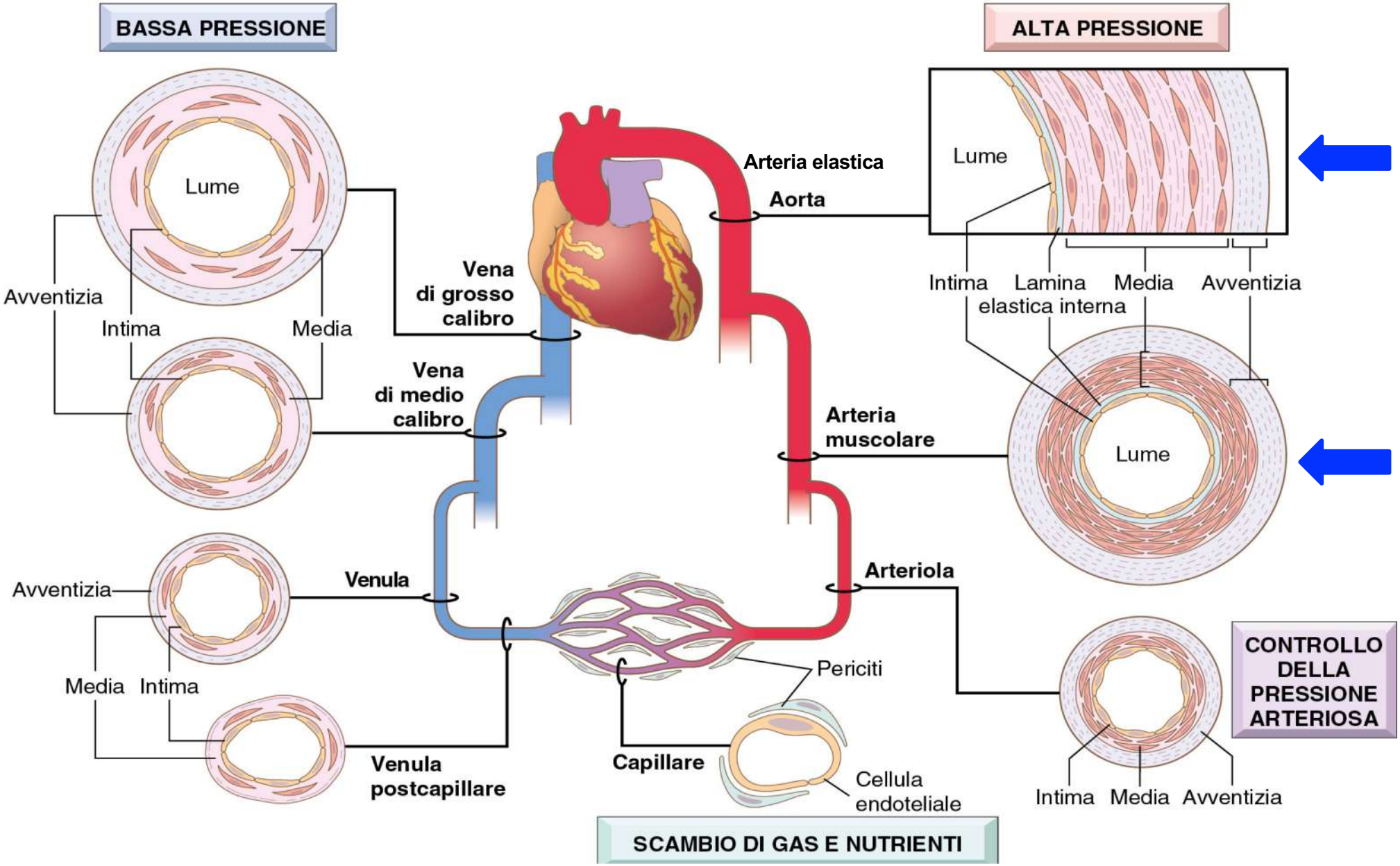
Athere = pappa

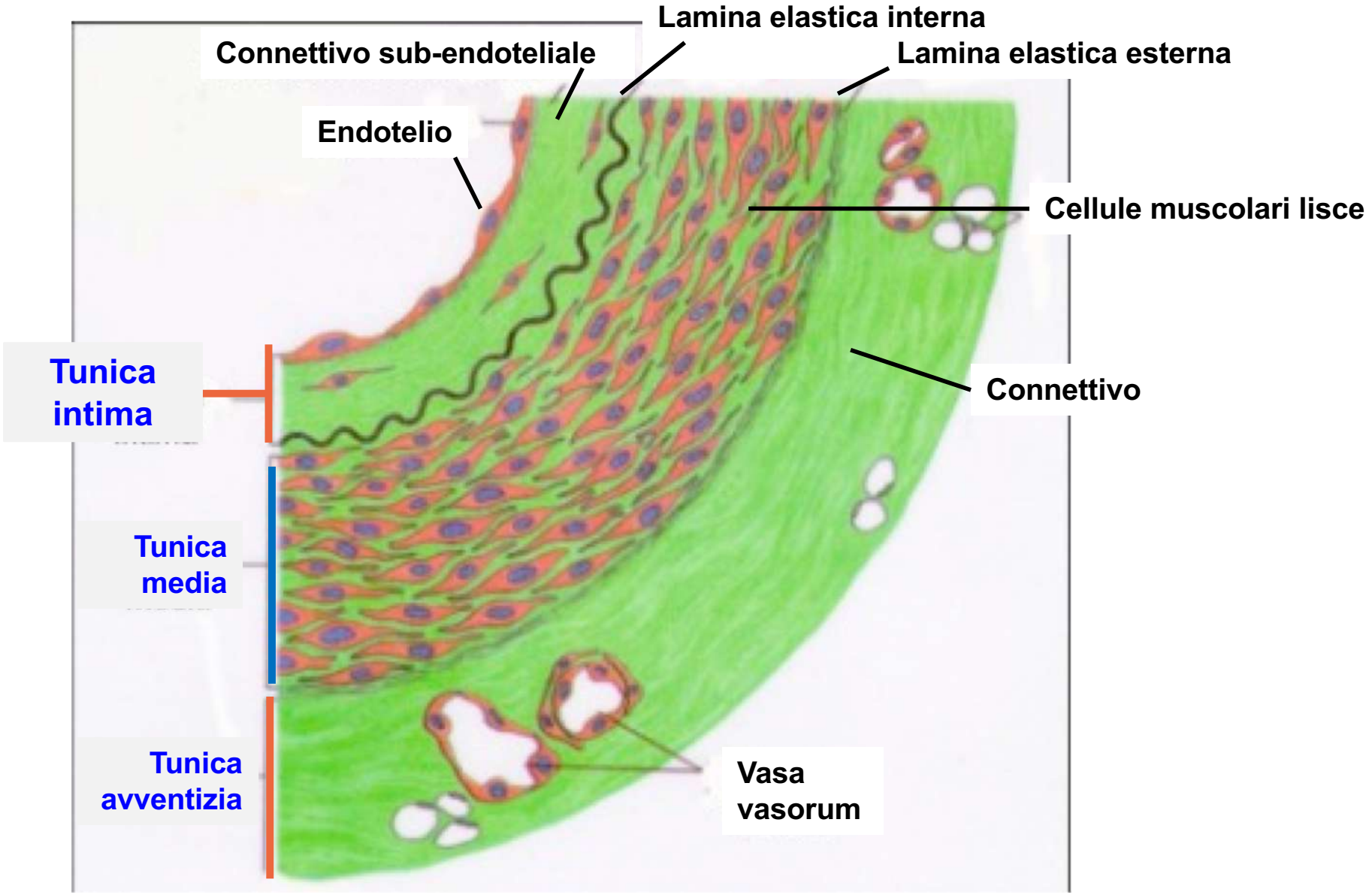
Sclerosis = indurimento

Specializzazione regionale dei vasi

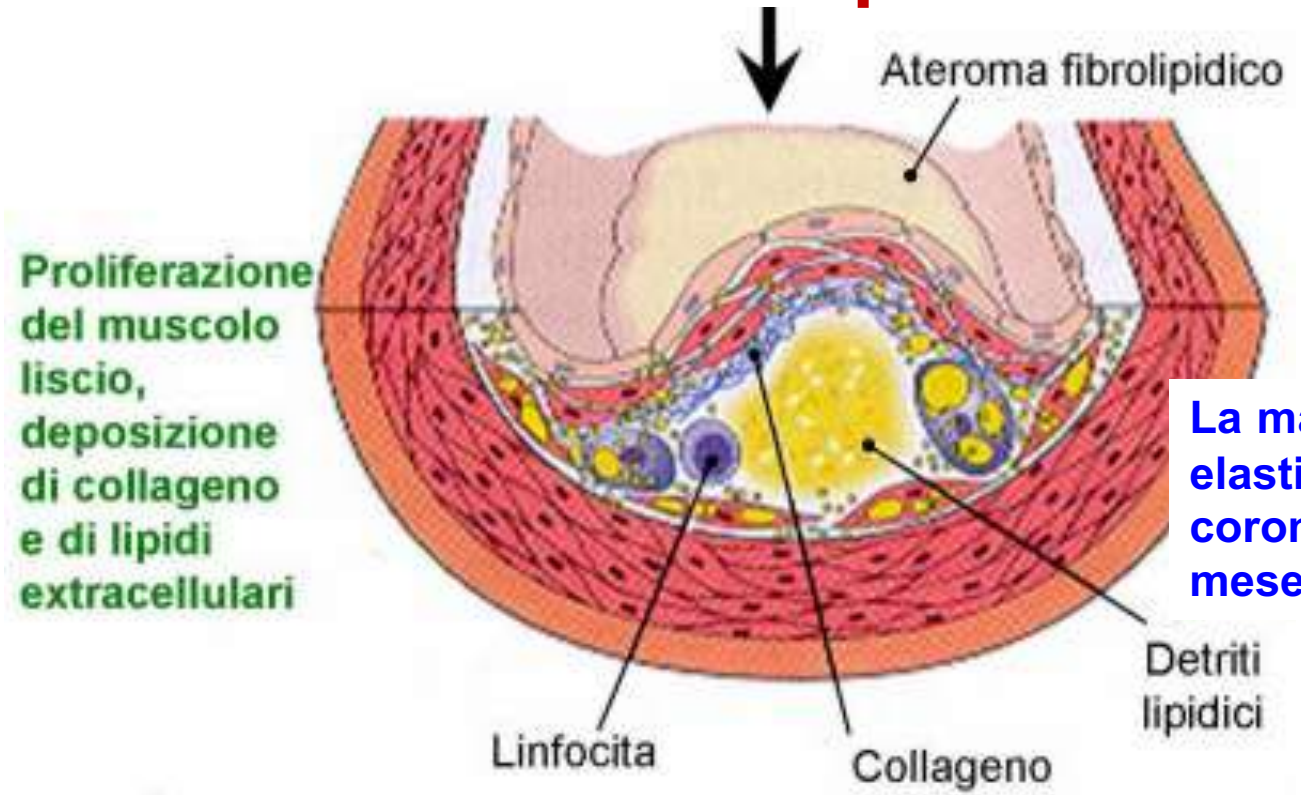


Tutti i vasi hanno la stessa struttura generale ma differiscono per spessore e composizione degli strati in dipendenza dai fattori emodinamici e dalle esigenze tissutali

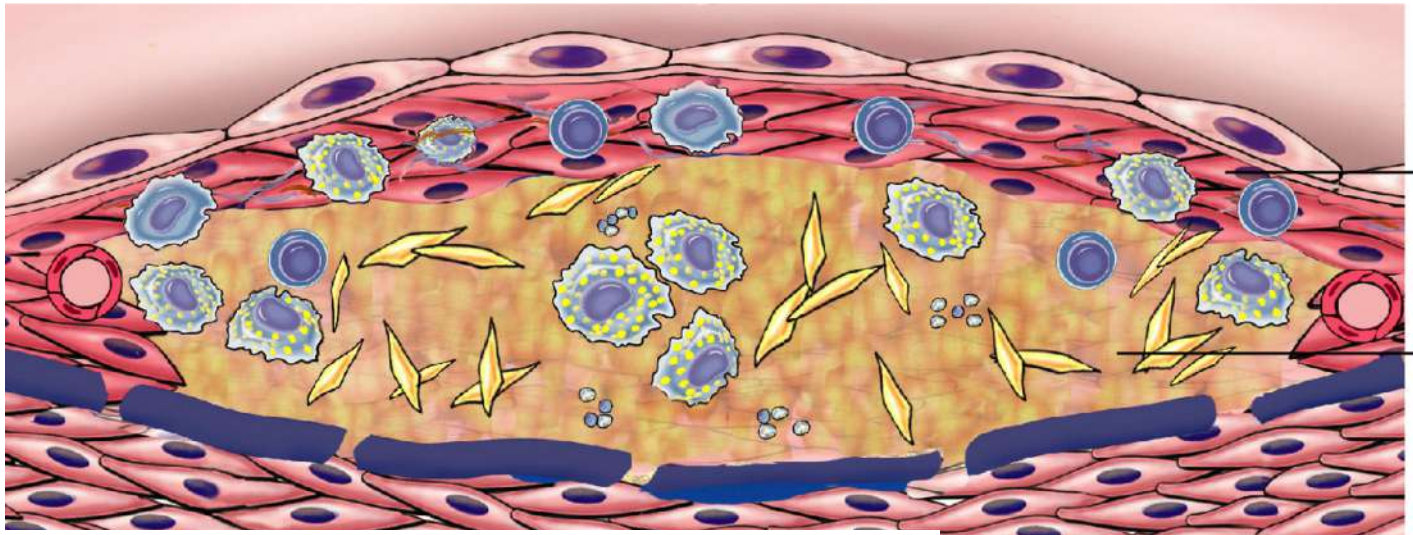
Sezione trasversale di un’arteria coronarica normale



