IX° Corso Nazionale Congiunto

ULTRASONOLOGIA VASCOLARE
DIAGNOSI E TERAPIA

CENTRO RESIDENZIALE UNIVERSITARIO
BERTINORO (FC)

30 marzo - 2 aprile 2011

Nuove acquisizioni sull'aterosclerosi: placca vulnerabile

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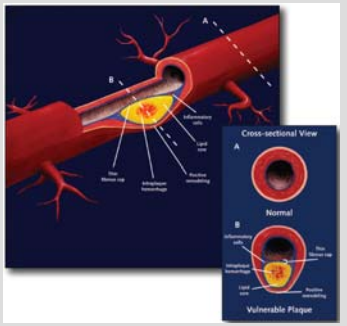
Centro Cardiologico Monzino IRCCS, Milano

CCM

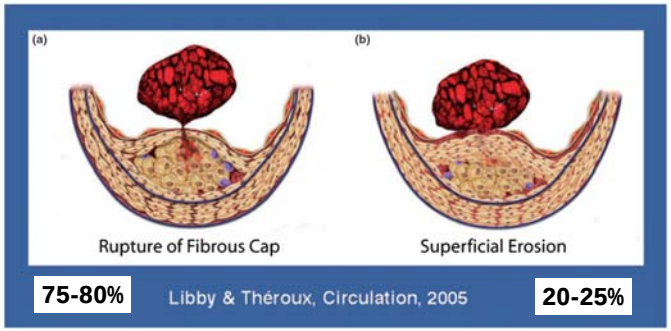
Vulnerable Plaque



…Plaque vulnerability was defined as the susceptibility of a plaque to rupture, thus causing a clinical cardiovascular event.

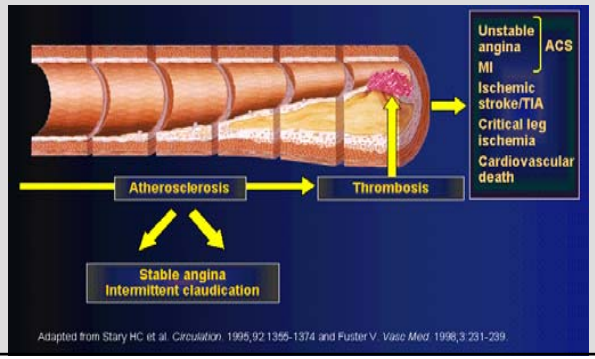
Muller JE et al, Circulation 1989

Plaque rupture *vs* plaque erosion

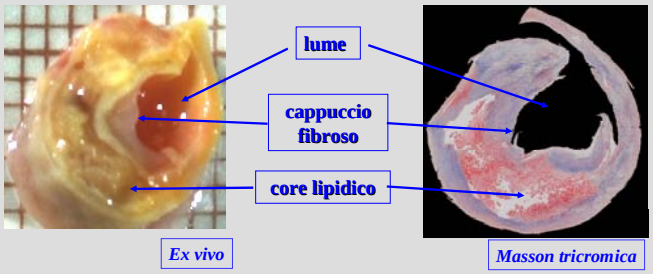


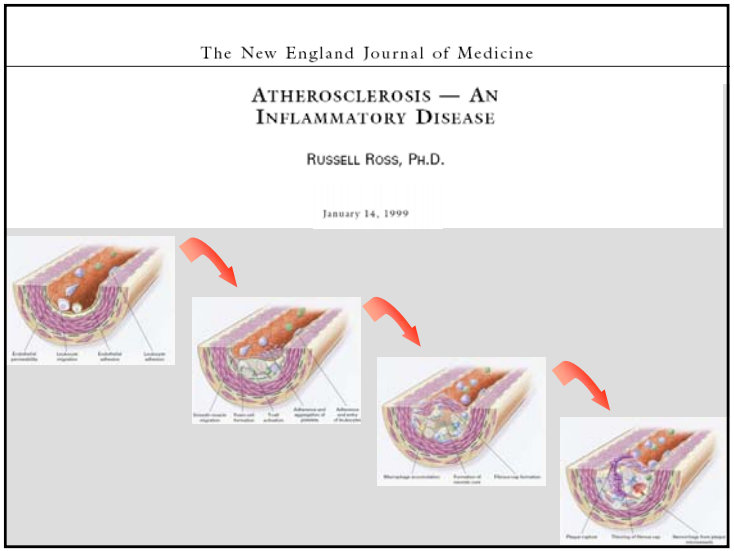
Atherothrombosis

A generalized progressive disease of large- and mid-size arteries that affects multiple vascular beds, including cerebral, coronary, and peripheral arteries



