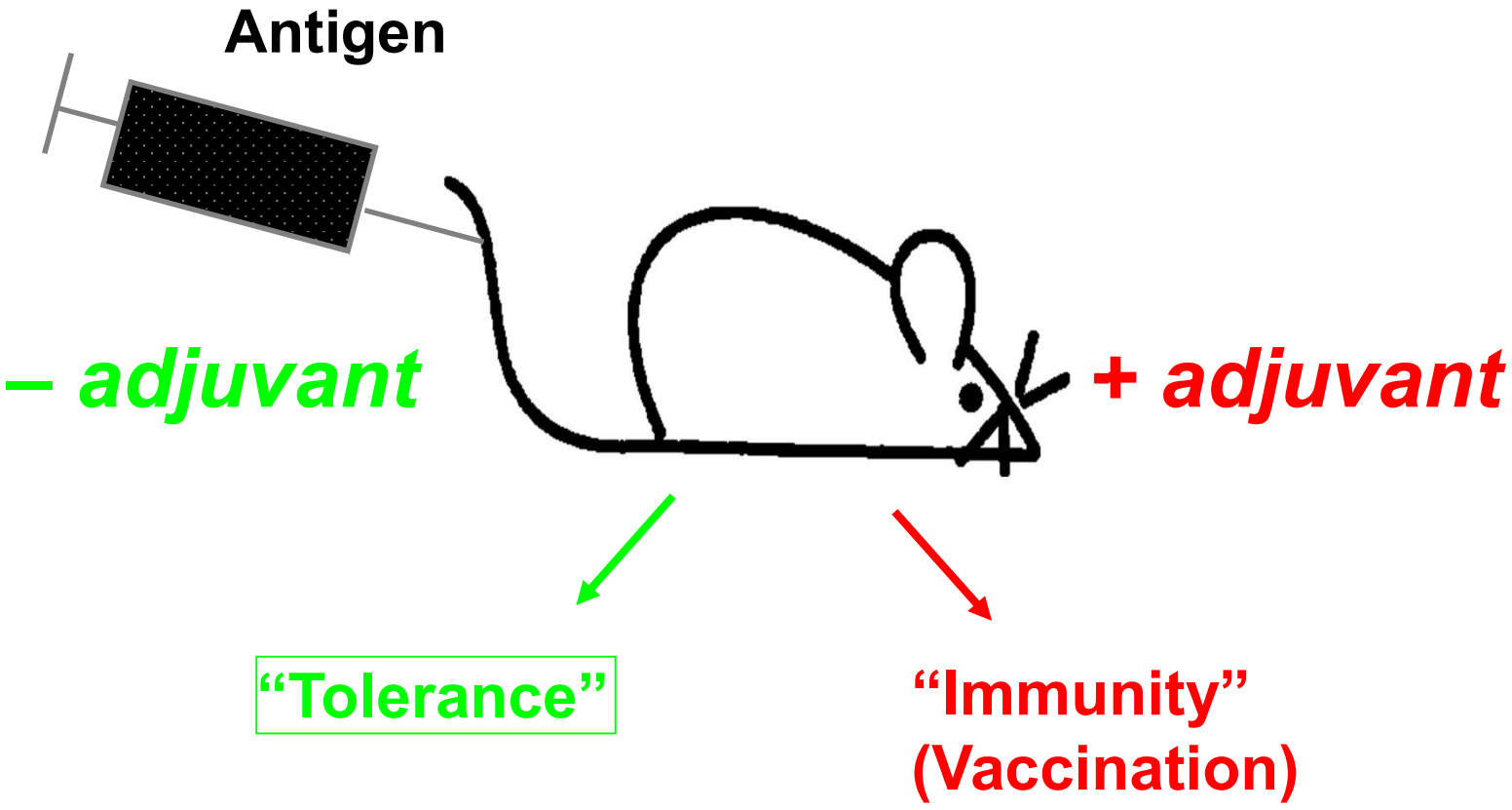
CD4 (Th1, Th2, Th17, Treg)

B cells

Atherosclerosis
Coronary artery disease
Cerebrovascular disease
Peripheral arterial disease
Inflammatory heart disease
Rheumatic heart disease

EFFECTOR IMMUNE RESPONSE

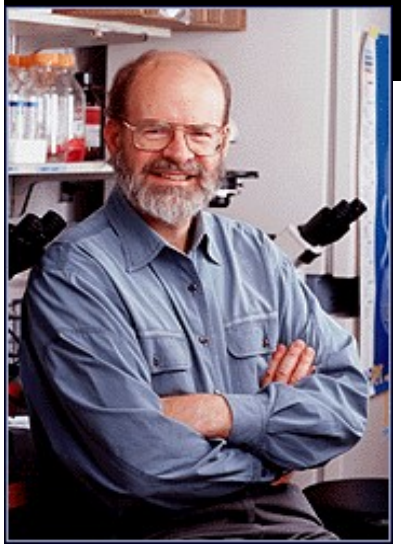
How is initiated the immune response?
The immunologist's dirty little secret



The antigen is not enough

to mount an adaptive immune response

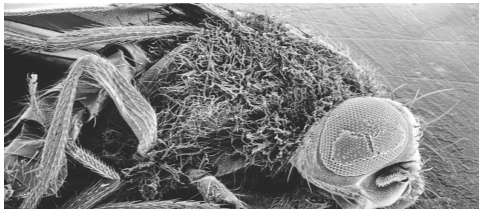
Induction of immunity and inflammation in response to pathogens



C. Janeway
(1943-2003)

Janeway Jr, C. A. 1989. Cold Spring Harb Symp Quant Biol. 54:1-13.

Pathogen molecular signatures (adjuvants)



B. Lemaitre…. J. Hoffmann. 1996. Cell.

Pathogen recognition receptors

Steady state Myeloid cell

Myeloid cell activation

Effector Myeloid cell

Inflammation

Resting T cell

T cell activation

Effector T cell

Adaptive response

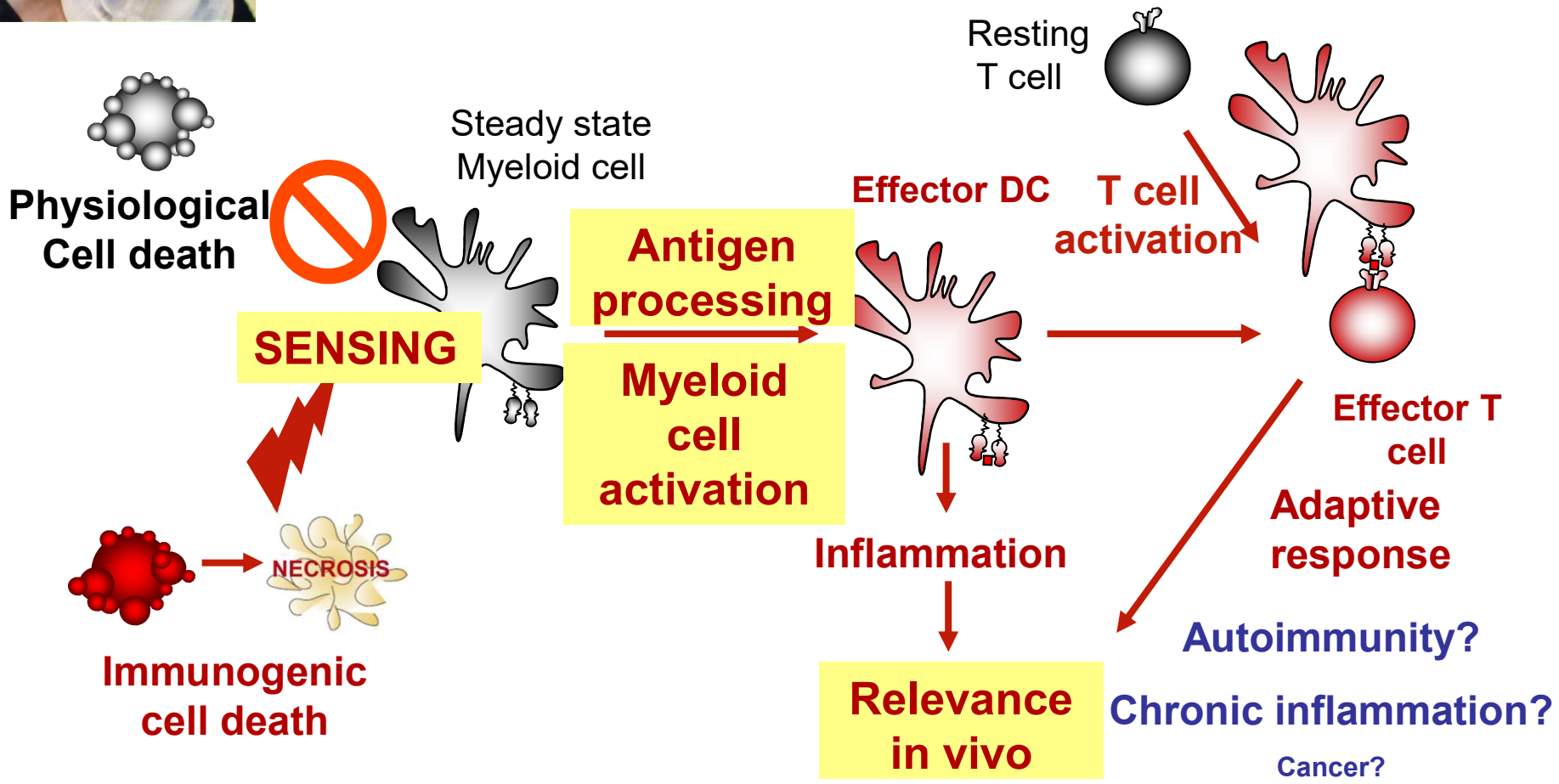
However, inflammation or immunity can occur in the absence of pathogens.

e.g., autoinflammatory / autoimmune diseases.

How do danger signals initiate/modulate the inflammatory and immune response?

"danger" signals are preformed endogenous adjuvants sequestered inside healthy cells and exposed or released upon necrotic cell death.

Matzinger (1994). Annu Rev Immunol *12*, 991



Our research questions

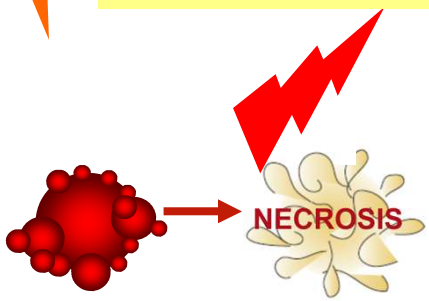
Pathogens & microbiota

Iborra et al. 2012. *J. Clin. Invest.*

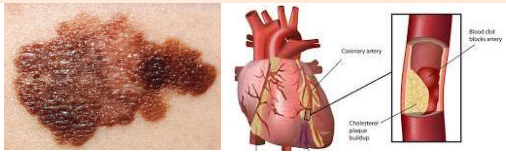
Blanco-Menéndez et al. 2015. *J. Immunol.*

Iborra & Martínez-López et al. 2016. *Immunity*

How do DC & MF sense tissue damage and microorganisms?



Tissue damage & Dysregulation

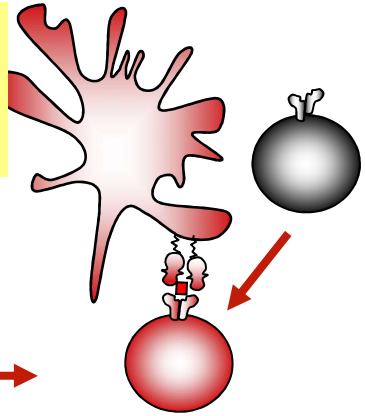


Martínez-López et al. 2015. *Eur. J. Immunol.*

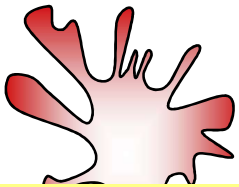
Sánchez-Paulete et al. 2016. *Cancer Discov.*

Iborra et al. 2016. *Immunity*

What is the specialized function of different DC subsets in initiating immunity?



Mechanisms Function



Immunity

Adaptive Response

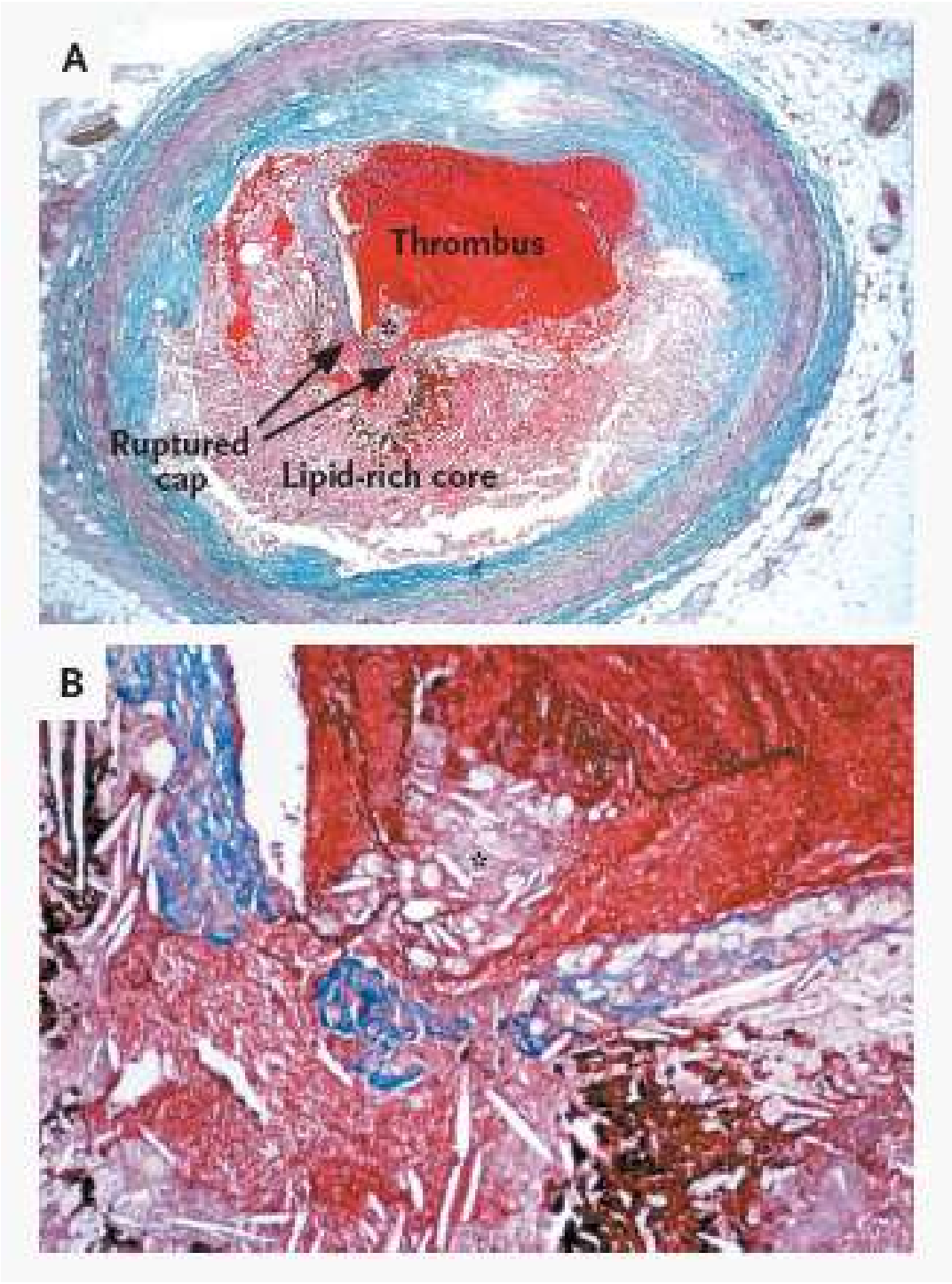
Can we target metabolism for manipulating DC function?

