Update on Inflammation in the Pathogenesis of Cardiometabolic Disease






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Brigham & Women's Hospital
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CMHC Cardiometabolic Health Congress

Keynote Session

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Disclosure of financial relationships

Peter Libby, MD

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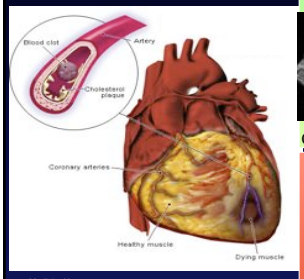
Speakers Bureau: None

Stock shareholder: None

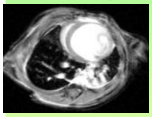
Scientific Advisory Board: Interleukin Genetics, Athera

Dr. Libby declines all personal compensation from pharma or device companies

Myocardial Healing and Remodeling: Critical Determinants of Outcomes

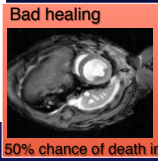


Good healing



Good prognosis

Bad healing

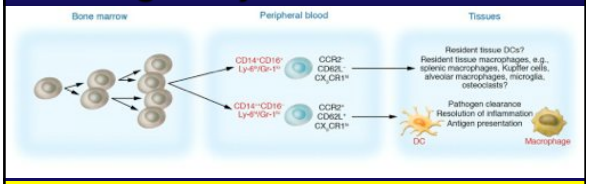


50% chance of death in next year

MedicineNet.com;
Janice and Marc Pfeffer

Monocyte/ Macrophage Heterogeneity in Atherosclerosis

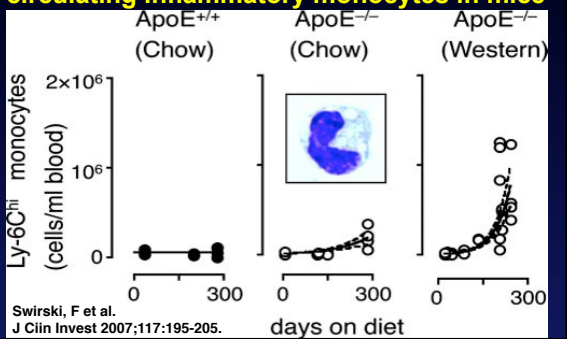
Mononuclear Phagocyte Heterogeneity in Atherosclerosis



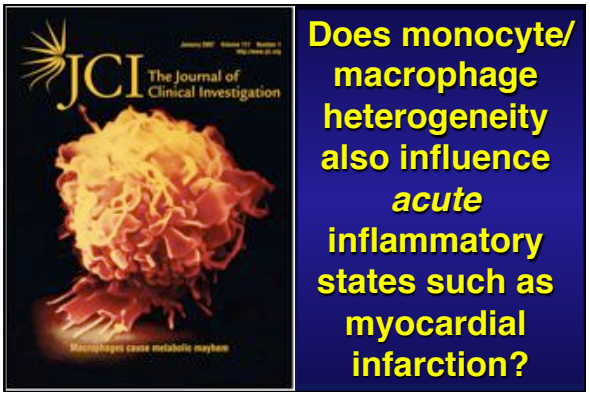
Monocytes that bear high levels of the surface marker Ly-6C have particularly pro-inflammatory functions

Siamon Gordon, J. Clin. Invest. 2007;117:89-93

Hyperlipidemia markedly expands circulating inflammatory monocytes in mice

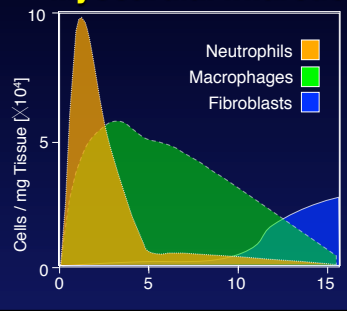


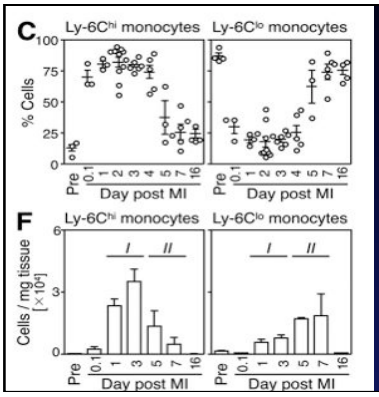
Swirski, F et al.
J Ciin Invest 2007;117:195-205.