Ateroma: lesione tipica dell'aterosclerosi

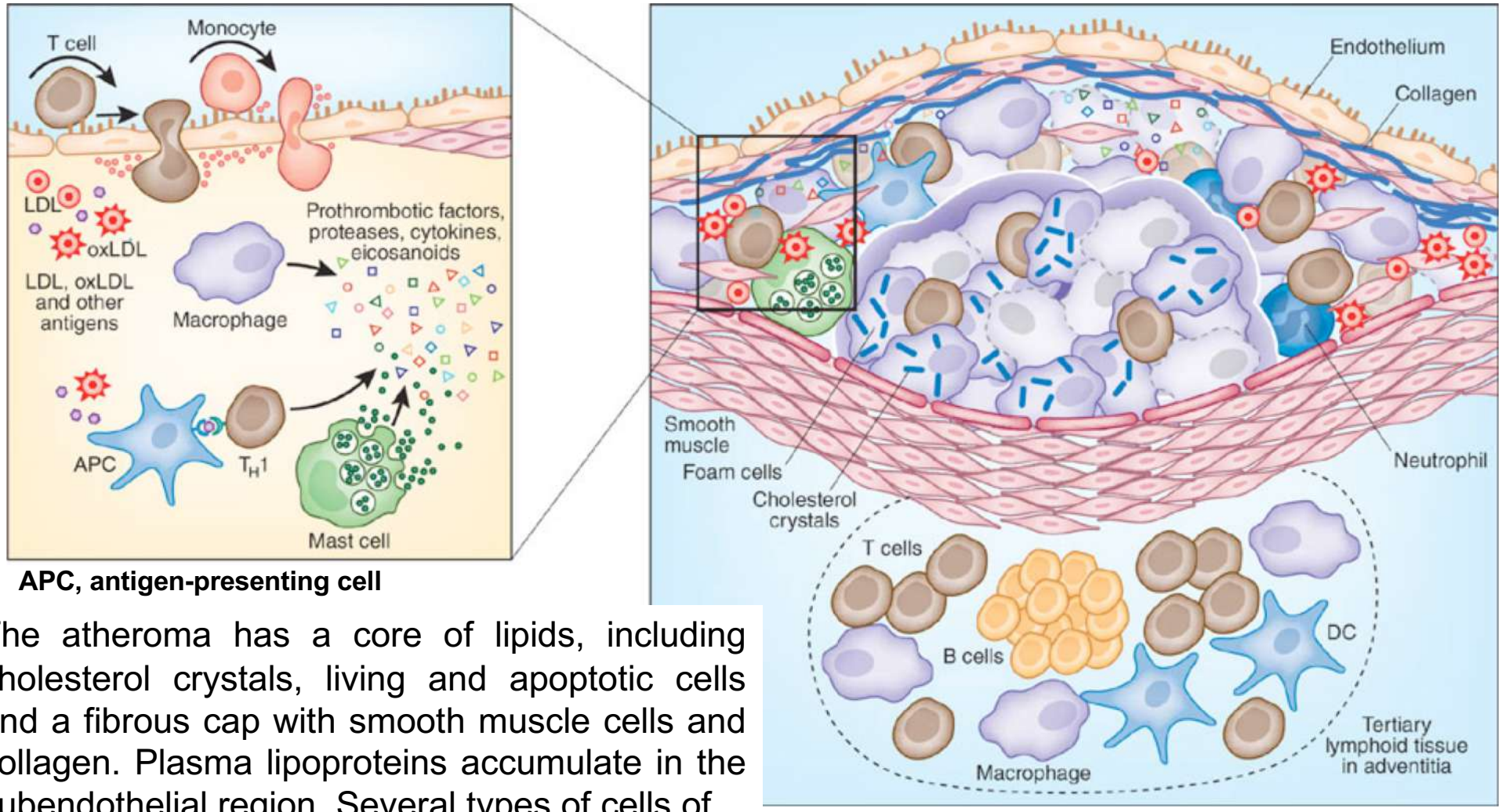


La malattia colpisce le arterie elastiche e muscolari (aorta, coronarie, cerebrali, carotide, mesenteriche e femorali)



Struttura della placca ateromatosica

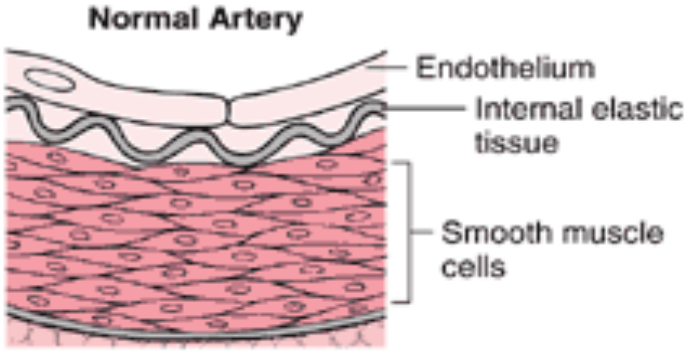
Componenti cellulari della placca ateromatosa



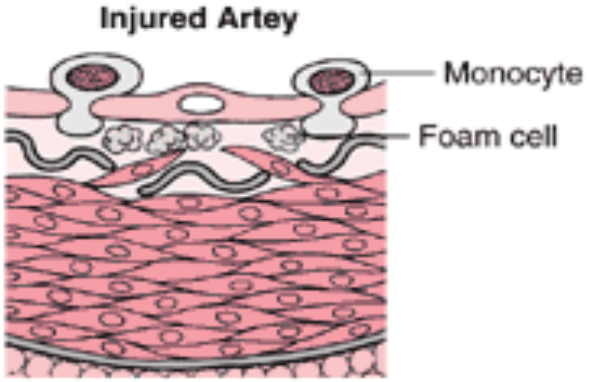
APC, antigen-presenting cell

The atheroma has a core of lipids, including cholesterol crystals, living and apoptotic cells and a fibrous cap with smooth muscle cells and collagen. Plasma lipoproteins accumulate in the subendothelial region. Several types of cells of the immune response are present throughout the atheroma including macrophages, T cells, mast cells and DCs. The atheroma builds up in the intima, the innermost layer of the artery. Outside the intima, the media contains smooth muscle cells that regulate blood pressure and regional perfusion, and further abluminally, the adventitia continues into the surrounding connective tissue. Here, cells of the immune response accumulate outside advanced atheroma and may develop into tertiary lymphoid structures with germinal centers.

Architettura di un’arteria di medio/grosso calibro

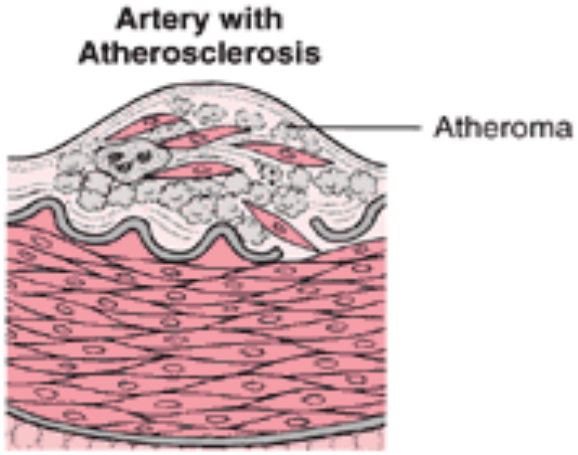


Normale



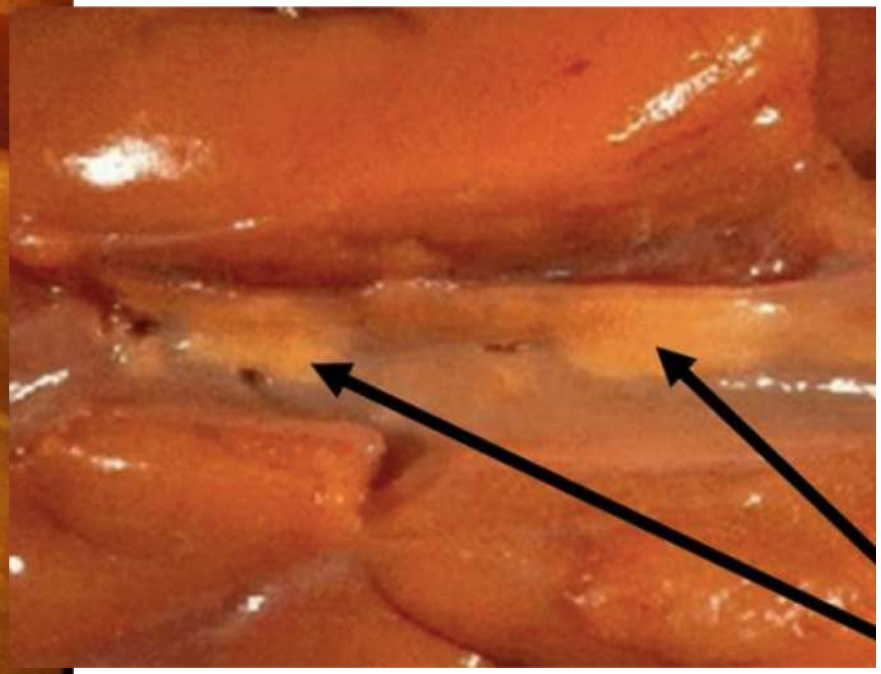
con lesione iniziale o precoce (stria lipidica)

