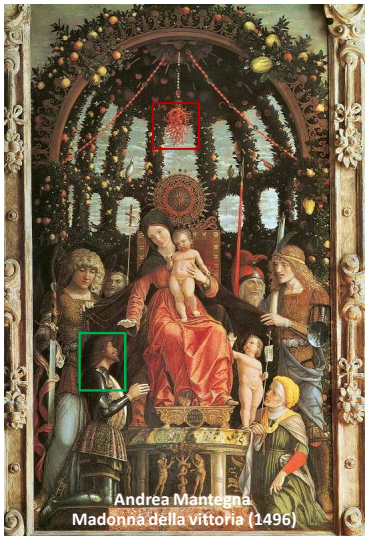
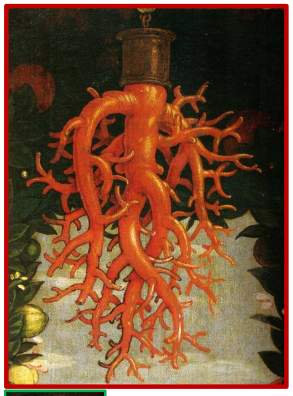




Francesco II Gonzaga

Arteriosclerosi e Aterosclerosi non sono sinonimi

I disegni e molti schemi sono stati realizzati dal prof. Ernesto Damiani

Arteriosclerosi è un genere di malattia

Comprende diverse malattie distinte morfologicamente, tutte caratterizzate da indurimento della parete arteriosa

Genere: Arteriosclerosi

Specie: **arteriolosclerosi** **aterosclerosi** **sclerosi calcifica di Mönckenberg**

Aterosclerosi è una singola specie di malattia

È la sclerosi di un precedente ateroma

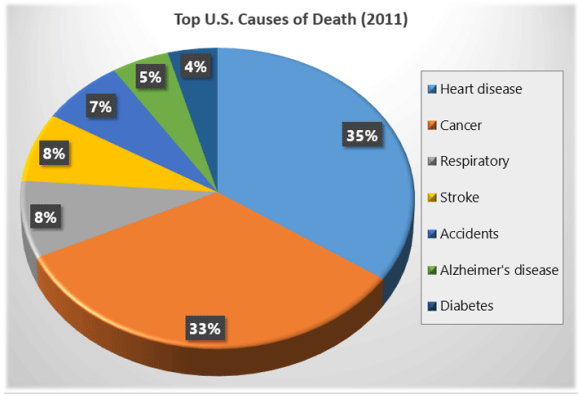
Αθήρα, poltiglia
-ωμα, rigonfiamento da raccolta

Rigonfiamento da raccolta di poltiglia giallastra

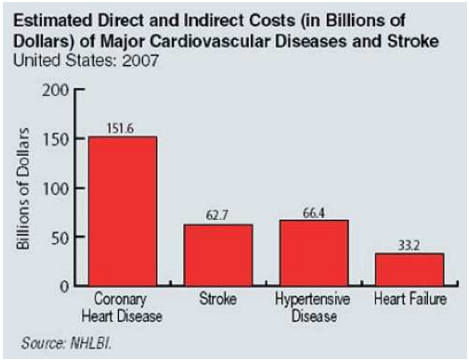
Aterosclerosi

Σκλερός, duro
È la sclerosi di un ateroma

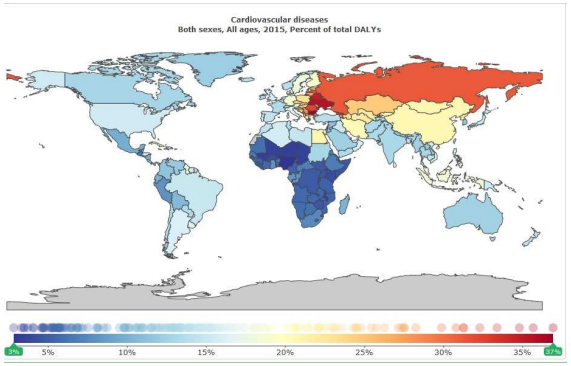
Alcuni dati epidemiologici



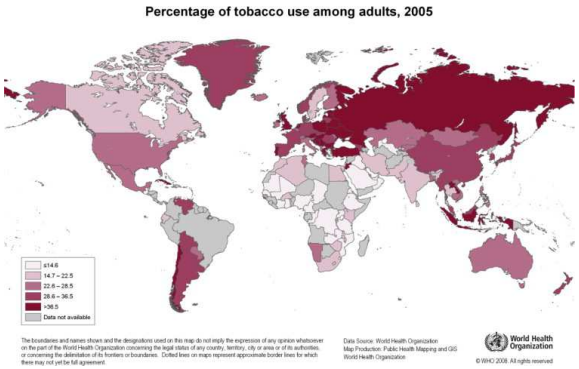
Spesa sanitaria riconducibile alle malattie cardiovascolari



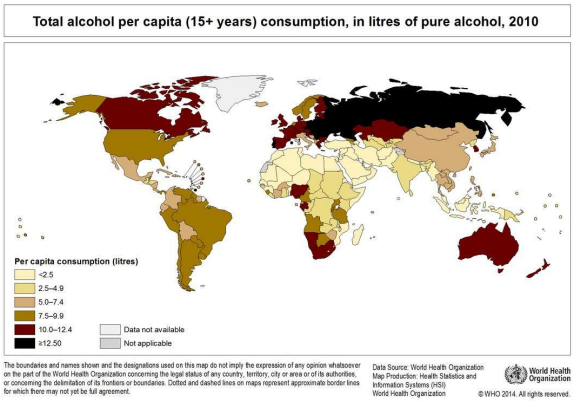
Malattia dei paesi ricchi?

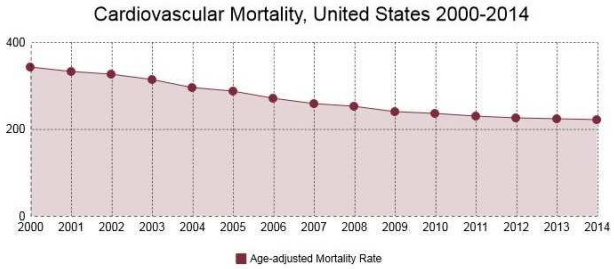


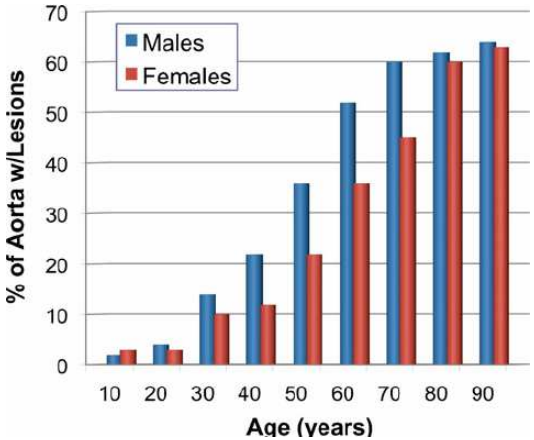
Tabagismo (tabacco e fumo)



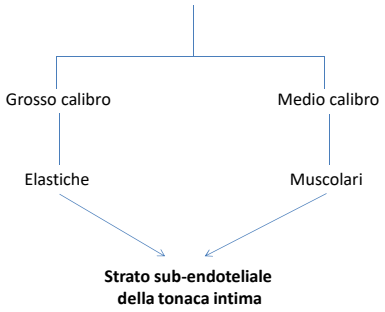
Consumo di alcol



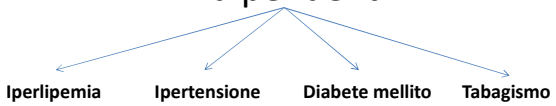




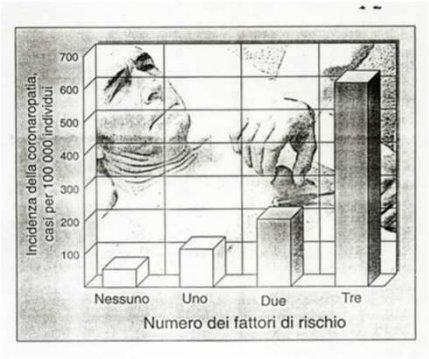
Arterie



Fattori di rischio indipendenti



L'associazione tra fattori di rischio aumenta l'incidenza in maniera esponenziale



La proteina C-reattiva è un fattore di rischio?

No

È un marcatore di flogosi

Riflette la progressione della malattia

Come fanno fattori di rischio così diversi a dare lo stesso risultato?

Agiscono tutti sull'endotelio

Response to injury hypothesis

Iperlipemia **Ipertensione** **Diabete mellito** **Tabagismo**

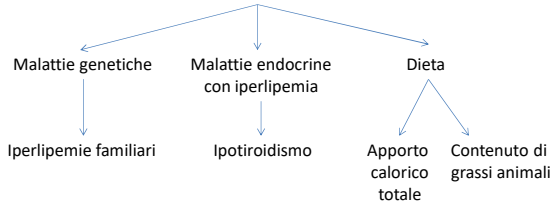
Danno endoteliale

L'endotelio risponde al danno innescando il processo patologico che porta nel tempo alla formazione della lesione aterosclerotica

Ruolo dell'Iperlipemia

Evidenze

Iperlipemia



Particolarmente importanti i livelli di:

colesterolo totale < 200 mg/100 ml

LDL 130-159 mg/100 ml

HDL 35-39 mg/100 ml

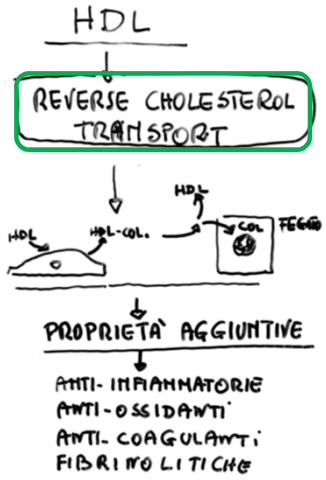
Valori ottimali

Test	Desirable	Borderline
Total cholesterol	<200	200-240
HDL cholesterol	>45	35-45
Triglycerides	<200	200-400
LDL cholesterol	<130	130-160
Cholesterol/HDL	<4.5	4.5-7.5
LDL/HDL	<3.0	3.5