Does monocyte/ macrophage heterogeneity also influence *acute* inflammatory states such as myocardial infarction?

Leukocyte Response Post Myocardial Infarction



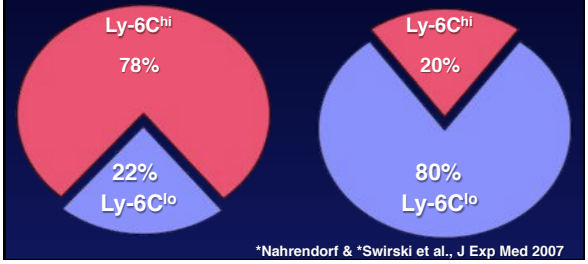


The ischemic myocardium mobilizes Ly-6Chi and Ly-6Clo monocytes in two distinct phases

Nahrendorf, M. et al. J. Exp. Med. 2007;204:3037-3047

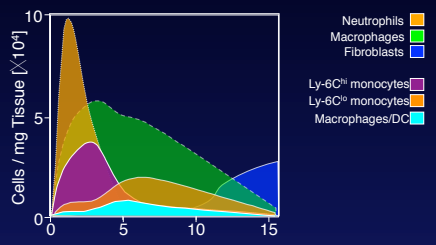
JEM

Sequential accumulation of Ly-6C^{hi} and Ly-6C^{lo} monocytes post myocardial ischemic injury



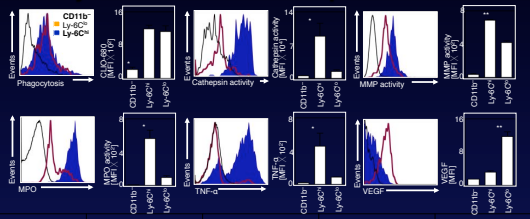
*Nahrendorf & *Swirski et al., J Exp Med 2007

Revised Leukocyte Response to Healing Post Myocardial Infarction



*Nahrendorf & *Swirski et al., J Exp Med 2007

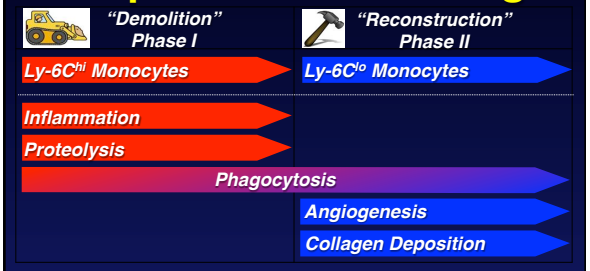
Monocyte subsets exhibit specific functions



	Proteolysis	Phagocytosis	Inflammation	Angiogenesis
Ly-6C^{hi}	+	+	+	–
Ly-6C^{lo}	–	+	–	+

*Nahrendorf & *Swirski et al., J Exp Med 2007

Revision of the monocyte response in MI healing



*Nahrendorf & *Swirski et al., J Exp Med 2007

Monocyte Heterogeneity in Healing of MI

The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions

Matthias Nahrendorf,[1,2] Filip K. Swirski,[2,4,5,6] Elena Aikawa,[2,6] Lars Stangenberg,[2] Thomas Wurdinger,[2,3] Jose-Luiz Figueiredo,[2] Peter Libby,[4,5,6] Ralph Weissleder,[1,2,6] and Mikael J. Pittet[1,2]

JEM VOL. 204, November 26, 2007

From where do the proinflammatory moncytes that appear in the myocardium hours after coronary ligation come?

Identification of Splenic Reservoir Monocytes and Their Deployment to Inflammatory Sites

Filip K. Swirski,[1*†] Matthias Nahrendorf,[1*] Martin Etzrodt,[2,3] Moritz Wildgruber,[1] Virna Cortez-Retamozo,[1] Peter Panizzi,[1] Jose-Luiz Figueiredo,[1] Rainer H. Kohler,[1] Aleksey Chudnovskiy,[1] Peter Waterman,[1] Elena Aikawa,[1] Thorsten R. Mempel,[1,3] Peter Libby,[4,5] Ralph Weissleder,[1,6†] Mikael J. Pittet[1†]

A current paradigm states that monocytes circulate freely and patrol blood vessels but differentiate irreversibly into dendritic cells (DCs) or macrophages upon tissue entry. Here we show that bona fide undifferentiated monocytes reside in the spleen and outnumber their equivalents in circulation. The reservoir monocytes assemble in clusters in the cords of the subcapsular red pulp and are distinct from macrophages and DCs. In response to ischemic myocardial injury, splenic monocytes increase their motility, exit the spleen en masse, accumulate in injured tissue, and participate in wound healing. These observations uncover a role for the spleen as a site for storage and rapid deployment of monocytes and identify splenic monocytes as a resource that the body exploits to regulate inflammation.