I lipidi (esteri del colesterolo) sono principalmente intracellulari



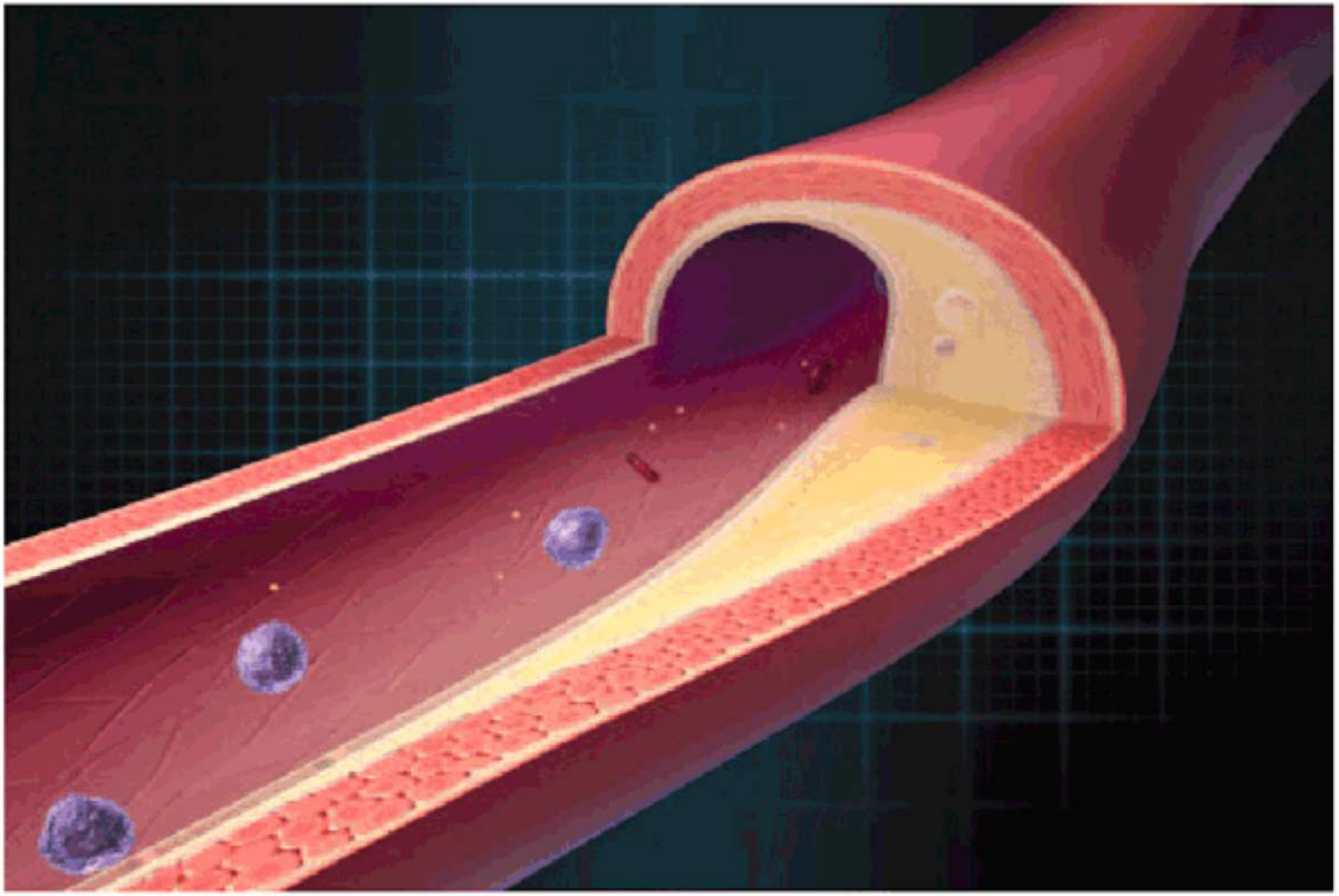
con placca fibrolipidica o ateroma


Fatty Streaks in intima of infant aorta



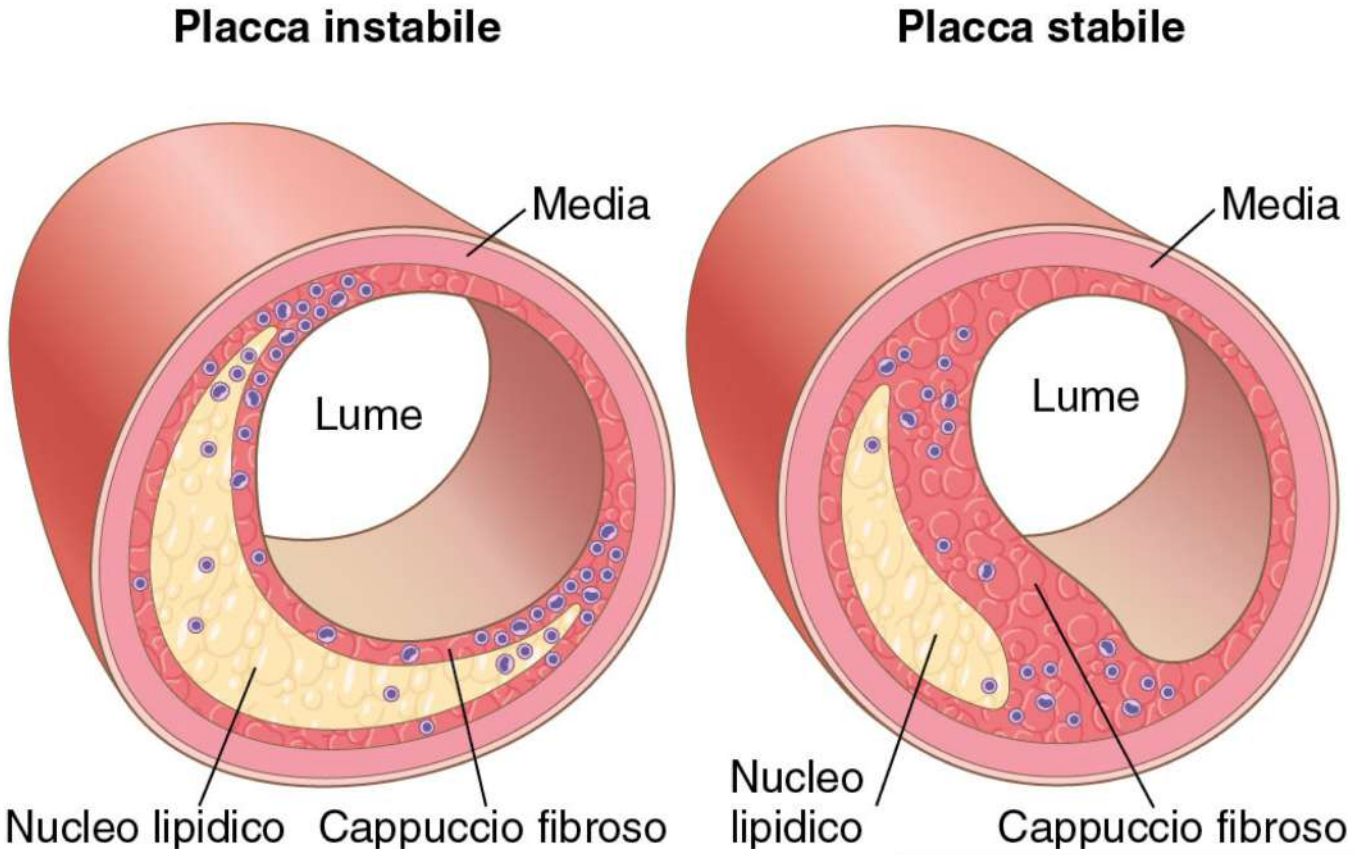

Aorta
Strie lipidiche presso gli orifici delle arterie intercostali

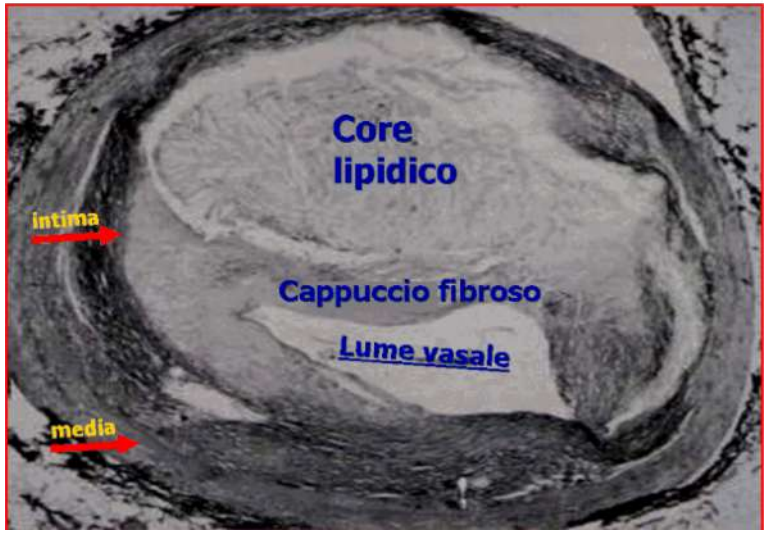
Large atheroma may not produce flow limiting stenosis



This image shows formation of a substantial atheroma in the arterial intima (yellow zone) with preservation of the lumenal flow channel. An outward bowing of the entire artery accommodates this growth of plaque to preserve the lumen until the later stages of the disease. This outward remodeling, also known as 'compensatory enlargement,' accommodates the growing atheroma.