Garaude et al. 2016. *Nat. Immunol.*

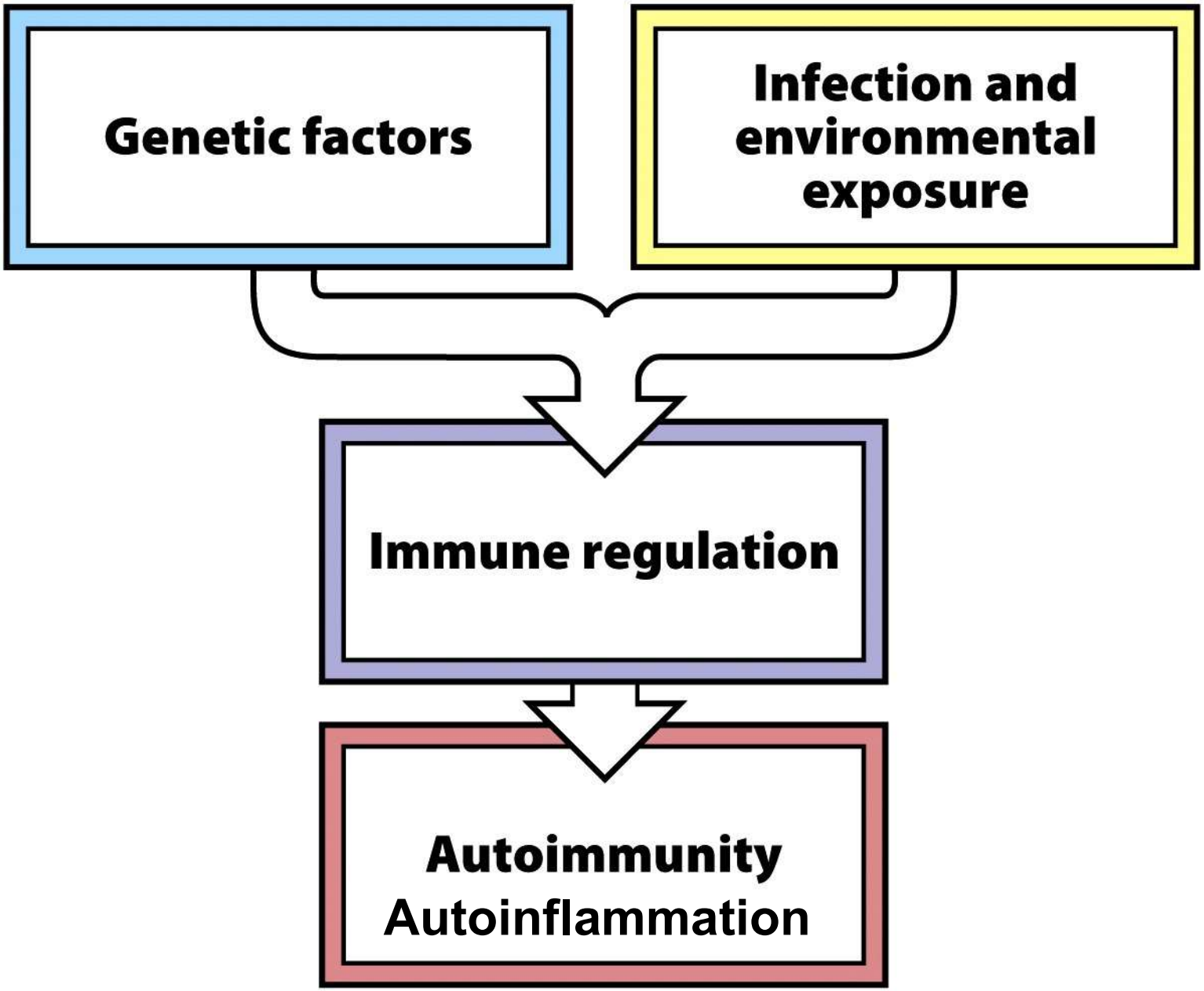
Inflammation

Innate response

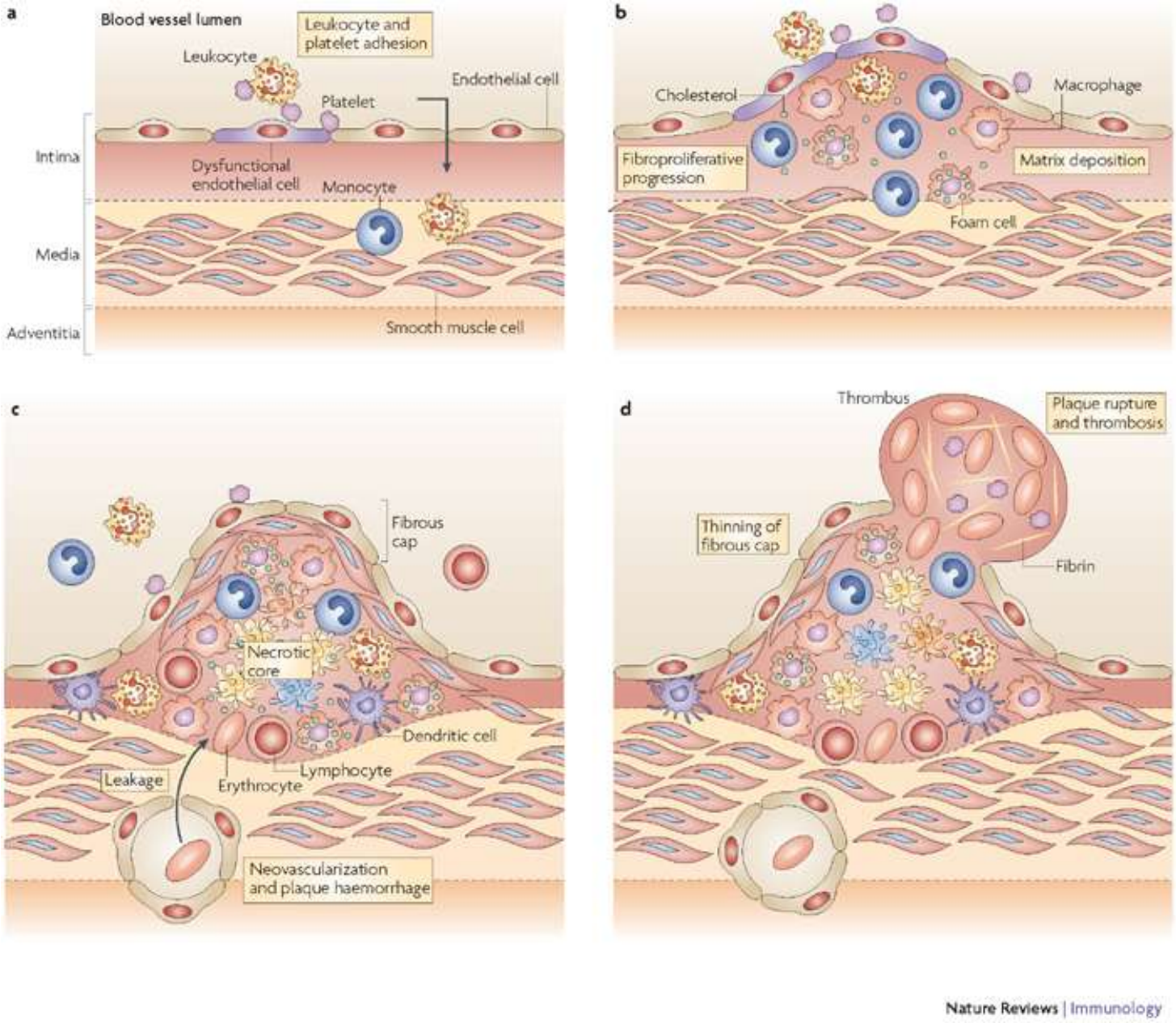
Relevance *in vivo*



Atherosclerotic lesion in a human artery: Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood.
Trichrome stain was used, rendering luminal thrombus and intraplaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in (the asterisk indicates cholesterol crystals).


Genetic factors
Infection and environmental exposure
Immune regulation
Autoimmunity
Autoinflammation

Development of atherosclerosis



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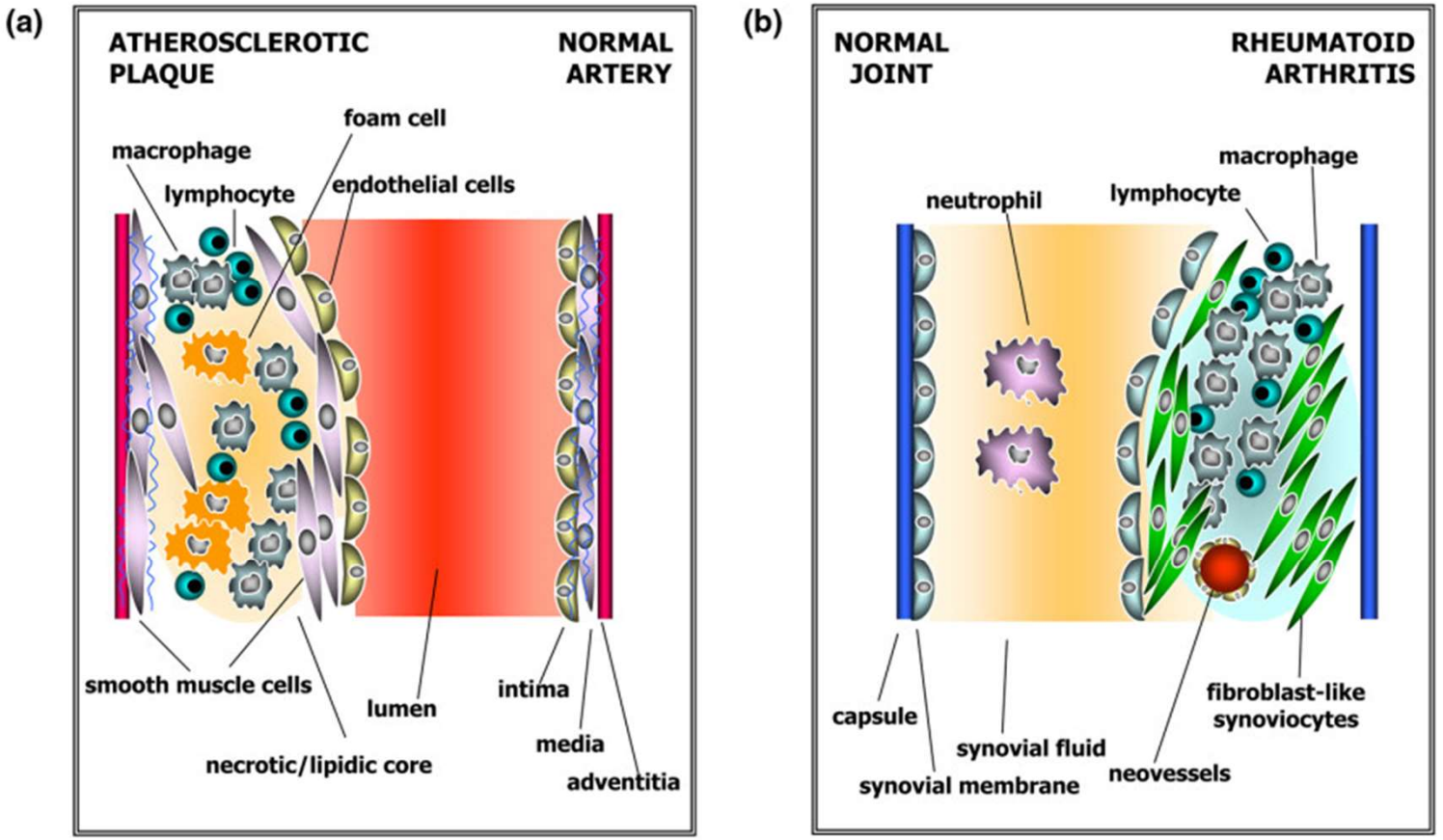
Atherosclerosis and autoimmunity



Cardiovascular disease = (chronic) Inflammation

- Chronic inflammation is positively linked to CVD
  - Elevated hs-CRP, proinflammatory cytokines {IL-6 and TNF-alpha} and chemokines
  - Increased incidence of CVD in those with:
    - Overt inflammatory conditions
      - Autoimmune disease, renal disease, allergic disease, coeliac disease, periodontal disease and inflammatory bowel disease
    - Fatty infiltration of liver
      - Persistent elevated GGT is predictive of metabolic syndrome
    - insulin resistance ←→ obesity
      - Adipocyte production of cytokines and chemokines.

Arthritis and cardiovascular risk

Table 1

Studies evaluating the risk of coronary heart disease in rheumatoid arthritis

[Reference] (year)	Study design	RA definition	*n*	Estimated risk
[18] (2001)	Prospective cohort	ACR 1987 criteria	236	3.86-fold of combined CV events (MI + revascularization + stroke)
[4] (2003)	Prospective cohort	ACR 1987 criteria	525	2-fold risk for MI 1.48-fold risk for stroke RA >10 years: 3-fold risk for MI
[84] (2003)	Cross-sectional survey	Rheumatologist diagnosis	9,093	2.15-fold risk for MI
[19] (2003)	Prospective cohort	Physician diagnosis	11,633	1.6-fold risk for MI
[5] (2005)	Retrospective cohort	ACR 1987 criteria	603	2-fold risk for MI 6-fold risk for unrecognized MI 2-fold risk sudden death
[85] (2007)	Retrospective cohort	ACR 1987 criteria	239	0.1% to 0.3%/year MI 0.07%/year stroke
[2] (2008)	Retrospective cohort	Rheumatologist diagnosis	4,363	3.2% prevalence MI 1.9% prevalence stroke

ACR, American College of Rheumatology; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; RA, rheumatoid arrthritis.