HUMAN ATHEROSCLEROTIC PLAQUE



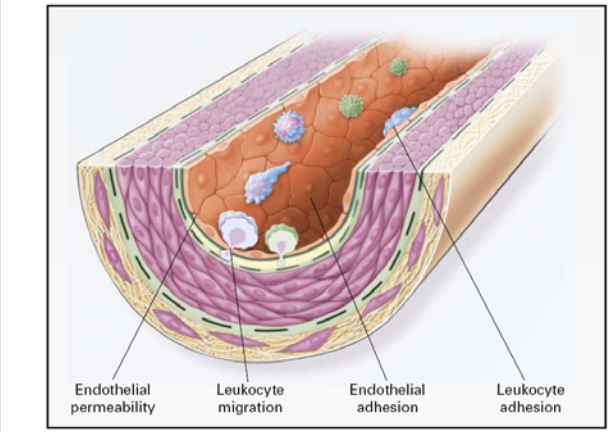


Inflammation and Atherosclerosis

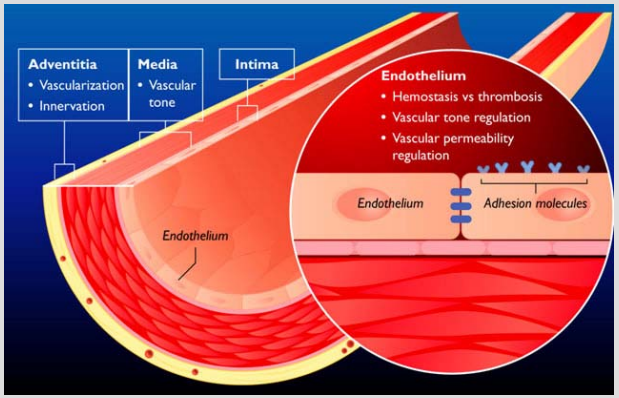
Inflammation in the vessel wall is now considered to play an essential role in the ***initiation, progression and final steps*** of atherosclerosis, namely ***plaque destabilization*** and eventually plaque rupture.

Atherothrombosis:
onset, evolution and rupture

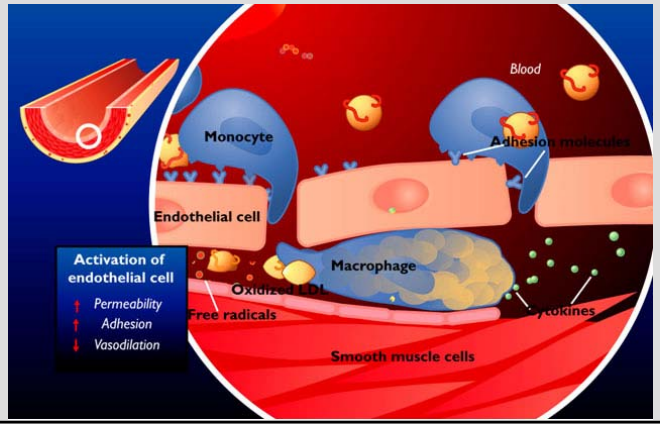
Endothelial Dysfunction in Atherogenesis



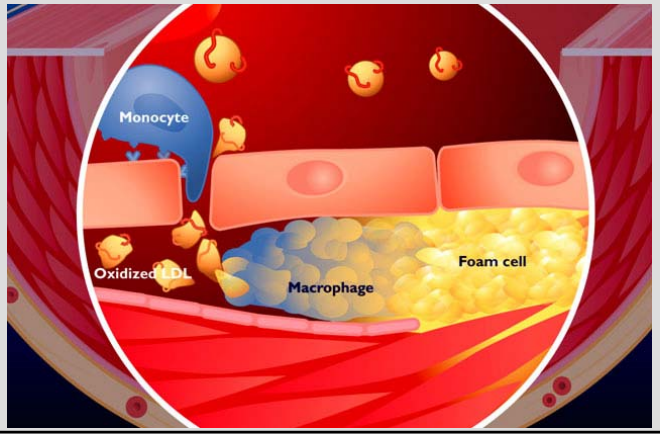
The normal endothelium does not in general support binding of white blood cells