Differenze tra placca aterosclerotica stabile e instabile

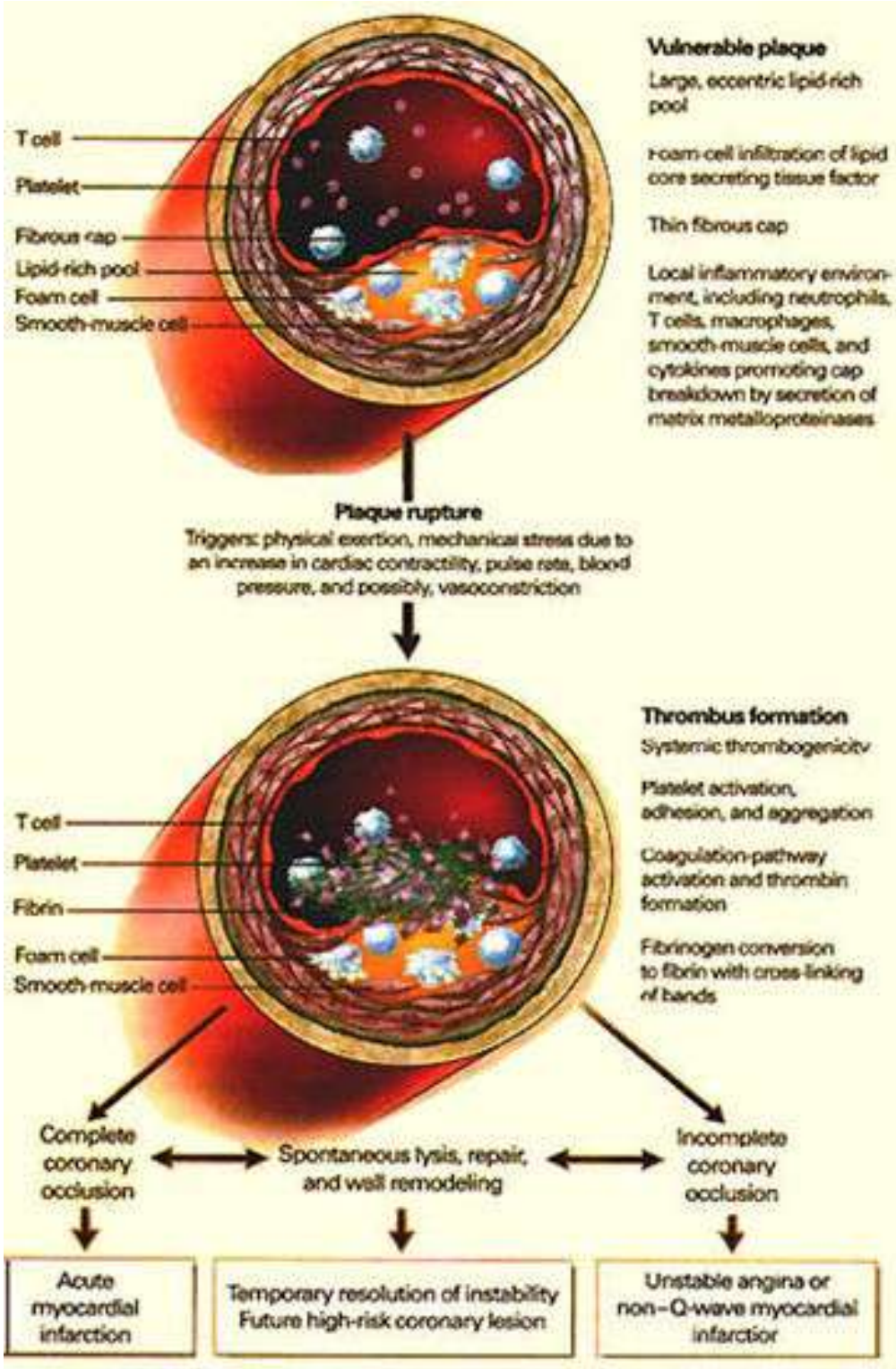




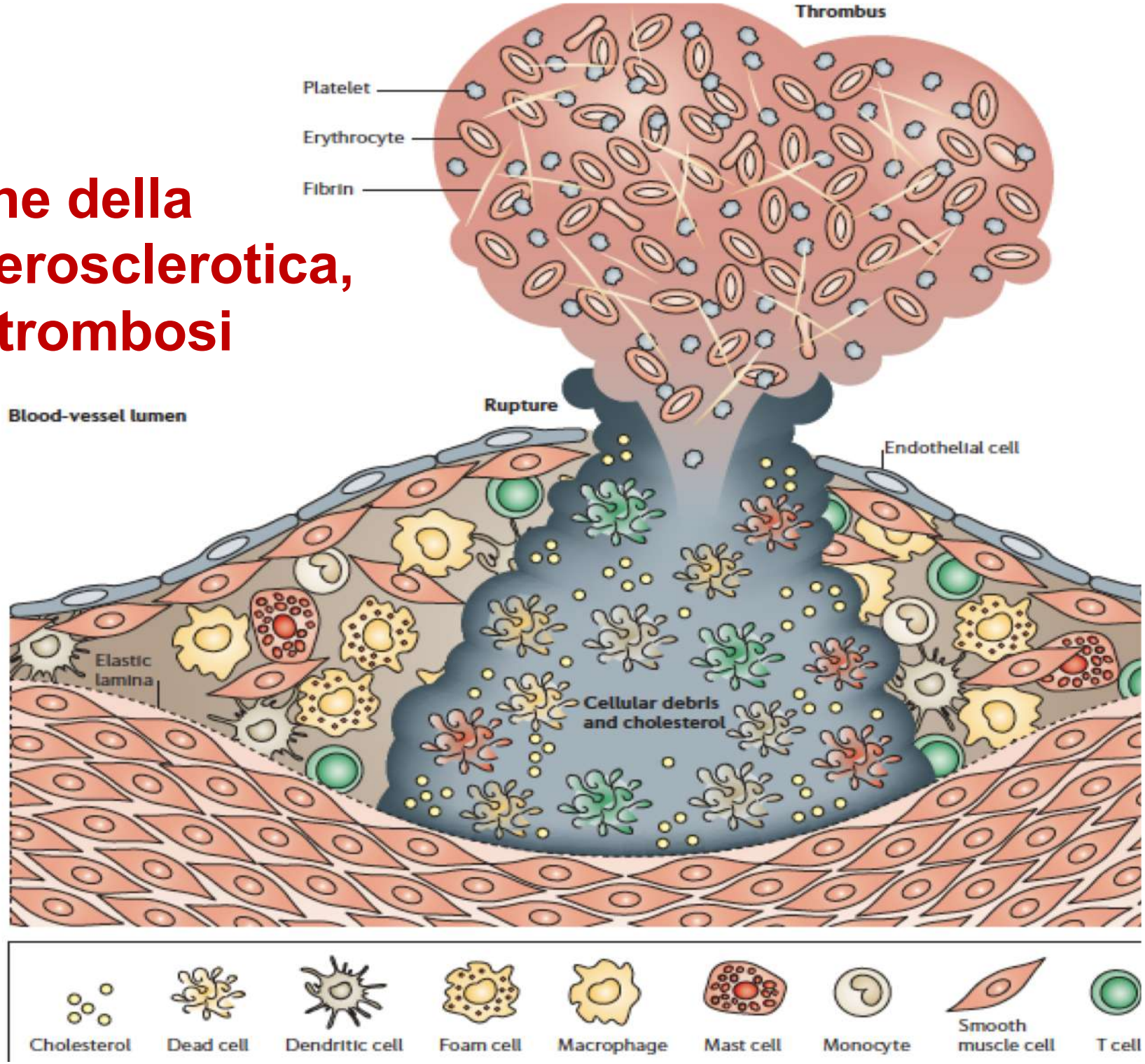
Placca instabile

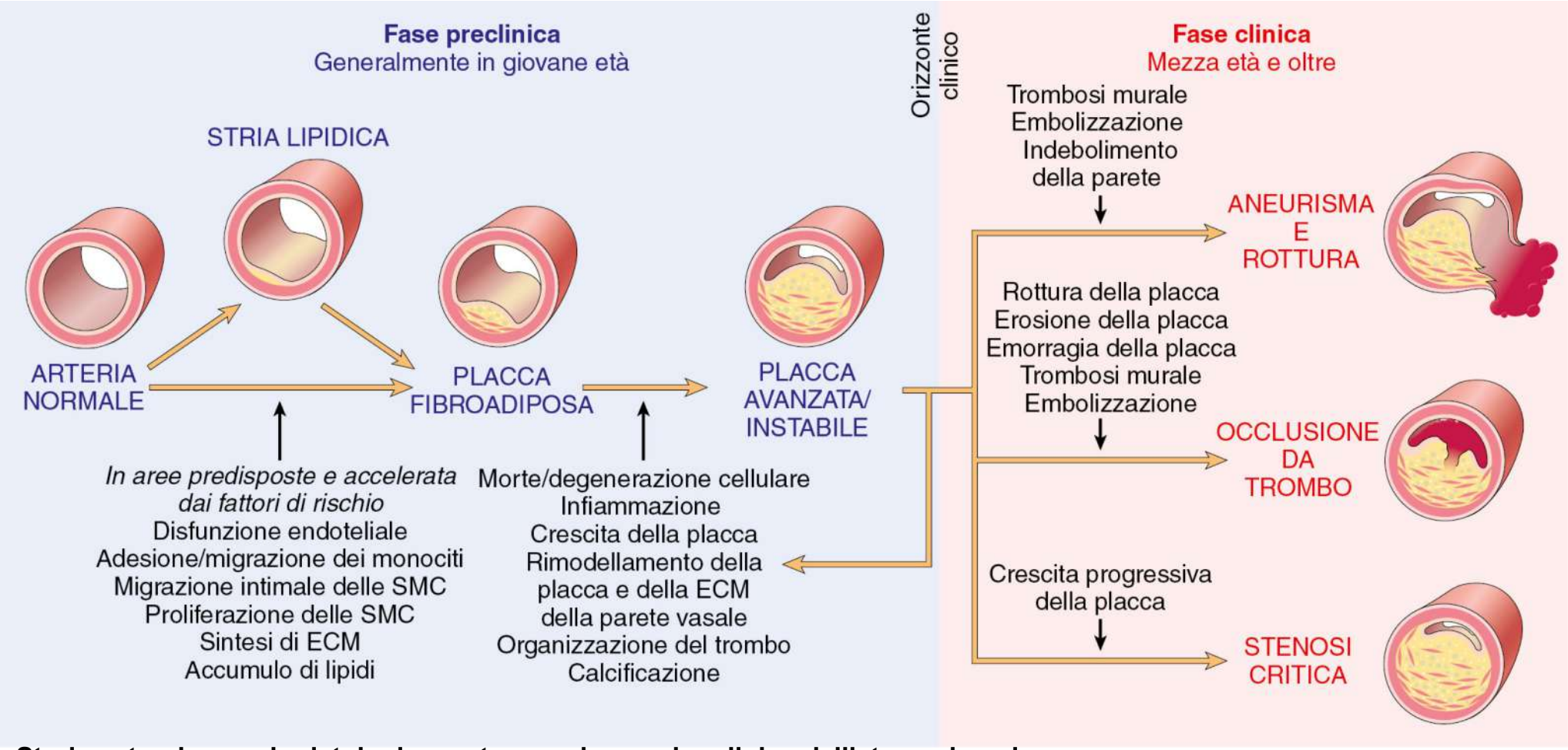
Rottura della placca

Formazione del trombo



Attivazione della placca aterosclerotica, rottura e trombosi



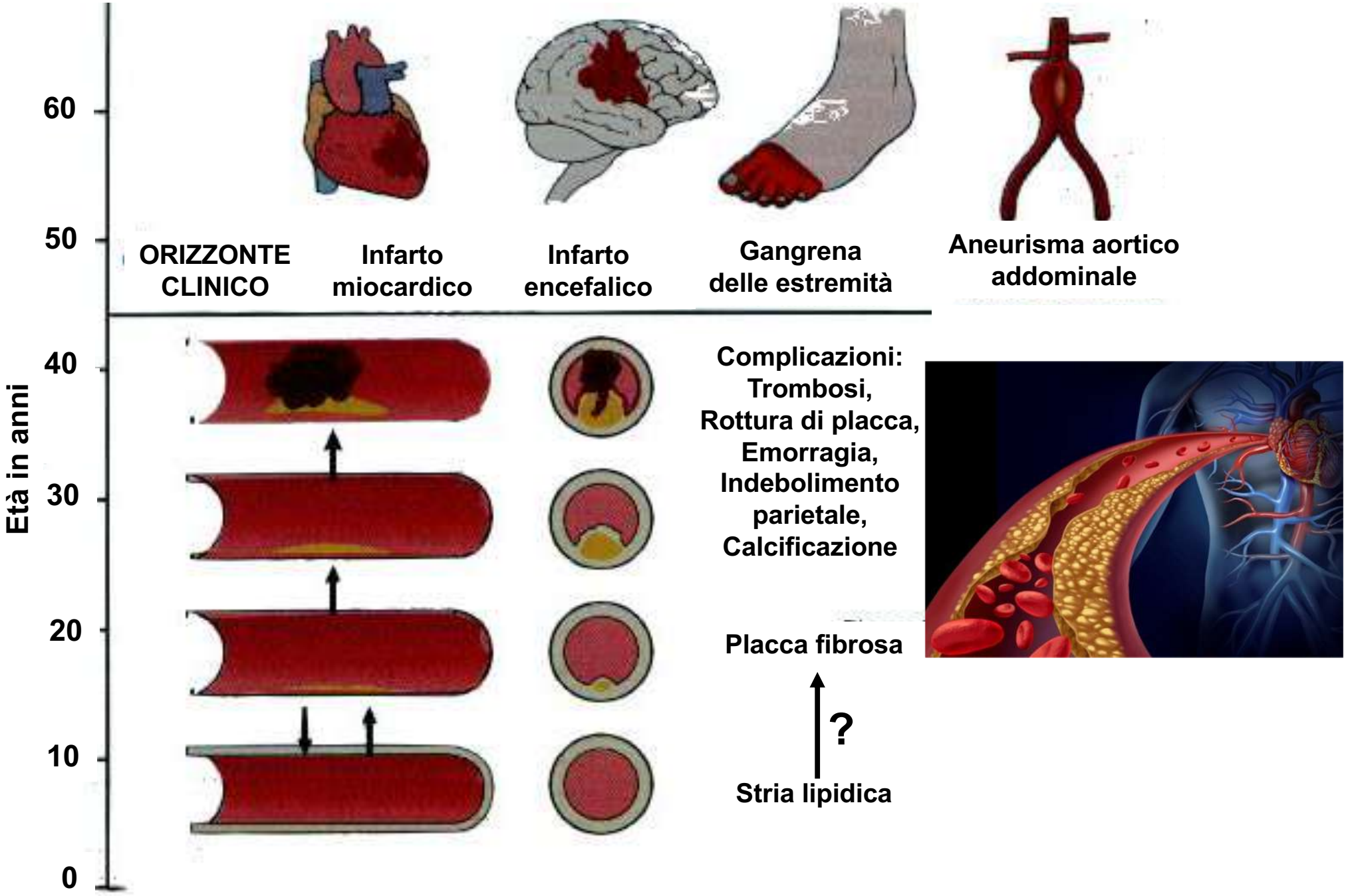


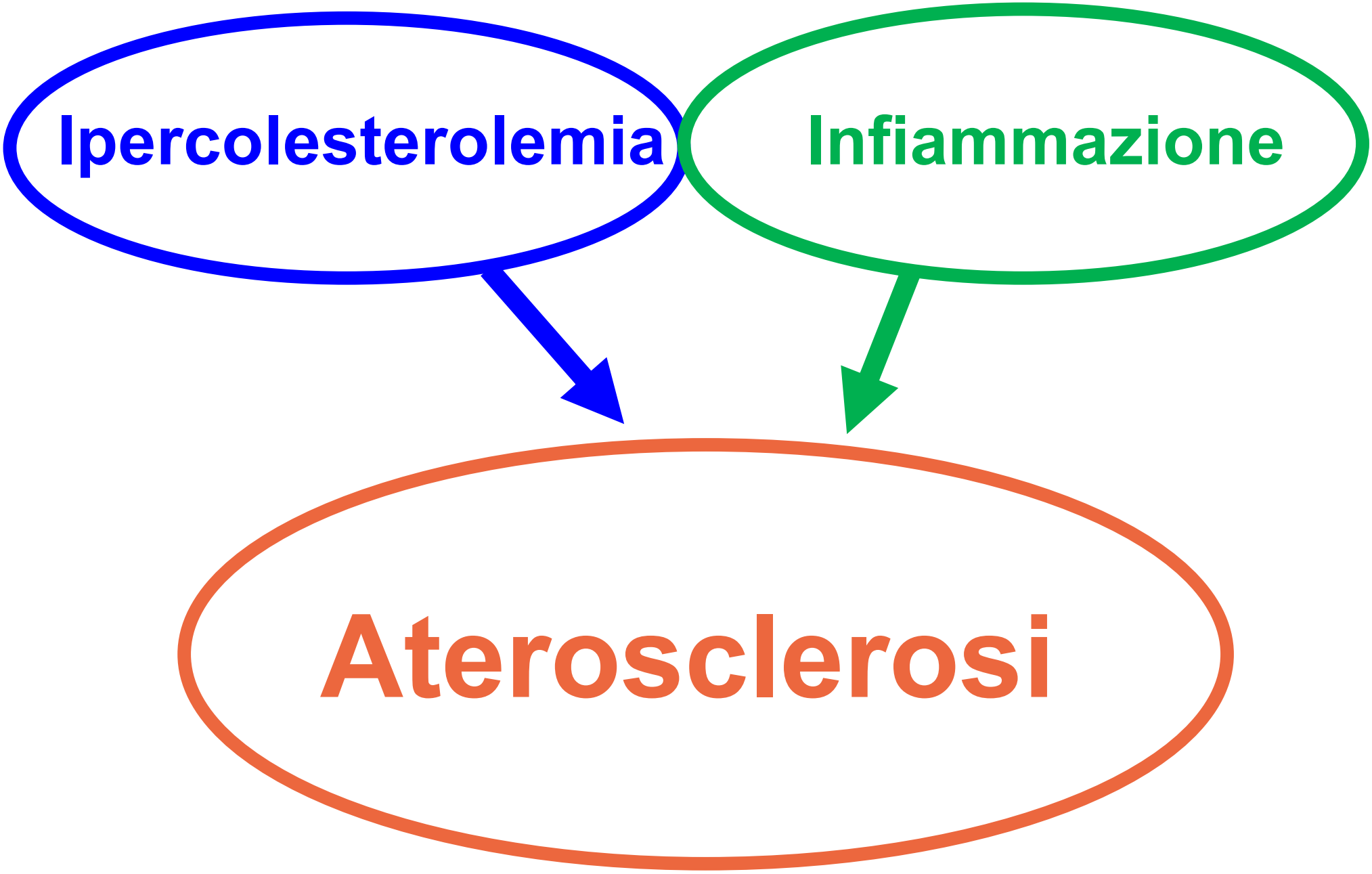
Storia naturale, quadro istologico, patogenesi e quadro clinico dell'aterosclerosi.
SMC= cellule muscolari lisce ECM=matrice extracellulare

Principali complicanze dell'aterosclerosi:

- cardiopatia ischemica acuta
- ictus cerebrale
- vasculopatia periferica

Dalla stria lipidica all'infarto




Ipercolesterolemia
Infiammazione
Aterosclerosi

Fattori di rischio nell'aterosclerosi

Costituzionali (non modificabili)

Difetti genetici

Familiarità tratti poligenici

Invecchiamento

Sesso maschile

Modificabili

Iperlipidemia soprattutto ipercolesterolemia/dieta ricca di grassi

Ipertensione

Fumo di sigaretta (attivo e passivo)

Diabete mellito

Infiammazione

LDL lipoproteina a bassa densità
(o colesterolo “cattivo”)
valore desiderabile <130 mg/dl
correlazione positiva tra un’alta concentrazione plasmatica di LDL (>130 mg/dl) ed il rischio di patologie cardiovascolari.