Lupus and cardiovascular risk

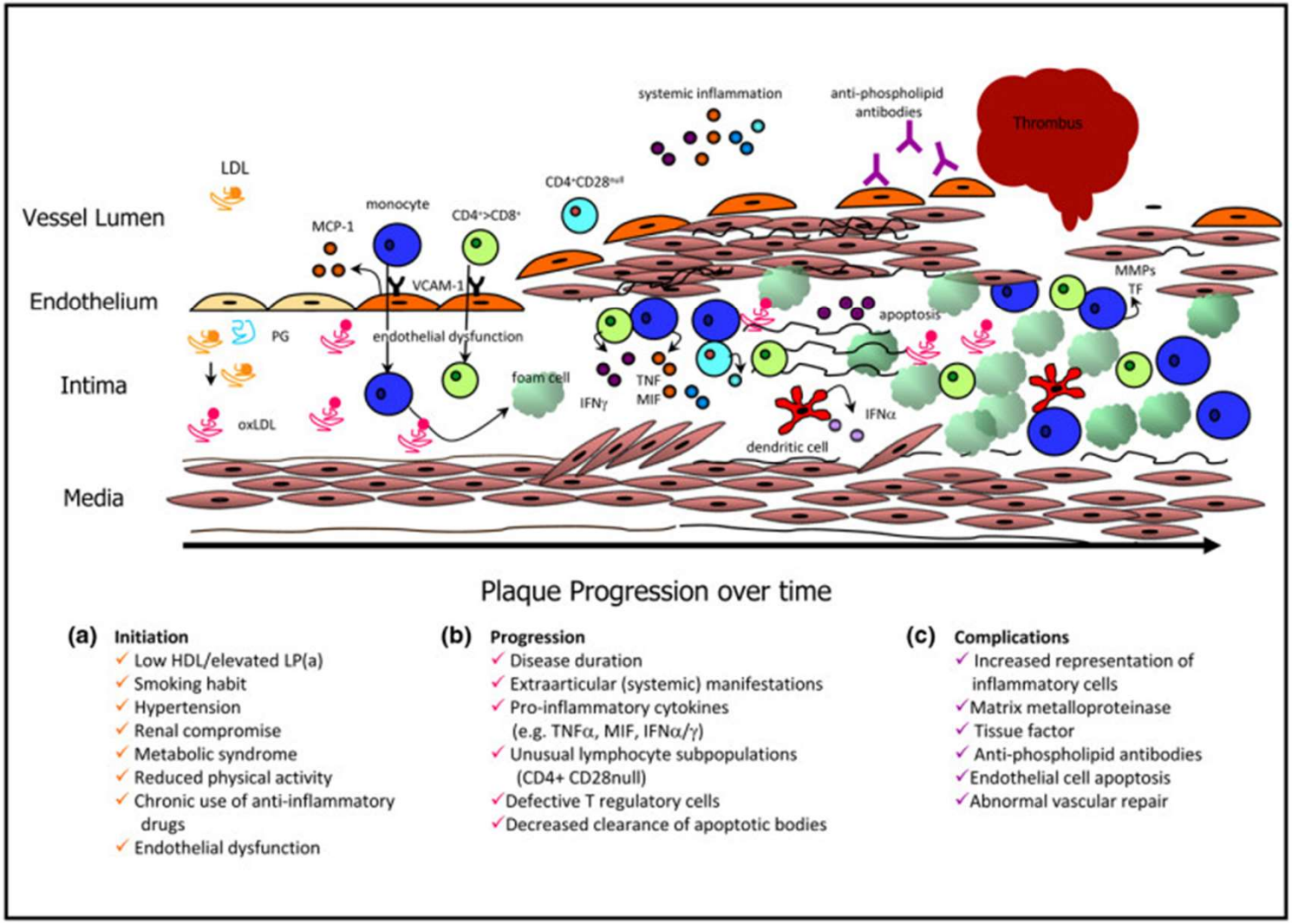
Table 2

Studies evaluating the risk of coronary heart disease in systemic lupus erythematosus

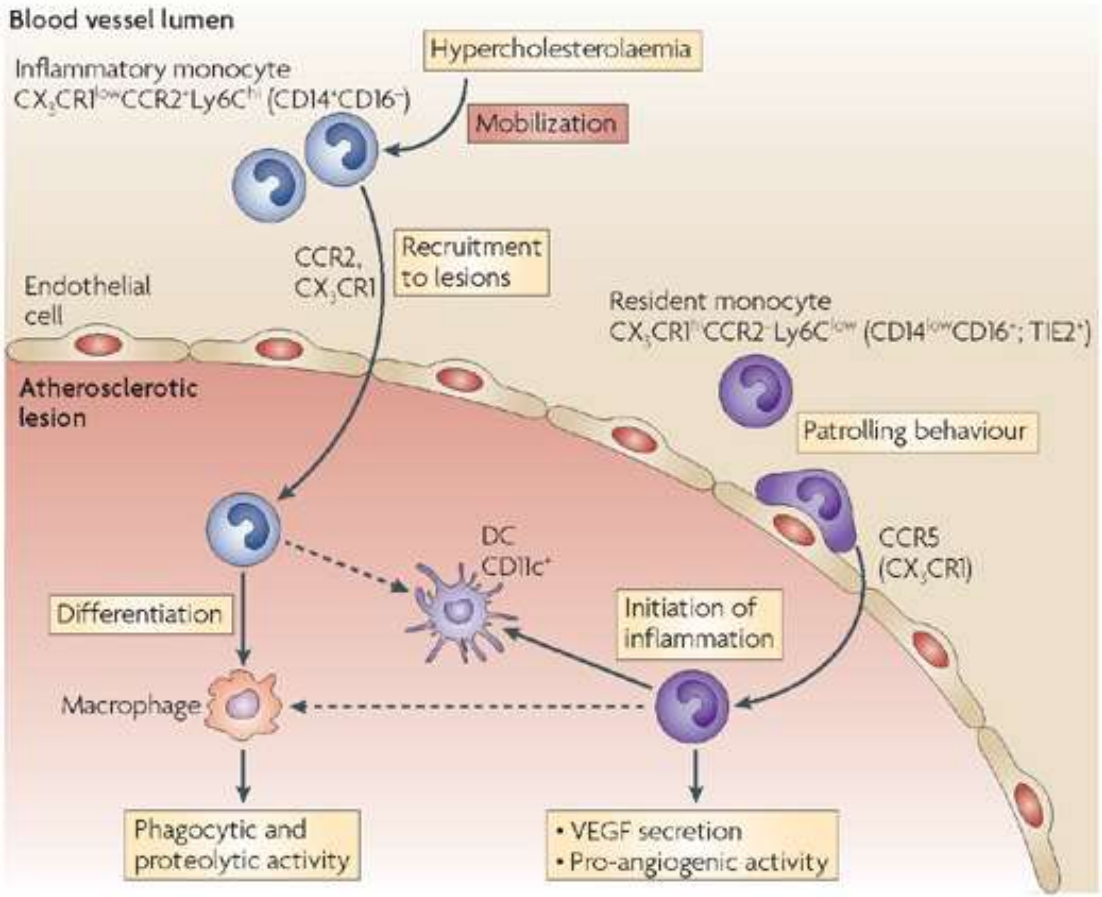
[Reference] (year)	Study design	SLE definition	*n*	Estimated risk
[11] (1997)	Prospective cohort	ACR criteria for SLE	498	5-fold risk for MI 50-fold risk in ages 35 to 44 years
[86] (1999)	Retrospective cohort	Rheumatologist diagnosis	8,742	2.27-fold risk for MI 3.8-fold risk for chronic heart failure
[12] (2001)	Retrospective cohort	Rheumatologist diagnosis	296	17.0-fold risk for CVD 10.1-fold risk for MI 7.9-fold risk for stroke
[87] (2004)	Cross-sectional, prospective	ACR criteria for SLE	202 (cross-sectional), 47 (prospective)	1.4-fold risk for CHD 0.6-fold risk for stroke 8.5% CHD events 10% stroke follow up
[88] (2004)	Case control	Physician diagnosis	770	1.46 risk for MI

ACR, American College of Rheumatology; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; SLE, systemic lupus erythematosus.

Atherosclerosis evolution



Innate immunity in atherosclerosis



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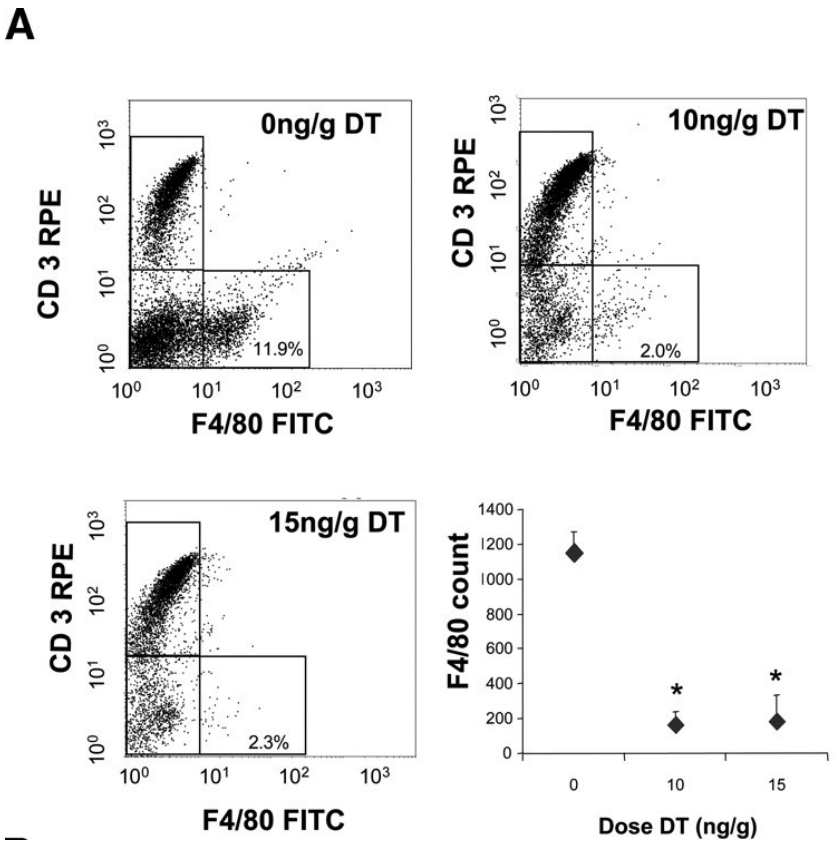
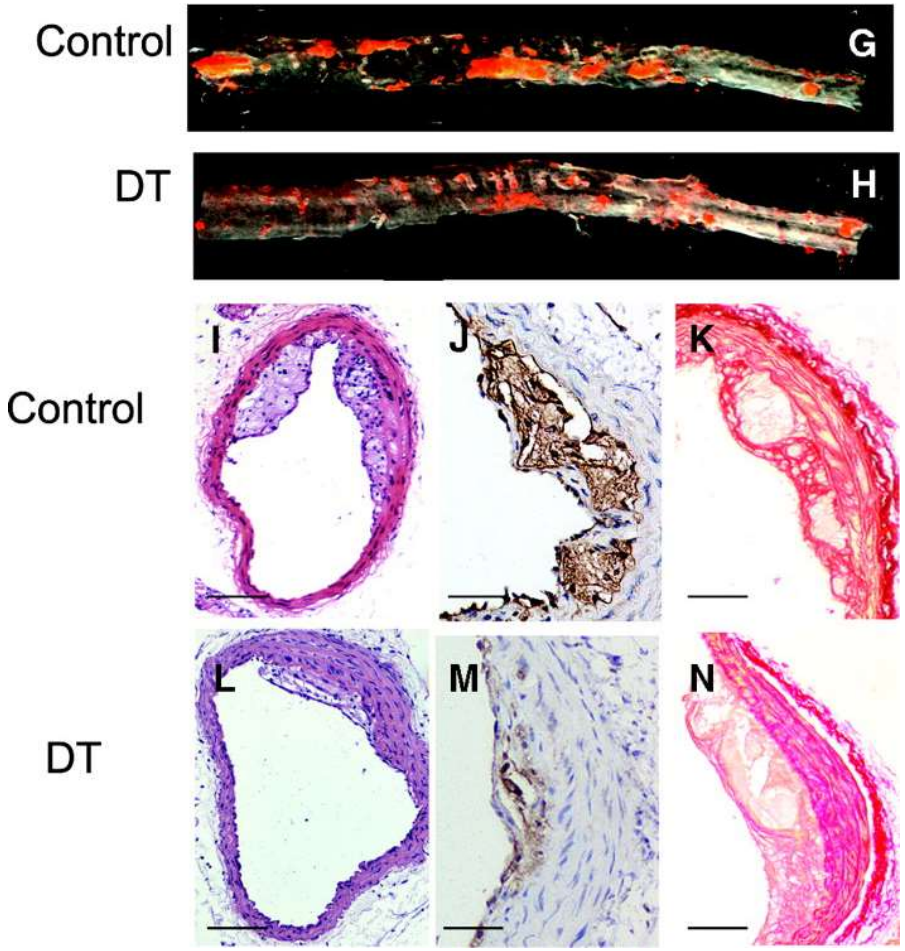
Innate immunity by macrophages is crucial!