31 JULY 2009 VOL 325 SCIENCE

What mechanism(s) modulate the mononuclear phagocyte response at d. 5-7 in the healing infarct?

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

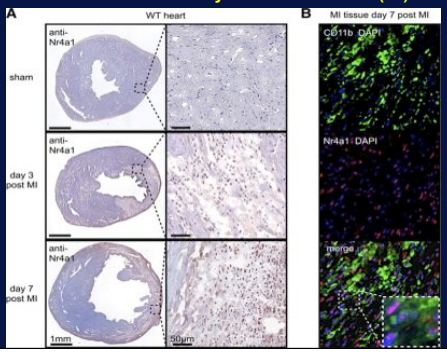
American Heart Association.

Ly-6C^high Monocytes Depend on Nr4a1 to Balance both Inflammatory and Reparative Phases in the Infarcted Myocardium

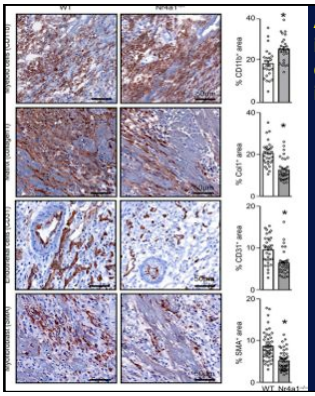
Ingo Hilgendorf, Louisa Gerhardt, Timothy C Tan, Carla Winter, Tobias AW Holderried, Benjamin G Chousterman, Yoshiko Iwamoto, Ronglih Liao, Andreas Zirlik, Marielle Scherrer-Crosbie, Catherine C Hedrick, Peter Libby, Matthias Nahrendorf, Ralph Weissleder and Filip K Swirski

Circ Res. published online March 13, 2014;

Nuclear receptor subfamily 4, group a, member 1 (Nr4a1) expressing myeloid cells accumulate in myocardial infarction (MI) tissue.



Hilgendorf I et al. Circulation Research. 2014;114:1611-1622

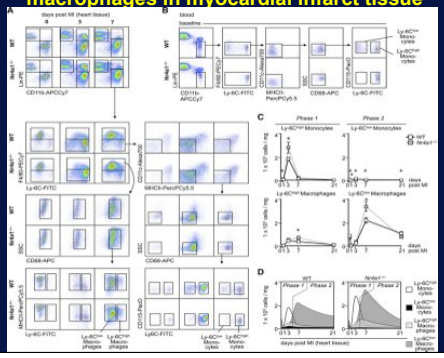


Adverse cardiac remodeling in Nr4a1−/− chimeric mice 7 days after myocardial infarction (MI).

7 days after myocardial infarction (MI). Immunohistochemical staining of MI tissue for CD11b, collagen 1 (Col1), CD31, and nonvascular smooth muscle α actin (SMA) in wild-type (WT) and *Nr4a1*$^{-/-}$ chimeric mice 7 days after MI. Results are mean±SEM, * $P \leq 0.05$, n=5 per group. Nr4a1 indicates Nuclear receptor subfamily 4, group a, member 1.

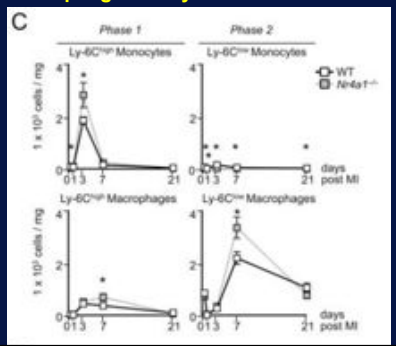
Hilgendorf I et al. Circulation Research. 2014;114:1611-1622

Enhanced accumulation of Nr4a1−/− monocytes and macrophages in myocardial infarct tissue