HDL lipoproteine ad alta densità
(o colesterolo “buono”)
valore desiderabile >40 mg/dl
correlazione negativa tra un’alta concentrazione plasmatica di HDL (>60 mg/dl) ed il rischio di patologie cardiovascolari. **Ruolo protettivo**

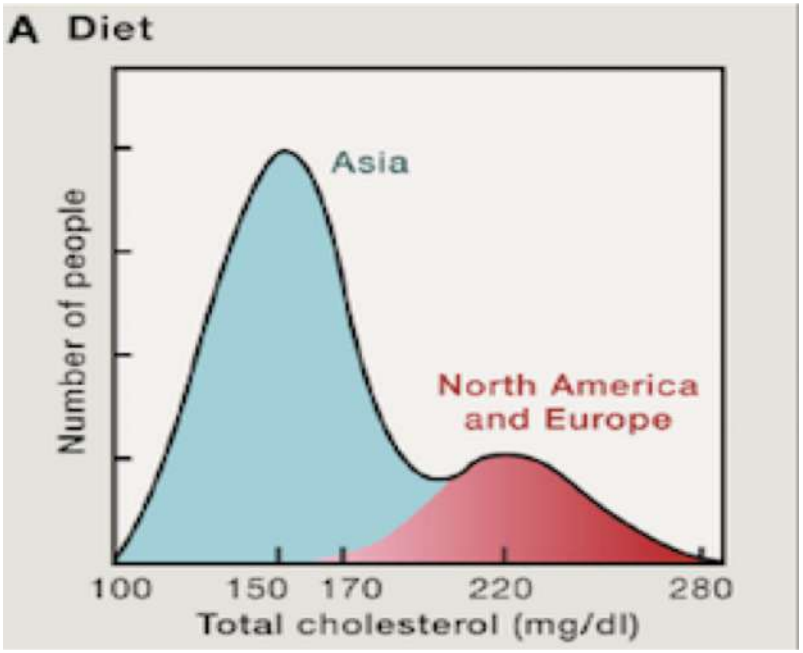
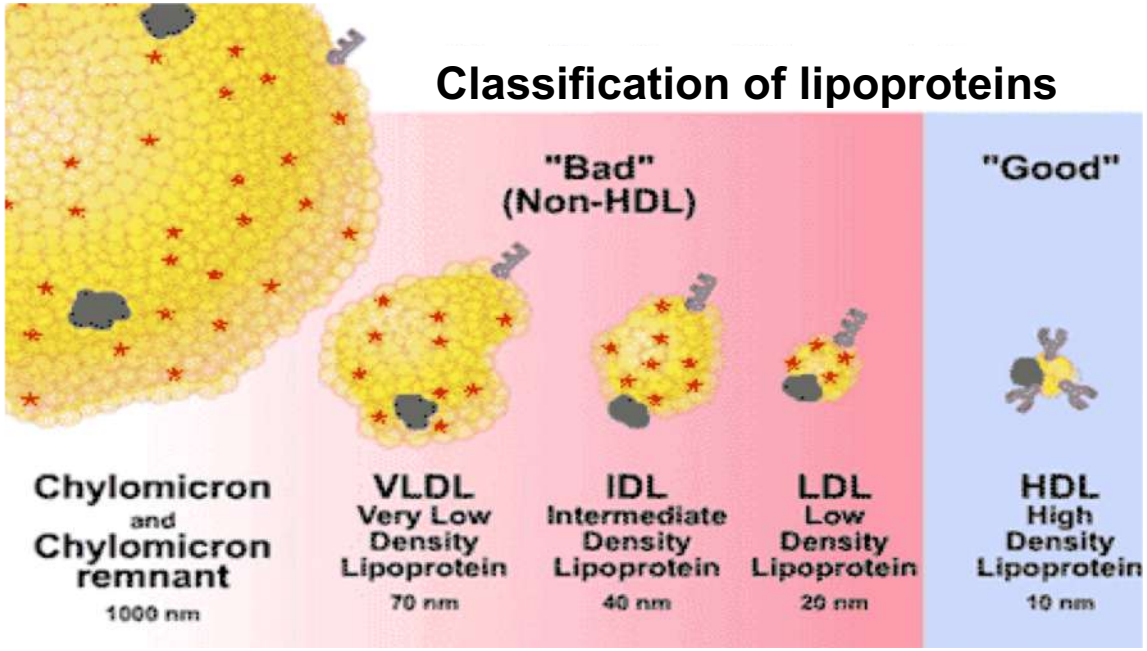
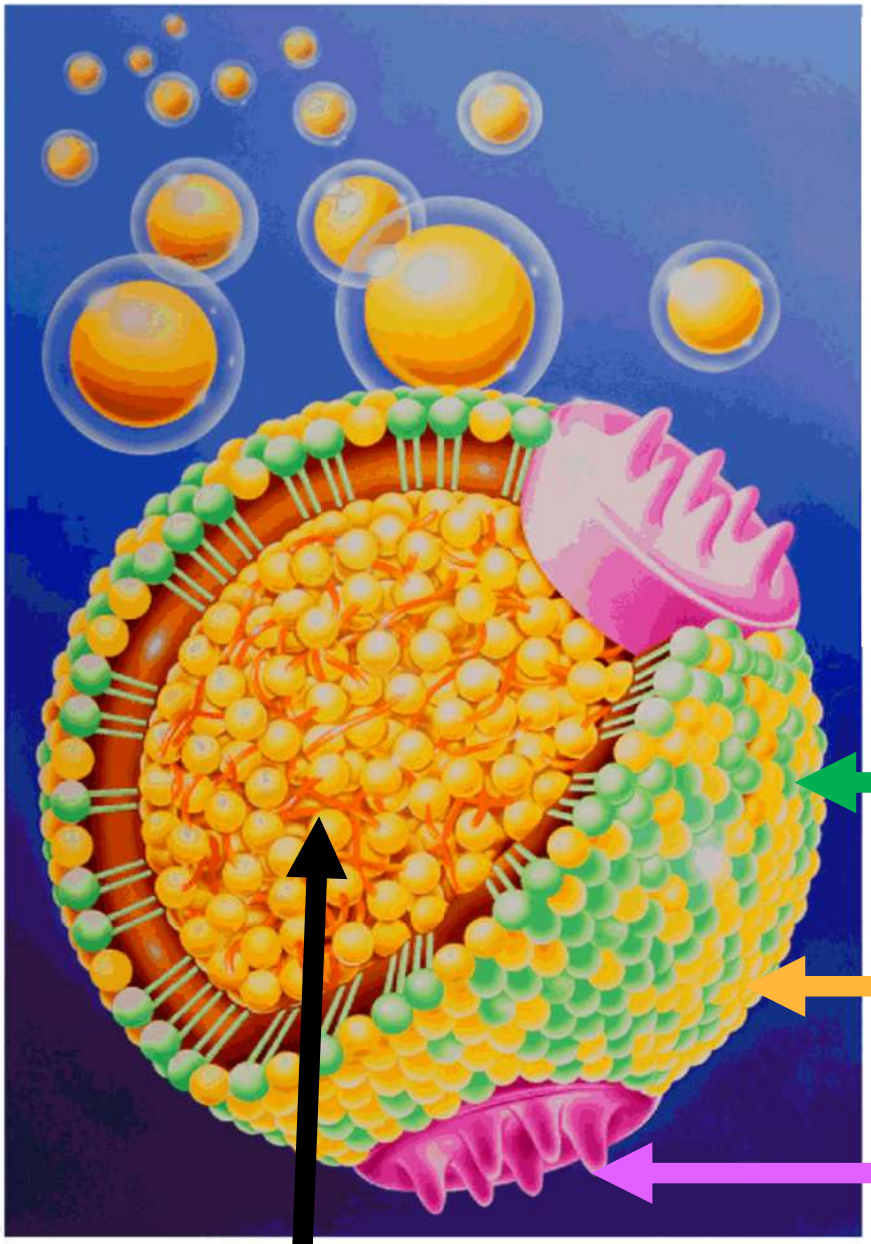


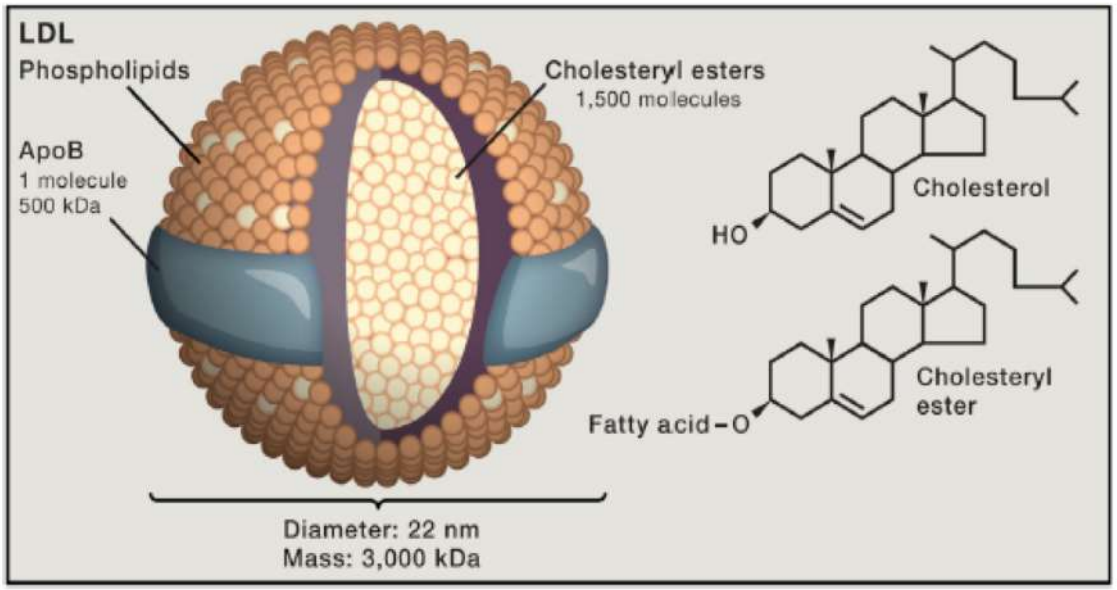
Diagram Illustrating the Effects of Diet on Plasma LDL and Coronary Disease
(A) Diet. Idealized depiction of the frequency distribution of plasma cholesterol levels in the human species as extrapolated from surveys of middle-aged people in major populations of the world. The higher the cholesterol level, the higher the risk for coronary disease, as denoted by the graded red shading.



Struttura di una lipoproteina a bassa densità (LDL)



JOHN BAVOSI / SCIENCE PHOTO LIBRARY / PHOTO RESEARCHERS, INC.