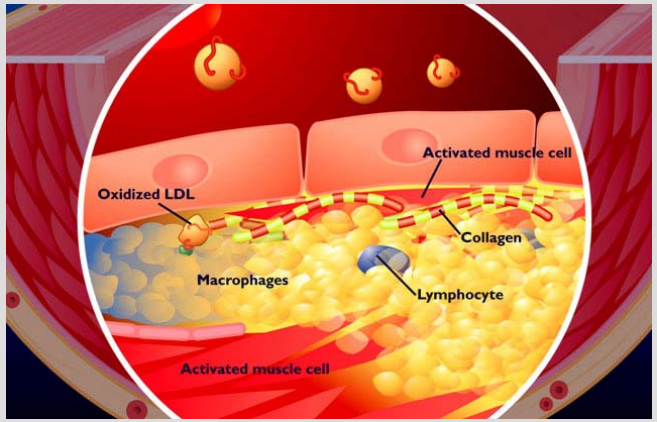
Vascular endothelium modification in atherosclerosis



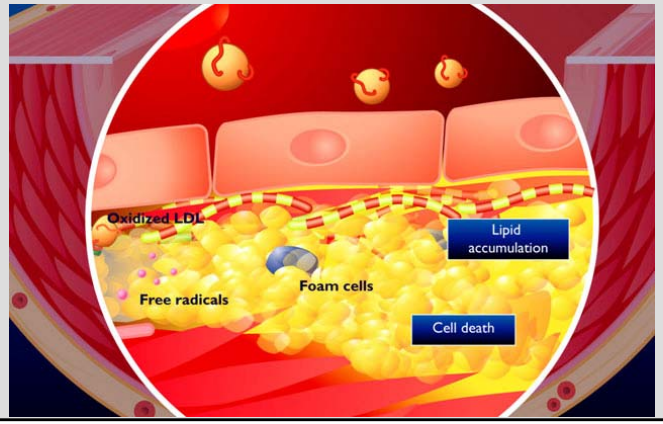
Plaque formation 1 — Fatty streak



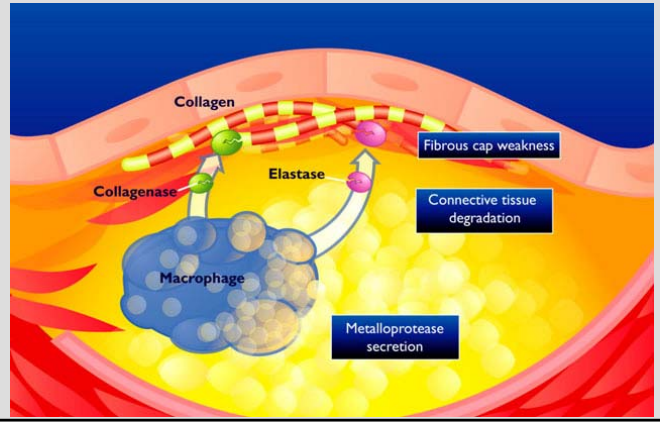
Plaque formation
2 — Fibrous cap



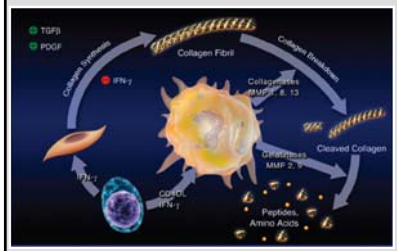
Plaque formation
3 — Lipid core

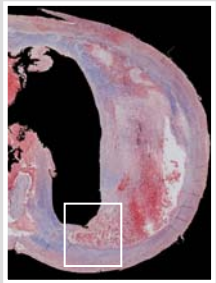


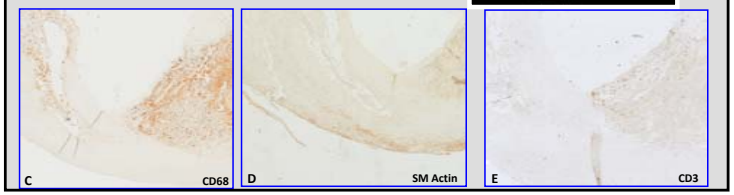
Vulnerable plaque
Key role of the macrophage in the degradation of the fibrous cap