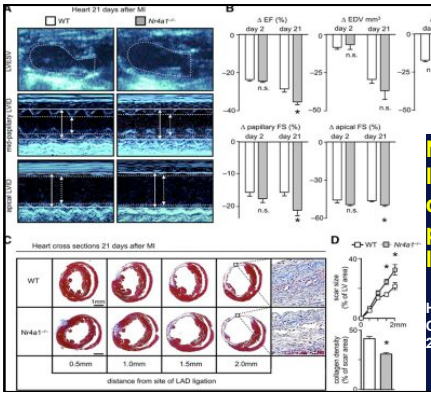


Hilgendorf I et al. Circulation Research. 2014;114:1611-1622

Enhanced accumulation of Nr4a1−/− monocytes and macrophages in myocardial infarct tissue



Hilgendorf I et al. Circulation Research. 2014;114:1611-1622



Nr4a1 limits left ventricular dysfunction post coronary ligation

Hilgendorf I et al. Circulation Research. 2014;114:1611-1622

Ly-6Chigh monocytes infiltrate the infarcted myocardium and, unlike Ly-6Clow monocytes, differentiate to cardiac macrophages.

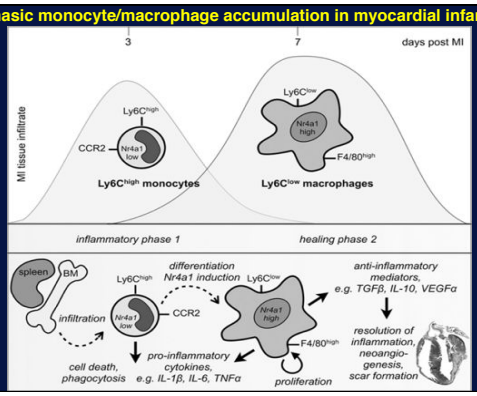
In the early, inflammatory phase of acute myocardial ischemic injury, Ly-6Chigh monocytes accrue in response to a brief Ccl2 burst.

In the second, reparative phase, accumulated Ly-6Chigh monocytes give rise to reparative Ly-6Clow F4/80high macrophages that proliferate locally.

In the absence of Nr4a1, Ly-6Chigh monocytes express heightened levels of Ccr2 on their surface, avidly infiltrate the myocardium, and differentiate to abnormally inflammatory macrophages, which results in defective healing and compromised heart function.

Hilgendorf et al. Circulation Research 114:1611-1622; 2014

Biphasic monocyte/macrophage accumulation in myocardial infarction



Hilgendorf et al. Circulation Research 114:1611-1622; 2014

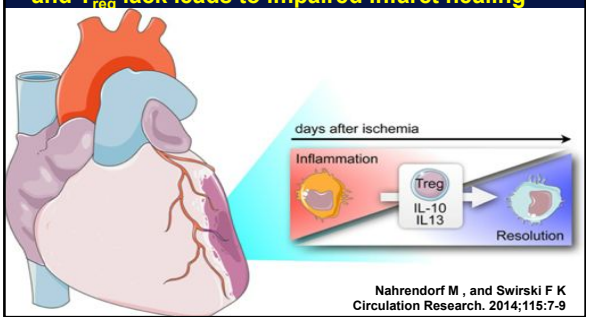
Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association.

Foxp3$^+$CD4$^+$ T Cells Improve Healing after Myocardial Infarction by Modulating Monocyte/Macrophage Differentiation

Johannes Weirather, Ulrich Hofmann, Niklas Beyersdorf, Gustavo C Ramos, Benjamin Vogel, Anna Frey, Georg Ertl, Thomas Kerkau and Stefan Frantz

Circ Res. published online April 30, 2014;

T-regulatory cells (T_{regs}) promote transition of macrophage polarization post coronary ligation and T_{reg} lack leads to impaired infarct healing



Nahrendorf M , and Swirski F K
Circulation Research. 2014;115:7-9

Is there crosstalk between acute inflammation peri-MI and plaque inflammation?