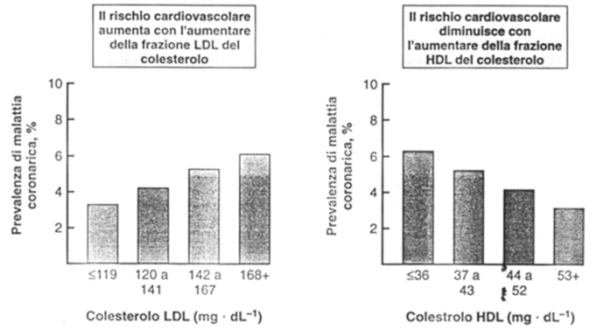
Source: Medical Essay (1993)

Colesterolo-LDL

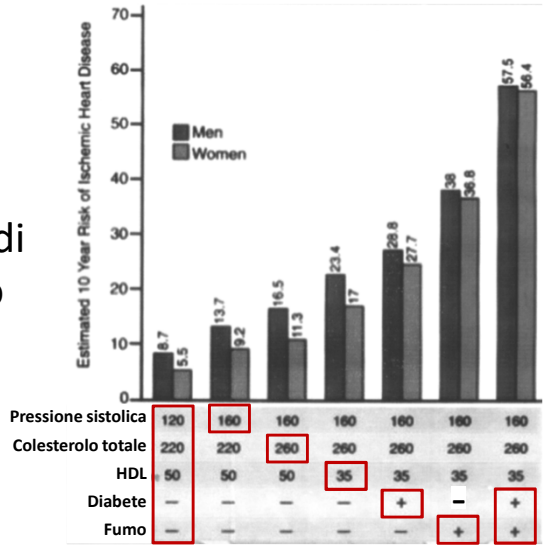
Colesterolo-HDL



Il rischio di aterosclerosi correla con il tipo di colesterolo



Fattori di rischio



https://www.escardio.org/Sub-specialty-communities/European-Association-of-Preventive-Cardiology-(EAPC)/News/hdl-cholesterol-ldl-cholesterol-and-coronary-atherosclerosis

HDL-cholesterol, LDL-cholesterol, and coronary atherosclerosis: observations from cardiac imaging studies

Comment by Konstantinos C. Koskinas, Population Science and Public Health Section
22 Feb 2021

Blood cholesterol is a well-recognised risk factor for the development and progression of atherosclerosis. Consistent evidence from genetic studies, epidemiologic observations, and randomised controlled trials (RCT) has unequivocally shown that **elevated plasma concentrations of atherogenic lipid, particularly low-density lipoprotein cholesterol (LDL-C), are causally linked to atherosclerotic cardiovascular disease (ASCVD)**(1). **Conversely, for higher-density lipoprotein cholesterol (HDL-C), higher levels are associated with a lower ASCVD risk.**

In their recent article, Kim and all analyzed coronary computed tomography angiography (CCTA) data from 5,130 non-diabetic Korean patients without known coronary artery disease in relation to HDL-C and LDL-C levels (2). Imaging outcomes included any obstructive plaque; presence of obstructive plaques in clinically most relevant locations (i.e. left-main or proximal left anterior descending artery); and multivessel obstructive lesions. **The authors found that patients with low levels (< 40 mg/dL) of HDL-C, as compared with those with higher levels (≥ 40 mg/dL), had a higher prevalence of obstructive plaques (by any of the aforementioned three definitions), but only in the subgroup of patients with LDL-C levels <130 mg/dL. In contrast, there was no difference in the prevalence of obstructive plaques in relation to HDL-C in the context of higher (≥ 130 mg/dL) LDL-C levels (2).**

Some aspects of the study methodology deserve consideration in interpreting these results. First, thresholds for considering LDL-C levels as "normal" or "elevated" are not the same for all individuals, but rather depend on each individual's cardiovascular risk: for patients with established ASCVD or at higher risk of developing ASCVD, lower LDL-C levels are generally recommenced (3). In the study by Kim et al, about 26% had a high ASCVD risk score, whereby recommended LDL goals according to current guidelines are not <130 mg/dL but lower (3). It would be of interest to explore whether favorable (high) HDL-C levels remain to be predictive of less advanced coronary atherosclerosis in the context of lower LDL-C levels (< 100 mg/dL) in these higher-risk primary-prevention individuals. Second, the long-established concept "the higher, the better" for HDL-C might may not apply for the entire spectrum of HDL-C levels, since extremely high HDL-C was paradoxically associated with high mortality in recent observational studies (4). With respect to coronary atherosclerosis by CCTA, this aspect cannot be addressed by applying a dichotomous approach for HDL-C (< vs. ≥40 mg/dL). Notwithstanding these considerations, and taking into account the observational, cross-sectional study design (thus showing associations but precluding any inference on causality), Kim et al. provide interesting data that add to the evidence base of HDL-C and its relation to ASCVD risk (2).

The inverse association between plasma HDL-C and the risk of ASCVD has been consistently shown in numerous epidemiological studies (5). In contrast, a causal role of HDL-C in ASCVD was not confirmed in Mendelian randomisation studies (6), although the latter evidence requires cautious interpretation given that most genetic variants associated with lower HDL-C are also associated with higher LDL-C and triglyceride levels. **Importantly, RCTs of medications that increase plasma HDL-C levels, e.g. cholesteryl ester transfer protein (CETP) inhibitors, failed to show a reduction in the risk of CV events (7,8). Along the same lines, directly infused HDL mimetics that raise HDL-C plasma level did not reduce the progression of atherosclerosis as measured by intravascular ultrasound (9)**.

Taken together, elevated HDL-C levels do associate with a lower risk of CVD in epidemiological studies, and consistently with fewer obstructive lesions in the CCTA study by Kim et al (2), but **there is currently no RCT or genetic evidence that raising plasma levels of HDL-C effectively reduces ASCVD risk. In contrast, lowering LDL-C level by 1.0 mmol/l (38.7 mg/dL) reduces the risk of major cardiovascular event by about 20% (10,11). Accordingly, current guidelines recommend LDL-C as the primary lipid analysis for screening, diagnosis, and management; HDL-C analysis is recommended to refine risk estimation (3). With respect to physician-patient communication, it is essential to explain to our patients that high levels of their "good" (HDL) cholesterol may indeed be protective, but this does not compensate for the adverse, pro-atherogenic effects of elevated levels of "bad" (LDL) cholesterol.**

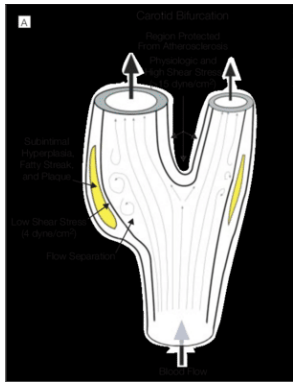
1. Ference BA et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459-2472.
2. Kim YG et al. High-density lipoprotein cholesterol and the risk of obstructive coronary artery disease beyond low-density lipoprotein cholesterol in non-diabetic individuals. Eur J Prev Cardiol. 2020;27(7):706-714.
3. Mach F et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111-188.
4. Madsen CM et al. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J. 2017;38(32):2478-2486.
5. Emerging Risk Factors Collaboration, Di Angelantonio E et al. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012;307:2499-2506.
6. Holmes MV et al. Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 2015;36:539-550.
7. Lincoff AM et al. ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med. 2017;376:1933-1942.
8. HPS/TIMI/REVEAL Collaborative Group, Bowman L et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med. 2017;377:1217-1227.
9. Tardif JC et al. Can HDL Infusions Significantly QUicken Atherosclerosis REgression (CHI-SQUARE) Investigators. Effects of the highdensity lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial. Eur Heart J. 2014;35:3277-3286.
10. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-1681.
11. Koskinas KC et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. Eur Heart J. 2018;39:1172-1180.

Ruolo dell'Ipertensione

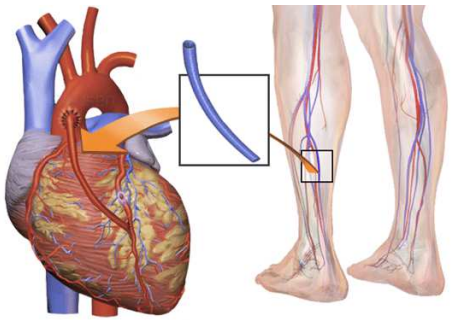
Evidenze

Sindrome del Carrefour

Localizzazione preferenziale alle biforcazioni



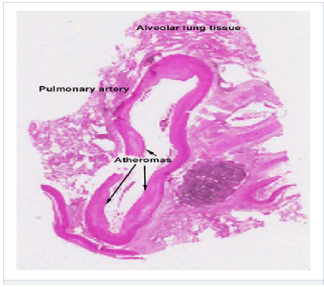
Il caso dei by-pass aorto-coronarico con la vena safena



Nel 92% dei casi la causa di occlusione del bypass è legata all'utilizzo di condotti venosi

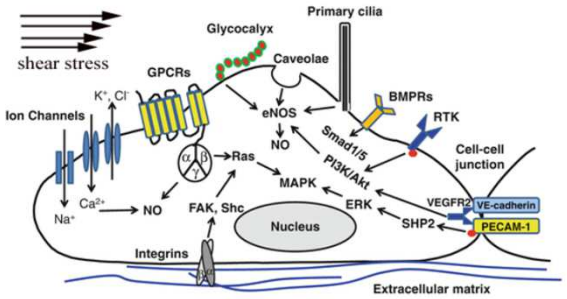
Il caso dell'arteria polmonare

*Prevalence of Pulmonary Atherosclerosis in Patients With **Chronic Thromboembolic Pulmonary Hypertension***, 2017

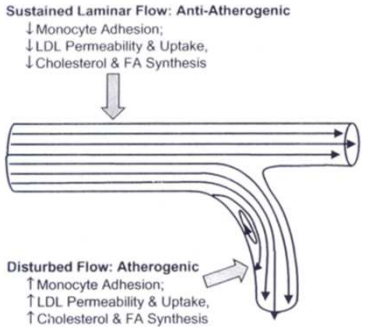


- Pulmonary atherosclerosis seems to be a common finding in patients with **CTEPH**. .. it might be suggested that **pathophysiological association exists** between venous thromboembolism and atherosclerosis.