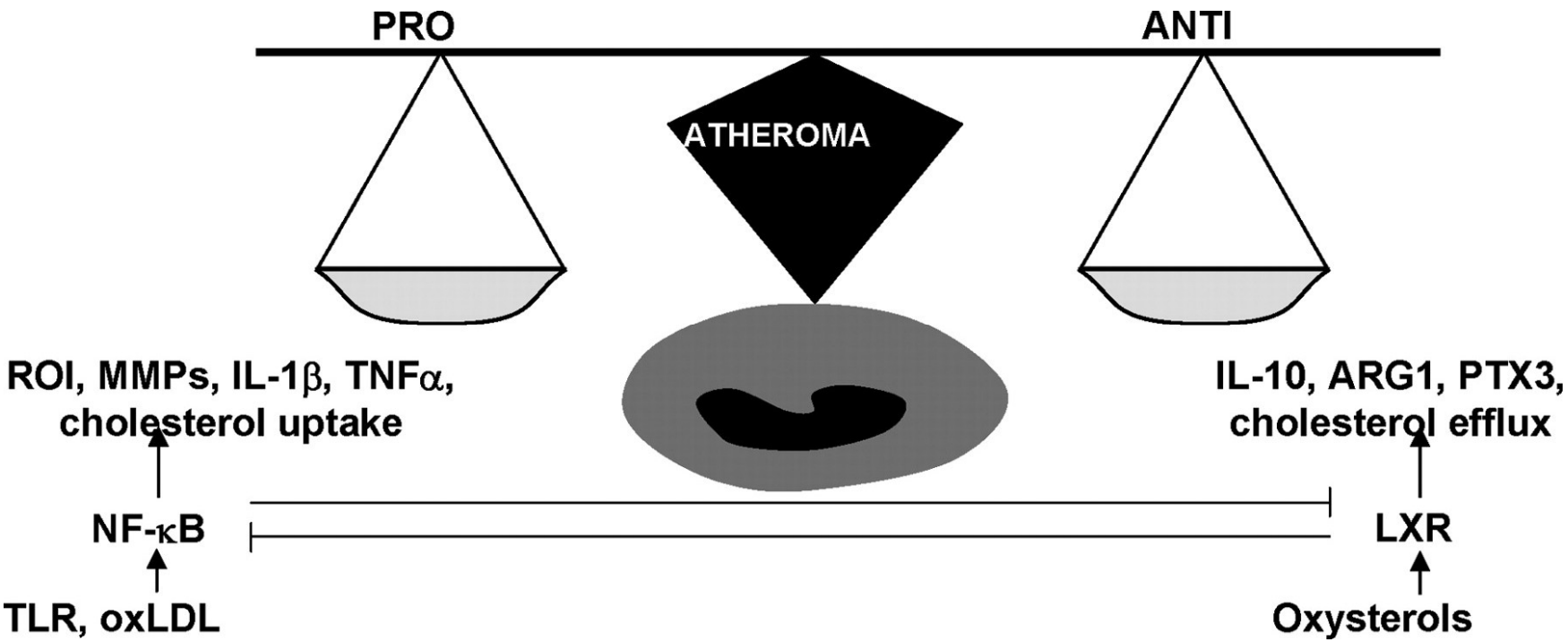




Stoneman, V. et al. Circ Res 2007;100:884-893

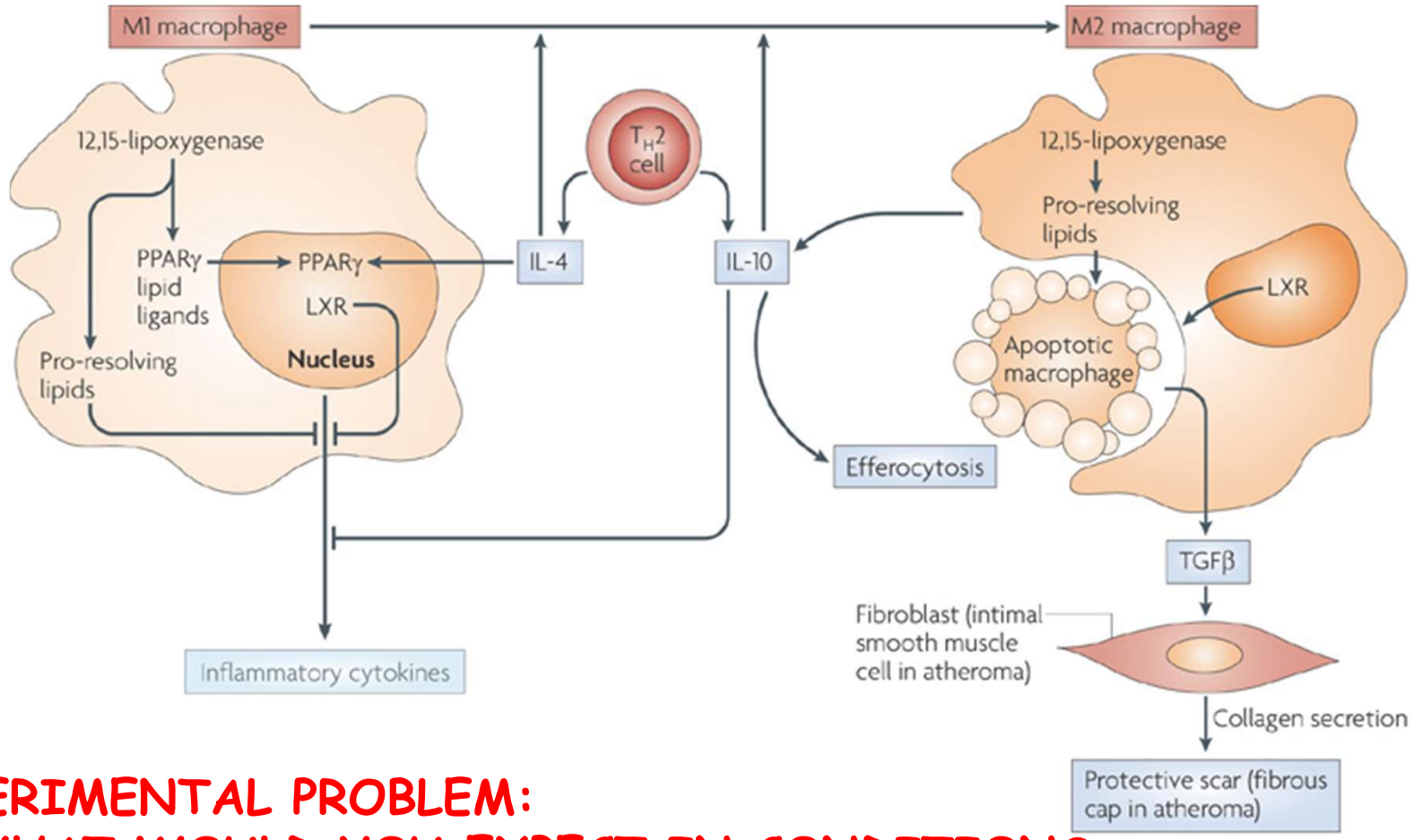
Macrophages are heterogeneous

The macrophage balance in atheroma formation and evolution



Mantovani, A. et al. Arterioscler Thromb Vasc Biol 2009;29:1419-1423

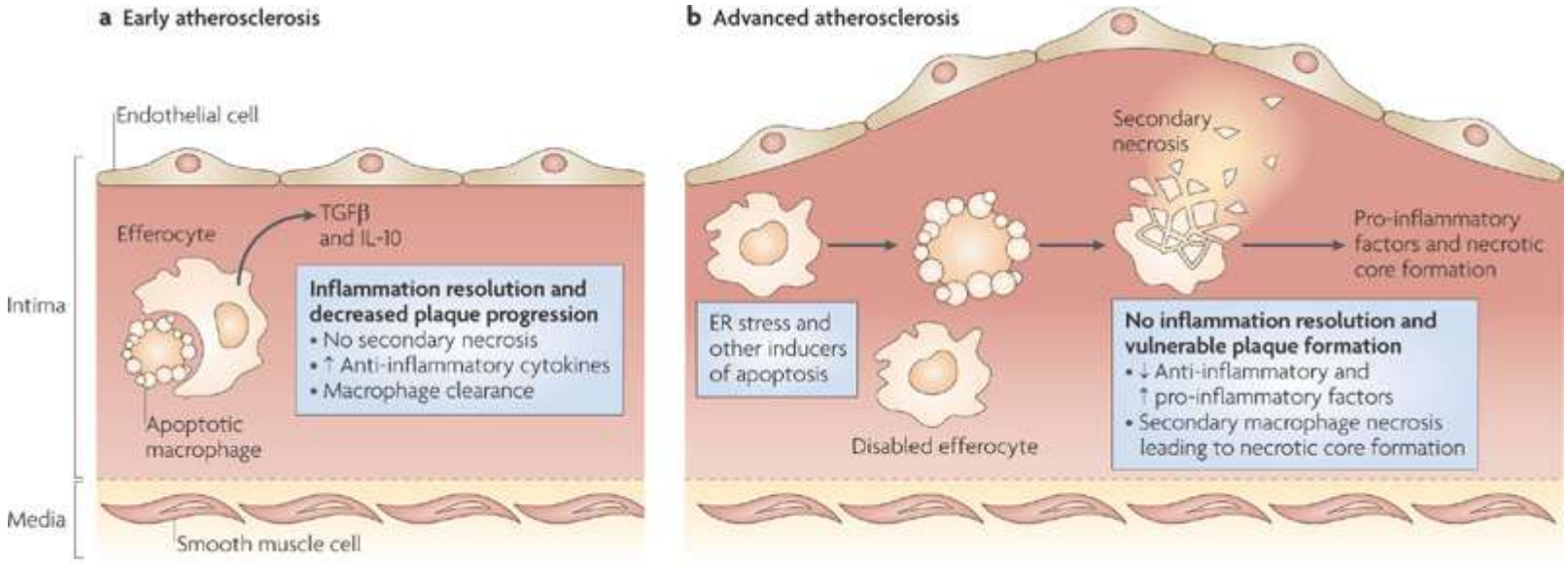
M1 versus M2 in atherosclerosis



EXPERIMENTAL PROBLEM:

1. WHAT WOULD YOU EXPECT IN CONDITIONS OF REDUCED EFFEROCYTOSIS???
2. HOW WOULD YOU ADDRESS THIS?

Resolution of inflammation by macrophages



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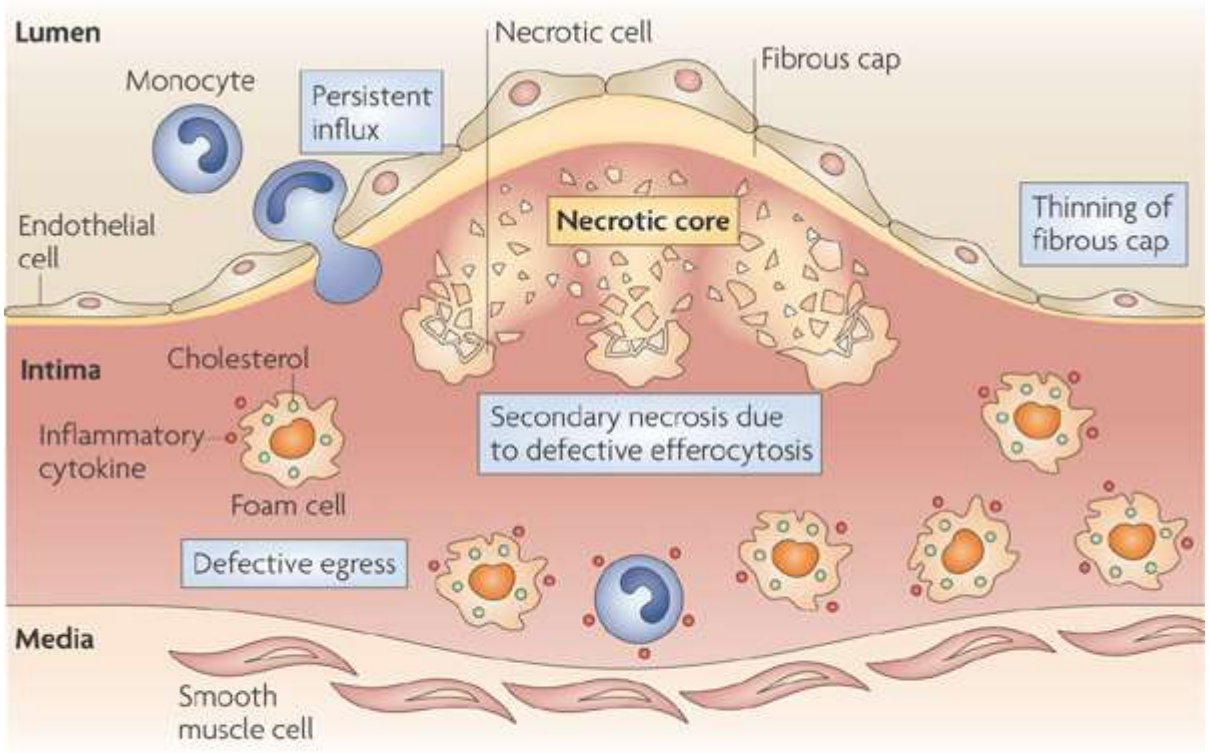
Failure in inflammation resolution by macrophages