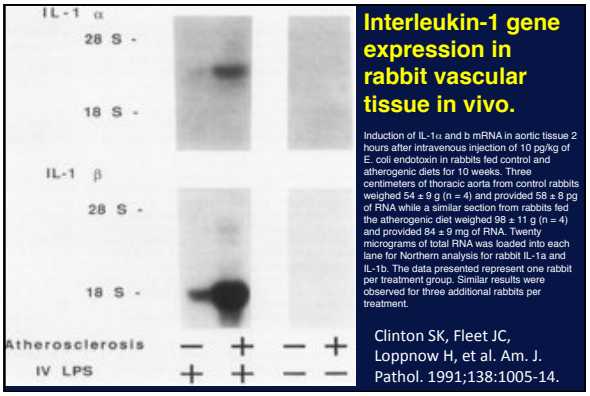
Hypothesis:
An *echo* in the arterial wall of the inflammation due to acute myocardial infarction aggravates atherosclerosis

Interleukin-1 Gene Expression in Rabbit Vascular Tissue *In Vivo*

Steven K. Clinton,* James C. Fleet,† Harald Loppnow,† Robert N. Salomon,† Burton D. Clark,‡ Joseph G. Cannon,† Alan R. Shaw,§ Charles A. Dinarello,‡ and Peter Libby¶

From the Dana-Farber Cancer Institute, Harvard Medical School, and the USDA Human Nutrition Research Center on Aging at Tufts University;† Boston, Massachusetts; Glaxo IMB,‡ Geneva, Switzerland, the Departments of Medicine and Cellular and Molecular Physiology,§ Tufts University and New England Medical Center, and the Vascular Medicine Unit,¶ Brigham and Women's Hospital, Boston, Massachusetts*

lar wall cells rather than mononuclear phagocytes probably account for the IL-1 activity induced by LPS. In addition, aortic tissue from rabbits fed an athero-genic diet showed an enhanced ability to accumulate IL-1 α and β mRNA and produce immunodetectible protein in response to LPS administration. These studies demonstrate inducible IL-1 gene expression in rabbit vascular tissue in vivo and support a local role for this cytokine in vascular pathophysiology. (Am J Pathol 1991, 138:1005–1014)



Interleukin-1 gene expression in rabbit vascular tissue in vivo.

Induction of IL-1α and b mRNA in aortic tissue 2 hours after intravenous injection of 10 pg/kg of E. coli endotoxin in rabbits fed control and atherogenic diets for 10 weeks. Three centimeters of thoracic aorta from control rabbits weighed 54 ± 9 g (n = 4) and provided 58 ± 8 pg of RNA while a similar section from rabbits fed the atherogenic diet weighed 98 ± 11 g (n = 4) and provided 84 ± 9 mg of RNA. Twenty micrograms of total RNA was loaded into each lane for Northern analysis for rabbit IL-1a and IL-1b. The data presented represent one rabbit per treatment group. Similar results were observed for three additional rabbits per treatment.

Clinton SK, Fleet JC, Loppnow H, et al. Am. J. Pathol. 1991;138:1005-14.

Atherogenic diets enhance endotoxin-stimulated interleukin-1 and tumor necrosis factor gene expression in rabbit aortae

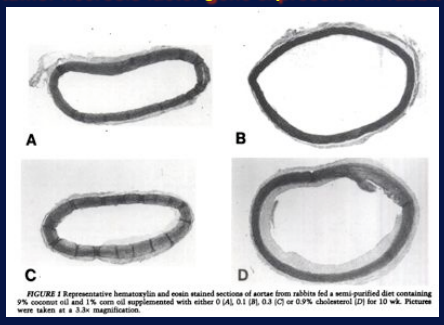
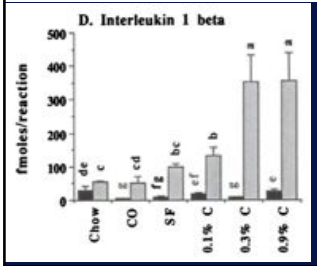


FIGURE 1 Representative hematoxylin and eosin stained sections of aortae from rabbits fed a semi-purified diet containing 9% coconut oil and 1% corn oil supplemented with either 0 (A), 0.1 (B), 0.3 (C) or 0.9% cholesterol (D) for 10 wk. Pictures were taken at a 3.3× magnification.

Fleet JC, Clinton SK, Salomon RN, Loppnow H, Libby P. J Nutr 1992;122:294-305.

