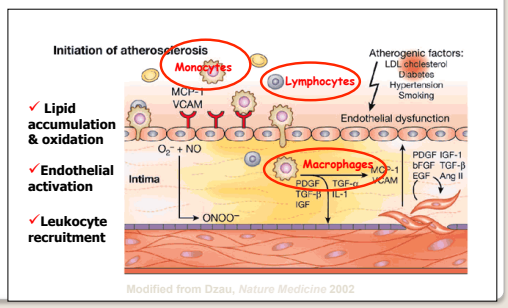
NFκB: THE HUB OF INNATE IMMUNITY IN ATHEROSCLEROSIS

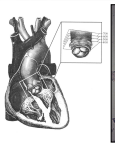
Claudia Monaco

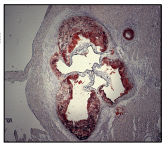
Atherosclerosis - I

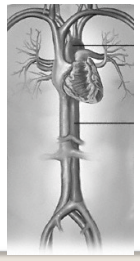


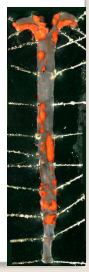
Modified from Dzau, *Nature Medicine* 2002

Experimental models of atherosclerosis: hyperlipidemia







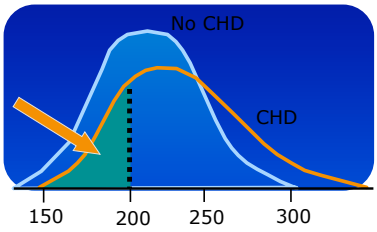


Human	ApoE or LDLR -/- Mouse
Hypercholesterolemia	Hypercholesterolemia
Diabetes	
Hypertension	
Smoking	
Obesity	
Metabolic syndrome	
Lack of exercise	
Genetic susceptibility	

Mouse models are monofactorial models of a multifactorial disease

Total Cholesterol Distribution: *CHD vs Non-CHD Population*

35% of CHD Occurs in People with TC<200 mg/dL (=5.2mmol/l)

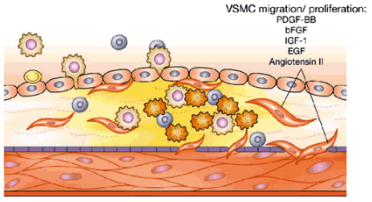


Total Cholesterol (mg/dL)
Framingham Heart Study—26-Year Follow-up

Castelli WP. Atherosclerosis 1996

Atherosclerosis - II

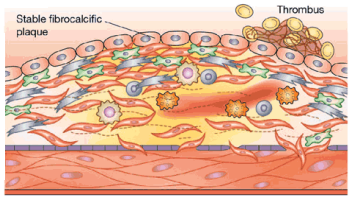
- ✓ **Foam cell formation**
- ✓ **SMC migration & proliferation**



Dzau, *Nature Medicine* 2002

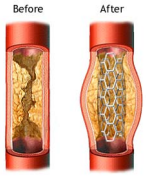
Atherosclerosis - III

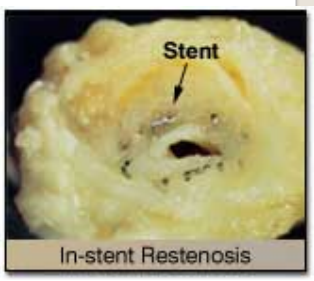
- ✓ **Extracellular matrix deposition**
- ✓ **Fibrous cap**
- ✓ **Lipidic core**