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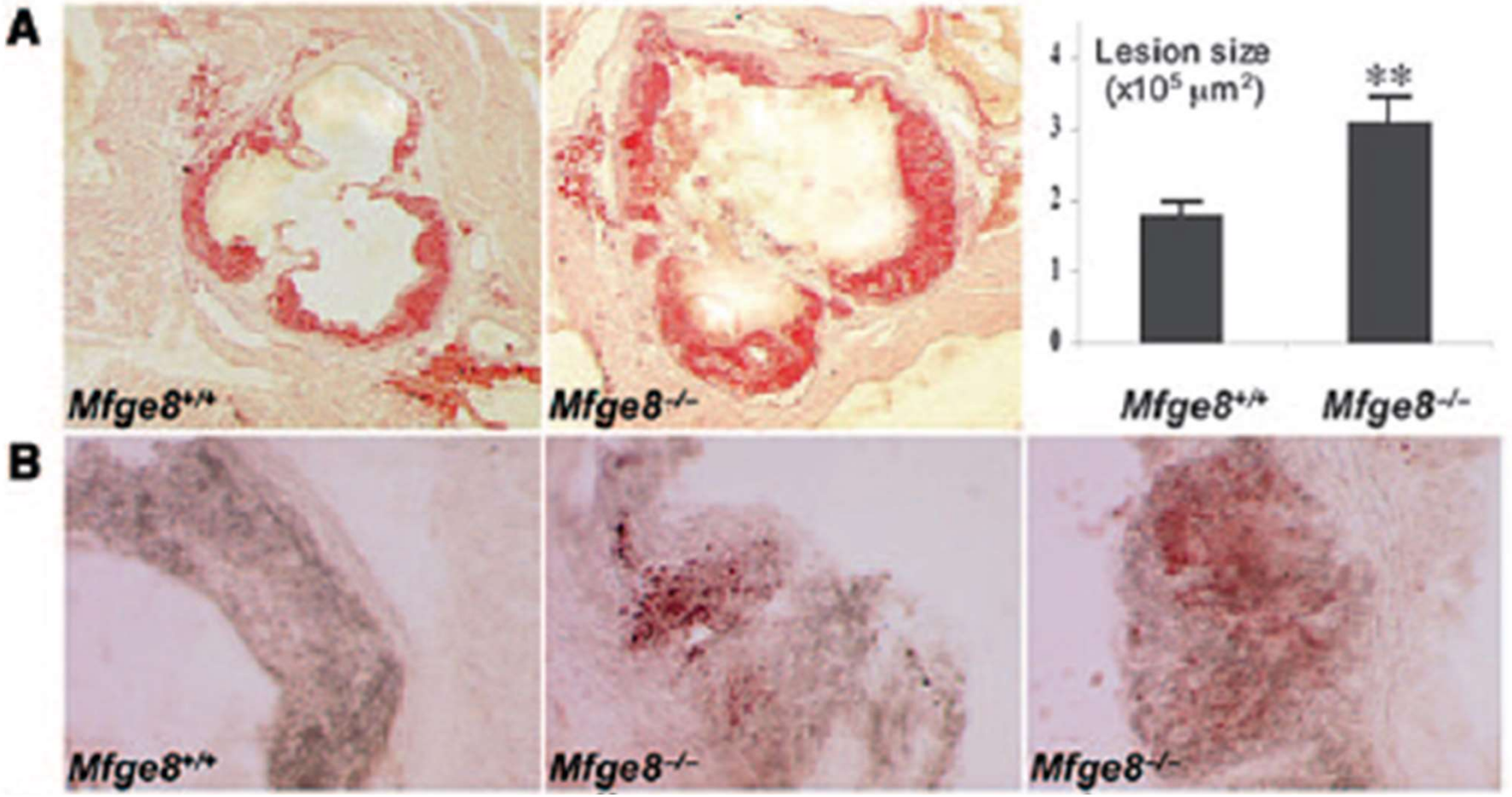
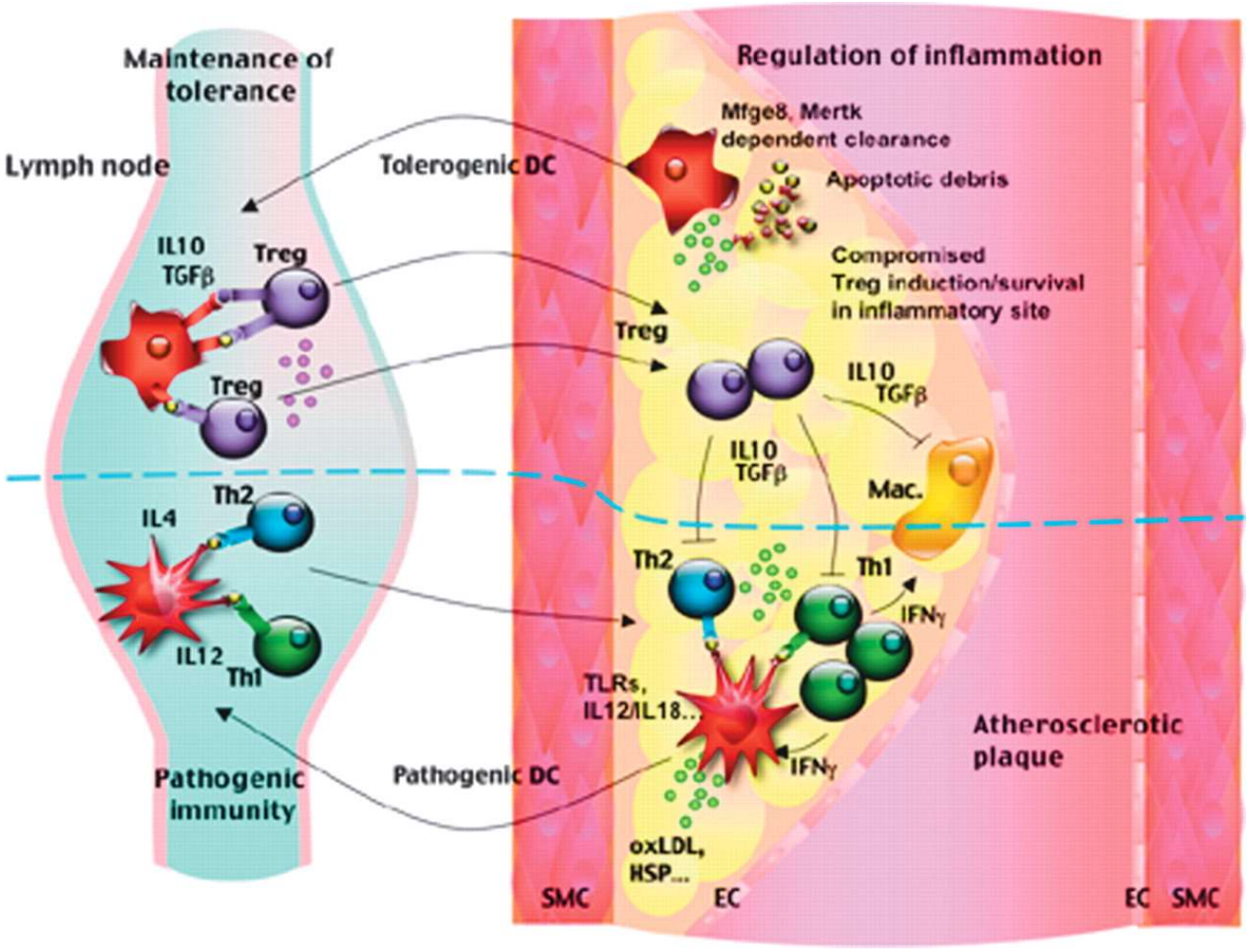
Failure in efferocytosis contributes to atherosclerosis



Ait Oufella et al. Circulation. 2007. 115:2168-77

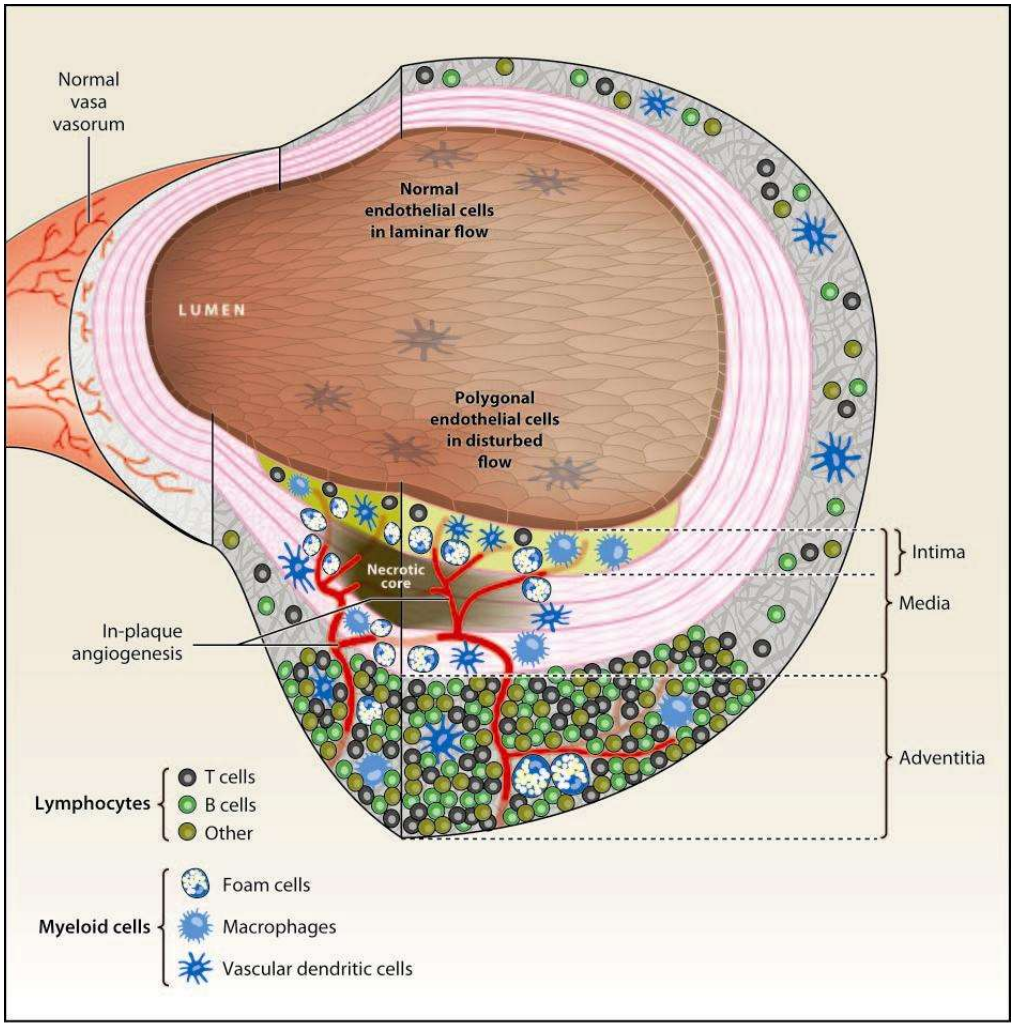
Adaptive immunity in atherosclerosis

Antigen presentation and induction of antigen-specific pathogenic and regulatory T cells in the context of atherosclerosis



Mallat, Z. et al. J. Lipid Res. 2009;50:S364-S369

Tertiary lymphoid organs



Galkina E, Ley K. 2009.
Annu. Rev. Immunol. 27:165–97

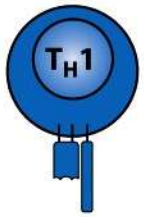
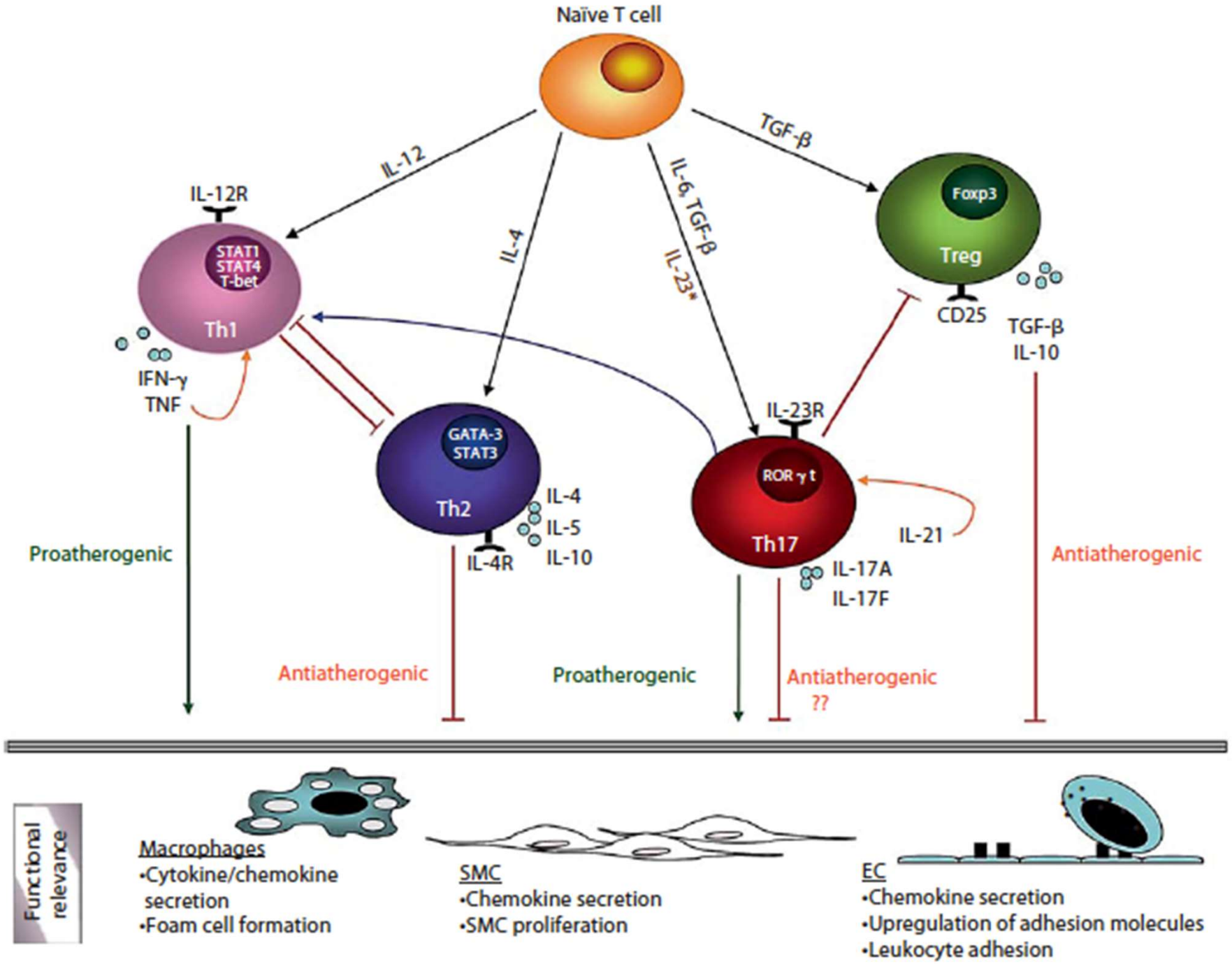
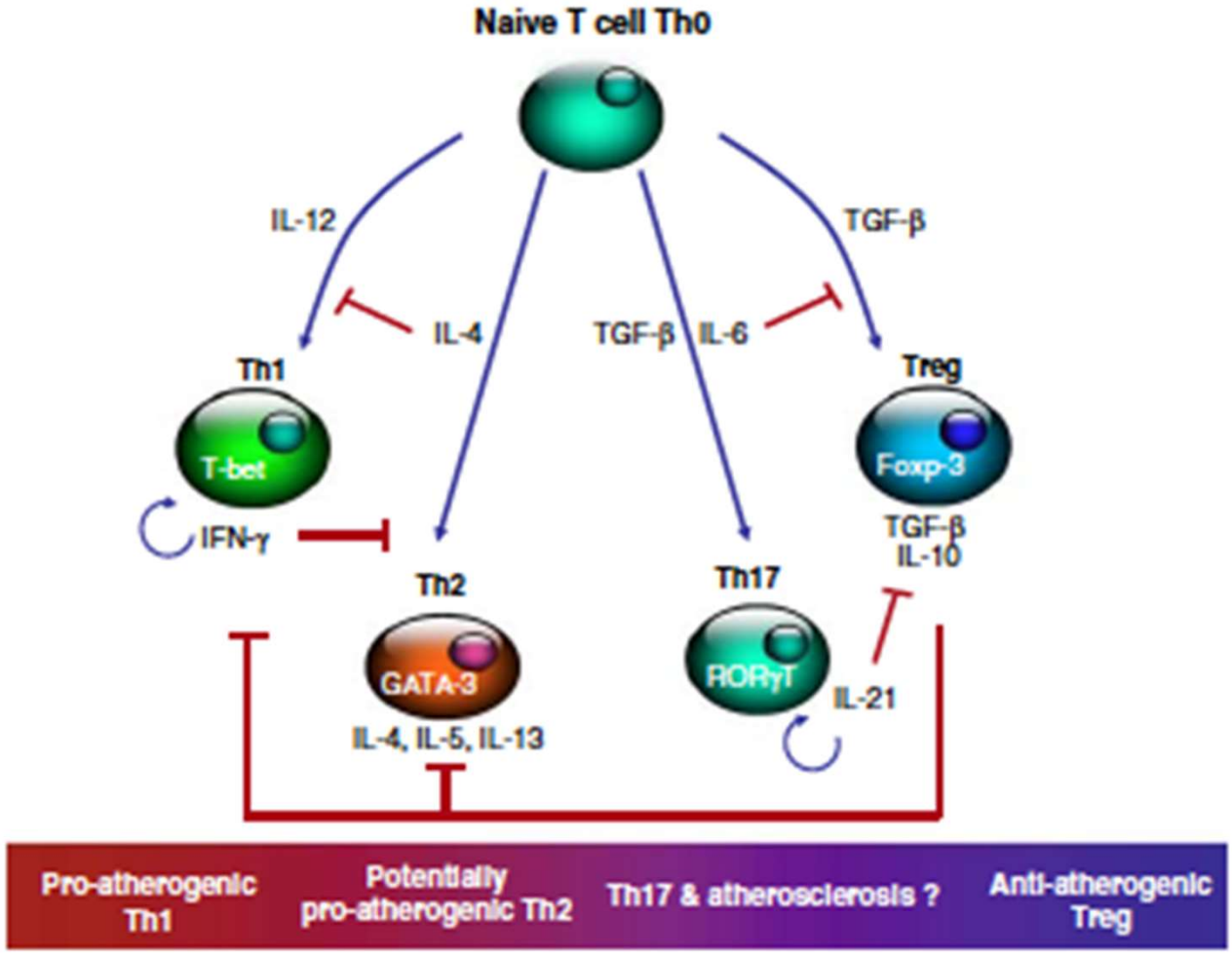
	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	CD4 regulatory T cells (various types)
Types of effector T cell					
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	Extracellular bacteria (e.g. *Salmonella enterica*)	