Le cellule endoteliali possiedono una molteplicità di *mechanotransducers*



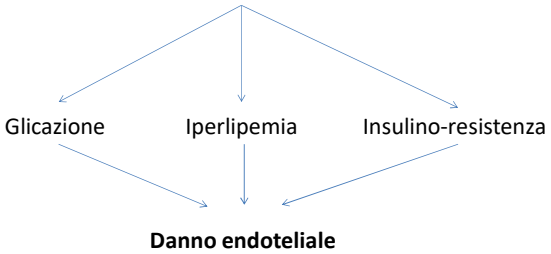
Le variazioni di flusso attivano vie di trasduzione del segnale aterogeniche



Ruolo del diabete mellito

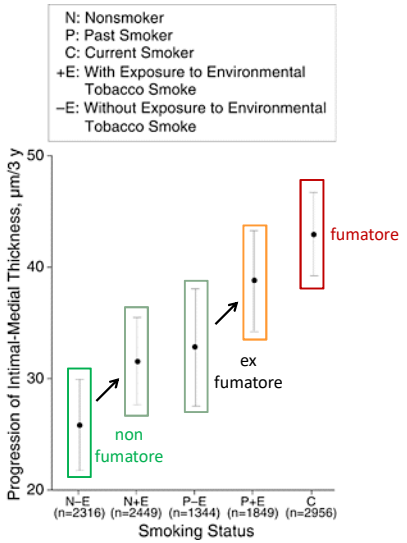
La **macroangiopatia** (aterosclerosi) è una classica complicanza del diabete mellito

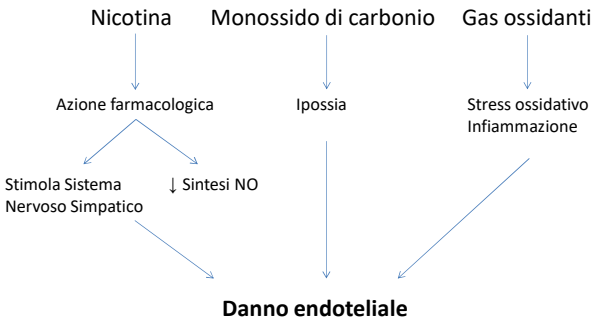
Diabete mellito



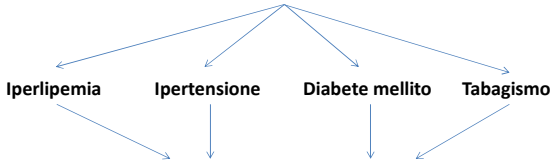
Ruolo del fumo di sigaretta

Evidenze





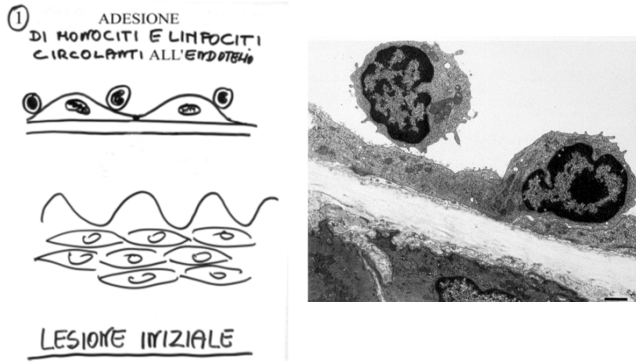
Response to injury hypothesis



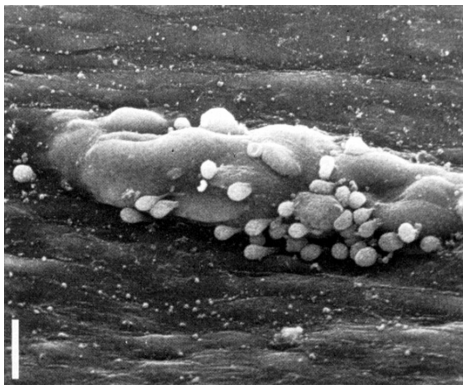
L'endotelio risponde al danno innescando il processo patologico che porta nel tempo alla formazione della lesione aterosclerotica

Istogenesi della placca

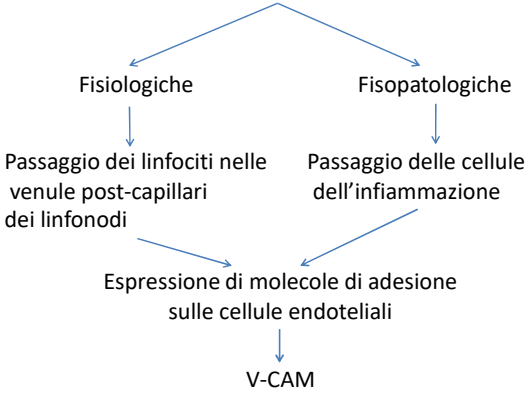
Il primo evento morfologicamente dimostrabile



Adesione dei monociti al microscopio a scansione



Il meccanismo dell'adesione è lo stesso che interviene in condizioni



All'adesione fa seguito la diapedesi dei monociti

Attivazione dei monociti

Monociti

Proliferano

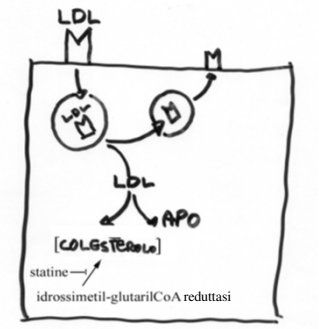
Differenziano in macrofagi

Ruolo di citochine e growth factors (*Macrophage e Granulocyte/Macrophage-Colony Stimulating Factors*) di produzione endoteliale

I macrofagi attivati espletano le loro fisiologiche funzioni

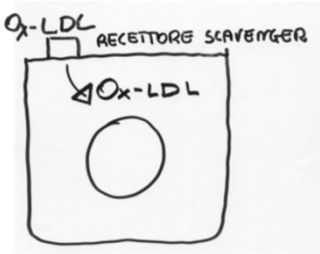
- Fagocitosi
  - Minimally modified-LDL
  - Oxidized LDL
- Secrezione di citochine e growth factors
  - monociti macrofagi
  - endotelio

Epatocita - Endocitosi mediata da recettore delle LDL



- È un meccanismo saturabile, regolato dalla $[colesterolo]_i$.
- Le statine inibiscono la idrossimetil-glutarilCoA reduttasi

Macrofagi – Fagocitosi mediata da recettore *scavenger*



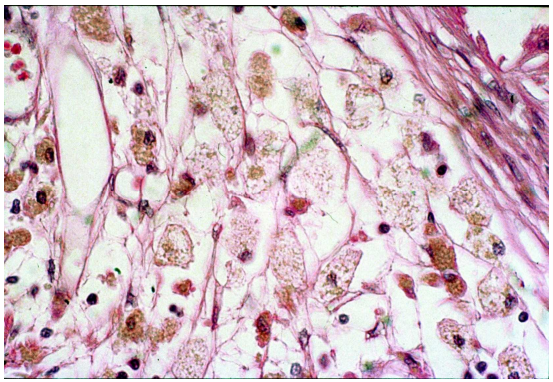
- Non saturabile
- Non regolata dalla concentrazione intracellulare di colesterolo

Nota: il ruolo delle LDL ossidate (ma non quello delle LDL) è stato ridimensionato. Oggi si da più importanza alle modificazioni dell'endotelio che favoriscono l'adesione e la extravasazione dei leucociti, e all'endocitosi di aggregazioni di LDL associate ai proteoglicani (vedi dopo e Libby, 2021)

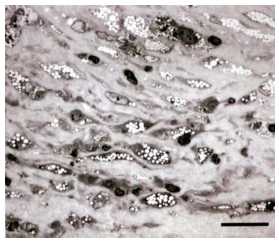
Expression of class A scavenger receptor is enhanced by high glucose in vitro and under diabetic conditions in vivo: one mechanism for an increased rate of atherosclerosis in diabetes.

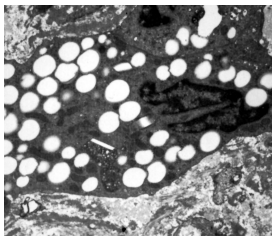
Fukuhara-Takaki K1, Sakai M, Sakamoto Y, Takeya M, Horiuchi S., J Biol Chem. 2005 Feb 4;280(5):3355-64.

I macrofagi si riempiono di lipidi e diventano cellule schiumose



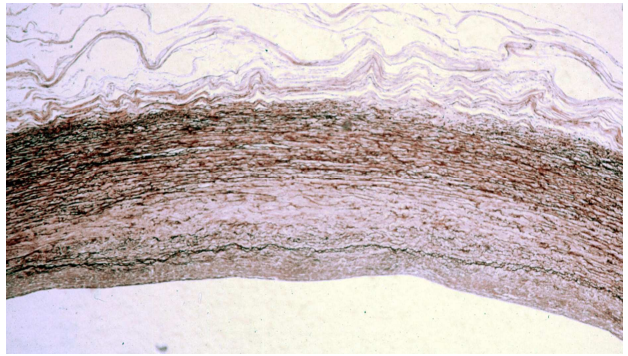
Cellule schiumose

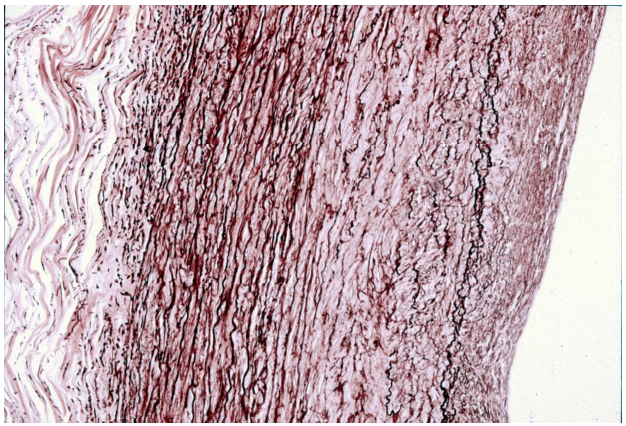


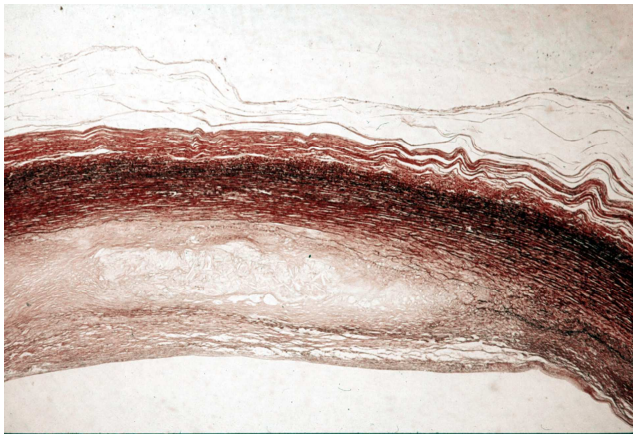


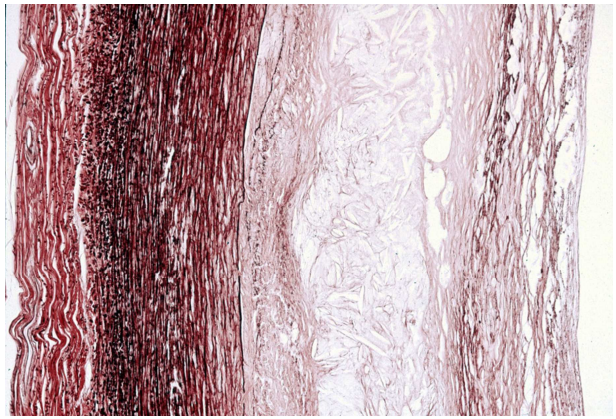
l'accumulo di cellule schiumose forma l'ateroma