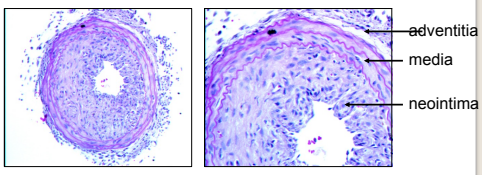
Dzau, *Nature Medicine* 2002

Restenosis reduces the success of interventions



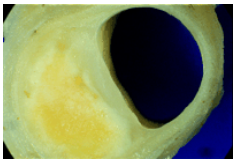


Neointima formation after collar injury

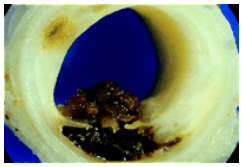


The two facets of atherosclerosis

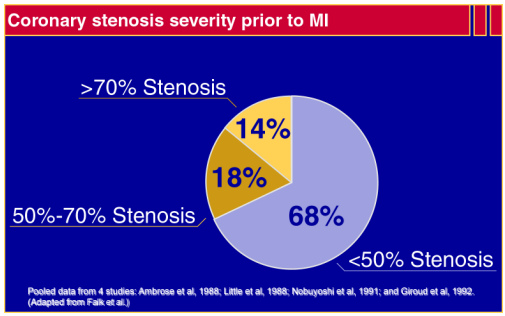
Stable



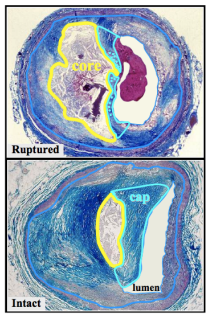
Unstable



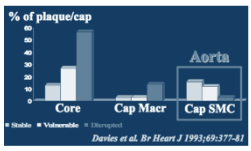
Myocardial Infarctions are caused by low-grade stenoses



The high risk atherosclerotic plaque



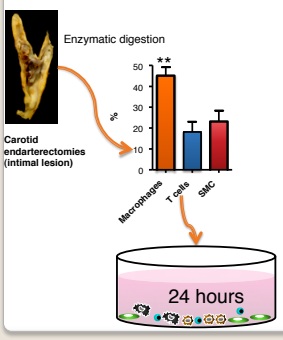
- ✓ Necrotic core >25% plaque area
- ✓ Fibrous cap < 65 μm
- ✓ Infiltration of inflammatory cells in the fibrous cap
- ✓ Loss of SMC in the fibrous cap



Site of Intimal Rupture or Erosion of Thrombosed Coronary Atherosclerotic Plaques Is Characterized by an Inflammatory Process Irrespective of the Dominant Plaque Morphology

Allard C. van der Wal, MD; Anton E. Becker, MD;
Chris M. van der Loos, PhD; Pranab K. Das, PhD

Functional studies in human atherosclerosis

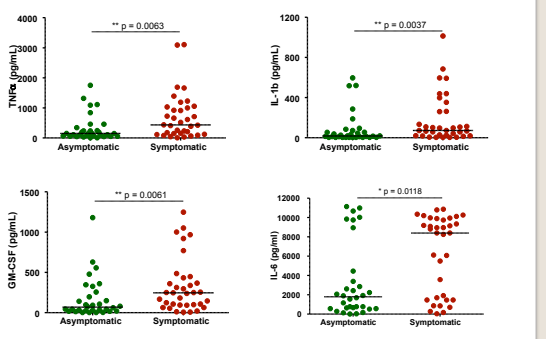


	Cytokine	% Detected
75-100 %	TNFα	98
	TNFβ	1
	IL1α	68
	IL1β	87
	IL2	3
	IL4	58
	IL5	1
	IL6	100
	IL10	94
50-75	IL12 (p40)	62
	IL12 (p70)	7
	IL15	4
	IL17	3
	IFNα2	56
25-50	IFNγ	14
	M-CSF	94
	GM-CSF	96
	IL11	0
	IL29	0
0-25	CCL2/MCP-1	100
	CX3CL1/FRACTALKINE	89
	CXCL10/IP-10	90
	CCL5/RANTES	96
	CXCL9/MIG	76
	CXCL7	100
	CXCL6	13
	CXCL11/ITAC	9
	CCL14a	100
	CCL19/ELC/MIP3b	0
	CCL20/LARC/MIP3a	67