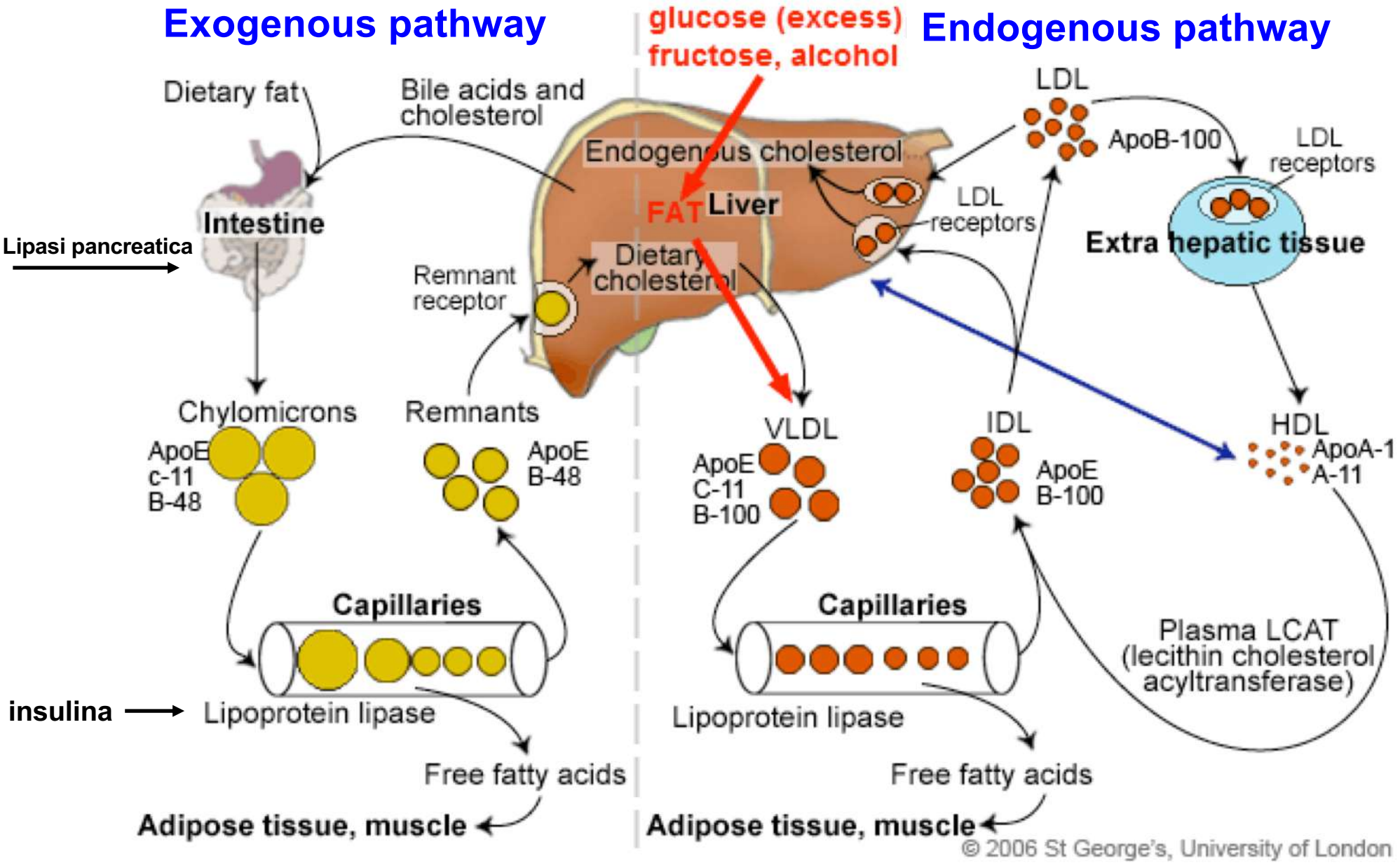
Fosfolipidi

Colesterolo libero

Apo(lipo)proteina B-100

Esteri del colesterolo e trigliceridi

Principali tappe metaboliche del trasporto del colesterolo e dei trigliceridi nel plasma



Captazione cellulare delle LDL tramite recettore LDLR e regolazione del metabolismo del colesterolo

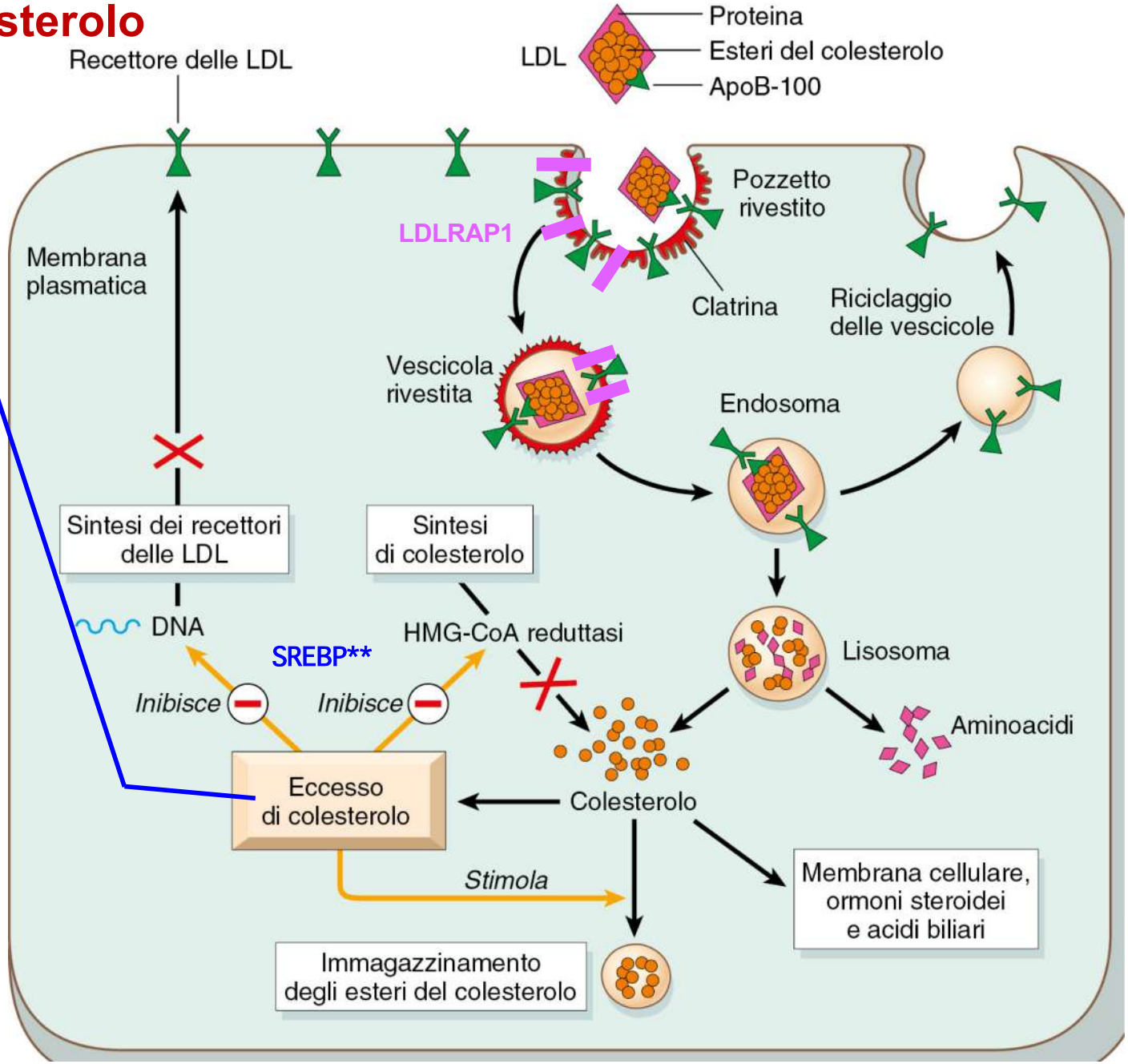
Eccesso di colesterolo

SREBP**

1. **Inibizione della 3-idrossi-3-metilglutaril coenzima A (HMG-CoA) reduttasi. Diminuisce la sintesi di colesterolo. HMG-CoA reduttasi è inibita dalle STATINE (farmaci per trattare ipercolesterolemia)**

2. **Inibizione della sintesi del recettore LDL**

3. **Attivazione dell'acil-CoA-aciltransferasi (ACAT o SOAT) ed esterificazione del colesterolo libero**



SREBPs (sterol regulatory element-binding proteins) fattori che attivano la trascrizione di LDLR e della HMG-CoA reduttasi e la sintesi degli acidi grassi

Dislipoproteinemie o alterazioni del metabolismo lipoproteico

Iperlipidemie primarie: alcuni esempi

- **Ipercolesterolemie dovute a difetti monogenici** (es. **ipercolesterolemia familiare**) con trasmissione autosomica dominante. Per:

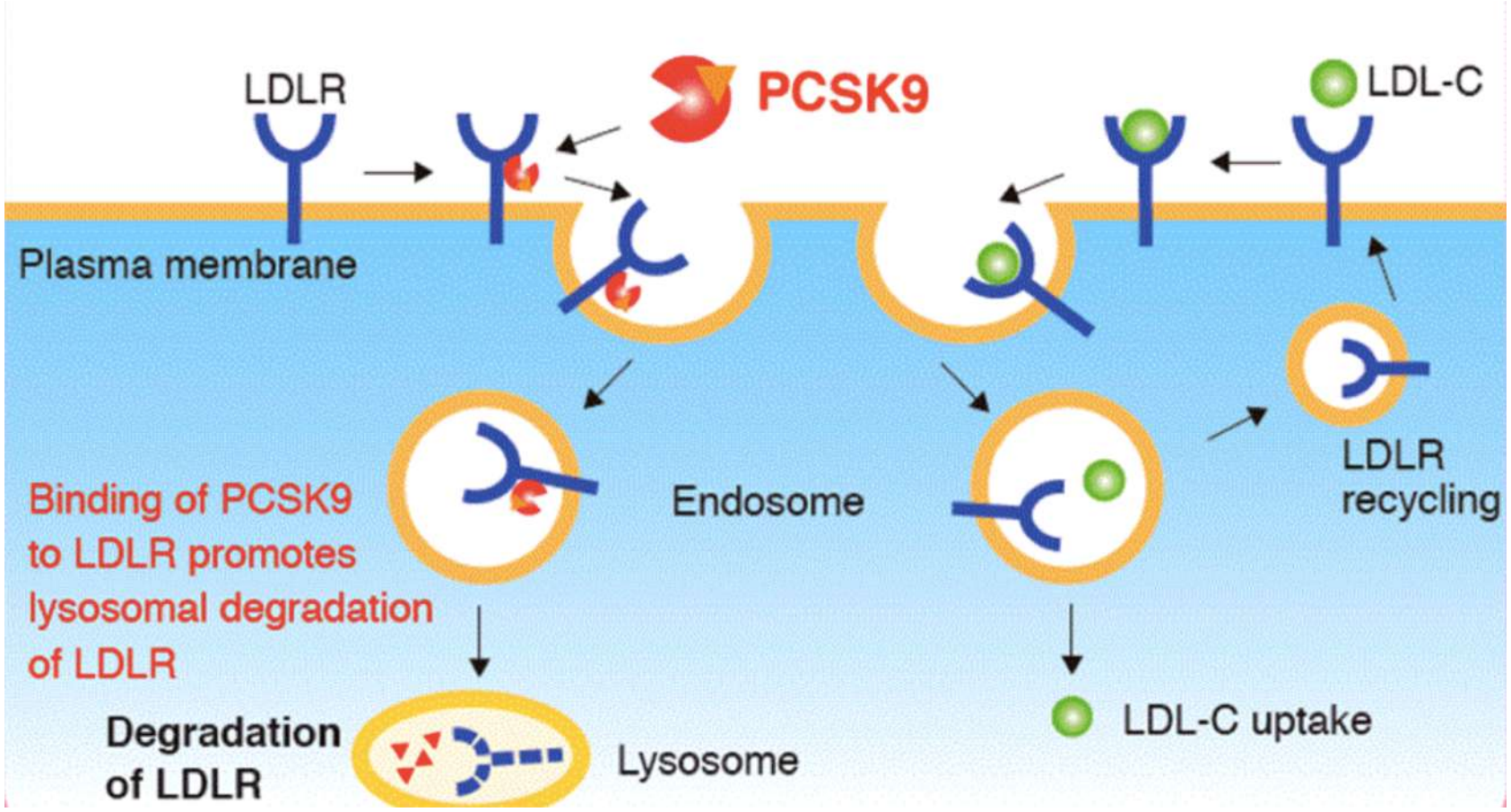
1. **Mutazioni del gene per il recettore LDL** (2580 varianti; divise per classi) determinano:
   a) assenza/carenza di LDLR;
   b) difetti nel trasporto da RE al Golgi;
   c) espressione di recettori LDL che non legano correttamente LDL;
   d) difetti nell'internalizzazione dei complessi LDL/LDLR che restano intrappolati negli endosomi perché LDL e recettore non si dissociano.
2. **Mutazione di ApoB** (896 varianti; es. sostituzione aminoacidica nella regione di legame al recettore aa 3500 Arg>Gln).
3. **Mutazioni "gain of function" di PCSK9** (proproteina della convertasi subtilisina/kexina tipo 9; proteina che favorisce la degradazione del LDLR) 351 varianti.
4. **Mutazioni di ApoE** (16 varianti).
5. **Mutazioni di LDLRAP1** (molto rare).

- **Ipercolesterolemia poligenica** è la forma più comune di ipercolesterolemia ed è una patologia multifattoriale.

- **Iperlipidemia familiare combinata (associata)** - il cui difetto primario è l'iperproduzione di ApoB che determina un eccesso di LDL e di VLDL.

- **Deficienza di lipasi lipoproteica (LPL)** malattia autosomica recessiva con assenza o ridotta funzionalità dell'enzima LPL. La patologia può anche essere causata da deficit di apoproteina CII che è essenziale per l'attivazione enzimatica della LPL.