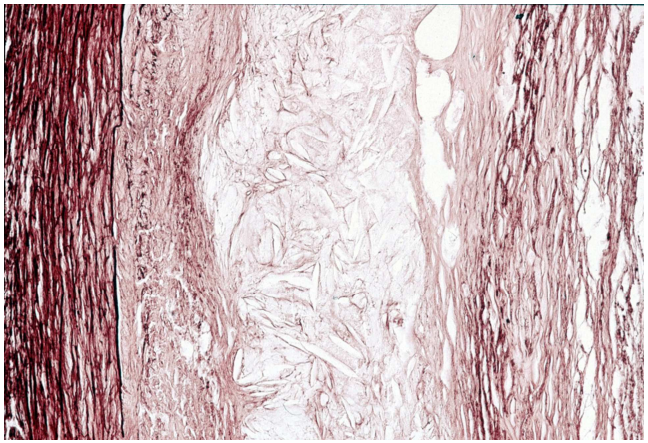
Ateroma dell'aorta





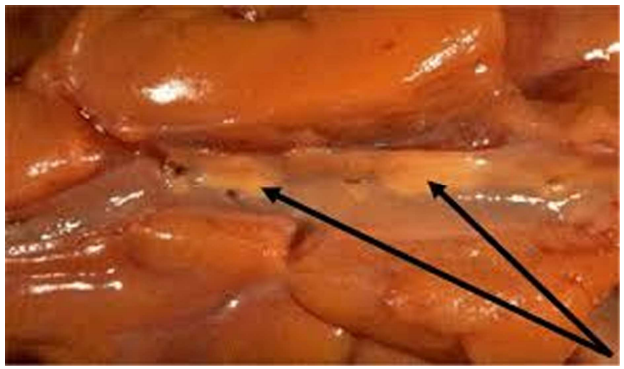




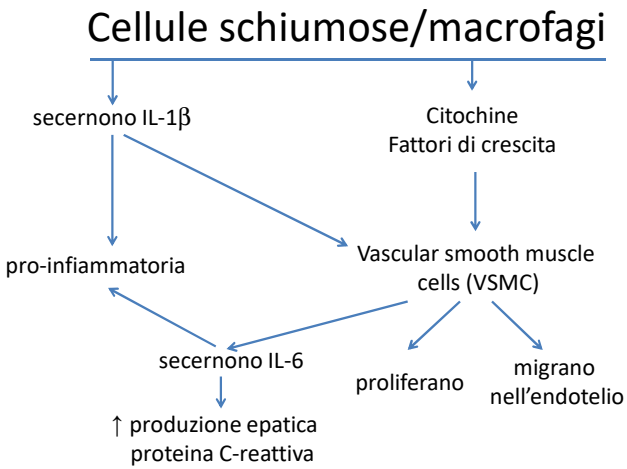


Ateroma

L'ateroma si evidenzia macroscopicamente come *strie lipidiche/Fatty streak* gialle non rilevate



Progressione della placca



RESEARCH

ATHEROSCLEROSIS Orecchioni *et al.*, *Science* **375**, 214–221 (2022) 14 January 2022

Olfactory receptor 2 in vascular macrophages drives atherosclerosis by NLRP3-dependent IL-1 production

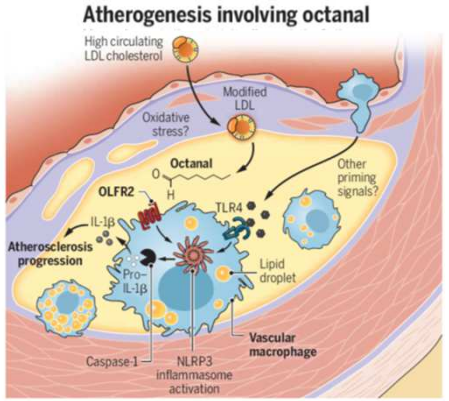
Marco Orecchioni[1], Kouji Kobiyama[1,2], Holger Winkels[1,3], Yanal Ghosheh[1], Sara McArdle[4], Zbigniew Mikulski[4], William B. Kiosses[4], Zhichao Fan[1,5], Lai Wen[1], Yunmin Jung[1], Payel Roy[1], Amal J. Ali[1], Yukiko Miyamoto[6], Matthew Mangan[7], Jeffrey Makings[1], Zhihao Wang[1], Angela Denn[4], Jenifer Vallejo[1], Michaela Owens[1], Christopher P. Durant[1], Simon Braumann[3], Navid Mader[8], Lin Li[9], Hiroaki Matsunami[10], Lars Eckmann[6], Eicke Latz[7], Zeneng Wang[9], Stanley L. Hazen[9,11], Klaus Ley[1,12]*

IMMUNOLOGY

The scent of atherosclerosis

Vascular macrophages sense an odorant to induce atherosclerotic plaque formation

By Katey J. Rayner[1,2] and Adil Rasheed[1,2]



Macrophages in the arterial wall are a hub of atherogenesis. Toll-like receptor 4 (TLR4) activation primes the NLRP3 (NACHT, LRR- and PYD domains-containing protein 3) inflammasome, which is fully activated by olfactory receptor 2 (OLFR2). Octanal, the OLFR2 ligand, is produced from oxidized low-density lipoprotein (oxLDL) cholesterol. This two-hit NLRP3 activation leads to interleukin-1β (IL-1β) production and exacerbation of atherosclerosis.

Atherosclerosis

Nerve remodelling at a distance

32 | Nature | Vol 605 | 5 May 2022

Courtney Clyburn & Susan J. Birren

Fatty structures called plaques can form in arteries, and are separated from nerves by the artery walls. But this is no barrier to communication – it seems that nerves interact with plaques and immune cells to drive cardiovascular disease. See p.152

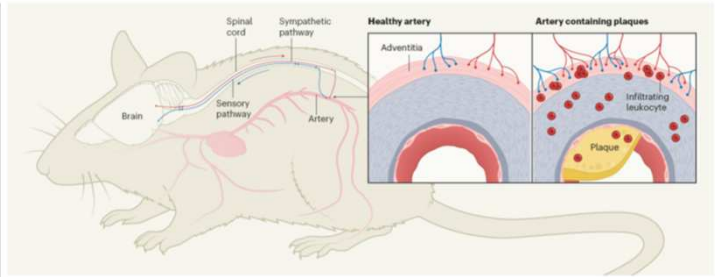


Figure 1 | Neuroimmune–cardiovascular interactions drive plaque formation. In healthy arteries, sensory (blue) and sympathetic (red) nerves are found in the adventitia (the artery outer layer). In arteries containing fatty build-ups called plaques, immune cells known as leukocytes infiltrate the inner plaque and through the arterial wall to the adventitia. Mohanta *et al.*[3] find an increased density of both sensory and sympathetic nerve fibres in these plaque-laden regions. The authors suggest that plaque-induced activation of sensory neurons in the adventitia leads to activation of sympathetic nerves in the brain. This, in turn, drives heightened activity and increased density of sympathetic projections to the artery, promoting further growth of plaques.