Monaco C PNAS U S A 2004;101:5634-9

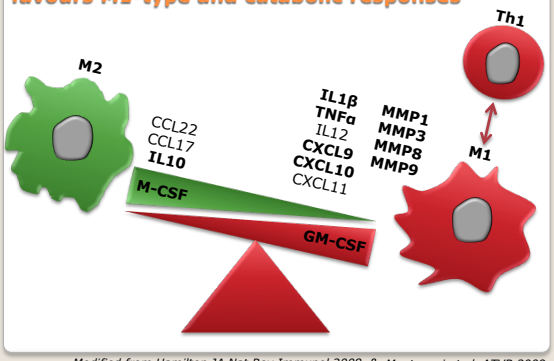
N=67

M1-type mediators relate to plaque activity



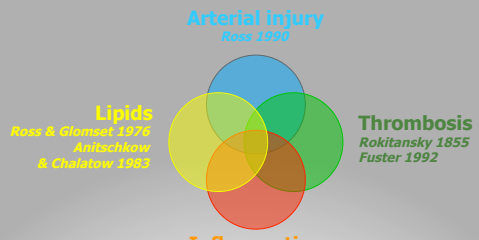
Shalhoub et al. (in preparation)

Cytokine milieu in high-risk atherosclerosis favours M1-type and catabolic responses



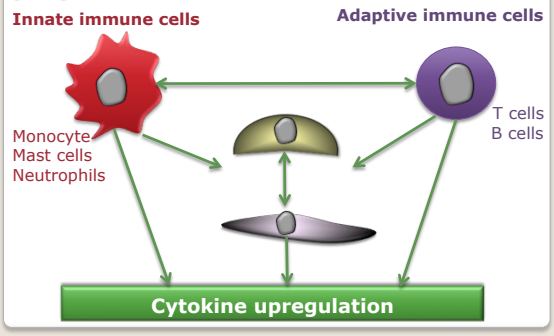
Modified from Hamilton JA Nat Rev Immunol 2008 & Mantovani et al. ATVB 2009

The pathogenic components of atherosclerosis

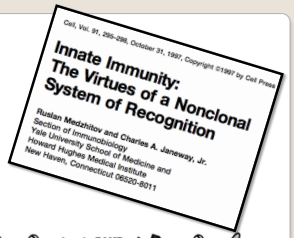


Q1: What drives cytokine production in human disease?

Both innate and adaptive immunity play a role in atherosclerosis

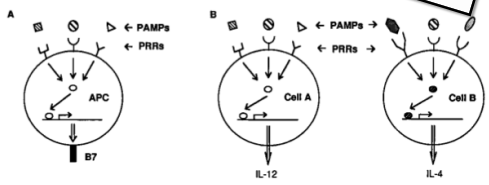


Innate immunity: the "dirty little secret" of immunology


Cell, Vol. 91, 295–298, October 31, 1997, Copyright ©1997 by Cell Press

Innate Immunity: The Virtues of a Nonclonal System of Recognition

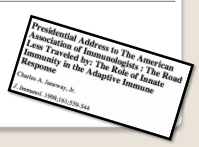
Ruslan Medzhitov and Charles A. Janeway, Jr.
Section of Immunobiology
Yale University School of Medicine and
Howard Hughes Medical Institute
New Haven, Connecticut 06520-8011



Innate immunity vs. adaptive immunity

Table I. *Innate and adaptive immunity*

Property	Innate Immune System	Adaptive Immune System
Receptors	Fixed in genome; rearrangement not necessary	Encoded in gene segments; rearrangement necessary
Distribution	Nonclonal; all cells of a class identical	Clonal; all cells of a class distinct
Recognition	Conserved molecular patterns (LPS, LTA, mannans, glycans)	Details of molecular structure (proteins, peptides, carbohydrates)
Self–non-self discrimination	Perfect: selected over evolutionary time	Imperfect: selected in individual somatic cells
Action time	Immediate activation of effectors	Delayed activation of effectors
Response	Costimulatory molecules; cytokines (IL-1β, IL-6); chemokines (IL-8)	Clonal expansion or anergy; IL-2; effector cytokines (IL-4, IFN-γ)

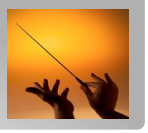

Presidential Address to The American Association of Immunologists : The Road Less Traveled by: The Role of Innate Immunity in the Adaptive Immune Response

Charles A. Janeway, Jr.