Atherogenic Diets Enhance Endotoxin-Stimulated Interleukin-1 and Tumor Necrosis Factor Gene Expression in Rabbit Aortae[1,2]

JAMES C. FLEET*, STEVEN K. CLINTON*[3], ROBERT N. SALOMON*[1], HARALD LOPPNOW* AND PETER LIBBY**[4]

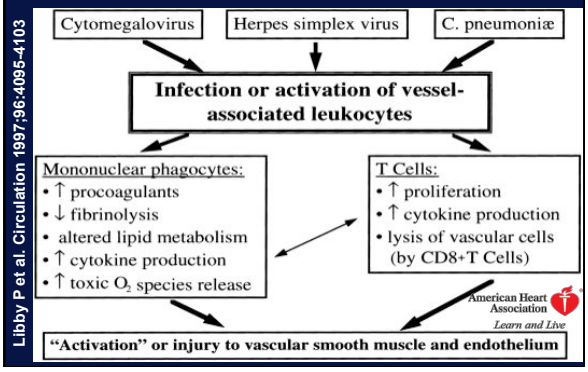


The "echo" phenomenon:

A systemic inflammatory stimulus, intravenous endotoxin, evokes a local cytokine response in arteries dependent on the amount of pre-existing atherosclerosis

J Nutr 1992;122:294-305.

Infectious agents by systemic and local effects can activate artery wall cells



Libby P et al. Circulation 1997;96:4095-4103

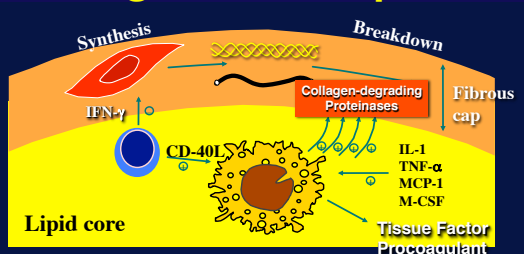
Myocardial infarction accelerates atherosclerosis

Partha Dutta[1]*, Gabriel Courties[1]*, Ying Wei[2], Florian Leuschner[1,3], Rostic Gorbatov[1], Clinton S. Robbins[1], Yoshiko Iwamoto[1], Brian Thompson[1], Alicia L. Carlson[1], Timo Heidt[1], Maulik D. Majmudar[1,4], Felix Lasitschka[5], Martin Etzrodt[1], Peter Waterman[1], Michael T. Waring[6,7], Adam T. Chicoine[6,7], Anja M. van der Laan[8], Hans W. M. Niessen[9], Jan J. Piek[8], Barry B. Rubin[10], Jagdish Butany[11], James R. Stone[1,12], Hugo A. Katus[3], Sabina A. Murphy[13], David A. Morrow[13], Marc S. Sabatine[13], Claudio Vinegoni[1], Michael A. Moskowitz[2], Mikael J. Pittet[1], Peter Libby[4], Charles P. Lin[1], Filip K. Swirski[1], Ralph Weissleder[1,14] & Matthias Nahrendorf[1]

During progression of atherosclerosis, myeloid cells destabilize lipid-rich plaques in the arterial wall and cause their rupture, thus triggering myocardial infarction and stroke. Survivors of acute coronary syndromes have a high risk of recurrent events for unknown reasons. Here we show that the systemic response to ischaemic injury aggravates chronic atherosclerosis. After myocardial infarction or stroke, *Apoe*$^{-/-}$ mice developed larger atherosclerotic lesions with a more advanced morphology. This disease acceleration persisted over many weeks and was associated with markedly increased monocyte recruitment. Seeking the source of surplus monocytes in plaques, we found that myocardial infarction liberated haematopoietic stem and progenitor cells from bone marrow niches via sympathetic nervous system signalling. The progenitors then seeded the spleen, yielding a sustained boost in monocyte production. These observations provide new mechanistic insight into atherogenesis and provide a novel therapeutic opportunity to mitigate disease progression.