VSMC

↓

Differenziano in un fenotipo sintetico

↙ ↘

Fagocitano come i macrofagi

Sintetizzano come fibroblasti

↙ ↘

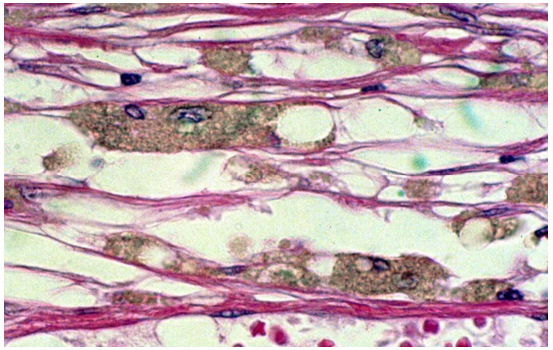
Collageno

Matrice

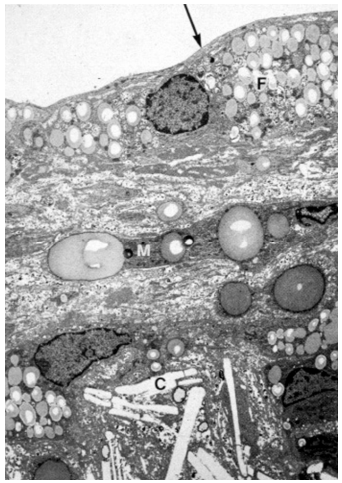
↓

Placca fibro-adiposa

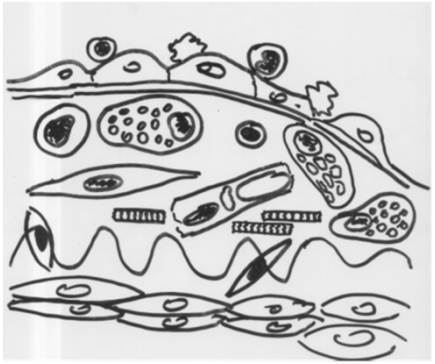
Miofibroblasti



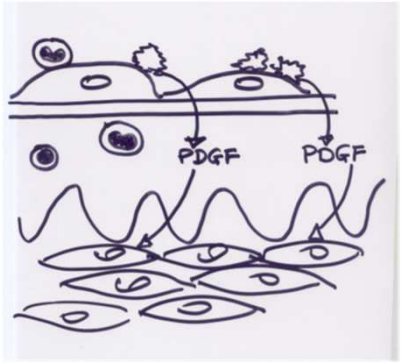
Cellule schiumose e miofibroblasti



Placca fibro-adiposa

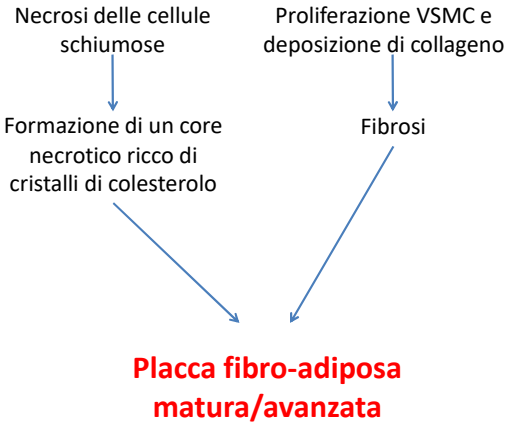


Ruolo delle piastrine nel reclutamento delle VSMC

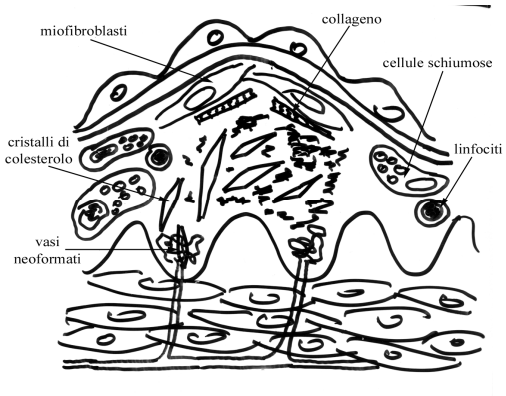


Altri GF? VEGF, FGF, TGFβ

Progressione a placca fibroadiposa matura/avanzata

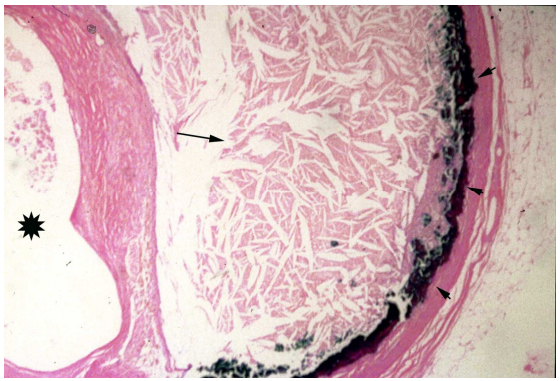


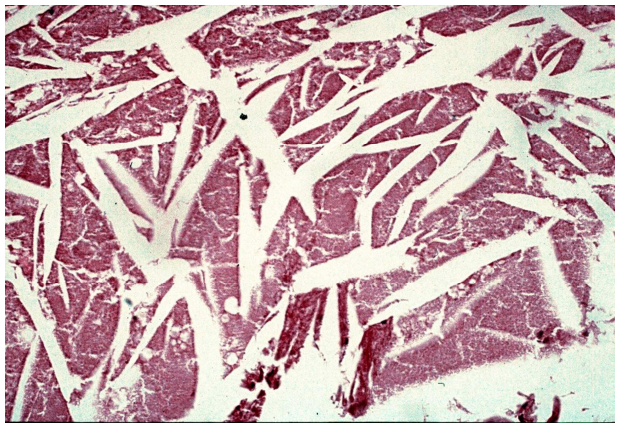
Placca fibroadiposa matura/avanzata



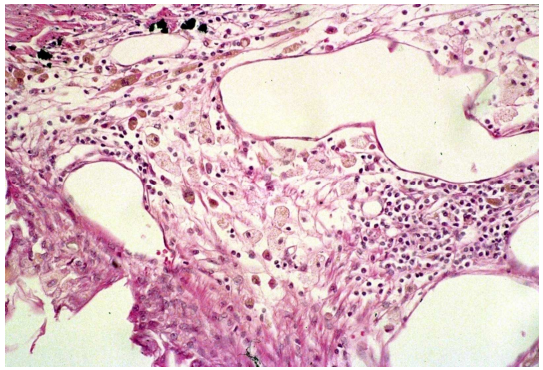
Anatomia della placca

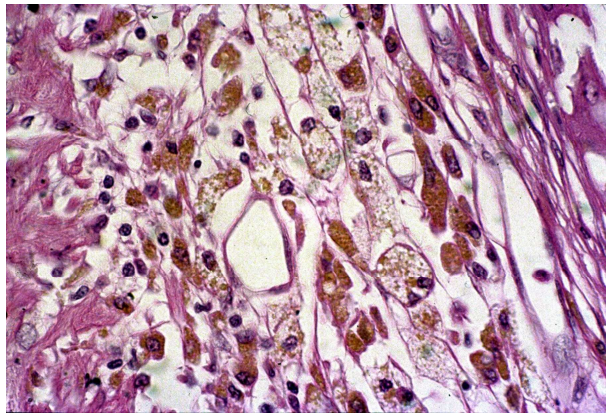
Il core necrotico-lipidico



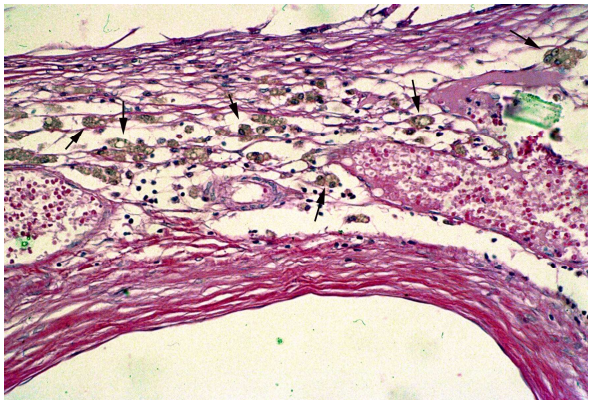


Le spalle





Il cappuccio fibroso

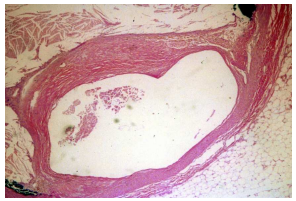


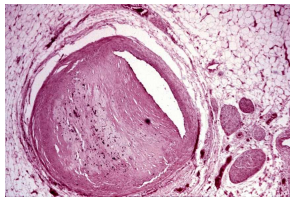
Cappuccio fibroso e stabilità della placca

Placche stabili e instabili

La stabilità indica la tendenza all'ulcerazione

Lo spessore del cappuccio fibroso condiziona la stabilità della placca

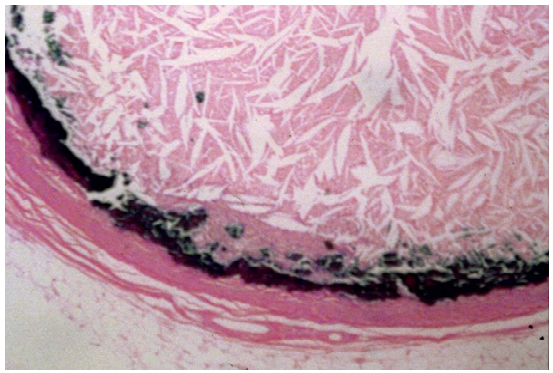


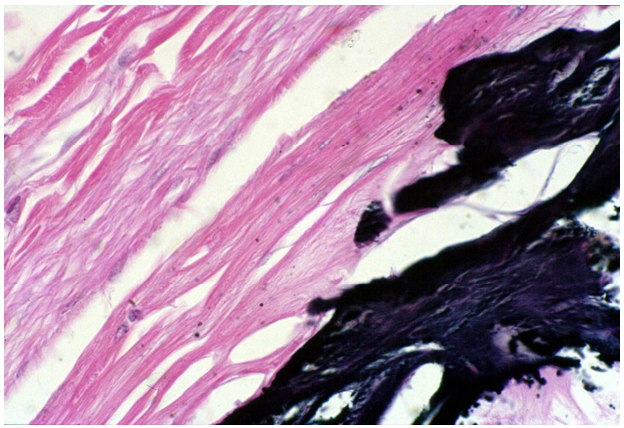


La localizzazione correla con la stabilità (tendenza all'ulcerazione) della placca

- Instabile
  - Alle biforcazioni
- Stabile
  - Mai alle biforcazioni

Calcificazione





Review 524 | Nature | Vol 592 | 22 April 2021

The changing landscape of atherosclerosis

Peter Libby

Emerging evidence has spurred a considerable evolution of concepts relating to atherosclerosis, and has called into question many previous notions. Here I review this evidence, and discuss its implications for understanding of atherosclerosis. The risk of developing atherosclerosis is no longer concentrated in Western countries, and it is instead involved in the majority of deaths worldwide. Atherosclerosis now affects younger people, and more women and individuals from a diverse range of ethnic backgrounds, than was formerly the case. The risk factor profile has shifted as levels of low-density lipoprotein (LDL) cholesterol, blood pressure and smoking have decreased. Recent research has challenged the protective effects of high-density lipoprotein, and now focuses on triglyceride-rich lipoproteins in addition to low-density lipoprotein as causal in atherosclerosis. Non-traditional drivers of atherosclerosis—such as disturbed sleep, physical inactivity, the microbiome, air pollution and environmental stress—have also gained attention. Inflammatory pathways and leukocytes link traditional and emerging risk factors alike to the altered behaviour of arterial wall cells. Probing the pathogenesis of atherosclerosis has highlighted the role of the bone marrow: somatic mutations in stem cells can cause clonal haematopoiesis, which represents a previously unrecognized but common and potent age-related contributor to the risk of developing cardiovascular disease. Characterizations of the mechanisms that underpin thrombotic complications of atherosclerosis have evolved beyond the 'vulnerable plaque' concept. These advances in our understanding of the biology of atherosclerosis have opened avenues to therapeutic interventions that promise to improve the prevention and treatment of now-ubiquitous atherosclerotic diseases.

Large-scale cohort investigations, such as the Framingham study, revealed risk factors for atherosclerosis that we now regard as 'traditional'[25]. However, long-term trends have modified risk factors such that these traditional factors no longer capture the contemporary reality of atherosclerosis. Genetic risk scores have undergone continuing refinement and incorporate increasingly expanded numbers of inherited variants that influence atherosclerotic events. As these genetic panels can predict risk from birth, they may inform the early targeted allocation of preventive measures in younger individuals who have an augmented genetic predilection to develop atherosclerotic disease[26]. Indeed, lifestyle measures appear to mitigate risk of cardiovascular events across the spectrum of estimated genetic risk. Yet, the ability of even the latest generation of genetic risk scores to improve prediction of atherosclerotic events over more traditional algorithms remains controversial[27,28].

Recent research has challenged and expanded on the traditional risk factors. With global trends towards a decrease in LDL and the introduction of highly effective therapies for lowering LDL, as well as inexpensive and efficacious antihypertensive therapies, these drivers of chronic risk contribute less today than in previous years. Most markedly and despite decades of belief that HDL protected from atherosclerosis, recent human genetic studies—and the failure of several independent pharmacological measures to raise HDL to reduce atherosclerotic events—have called into question the protective effect of HDL[29]. Mendelian randomization studies that have corrected for pleiotropy have, however, provided some support for the protective effect of HDL[30]. Moreover, functional attributes of HDL fractions that are not captured by steady-state measurements of total HDL cholesterol concentrations (such as the capacity to mediate cholesterol efflux or anti-inflammatory actions) may yet exert anti-atherosclerotic effects[31,32].