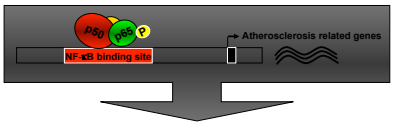
J Immunol, 1998;161:539-544

Nuclear factor κB (NFκB)

- Transcription factor involved in inflammatory gene expression
- "Director" of the inflammatory response

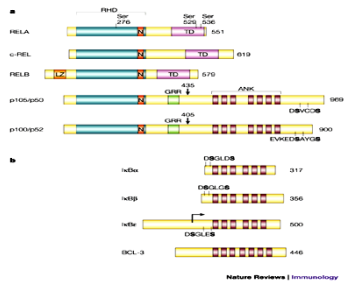


NFkB regulates the main biological events in the atherosclerotic plaque

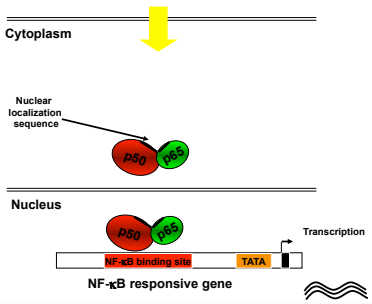


Recruitment of mononuclear cells	MCP-1, RANTES, MGSA/*gro*, E-selectin, ICAM-1, VCAM-1, MAdCAM-1
Inflammation & Immunity	IκBα, IL-1, IL-2, IL-6, IL-8, TNFα, G-CSF, M-CSF, GM-CSF, MCP-1, RANTES, MGSA/*gro*, MHC-I, MHC-II, CD80, CD86
Apoptosis & Proliferation	XIAP, c-IAP1, c-IAP2, Cyclin D
Thrombosis & vessel homeostasis	iNOS, COX-2, tissue factor, PAI-1, MnSOD, MMP-2, MMP-9, PTX3, RAGE

NFkB/Rel and IkB families

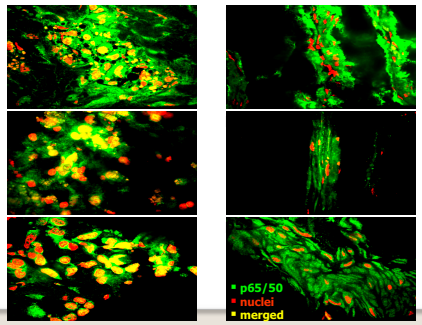


Model of NFkB activation



Activated NFκB in carotid plaques

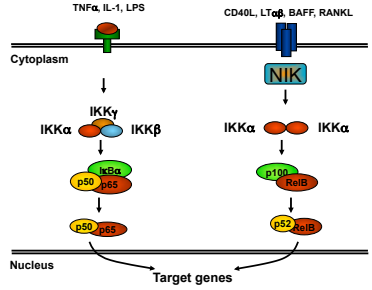
Carotid endarterectomies ; Immunoconfocal images (60x)



NFkB and acute coronary syndromes

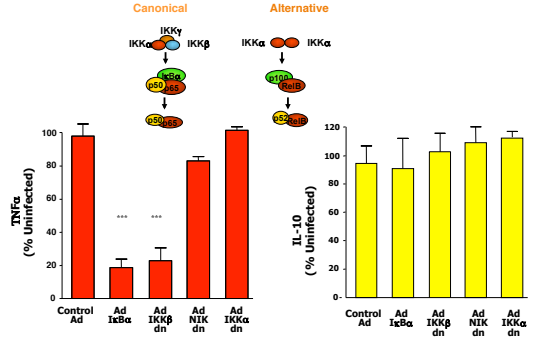
- Nuclear translocation of p65 is higher in unstable coronary atherectomies Wilson SH; *Atherosclerosis* 2002
- NFκB activation
  - in PBMC from peripheral circulation Ritchie M, *Circulation* 1998
  - in myocardial biopsies Valen G, *Cardiovasc Res* 2000