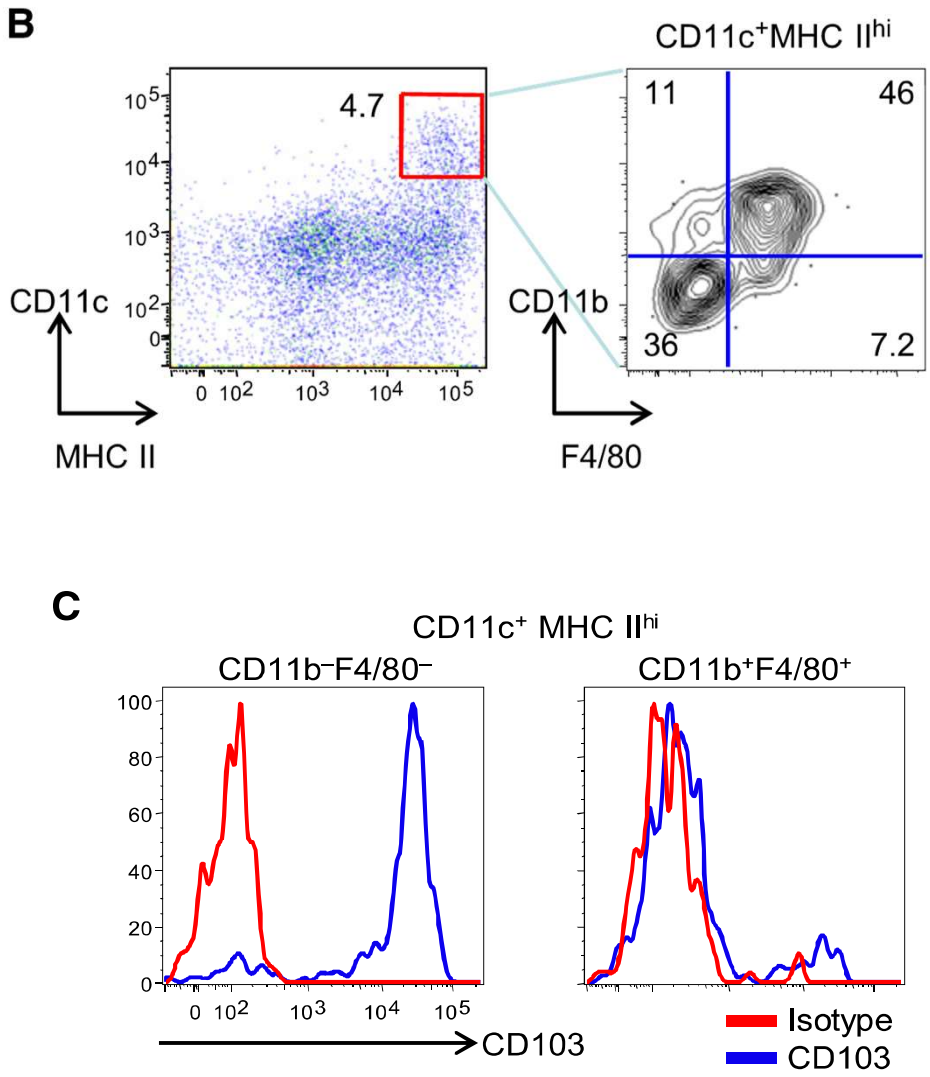
Figure 8-1 Immunobiology, 7ed. (© Garland Science 2008)


Naïve T cell
IL-12
IL-4
IL-6, TGF-β
IL-23*
TGF-β
IL-12R
STAT1
STAT4
T-bet
Th1
IFN-γ
TNF
Foxp3
Treg
CD25
TGF-β
IL-10
GATA-3
STAT3
Th2
IL-4
IL-5
IL-10
IL-4R
IL-23R
RORγt
Th17
IL-21
IL-17A
IL-17F
Proatherogenic
Antiatherogenic
Antiatherogenic
??
Proatherogenic
Antiatherogenic
Functional relevance
Macrophages
•Cytokine/chemokine secretion
•Foam cell formation
SMC
•Chemokine secretion
•SMC proliferation
EC
•Chemokine secretion
•Upregulation of adhesion molecules
•Leukocyte adhesion

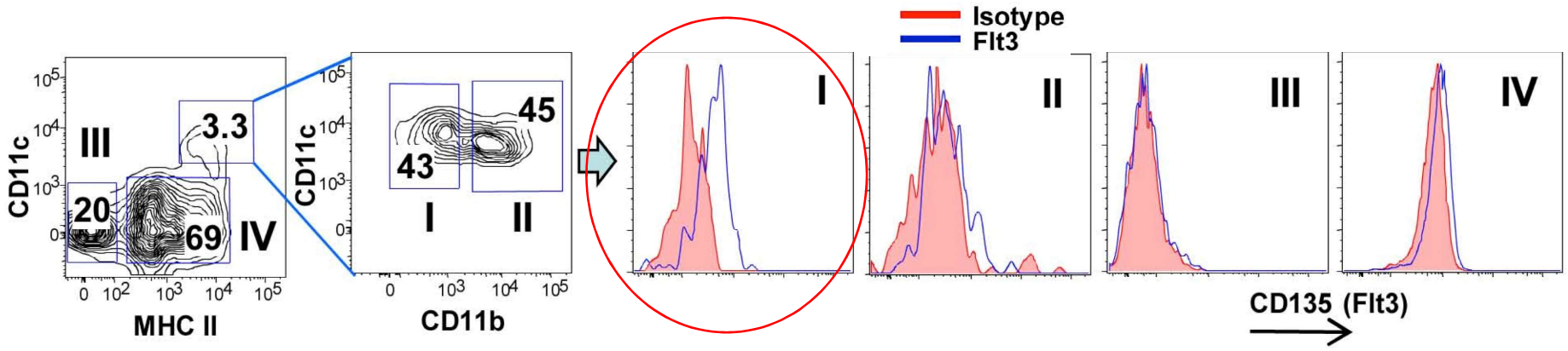
Adaptive immunity in atherosclerosis



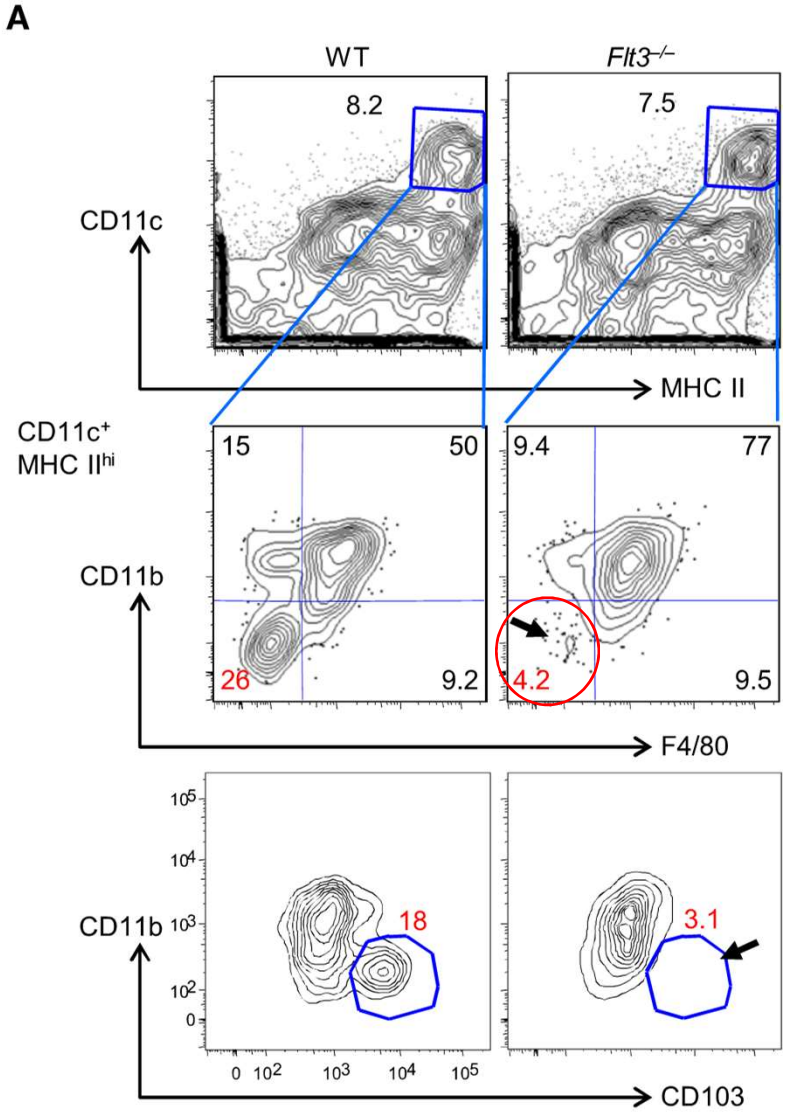
Two major subsets of dendritic cells (DCs) in the aorta



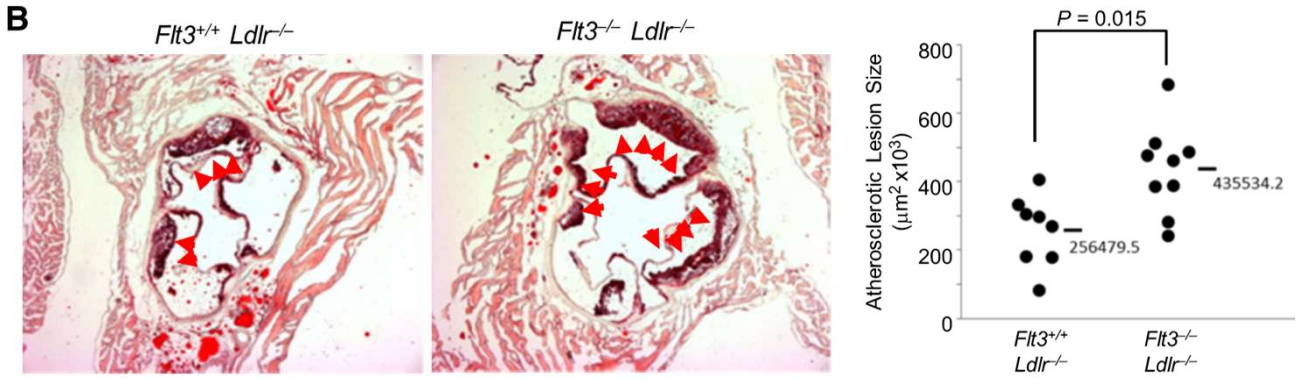
CD11c^{+} CD11b^{low} DC subset expresses Flt3



CD11c^{high} CD103+ aorta DC are Flt3 dependent



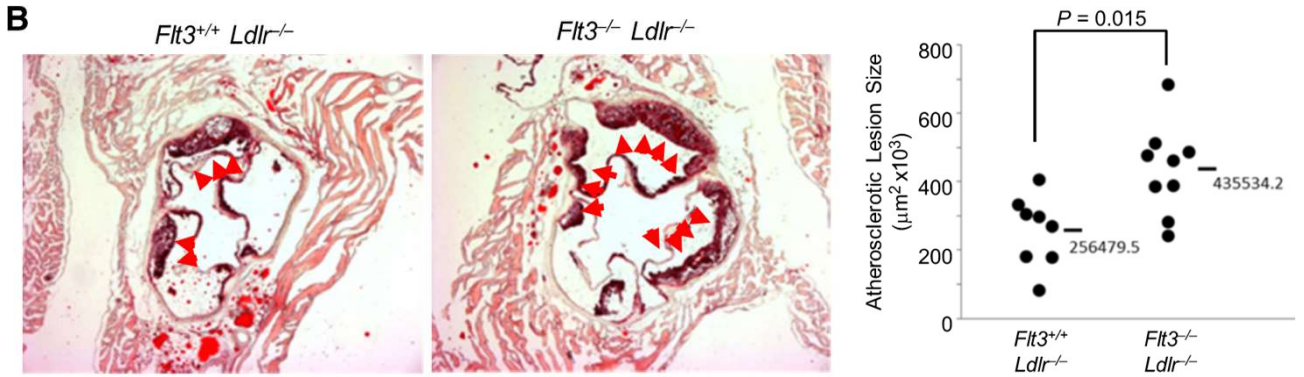
The absence of CD11c^{high} DC in aorta increases lesion size…

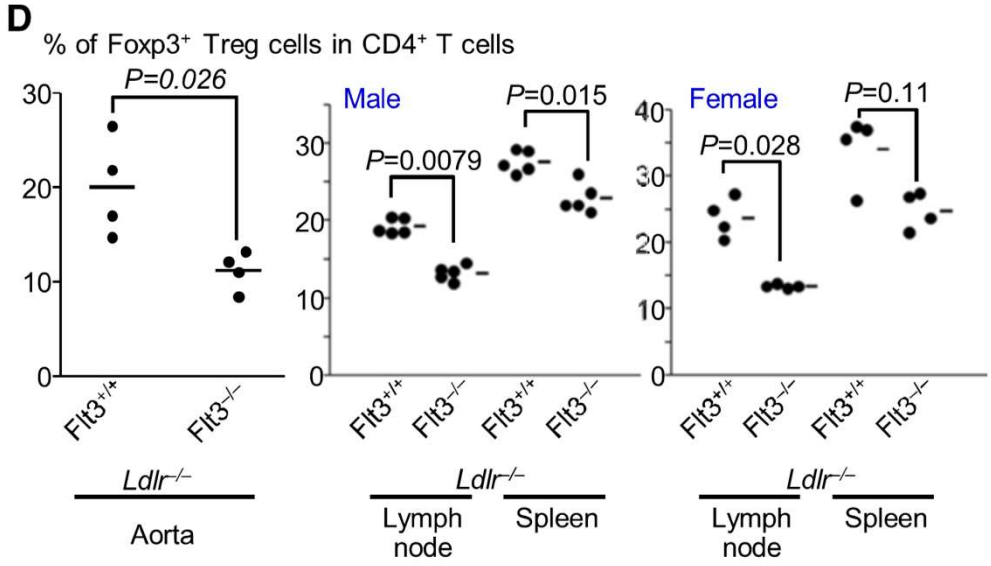


Questions:

1. WHY THE ABSENCE OF DC INCREASES LESION SIZE?
2. HOW WOULD YOU TEST THIS?

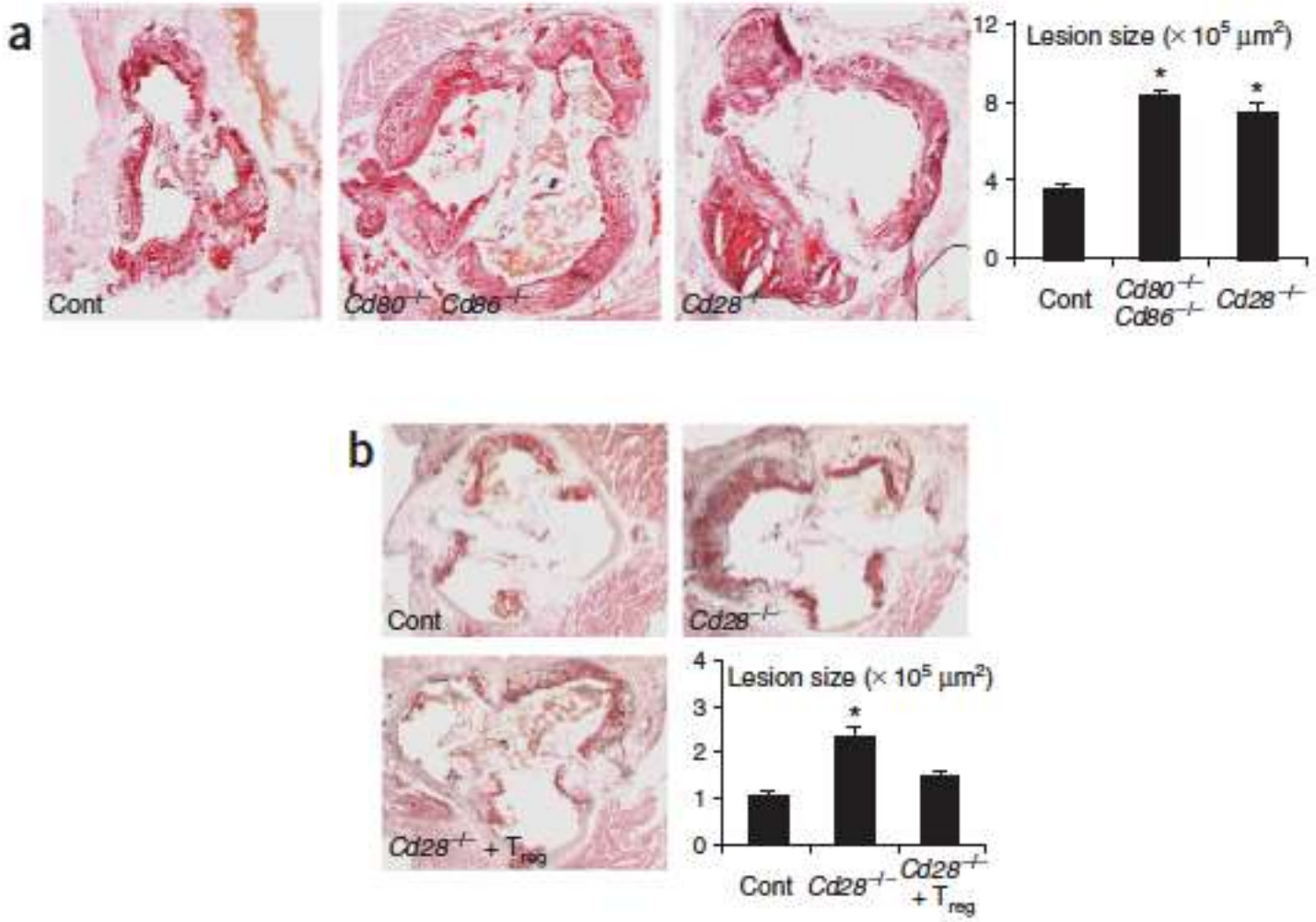
The absence of CD11c^{high} DC in aorta increases lesion size…





Treg as anti-atherogenic

No Tregs in the absence of CD80/CD86 or CD28

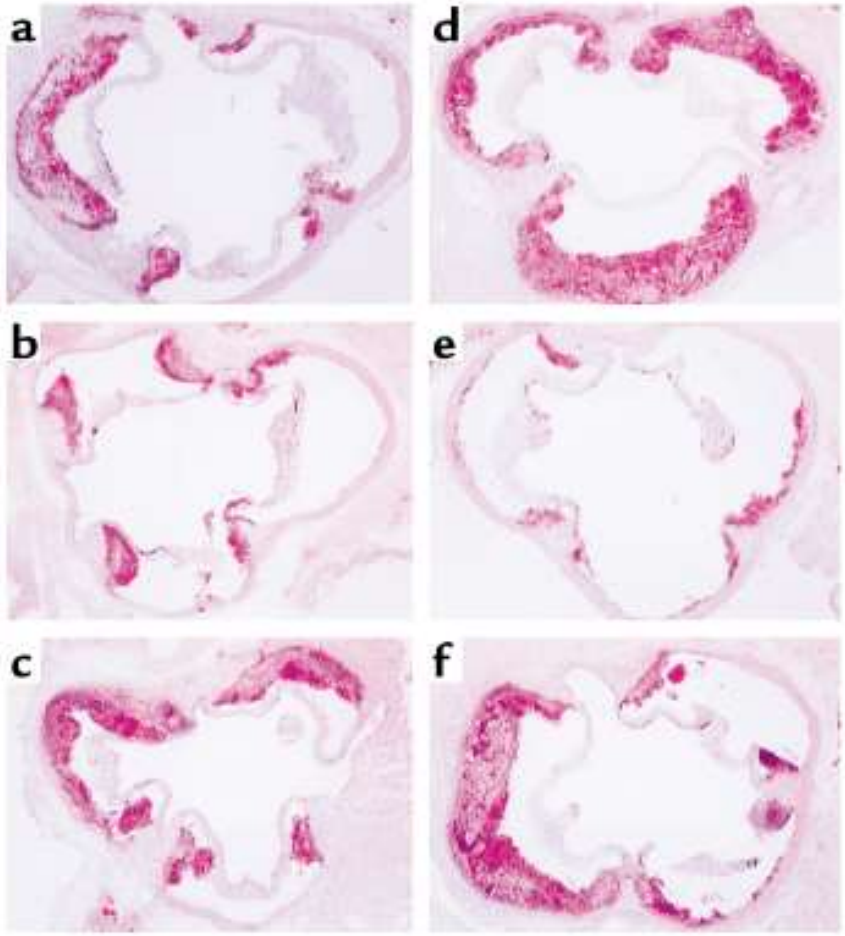


B cells in atherosclerosis

control

+ B cells ApoE-/-

+ T cells ApoE-/-

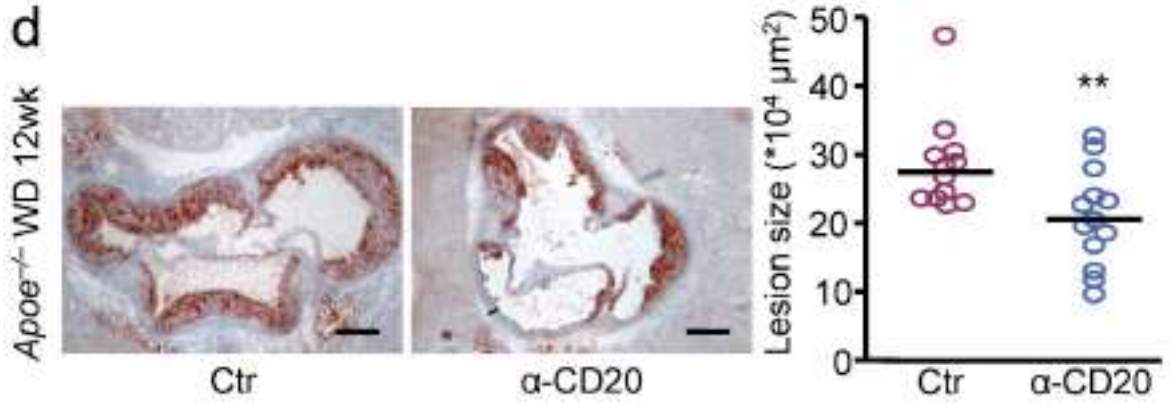


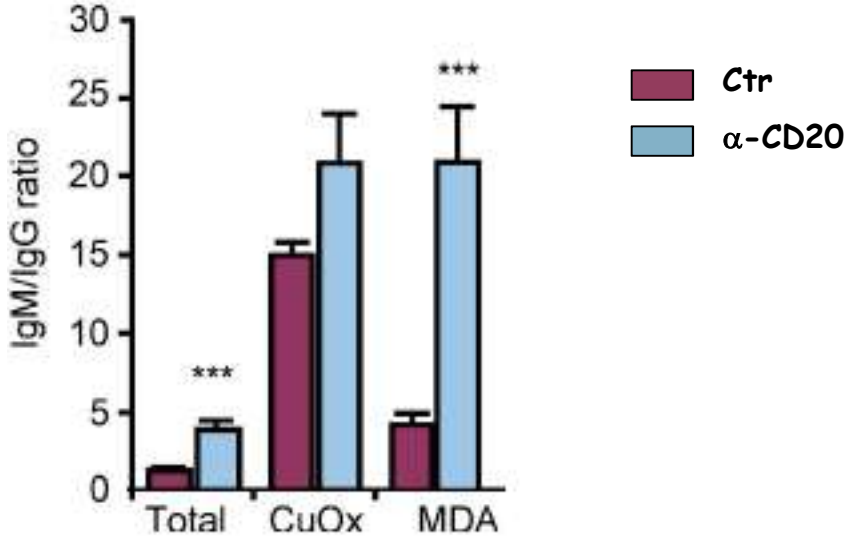
Sham mice splenectomized

INTERPRETATION of the experiment:

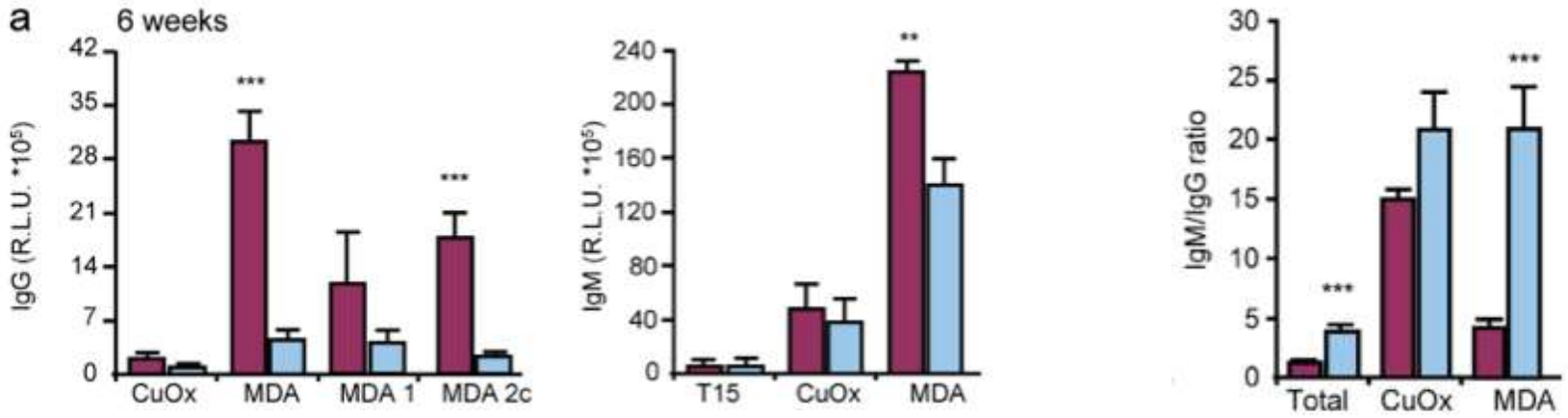
1. What is the role of B cells in atherosclerosis?
2. Why?