The risk of plasma triglyceride concentration (a biomarker of a class of lipoproteins that include the TGRL) was passed over for many years, as the belief in the protective effect of HDL rendered it logical to adjust triglycerides for HDL—a precaution that attenuated the risk attributed to TGRL[33]. Triglycerides and HDL tend to vary inversely, and a recent ranking[34,35] of the relevant risk factors demotes HDL as a protective factor and points to TGRL as a potent predictor of cardiovascular risk. Moreover, in contrast to the situation with HDL, contemporary and concordant human genetic studies strongly support a causal role for TGRL in atherosclerosis and its complications[36]. A variety of inherited sequence variations that affect lipoprotein lipase, or factors that modulate the activity of this enzyme, alter the rate of atherosclerotic events, and these findings furnish strong human genetic evidence for the causal role of TGRL in their pathogenesis. Apolipoprotein CIII, ANGPTL3 and

ANGPTL4 inhibit the ability of lipoprotein lipase to hydrolyse triglycerides in TGRL, and thus cause accumulation of these particles. By contrast, apolipoprotein V augments the activity of lipoprotein lipase and enhances TGRL clearance[37,38]. The activity of lipoprotein lipase thus regulates plasma triglyceride concentrations. Gain- or loss-of-function variants in this pathway that raise TGRL track with increased numbers of atherosclerotic events, and those that lower TGRL correlate with improved outcomes. The triglyceride component of TGRL does not appear to account for their atherogenicity[10]. TGRL, as with LDL, bear apolipoprotein B; they also contain cholesterol, and can deliver it effectively to macrophages in the atheroma. TGRL provoke inflammation, in part owing to their apolipoprotein CIII content. TGRL concentrations correlate better with inflammatory status than does LDL itself[39,40]. This refocusing on TGRL as a causal risk factor, and lack of actionability of altering HDL thus far, has notable therapeutic implications.

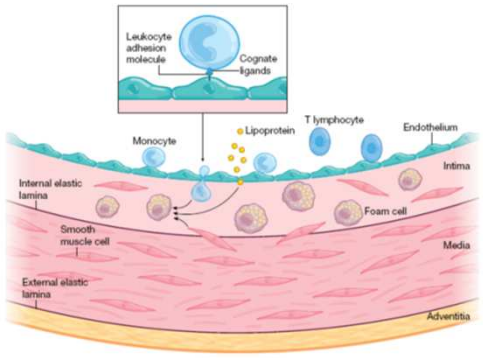


Fig. 1 | Initiation of atherosclerosis. The normal artery comprises three layers: the innermost intima (in close contact with the bloodstream), the tunica media, and the outer coat and adventitia. Under homeostatic conditions, the endothelial monolayer that lines the intima does not gather blood leukocytes. When activated by proinflammatory cytokines or other irritative stimuli related to cardiovascular risk factors, endothelial cells can express a leukocyte adhesion molecule (such as VCAM-1) that interacts with its cognate ligands (VLA4) to promote the rolling, and eventually adherence, of blood monocytes and lymphocytes to the endothelial layer. Chemoattractant cytokines can direct the migration of these bound leukocytes into the intima. Within the intima, foam cells form by uptake of lipids. Some of these lipid-laden foam cells arise from blood monocytes that have matured into macrophages. Recent evidence[165] in mice indicates that smooth muscle cells can undergo metaplasia, and give rise to foam cells that bear markers in common with those of macrophages. T lymphocytes—although fewer in number than the foam cells—produce mediators that orchestrate many functions of these innate immune cells. In humans (but not in many of the small animals that are often used experimentally), the intima contains resident smooth muscle cells. Other smooth muscle cells (that are usually located in the media) can penetrate into the intima, where they join resident smooth muscle cells to promote the accumulation of extracellular matrix that these cells synthesize within the expanding intima.

Ruolo della flogosi e
della risposta immune
nella patogenesi della placca

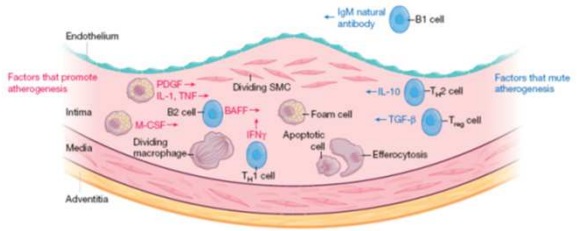


Fig. 2 | The progression of atherosclerosis reflects and interplay between factors that promote or mitigate atherogenesis. This diagram summarizes results from experimental studies in mice, and observations on human atherosclerotic plaques. Pathways thought to promote lesion formation (factors in red) are shown on the left, and mechanisms that may moderate atherogenesis (factors in blue) are on the right. Smooth muscle cells and macrophages can proliferate as the intimal lesion grows. PDGF promotes the migration and replication of smooth muscle cells, and then production of extracellular matrix. All cells in the atheromatous plaque can secrete cytokines, examples of which include IL-1, TNF and M-CSF (also known as CSF1). Activated T-helper 1 (T_H1) lymphocytes produce IFNγ, which can stimulate mononuclear phagocytes and aggravate atherosclerosis. Other types of cell produce countervailing mediators. B1 lymphocytes can secrete IgM natural antibody; T-helper 2 (T_H2) lymphocytes produce the anti-inflammatory cytokine IL-10; and regulatory T (T_{reg}) cells can secrete TGFβ. These mediators can antagonize cellular proliferation, promote extracellular matrix synthesis and quell inflammation. Mononuclear phagocytes can engulf dying or dead cells that arise through apoptosis, through a process known as efferocytosis. Inefficient efferocytosis favours the accumulation of debris from dead or dying cells, and promotes formation of the central lipid core of the atherosclerotic plaque. B2 lymphocytes secrete mediators (such as BAFF, a member of the TNF family) that can aggravate atherogenesis. This diagram shows only a subset of the mediators that have been implicated in promoting or antagonizing aspects of atherogenesis. Current research suggests an ongoing struggle between proliferation and death, involving proinflammatory, anti-inflammatory and proresolving mediators—generally through a prolonged course of many years in the evolution of the human atherosclerotic plaque.

Conclusione

La flogosi e la risposta immunitaria cellulo-mediata influenzano la progressione della malattia, che non è necessariamente irreversibile

Table 1 | Changing views on atherosclerosis

Past	Present
Atherosclerosis predominantly affects developed countries	Developing countries now bear the greatest burden of atherosclerosis
Coronary thrombosis affects primarily middle-aged white men	Women, younger individuals, individuals from a range of ethnic backgrounds and the very old suffer increasingly from acute coronary syndromes
Atherosclerosis is a lipid storage disease	Inflammation links dyslipidaemia and other risk factors to atherogenesis
Oxidized LDL drives atherosclerosis	Native or aggregated LDL drives atherogenesis
HDL cholesterol protects against atherosclerosis	TGRL participate causally in atherosclerosis
Thin-capped fibroatheromata are vulnerable plaques	The 'vulnerable plaque' is a misnomer; superficial erosion is an increasing cause of arterial thrombosis
Atherosclerosis is an inevitable, steady and degenerative accompaniment to ageing	Atherosclerosis evolves episodically, can regress, and lifestyle and medical measures can modulate the process

Triglyceride-Rich Lipoprotein

Conseguenze funzionali della placca aterosclerotica

↓

↓ della dimensione del lume

↓

↓ del flusso

↓

Ischemia

Ischemia

Ridotto apporto di sangue arterioso

Ipossia + ridotto apporto di nutrienti + ridotta rimozione di cataboliti

Il grado dell'ischemia non correla linearmente con la riduzione del lume

Per essere emodinamicamente significativa la riduzione del lume deve essere >70 %

Complicazioni della placca aterosclerotica

↓

Eventi acuti che insorgono su una situazione cronica

↓

↓ del flusso arterioso sotto la soglia dell'ischemia

Trombosi

- Placca ulcerata
- Placca non ulcerata

L'incidenza delle trombosi correla positivamente con i livelli ematici di LPa (LDL)

↓

ApoB100

S

S — GPapo(a)