Classical and alternative pathway of NFκB activation

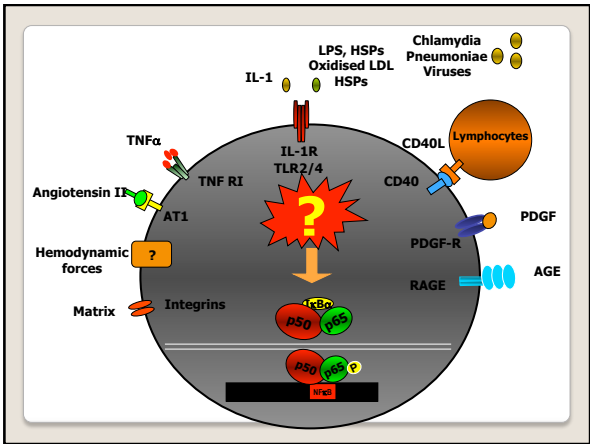


Modified from Karin M, Nat Rev Drug Discov. 2004

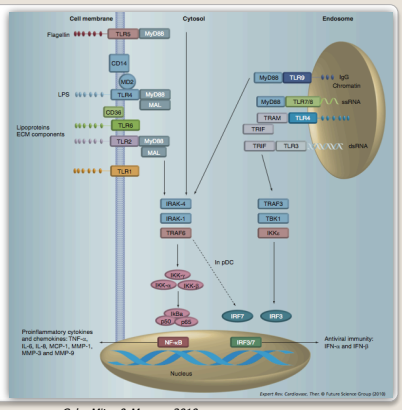
Selective inhibition of pro-inflammatory cytokines by NFκB blockade



Monaco C PNAS U S A 2004;101:5634-9

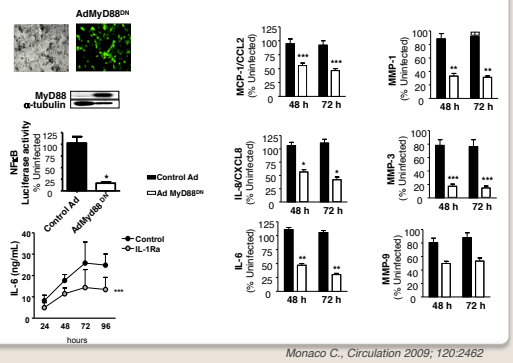


Toll-like Receptor signalling



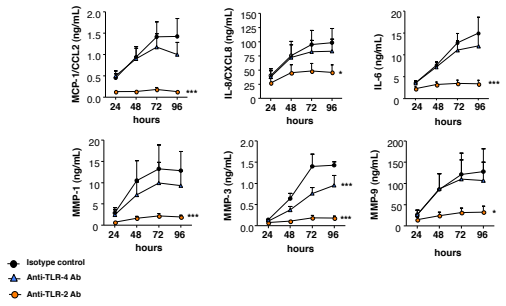
Cole, Mitra & Monaco 2010

MyD88 drives cytokine and MMP production

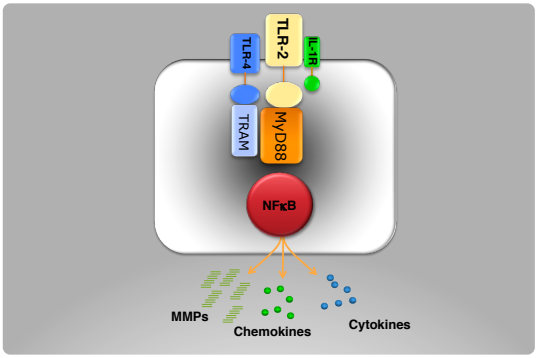


Monaco C., Circulation 2009; 120:2462

Persistent cytokine and MMP production in human atherosclerosis is driven by TLR2



Monaco C., Circulation 2009; 120:2462

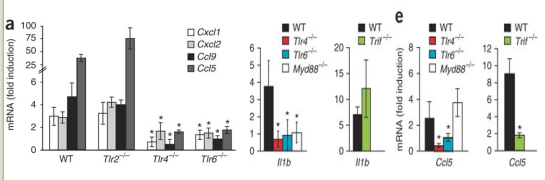


TLRs drive local inflammation

OxLDL and amyloid β promote inflammation through Toll-like receptors

Oxidised LDL

Amyloid-β



Stewart CR Nature Immunology 2010

- NFκB and pattern recognition receptors are the most powerful inducers of inflammation known so far.
- Innate immunity drives inflammation in the atherosclerotic plaque.

Conclusions