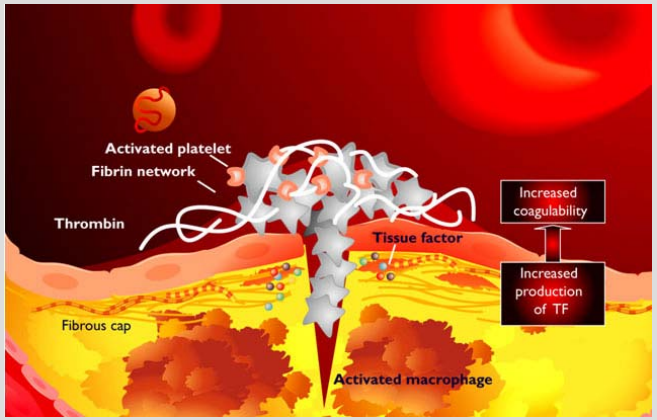
Degradation of the fibrous cap



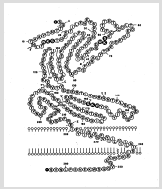




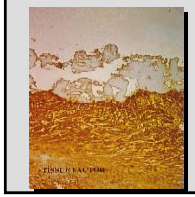
Thrombus formation
Tissue Factor expression within the plaque



Tissue Factor in Atherosclerosis

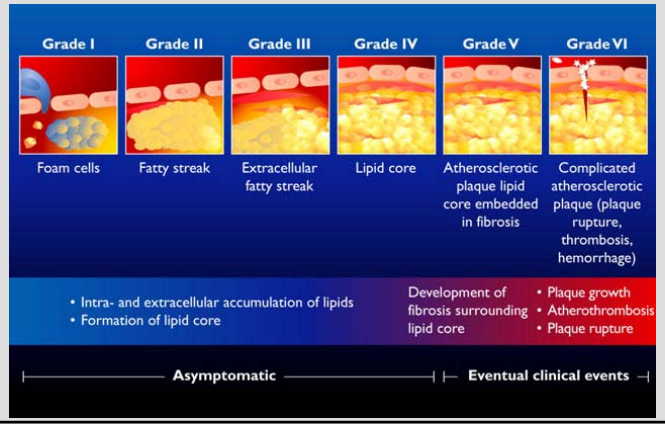


- ✓ **Tissue Factor (TF) is one of the major determinants of the activation of coagulation cascade at site of atherosclerotic plaque rupture.**

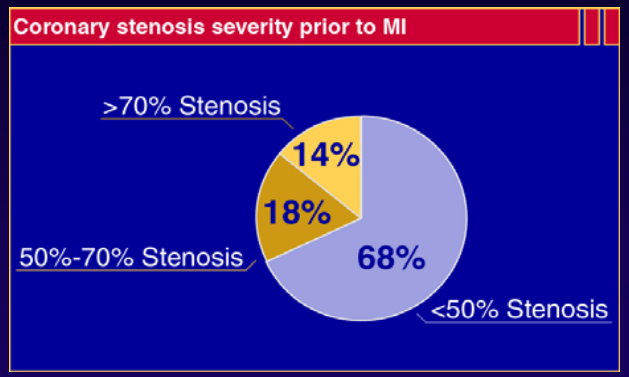


- ✓ **Several data indicate a positive correlation between atherosclerotic plaque thrombogenicity and Tissue Factor expression within the plaque.** *V. Toschi et al, Circulation 1997*

Atherothrombosis:
a Immunoinflammatory, Fibroproliferative and Progressive Process

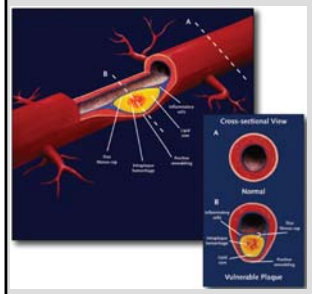


Most Myocardial Infarctions Are Caused by Low-Grade Stenoses



Pooled data from 4 studies: Ambrose et al, 1988; Little et al, 1988; Nobuyoshi et al, 1991; and Giroud et al, 1992. (Adapted from Falk et al.)