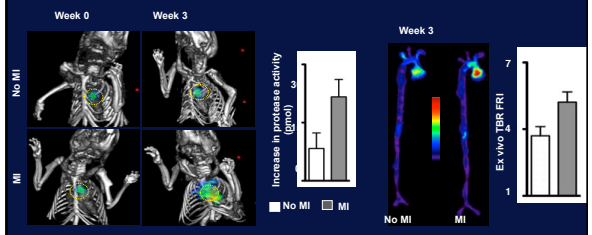
19 JULY 2012 I VOL 487 I NATURE I 325

Molecular Biology of the High-Risk Plaque



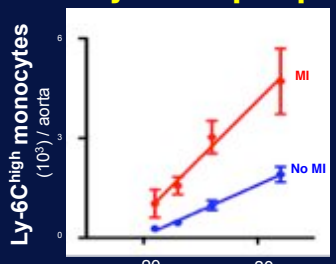
After Libby P. Circulation 1995

MI enhances protease activity in plaque

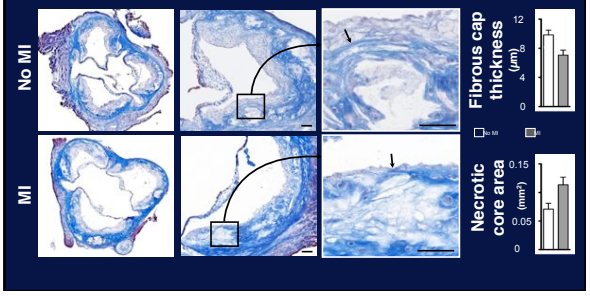


Dutta et al. Nature 487:325; 2012

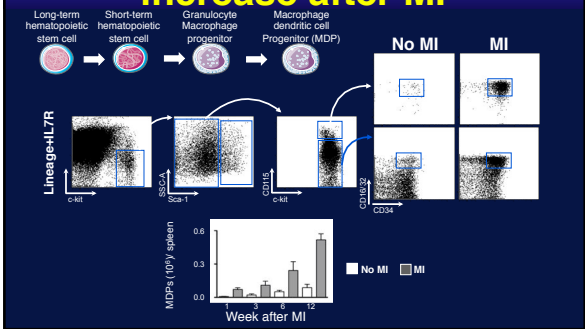
MI enhances pro-inflammatory monocytes in plaque

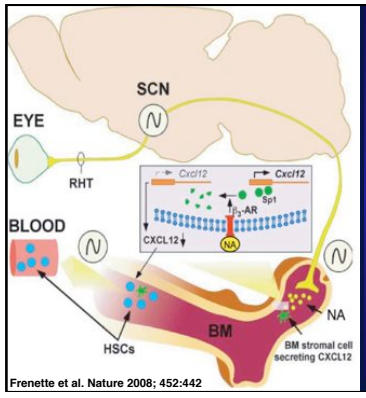


Post MI, plaque necrotic cores enlarge and fibrous caps thin



Progenitor numbers in spleen increase after MI



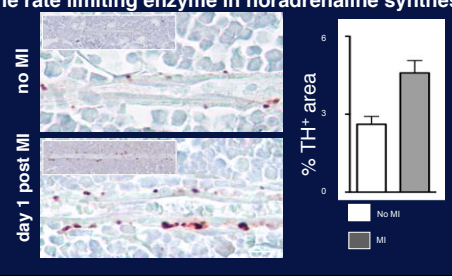


Frenette et al. Nature 2008; 452:442

What are the signals for progenitor release from bone marrow?

Progenitor release from bone marrow: *triggered by adrenergic signaling?*

Bone marrow tyrosine hydroxylase (TH):
The rate limiting enzyme in noradrenaline synthesis



β_3 blocker treatment reduces progenitor release from bone marrow

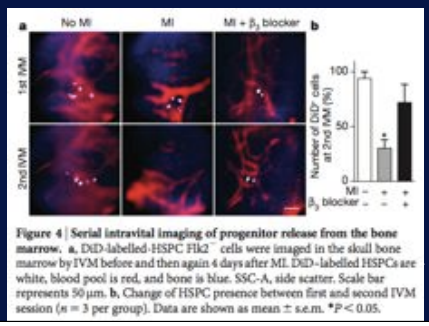
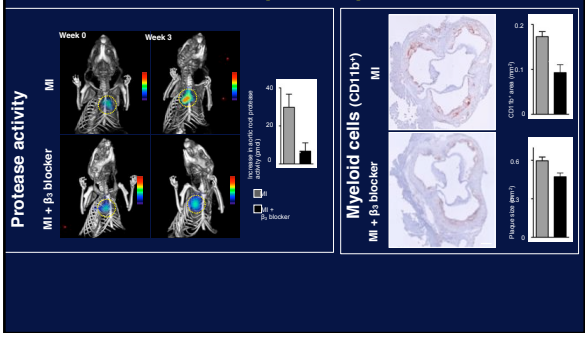
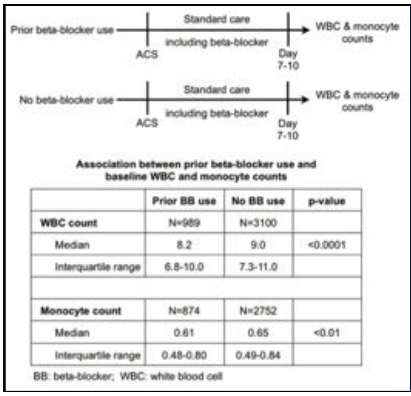