↓

Interferisce negativamente con la fibrinolisi

↓

Favorisce la formazione dei trombi

Vasospasmo

↓

Piastrine

↓

TXA2

↓

Vasocostrizione

Emorragia sub-intimale

↓

Rottura dei *vasa vasorum*

↓

Ostruzione completa del lume

↓

Morte improvvisa

Cholesterol-crystal embolism

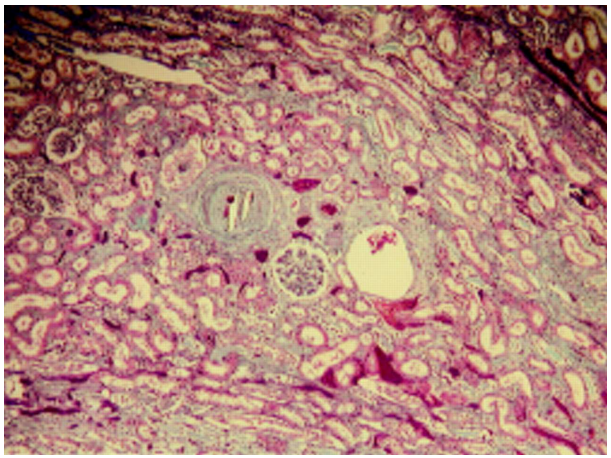
↓

Materiale grassoso è rilasciato dalla placca ulcerata

spontaneamente — manovre terapeutiche

Occlusione a valle

Rene



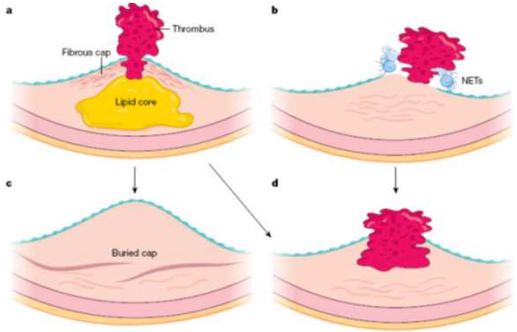


Fig. 3 | Thrombotic complications of atherosclerosis and evolution of the atherosclerotic plaque. a, Plaque rupture. This involves a fracture or fissure of the fibrous cap that overlies the lipid core of the plaque. This physical disruption permits contact of blood coagulation factors with thrombogenic material (principally the potent procoagulant tissue factor) within the plaque. The ensuing thrombosis can obstruct blood flow and lead to cardiac ischaemia. This mechanism accounts for about two-thirds of acute myocardial infarction, but appears to be waning; current preventive therapies lead to a reduction in accumulation of lipid within plaques and to the reinforcement of the fibrous cap. **b**, Superficial erosion. This cause of coronary artery clot formation involves a sloughing or desquamation of the endothelial monolayer. Granulocytes trapped in the plaque or adherent to the intimal basement membrane can form neutrophil extracellular traps (NETs). NETs are strands of nuclear DNA that have unwound, present various neutrophil granular proteins and bear other proteins that they bind from the blood, forming a solid-state reactor on the intimal surface. NETs can propagate inflammation and thrombosis. **c**, **d**, Plaques can heal, which augments the bulk of the plaque and promotes the formation of flow-limiting stenosis in previously disrupted arteries. During thrombosis, platelets release PDGF and TGFβ, which promote the synthesis of extracellular matrix proteins that contribute to fibrosis and plaque growth. **c**, Ruptured plaques that have healed often show morphologic evidence of the rupture underneath a layer of more recently deposited extracellular matrix (a 'buried' fibrous cap). **d**, Plaques can also grow through incorporation of a thrombus. Lesions can also calcify (not shown), in part owing to cell-derived microvesicles that can nucleate this process. Regions of spotty calcification imaged by computed tomography correlate with an increased risk of a thrombotic event. In contrast to smaller deposits of calcium, macroscopic plates of calcium may stabilize plaques from mechanical disruption (rather than create inhomogeneity in stresses that promotes thrombotic complications due to plaque disruption).

Complicanza di lungo periodo

↓

Aneurisma arterioso

↓

Aorta toracica — Aorta addominale

Appendice
(opzionale)

Targeting inflammation in atherosclerosis — from experimental insights to the clinic

Oliver Soehnlein[1,2,3] *and Peter Libby*[4]

Abstract | Atherosclerosis, a dominant and growing cause of death and disability worldwide, involves inflammation from its inception to the emergence of complications. Targeting inflammatory pathways could therefore provide a promising new avenue to prevent and treat atherosclerosis. Indeed, clinical studies have now demonstrated unequivocally that modulation of inflammation can forestall the clinical complications of atherosclerosis. This progress pinpoints the need for preclinical investigations to refine strategies for combatting inflammation in the human disease. In this Review, we consider a gamut of attractive possibilities for modifying inflammation in atherosclerosis, including targeting pivotal inflammatory pathways such as the inflammasomes, inhibiting cytokines, manipulating adaptive immunity and promoting pro-resolution mechanisms. Along with lifestyle measures, pharmacological interventions to mute inflammation could complement traditional targets, such as lipids and hypertension, to make new inroads into the management of atherosclerotic risk.

NATURE REVIEWS | DRUG DISCOVERY VOLUME 20 | AUGUST 2021 | 589

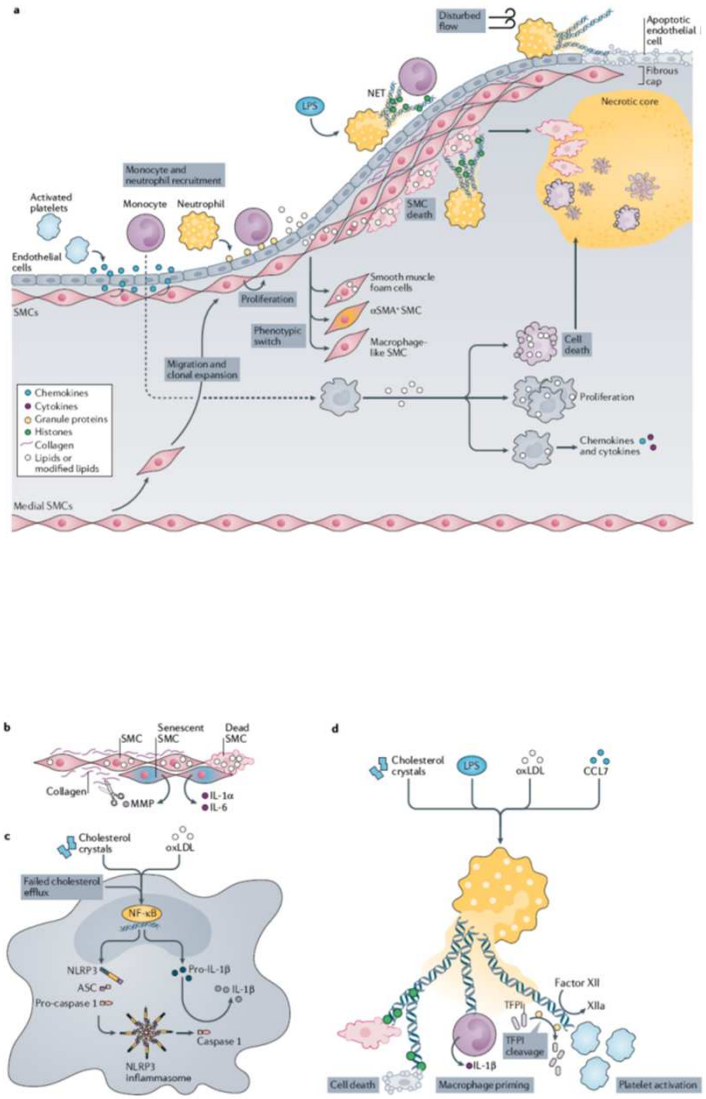


Fig. 1 | **Integration of inflammatory processes during atherosclerosis development.** **a** | Overview of inflammatory processes. At the early stages of atherosclerosis, activated platelets secrete chemokines (such as C-C motif chemokine 5 (CCL5)) that promote adhesion of monocytes and neutrophils. Neutrophils themselves secrete chemotactic granule proteins (including cathelicidin, cathepsin G and CCL2), thus paving the way for arterial monocyte infiltration. The chemokine milieu is supplemented by chemokines secreted by activated smooth muscle cells (SMCs), such as CCL2 and CCL5. In progressing atherosclerotic lesions, medial SMCs migrate towards the developing fibrous cap where they undergo clonal expansion. SMC lipid loading triggers phenotype switching towards SMCs that express α-smooth muscle actin (αSMA$^+$ SMCs), macrophage-like SMCs and smooth muscle foam cells. Heightened lipid loading of SMCs induces SMC apoptosis and — if not cleared quickly — necrosis. SMCs also undergo cell death after interaction with histone H4 presented in neutrophil extracellular traps (NETs). NET-associated cytotoxicity is observed during plaque erosion when NETs released at sites of disturbed flow induce endothelial cell desquamation. In systemic infections with Gram-negative organisms, which produce lipopolysaccharide (LPS), NET-associated histones promote the adhesion of monocytes, hence contributing to accelerated plaque growth under these conditions. Monocyte-derived macrophages ingest modified lipids and, in response, secrete inflammatory chemokines and cytokines. Excessive lipid uptake triggers macrophage proliferation or even cell death. **b–d** | Core inflammatory processes fuelled by SMCs (part **b**), macrophages (part **c**) and neutrophils (part **d**). **b** | Cholesterol uptake induces cell death in SMCs. SMC death, in turn, reduces the amount of extracellular matrix that is produced, which further fuels SMC death. Senescent SMCs release pro-inflammatory cytokines and matrix-degrading enzymes, including matrix metalloproteinases (MMPs). **c** | Priming and activation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome. Priming by cholesterol crystals, modified lipids such as oxidized low-density lipoproteins (oxLDL) or impaired cholesterol efflux triggers the nuclear factor-κB (NF-κB) signalling pathway, promoting the transcription of NLRP3 and pro-IL-1β. Assembly of the NLRP3 inflammasome induces activation of caspase 1, which cleaves pro-IL-1β into mature IL-1β. **d** | Release of NETs is licensed by cholesterol crystals, LPS, modified lipids and chemokines such as CCL7. NETs exert cytotoxicity by means of NET-resident histones, prime the NLRP3 inflammasome in macrophages and induce coagulation by cleavage of factor XII and tissue factor pathway inhibitor (TFPI), and by direct platelet activation.

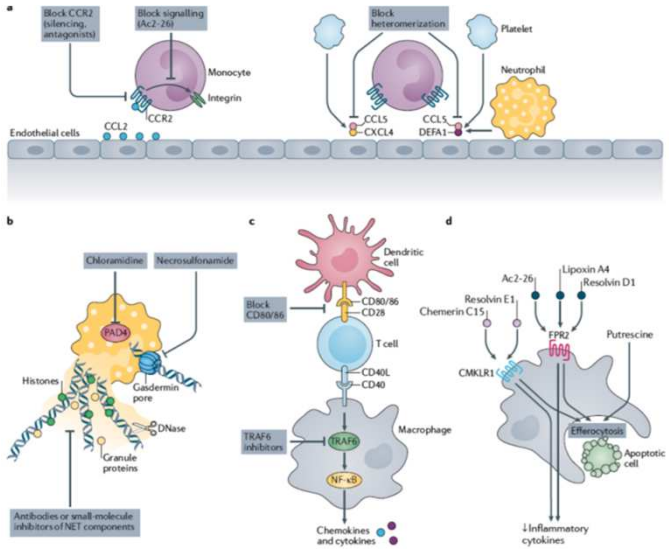


Fig. 2 | **Preclinical strategies to limit cardiovascular inflammation and stimulate its resolution. a** | Reducing monocyte recruitment. Silencing of C-C chemokine receptor 2 (CCR2) or timed inhibition of CCR2 signalling reduces monocyte adhesion. Overriding chemokine receptor signalling, for example with the small molecule Ac2-26, reduces integrin activation and monocyte arrest. Heterodimers of C-C motif chemokine 5 (CCL5) and C-X-C motif chemokine 4 (CXCL4) as well as of CCL5 and neutrophil defensin 1 (DEFA1) promote monocyte adhesion. Small peptides that disrupt these interactions reduce monocyte adhesion during cardiovascular inflammation. **b** | Inhibiting neutrophil extracellular traps (NETs). Inhibition of protein-arginine deiminase type 4 (PAD4) halts NET release. DNase I cleaves DNA strands in NETs. Neutralization of gasdermin D prevents NET discharge. Neutralization of NET-resident proteins by antibodies or small-molecule inhibitors reduces NET-driven inflammation. **c** | Examples of strategies to inhibit immune checkpoints. Neutralization of CD80/86 can reduce T cell and dendritic cell responses. The CD40–CD40 ligand (CD40L) interaction activates macrophages via intracellular TNF receptor-associated factor 6 (TRAF6) signalling, a cascade that can be inhibited with small molecules. **d** | Increasing inflammation resolution. Putrescine improves the ability of macrophages to engulf dead cells. Resolving *N*-formyl peptide receptor 2 (FPR2) agonists (Ac2-26, lipoxin A4, resolvin D1) and chemokine-like receptor 1 (CMKLR1) agonists (chemerin C15, resolvin E1) lower the production of inflammatory cytokines and improve the efferocytosis capacity. NF-κB, nuclear factor-κB.