Vulnerable Plaque



high-risk plaque is described as <u>thin-cap fibroatheroma (TCFA)</u>

- lipid-rich atheromatous core
- thin fibrous cap (<65µm) with macrophage and lymphocyte infiltration (inflammation)
- decreased smooth muscle cell content
- extensive positive remodeling of the arterial wall.

Consensus of the Fist International Vulnerable Plaque Meeting held in Santorini in 2003.
Schaar JA et al, Eur Heart J 2004

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

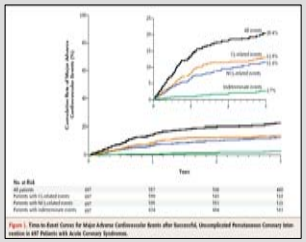
…The primary purpose of this natural-history study was to provide prospective *in vivo* confirmation of the hypothesis that acute coronary syndromes arise from atheromas with certain histopathological characteristics, and that these characteristics are not necessarily dependent on the degree of angiographic stenosis at that site.

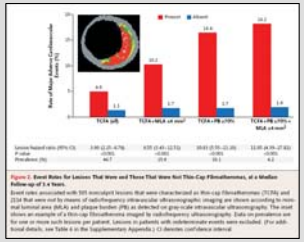
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

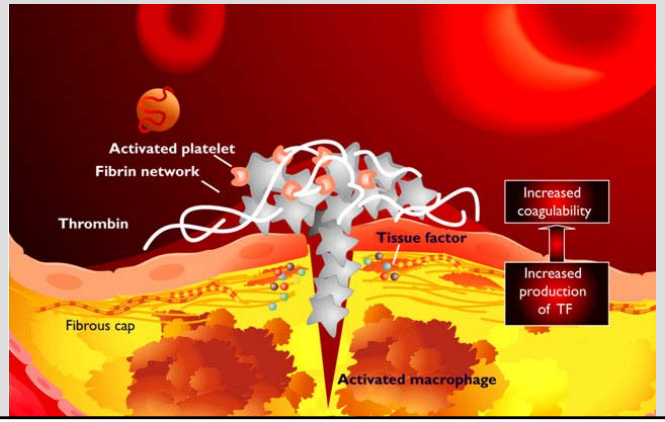




*Despite continuous improvements in the catheter-based treatment of coronary artery disease (CAD), our field continues to struggle with the concept that **percutaneous intervention may not prevent myocardial infarction or death in the stable patient**. The main reason behind this controversial but rather accepted statement is that **life-threatening coronary events arise most frequently from lesions that escape proper diagnosis and treatment**. As a result, <u>our efforts in clinical practice are almost totally consumed by the treatment of lesions that have limited impact on the natural history of atherothrombosis and CAD</u>. Thus, it is imperative to reflect on this paradox, and do something about it….*

Moreno PR, Cir Cardiovasc Interv 2009

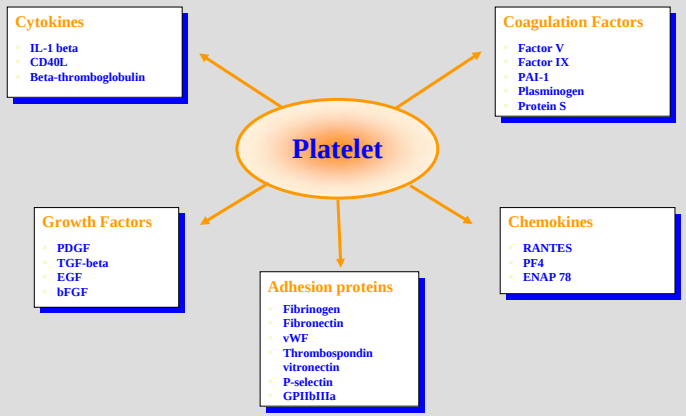
Thrombus formation
Platelet adhesion and activation



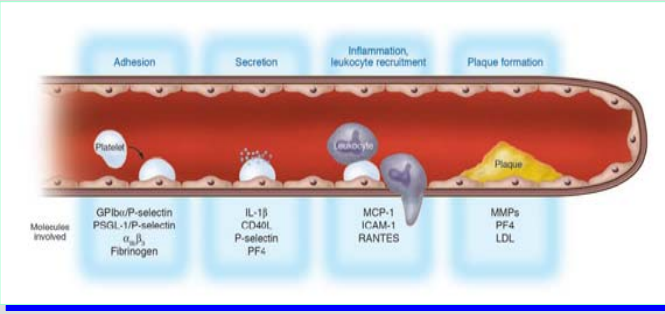
New concepts in Atherothrombosis…

…Platelets are multifunctional cells that use elaborate molecular pathways to regulate a variety of thrombotic and inflammatory responses