…but mature B cell depletion results in attenuated lesions

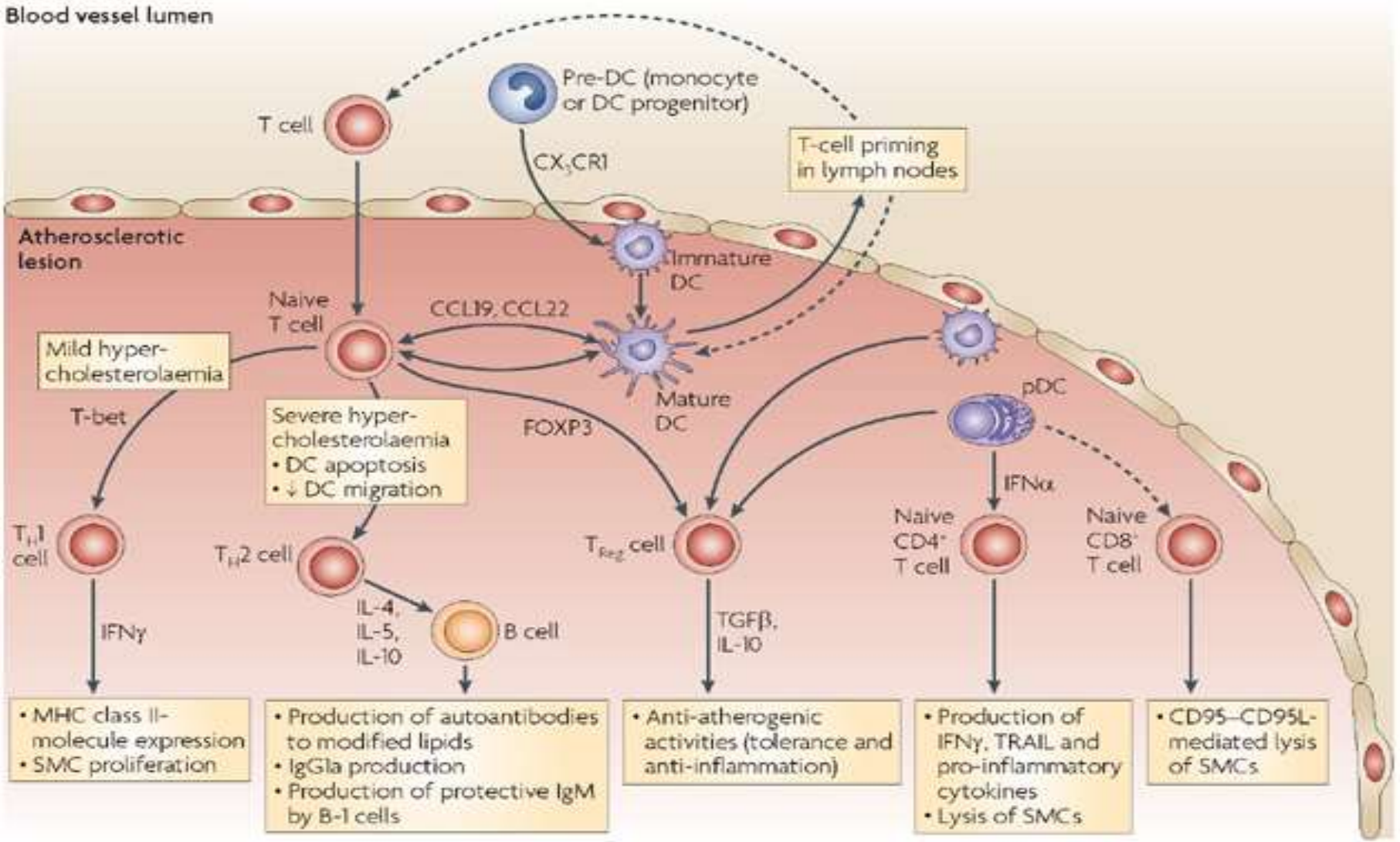




CD20 Ab-mediated B cell depletion preserves IgM over IgG



Adaptive immunity and atherosclerosis

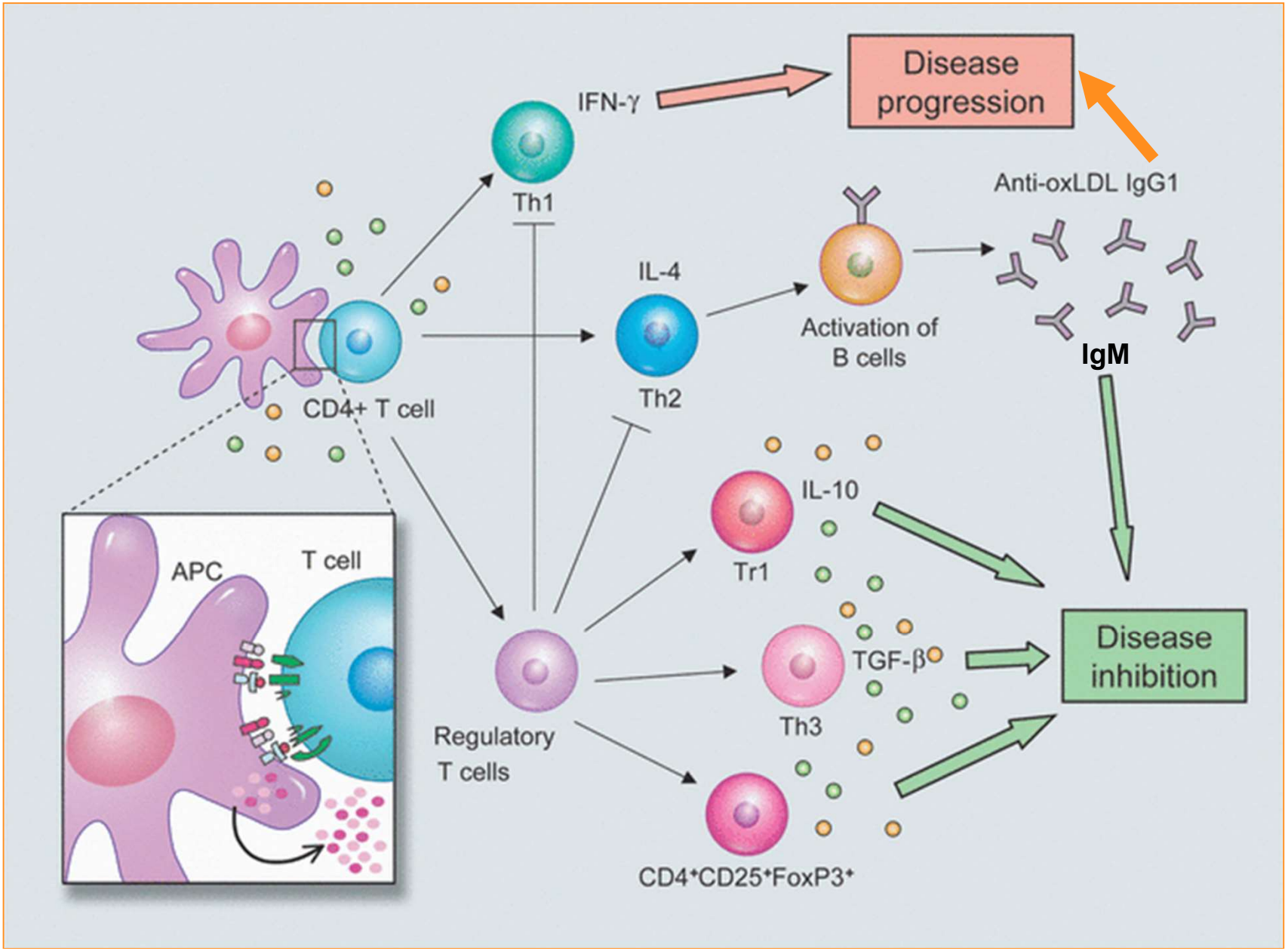


Nature Reviews | Immunology

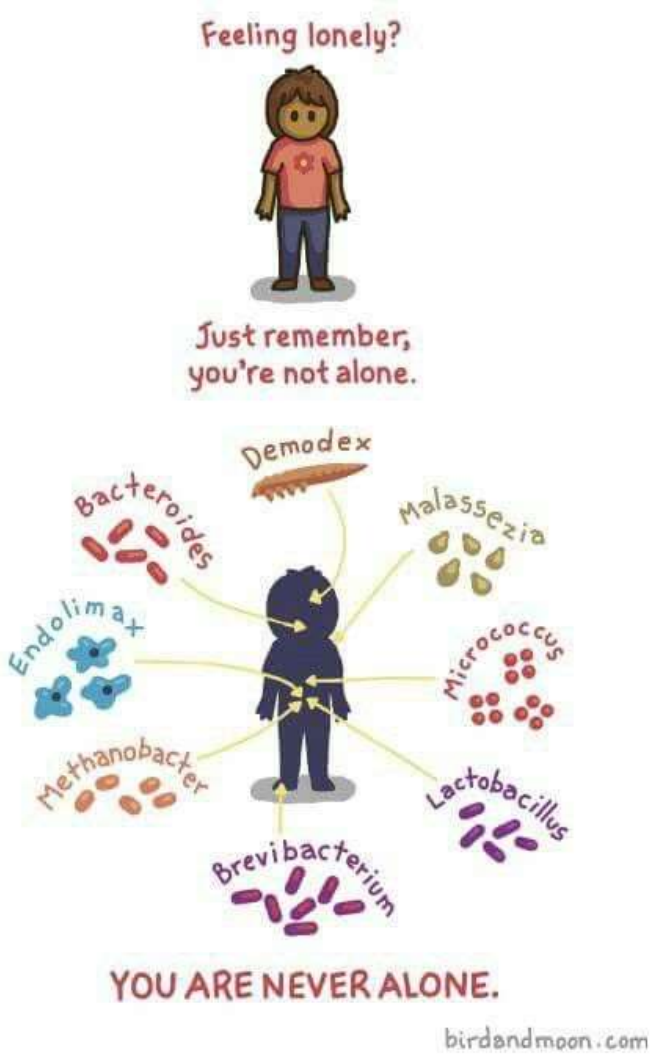
Immunotherapy in atherosclerosis?

HOW WOULD YOU PERFORM IMMUNOTHERAPY IN ATHEROSCLEROSIS?

Immunotherapy in atherosclerosis

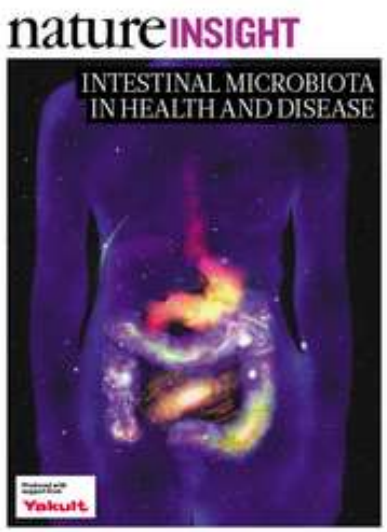


We are not alone…



10 times more cells than in our body
Sender, R. *et al. Cell* (2016)

500 times more genes than human genome
Li, J. *et al*. *Nature Biotechnology* (2014)



July 2016

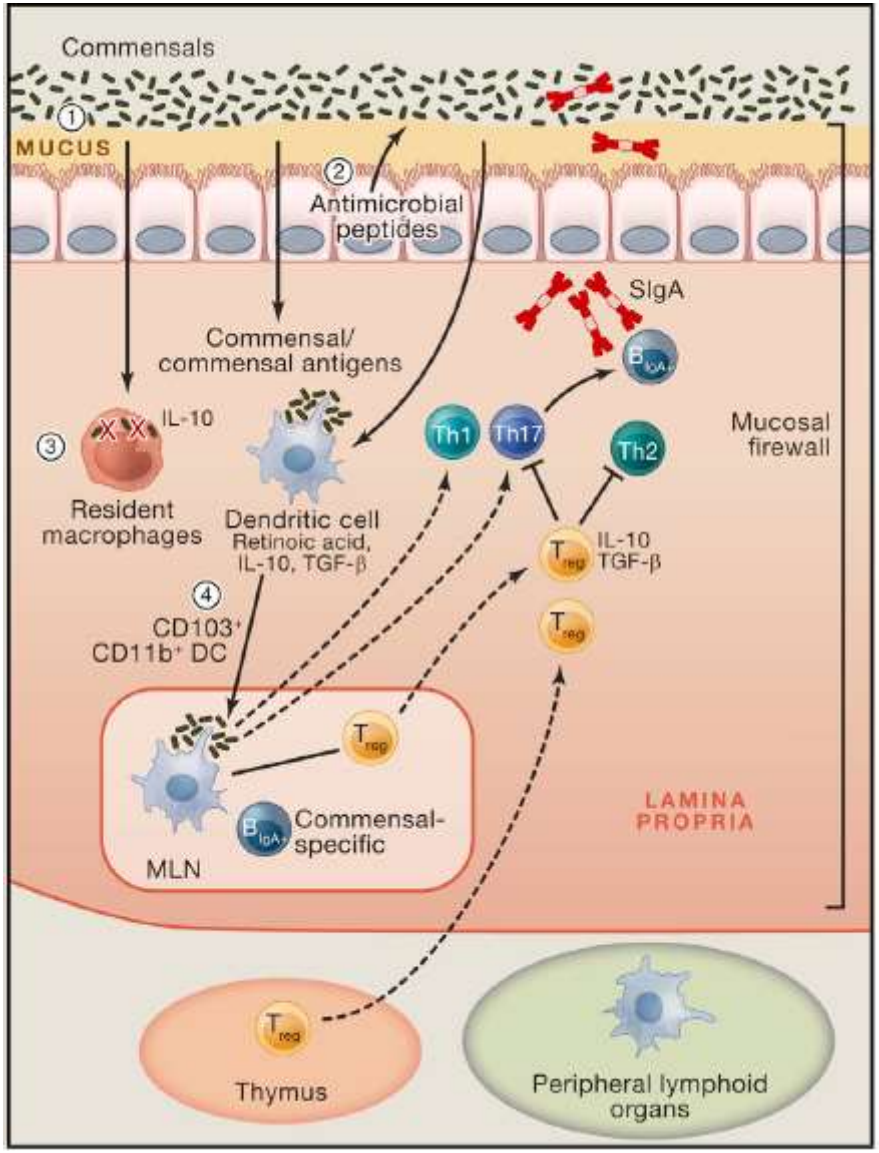
April 2016

“Mucosal Firewall”

Mucus
McGuckin *et al*.,
Nature Reviews Microbiology
(2011)

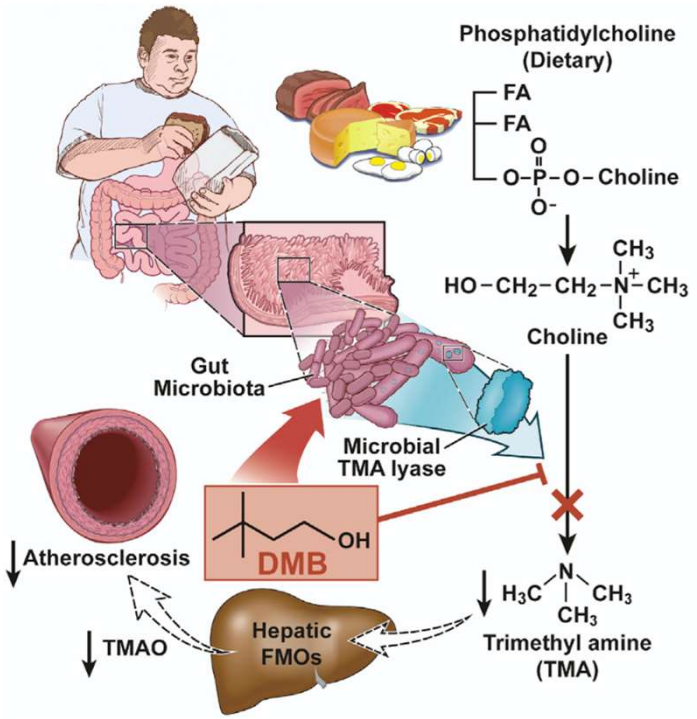
Antimicrobial peptides (RegIIIγ)
Hooper, L.& Macpherson, A.
***Nature Reviews Immunolgy* (2010)**

IgA specific for commensals
Macpherson, A. & Uhr, T.
***Science* (2004)**



Belkaid, Y. & Hand, T. W.
***Cell* (2014)**

Role of microbiota in atherosclerosis?



Basis: Metabolites generated by microbiota promote insulin resistance and atherosclerosis (e.g. branched-chain amino-acids, BCAA; trimethylamine N-oxide, TMAO)

Pedersen et al. 2016. *Nature*

Wang et al. 2015. *Cell*

Research question: Which are the microbiome patterns and gut microbiota-related metabolites linked to atherosclerosis?

Hypothesis: ***Atherosclerosis progression associates to new gut microbiota-related metabolites and specific microbiome patterns***

1. **Explore metabolites in the serum of PESA (Progression of Early Subclinical Atherosclerosis) volunteers. Is there association of atherosclerosis progression (or regression) with metabolites in serum? Are they microbiota-dependent?**

2. **Analyze microbiome in selected groups (low athero, high athero, fast progressors). Is there association of microbiota with early subclinical atherosclerosis?**