Table 1 | **Overview of selected clinical studies targeting inflammatory pathways in cardiovascular disease**

Trial	Study population	Study design	Outcome	Ref.
ASSAIL-MI	First-time STEMI presenting within 6 h of the onset of chest pain	Single dose of tocilizumab (IL-6 antibody) vs placebo	Improved myocardial salvage in patients assigned to tocilizumab	NCT03004703
CANTOS	Stable CAD, persistent elevation of hsCRP (>2 mg/l)	Canakinumab (IL-1β antibody) subcutaneously vs placebo	Canakinumab lowered plasma CRP, IL-1 and IL-6 Reduction in cardiovascular events, cancer and gout attacks Small increase in fatal infections	NCT01327846 (REF.[7])
CIRT	Stable CAD and persistent evidence of inflammation, type 2 diabetes or metabolic syndrome	Low-dose (15–20 mg) methotrexate (a purine metabolism inhibitor) once per week vs placebo	Halted prematurely for futility No change in plasma IL-1β, IL-6 and hsCRP No reduction in cardiovascular events	NCT02576067 (REF.[93])
COLCOT	Recent myocardial infarction (<30 days)	Low-dose (0.5 mg/day) colchicine (a tubulin disrupter) vs placebo	Reduction in cardiovascular death and cardiovascular events Increase in pneumonia	NCT02551094 (REF.[7])
CLEAR-Synergy	STEMI with primary PCI	SYNERGY bioabsorbable polymer drug eluting stent plus colchicine and spironolactone or placebo	Ongoing, estimated completion in early 2025	NCT03048825
CONVINCE	Adults >40 years of age with an ischaemic stroke or TIA not caused by cardiac embolism	Low-dose (0.5 mg/day) colchicine plus usual care or standard care alone	Ongoing, estimated completion in autumn 2021	NCT02898610
LATITUDE-TIMI 60	Patients hospitalized with acute myocardial infarction	Losmapimod (a selective inhibitor of p38α/β mitogen-activated protein kinases) twice per day vs placebo	No reduction in major ischaemic cardiovascular events	NCT02145468 (REF.[93])
LoDoCo	Stable CAD	Low-dose (0.5 mg/day) colchicine plus usual care or standard care alone	Significant reduction in ACS	[94]
LoDoCo2	Chronic coronary disease	Low-dose (0.5 mg/day) colchicine plus usual care or standard care plus placebo	Reduction in cardiovascular events	ACTRN12614000093684 (REF.[7])
LILACS	Stable ischaemic heart disease and ACS	Low-dose IL-2 ($0.3–3 \times 10^6$ I.U./day)	Phase I/II ongoing	NCT03113773
FUTURE 1	Psoriatic arthritis (prospective randomized)	Secukinumab (IL-17A antibody) vs placebo	Improved arthritis score Increase in infections Non-significant increase in MACE	NCT01392326 (REF.[108])
Tocilizumab in NSTEMI	NSTEMI	Single dose of tocilizumab (IL-6 receptor antibody) vs placebo	Reduction in hsCRP and troponin T release	NCT01491074 (REF.[109])

ACS, acute coronary syndromes; CAD, coronary artery disease; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CIRT, Cardiovascular Inflammation Reduction Trial; COLCOT, Colchicine Cardiovascular Outcomes Trial; CRP, C-reactive protein; hsCRP, CRP measured with a highly sensitive assay; MACE, major adverse cardiac event; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

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Thematic Review Series: Living History of Lipids

ApoE knockout and knockin mice: the history of their contribution to the understanding of atherogenesis

Godfrey S. Getz[1,*] and Catherine A. Reardon[†]

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Abstract ApoE is a multifunctional protein that is expressed by many cell types that influences many aspects of cardiovascular physiology. In humans, there are three major allelic variants that differentially influence lipoprotein metabolism and risk for the development of atherosclerosis. *Apoe*-deficient mice and human apoE isoform knockin mice, as well as hypomorphic *Apoe* mice, have significantly contributed to our understanding of the role of apoE in lipoprotein metabolism, monocyte/macrophage biology, and atherosclerosis. This brief history of these mouse models will highlight their contribution to the understanding of the role of apoE in these processes. These $Apoe^{-/-}$ mice have also been extensively utilized as an atherosensitive platform upon which to assess the impact of modulator genes on the development and regression of atherosclerosis.—Getz, G. S., and C. A. Reardon. ApoE knockout and knockin mice: the history of their contribution to the understanding of atherogenesis. *J. Lipid Res.* 2016. 57: 758–766.

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Severe Hypercholesterolemia and Atherosclerosis in Apolipoprotein E–Deficient Mice Created by Homologous Recombination in ES Cells

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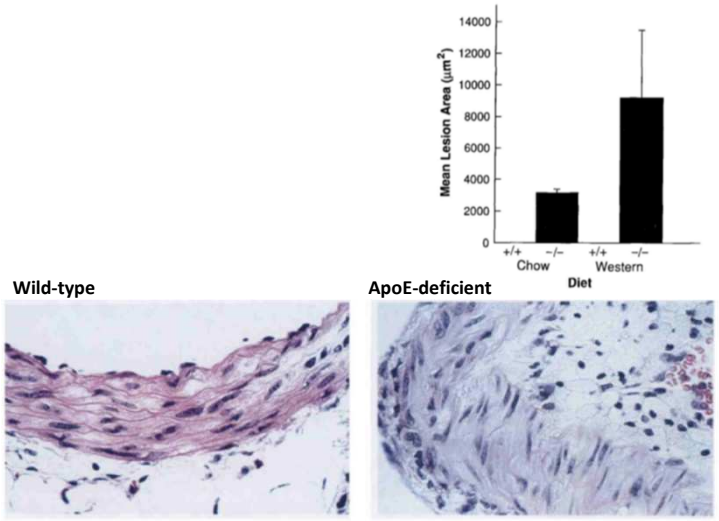
apoE-deficient mice have been created by homologous recombination in ES cells. On a low fat, low cholesterol chow diet these animals have plasma cholesterol levels of 494 mg/dl compared with 60 mg/dl in control animals, and when challenged with a high fat Western-type diet, these animals have plasma cholesterol levels of 1821 mg/dl compared with 132 mg/dl in controls. This marked hypercholesterolemia is primarily due to elevated levels of very low and intermediate density lipoproteins. At 10 weeks of age, apoE-deficient mice have already developed atherosclerotic lesions in the aorta and coronary and pulmonary arteries. apoE-deficient mice are a promising small animal model to help understand the role of apoE in vivo and the genetic and environmental determinants of atherosclerosis.



Modello sperimentale

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Topo KO ApoE

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La malattia si sviluppa in 3-5 mesi

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Infarto miocardico

Razionale

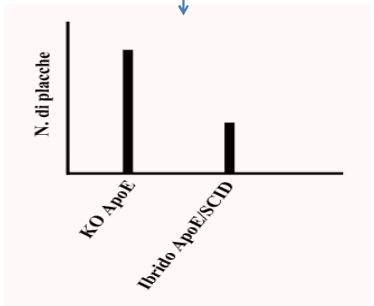
Macrofagi → APC

Linfociti → Cellule effettrici

ox-LDL → Antigene

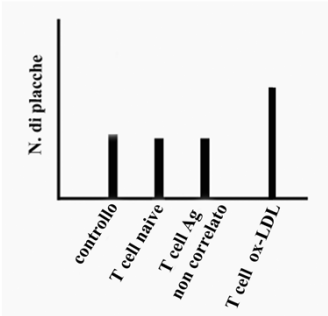
Il topo KO-ApoE è ibridizzato con il topo SCID

Severe Combined Immunodeficiency



Trasferimento passivo dell'immunità

Linfociti CD4+ anti ox-LDL trasferiti nei topi ibridi



Transfer of CD4⁺ T Cells Aggravates Atherosclerosis in Immunodeficient Apolipoprotein E Knockout Mice

Xinghua Zhou, MD, PhD; Antonino Nicoletti, PhD; Rima Elhage, PhD; Göran K. Hansson, MD, PhD

Conclusions—CD4⁺ T cells carry disease-promoting immunity in atherosclerosis. (*Circulation.* 2000;102:2919-2922.)

Adoptive Transfer of CD4⁺ T Cells Reactive to Modified Low-Density Lipoprotein Aggravates Atherosclerosis

Xinghua Zhou, Anna-Karin L. Robertson, Charlotta Hjerpe, Göran K. Hansson

Objective—Atherosclerosis is associated with immune responses to oxidized low-density lipoprotein (oxLDL). The presence of activated macrophages and T cells in lesions suggests that cell-mediated immune reactions are taking place during the disease process. However, the role of specific immune responses has remained unclear. We have previously shown that transfer of CD4⁺ T cells from apolipoprotein E knockout mice (apoE$^{-/-}$) into immunodeficient apoE$^{-/-}$ *scid/scid* mice accelerates disease.

Methods and Results—To test whether this effect is dependent on specific disease-associated antigens, purified CD4⁺ T cells from oxLDL-immunized mice were transferred into apoE$^{-/-}$ *scid/scid* mice. CD4⁺ T cells from mice immunized with a nonrelevant antigen, keyhole limpet hemocyanin (KLH), and naïve CD4⁺ T cells were used as controls. After 12 weeks, all mice that received T cells had larger lesions than untouched apoE$^{-/-}$ *scid/scid* controls. However, mice receiving CD4⁺ T cells from oxLDL immunized mice had substantially accelerated lesion progression compared with those receiving naive or KLH-primed T cells. Circulating levels of interferon-γ were increased in proportion to the acceleration of atherosclerosis.

Conclusion—These data show that adoptive transfer of purified CD4+ T cells from oxLDL-immunized mice accelerates atherosclerosis. They support the notion that Th1 cellular immunity is proatherogenic and identify oxLDL as a culprit autoantigen. (*Arterioscler Thromb Vasc Biol.* 2006;26:864-870.)

Cosa succede se rimuoviamo il controllo inibitorio sulla risposta immunitaria?

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KO ApoE
KO recettore TGFβ

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Placca altamente instabile