Factors released by activated human platelets



Platelet contribution to vessel inflammation leading to atherogenesis and eventually to plaque rupture and thrombosis



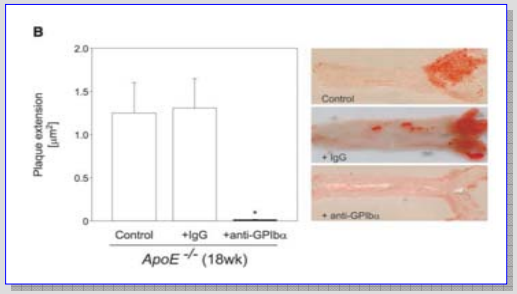
Platelets provide the inflammatory basis for plaque formation before physically occluding the vessel by thrombosis upon plaque rupture.

Gawaz M J Clin Invest 2005, 115:3378

A Critical Role of Platelet Adhesion in the Initiation of Atherosclerotic Lesion Formation

Steffen Massberg,[1,4] Korbinian Brand,[2] Sabine Grüner,[1] Sharon Page,[2] Elke Müller,[1] Iris Müller,[1] Wolfgang Bergmeier,[3] Thomas Richter,[4] Michael Lorenz,[1] Ildiko Konrad,[1] Bernhard Nieswandt,[3] and Meinrad Gawaz[1,4]

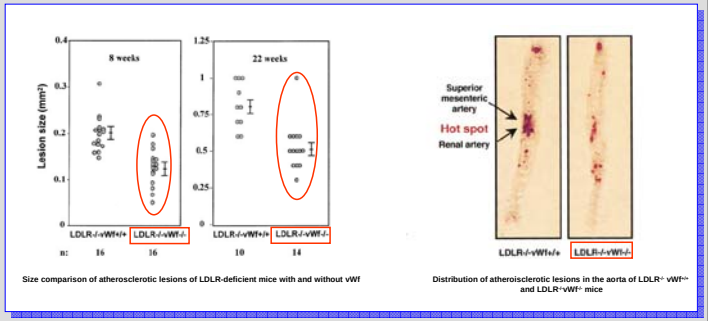
J. Exp. Med. © The Rockefeller University Press • 00
Volume 196, Number 7, October 7, 2002 887–896



Localized reduction of atherosclerosis in von Willebrand factor–deficient mice

Nassia Methia, Patrick André, Cécile V. Denis, Maria Economopoulos, and Denisa D. Wagner

(Blood. 2001;98:1424-1428)



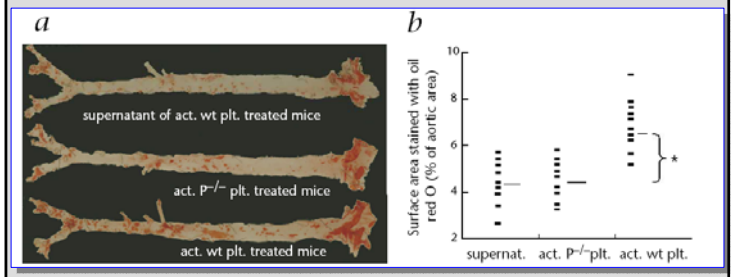
Size comparison of atherosclerotic lesions of LDLR-deficient mice with and without vWf

Distribution of atheroisclerotic lesions in the aorta of LDLR-/- vWf+/+ and LDLR-/-vWf-/- mice

Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E

Yuqing Huo[3], Andreas Schober[2], S. Bradley Forlow[3], David F. Smith[3], Matthew Craig Hyman[3], Steffen Jung[3], Dan R. Littman[4], Christian Weber[2] and Klaus Ley[1]

NATURE MEDICINE • VOLUME 9 • NUMBER 1 • JANUARY 2003



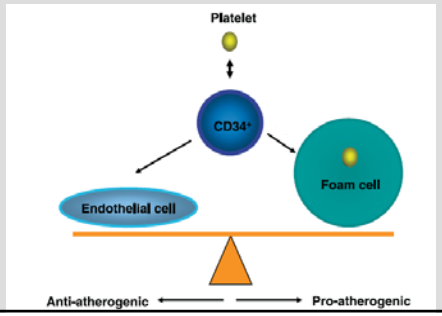
…our results indicate that circulating activated platelets and platelet-leukocyte/monocyte aggregates promote formation of atherosclerotic lesions.