Figure 4 | Serial intravital imaging of progenitor release from the bone marrow. a, DiD-labelled HSPC Flk2$^-$ cells were imaged in the skull bone marrow by IVM before and then again 4 days after MI. DiD-labelled HSPCs are white, blood pool is red, and bone is blue. SSC-A, side scatter. Scale bar represents 50 μm. b, Change of HSPC presence between first and second IVM session ($n = 3$ per group). Data are shown as mean ± s.e.m. *$P < 0.05$.

β_3 blocker treatment limits acceleration of atherosclerosis post experimental MI



β-adrenergic blocker administration associates with reduction in white blood cel and monocyte counts in patients after an acute coronary syndrome.



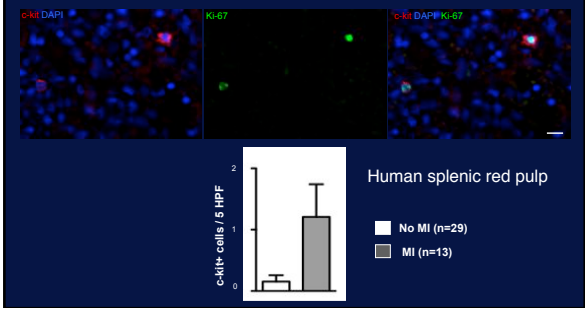
Association between prior beta-blocker use and baseline WBC and monocyte counts

	Prior BB use	No BB use	p-value
WBC count	N=989	N=3100	
Median	8.2	9.0	<0.0001
Interquartile range	6.8-10.0	7.3-11.0	
Monocyte count	N=874	N=2752	
Median	0.61	0.65	<0.01
Interquartile range	0.48-0.80	0.49-0.84	

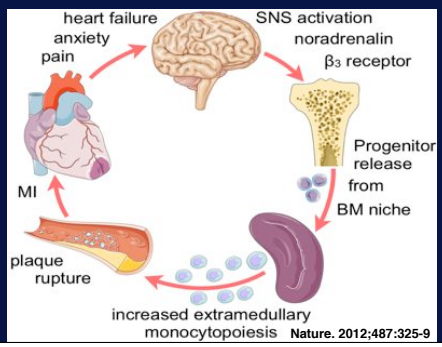
BB: beta-blocker; WBC: white blood cell

Nature. 2012;487:325-9

Increased splenic progenitor proliferation in patients after MI



MI enhances atherosclerosis



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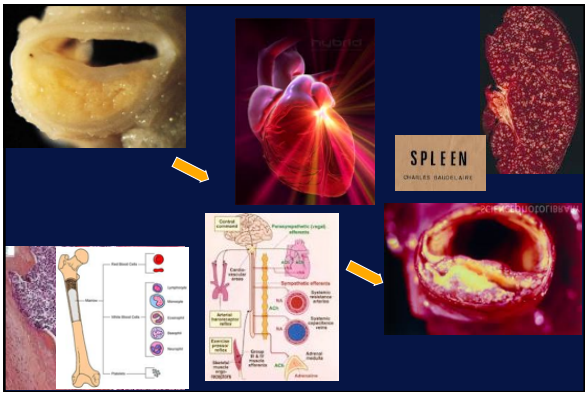

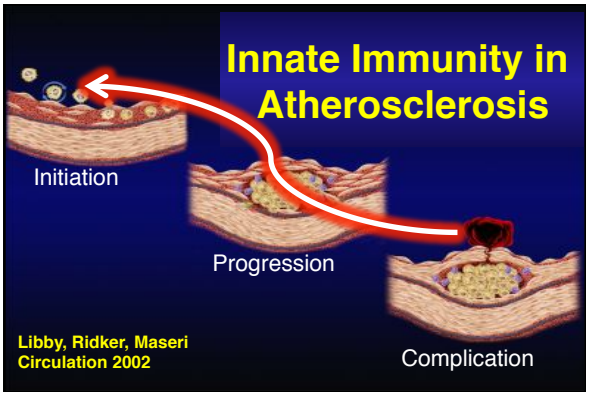
Innate Immunity in Atherosclerosis
Initiation
Progression
Complication
Libby, Ridker, Maseri
Circulation 2002


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