The FASEB Journal • FJ Express Full-Length Article Vol. 20 December 2006

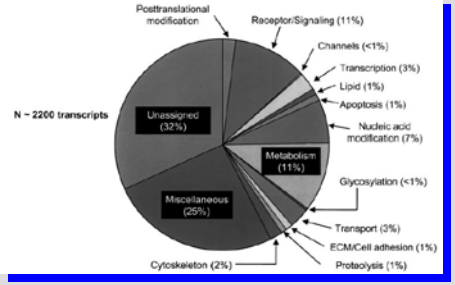
Platelets induce differentiation of human CD34+ progenitor cells into foam cells and endothelial cells

Karin Daub,* Harald Langer,* Peter Seizer,* Konstantinos Stellos,* Andreas E. May,* Pankaj Goyal,† Boris Bigalke,* Tanja Schönberger,* Tobias Geisler,* Dorothea Siegel-Axel,* Robert A. J. Oostendorp,‡ Stephan Lindemann,* and Meinrad Gawaz*,1

*Medizinische Klinik III, Eberhard Karls Universität Tübingen, Tübingen, Germany; †Institute for Prevention of Cardiovascular Diseases, University of Munich, Munich, Germany; and ‡Medizinische Klinik III, Klinikum rechts der Isar München, Technische Universität, Munich, Germany



The platelet transcriptome



Affymetrix HG-U95Av2 probe set (about 12.600 genes) identified the expression of 2147 (range, 13%-17%) platelet-expressed transcripts, less than half the number (30%-50%) expected for nucleated cells.

Of these, approximately 22% collectively are involved in metabolism and receptor/signaling, with a clear overrepresentation of genes with unassigned function (32%).

Gnatenko DV, et al. *Blood* 2003;101:2285-93

Activated platelets mediate inflammatory signaling by regulated interleukin 1β synthesis.

Lindemann S, et al. *J Cell Biol 2001;154(3):485-90*

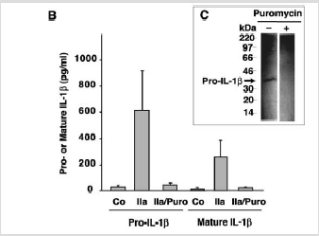
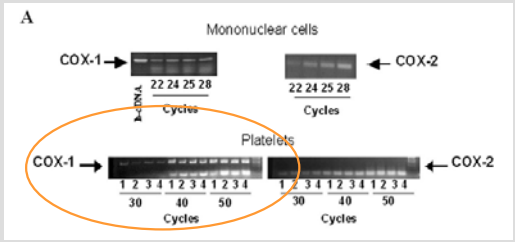


Figure 2. IL-1 is synthesized by platelets in fibrin clots. (B) Total IL-1 (mean±SEM,n=6) synthesized by resting platelets (Co) or platelets activated with thrombin (IIa) (8 h) in the presence or absence of puromycin (Puro;100 μM) was determined by ELISA. (C) Platelets were pretreatedwith puromycin or DMSO, activated with thrombin, and incubated in the presence of [35S]methionine for 8 h. The cells were then lysed and the proteins were immunoprecipitated with an antibody that preferentially recognizes pro–IL-1β. A single labeled protein with amolecular mass corresponding to pro–IL-1_was identified (arrow).

IL-1β mRNA is translated into protein by activated platelets during fibrin clot formation.

De Novo Synthesis of Cyclooxygenase-1 Counteracts the Suppression of Platelet Thromboxane Biosynthesis by Aspirin

V. Evangelista et al.
***Circ Res.* 2006; 593-595**



Activities of Platelets at the vascular interface

Platelets are multifunctional cells that use elaborate molecular pathways to regulate a variety of thrombotic and inflammatory responses

Platelets in atherothrombosis

The contribution of platelets in atherothrombosis is no more linked only to the last step of the process (thrombus formation upon plaque rupture).

Platelets play key roles since the early stage of the disease, when they contribute to endothelial and monocyte activation, leading to plaque progression.