Azione della PCSK9 (proproteina della convertasi subtilisina/kexina tipo 9)



Uso terapeutico di inibitori di PCSK9 (anticorpi monoclonali che fungono da farmaci ipolipemizzanti) Es. Alirocumab o Evolocumab

Iperlipidemie secondarie

Causa:

fattori ormonali (gravidanza, ipotiroidismo);

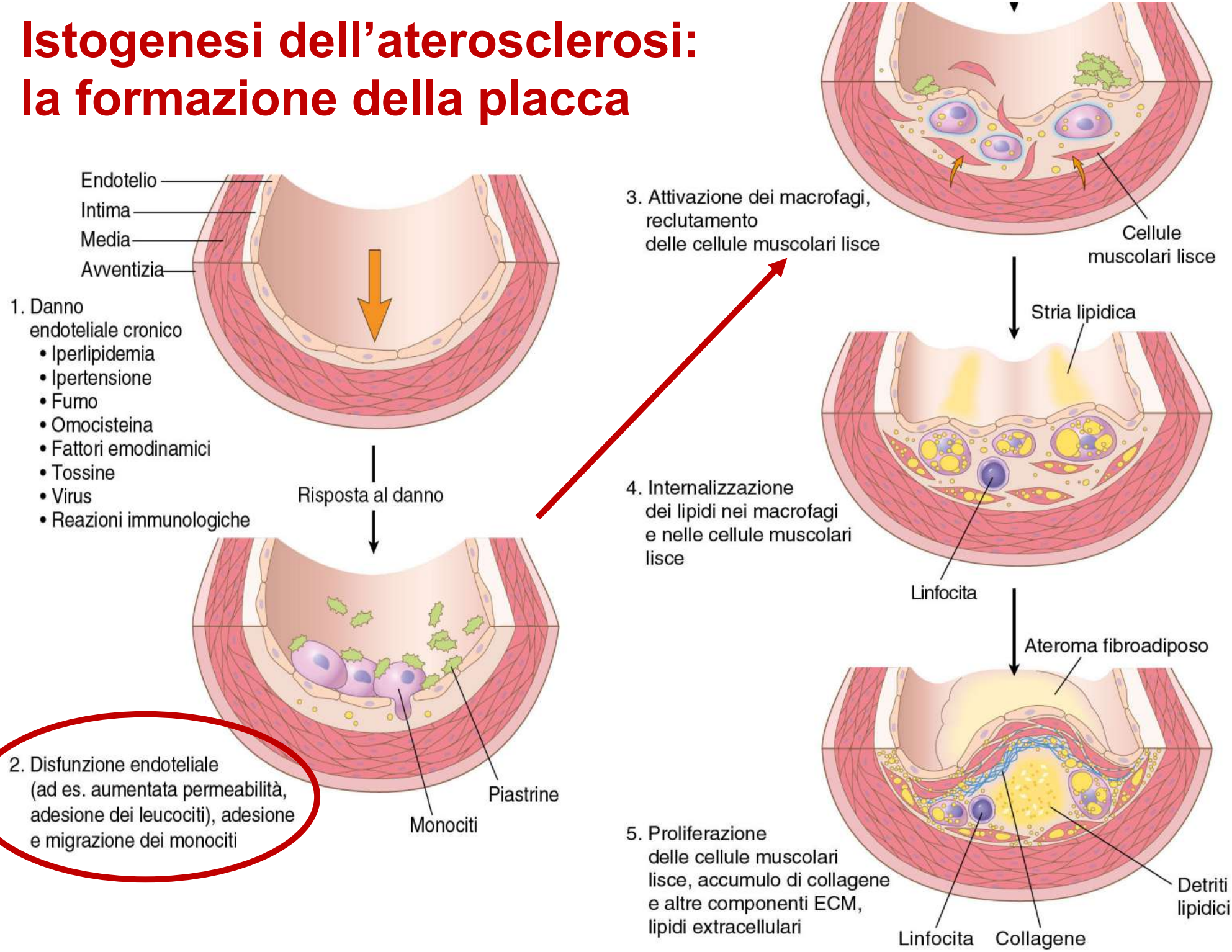
fattori nutrizionali (obesità, abuso di alcool, diabete);

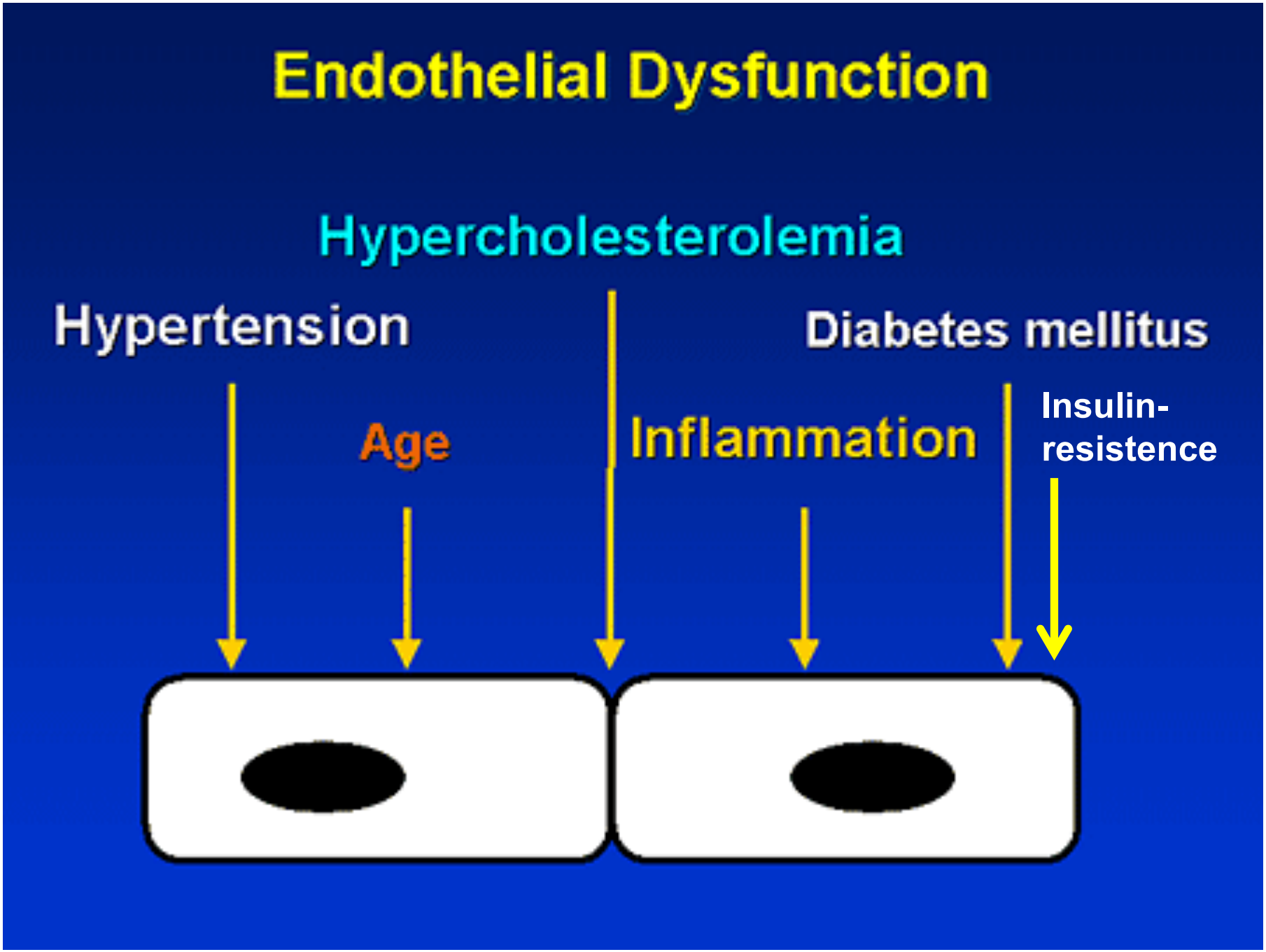
disfunzioni renali (insufficienza renale cronica);

malattie epatiche (cirrosi biliare primaria; ostruzione biliare);

iatrogena (beta-bloccanti, diuretici, progestinici).

Istogenesi dell'aterosclerosi: la formazione della placca




Endothelial Dysfunction
Hypercholesterolemia
Hypertension
Diabetes mellitus
Age
Inflammation
Insulin-
resistence

Disfunzione endoteliale

la risposta delle cellule endoteliali a stimoli di diversa natura induce:

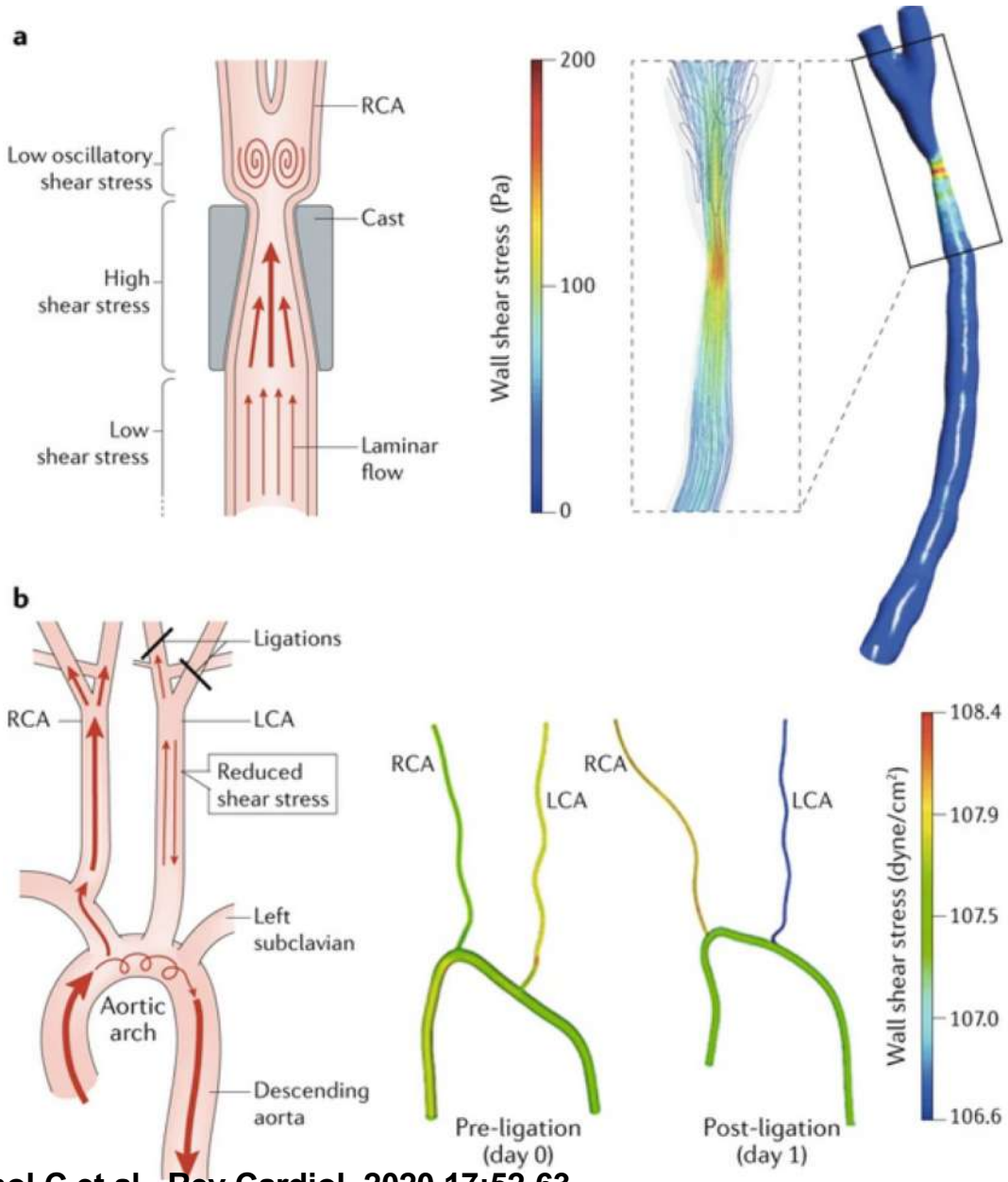
- attivazione di geni che ne alterano le proprietà specifiche (maggiore permeabilità ed espressione di molecole di adesione)
- alterazione delle proprietà antiaggreganti
- produzione di citochine, chemochine, fattori di crescita

formazione della placca ateromatosa

- **prodotti lipidici modificati**
- fattori emodinamici
- prodotti batterici
- virus
- componenti del complemento
- citochine
- prodotti della glicazione avanzata (diabete)
- omocisteina
- prodotti della combustione delle sigarette

Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes

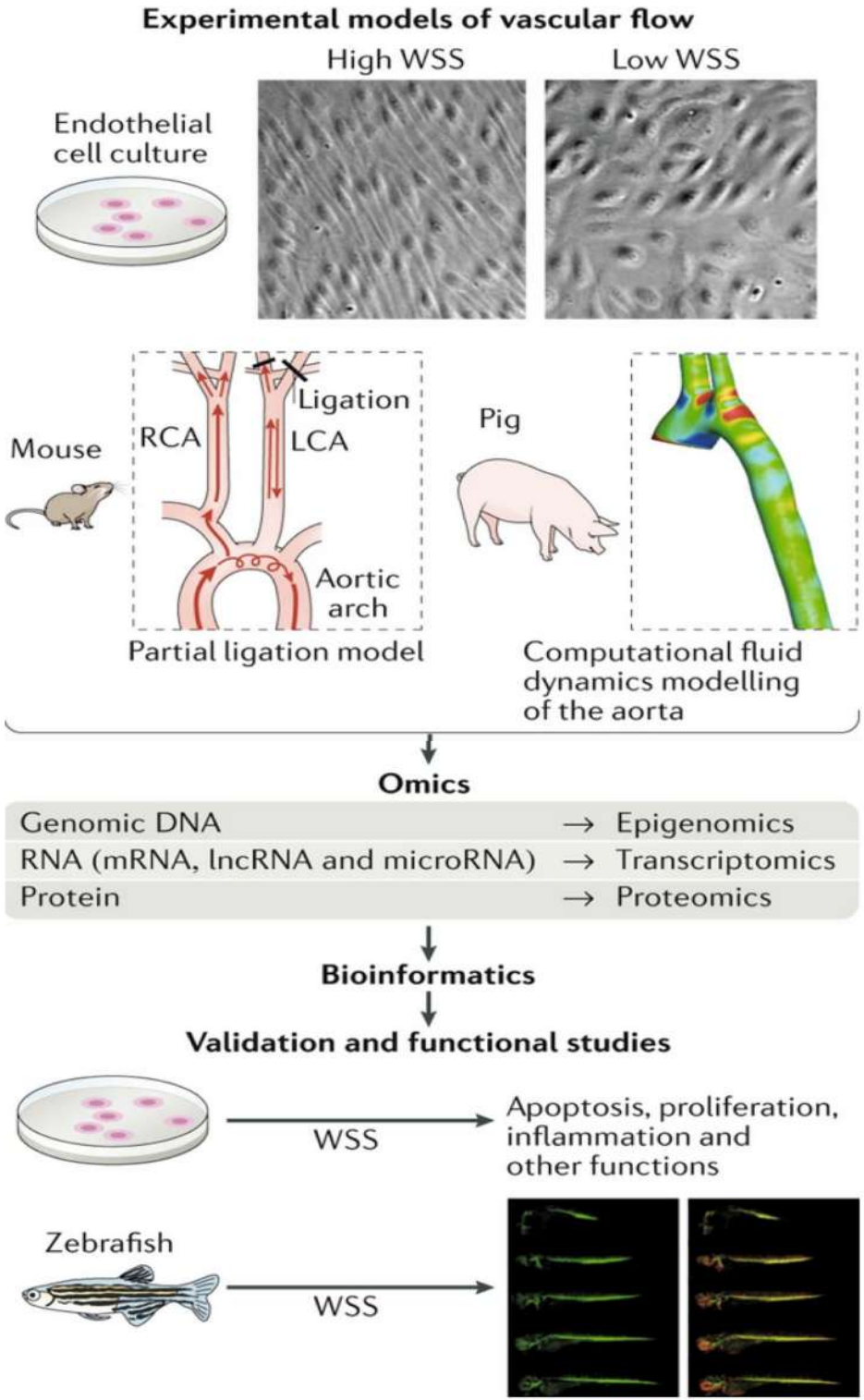
In vivo manipulation of shear stress



a | Schematic representation of the cast model (left panel) in which a constrictive cuff is placed in the right carotid artery (RCA) of **hypercholesterolaemic mice** to modify blood flow. Computational fluid dynamics modelling shows that the constrictive cuff generates low laminar shear stress upstream of the stenosis and low oscillatory shear stress downstream (right panel).

b | Schematic representation of the partial ligation model (left panel) in which three of the four branches of the left carotid artery (LCA) are ligated, leading to a reduction in shear stress in the LCA. Computational fluid dynamics modelling shows that partial ligation of the LCA significantly reduces shear stress (right panel).

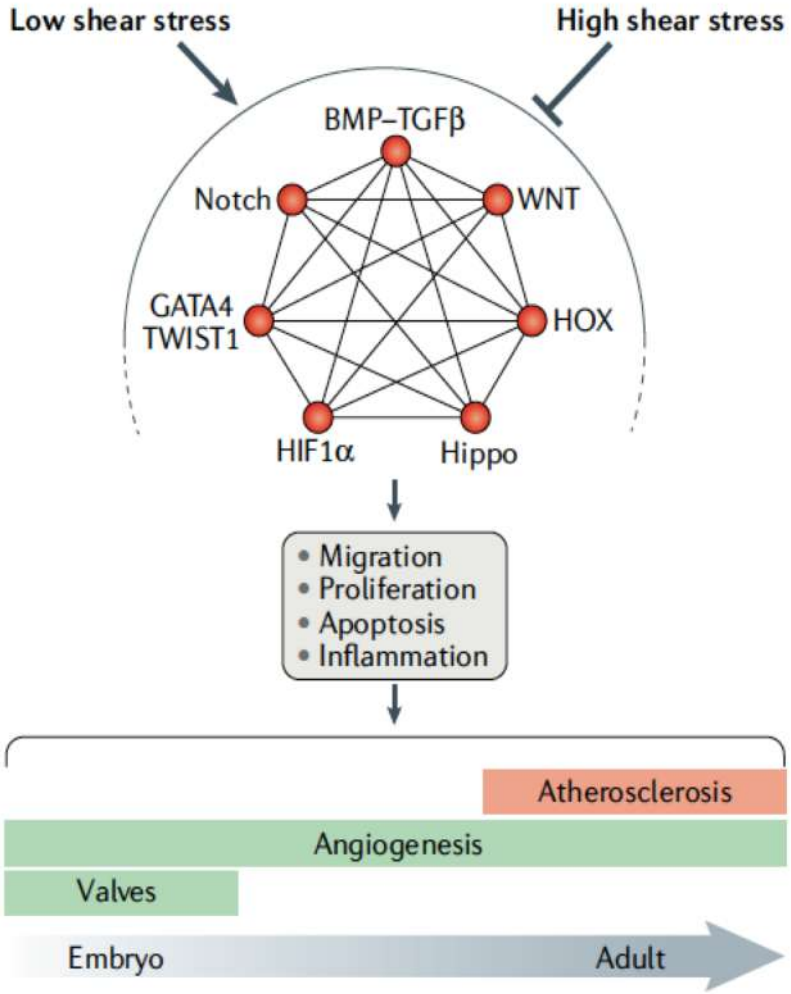
Souilhol C et al. Rev Cardiol. 2020 17:52-63.



Systems biology approach to identify mechanosensitive pathways in vascular endothelium

Schematic pathway for systems biology studies of endothelial cell responses to flow. First, **omics studies** are performed to define the level of mRNAs, long non-coding RNAs (lncRNAs) and microRNAs (transcriptomics), protein levels and modifications (proteomics), and chromatin and DNA alterations (epigenomics) that are **regulated by flow**. These studies have been done in mouse, pig and cell-culture models of vascular flow. Second, bioinformatic analyses are performed to define cell functions and pathways that are enriched under particular flow conditions. Third, model systems, such as cultured endothelial cells or zebrafish embryos, can be used for functional screening of shear stress-regulated genes to understand their role in **vascular mechanoresponses**. LCA, left carotid artery; RCA, right carotid artery; WSS, wall shear stress.

Souilhol C et al. Rev Cardiol. 2020 17:52-63.



- Shear stress regulates atherosclerosis by altering endothelial cell physiology.
- Systems biology approaches have identified multiple shear stress-regulated pathways in the endothelium, including several pathways classically known to be involved in **embryogenesis**.
- Blood flow-mediated regulation of developmental pathways orchestrates valve formation and angiogenesis to optimize tissue perfusion.
- By contrast, in arteries in adults, these blood flow-regulated pathways lead to inflammation, vascular dysfunction and atherosclerosis.

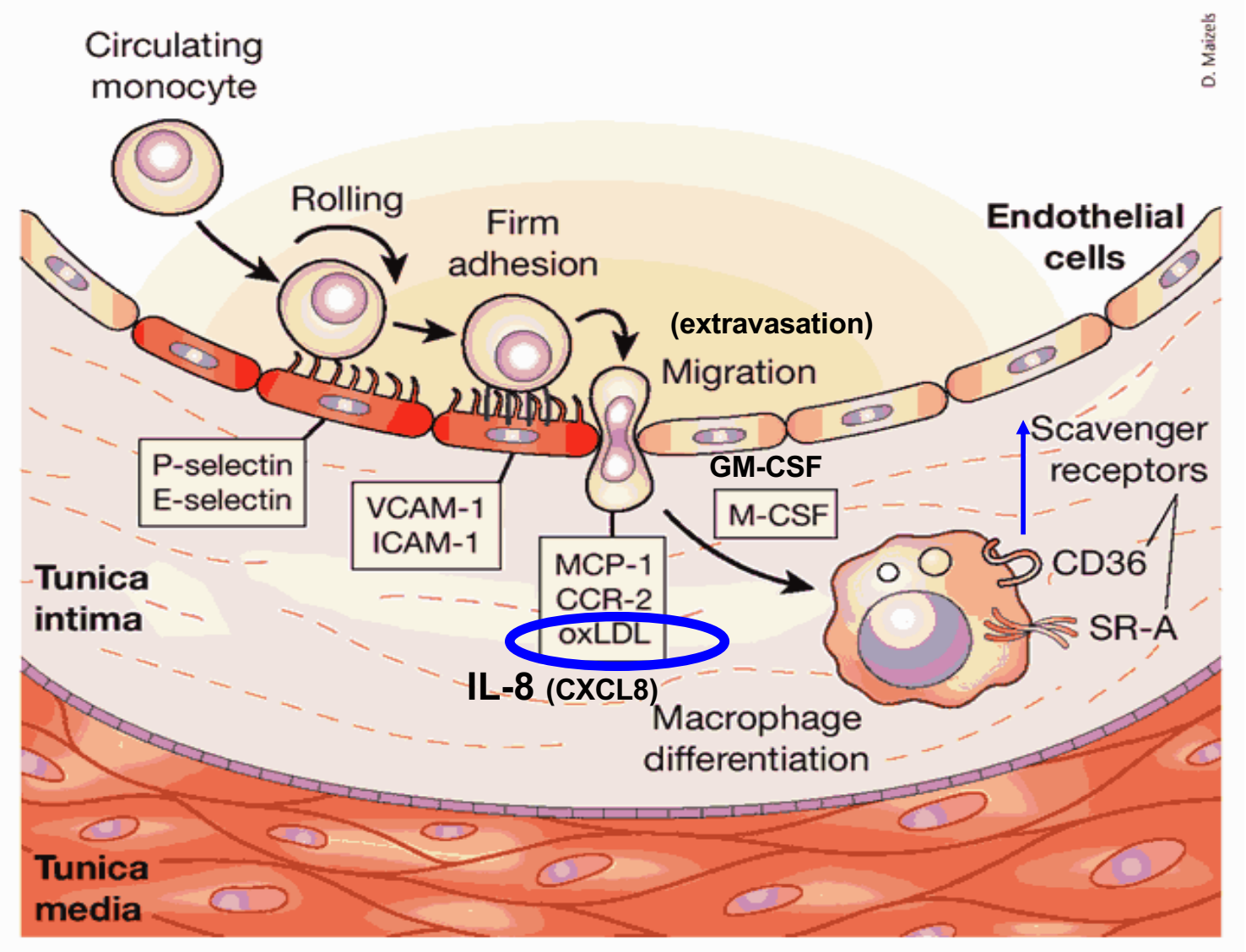
Low shear stress activation of a network that drives angiogenesis and atherosclerosis

Shear stress regulates multiple signalling pathways with a classical role in **embryonic development**, including members of the bone morphogenetic protein (BMP)–transforming growth factor-β (TGFβ) superfamily, hypoxia-inducible factor 1α (HIF1α), Notch, Hippo–Yes-associated protein (YAP)–transcriptional co-activator with PDZ-binding motif (TAZ), WNT, transcription factor GATA4 and twist-related protein 1 (TWIST1).

In general, low or oscillatory shear stress is an activating signal for these pathways, whereas high shear stress is inhibitory. Mechanical regulation of developmental pathways is essential for angiogenic processes in embryos and adults, ensuring that vessels are stabilized under high-flow conditions. Although most regions of adult arteries are exposed to high shear stress, branches and bends are exposed to low shear stress. **Low shear stress causes inappropriate activation of developmental signalling pathways, leading to increased inflammation and vascular permeability, which are the hallmarks of early atherogenesis.** HOX, homeobox.

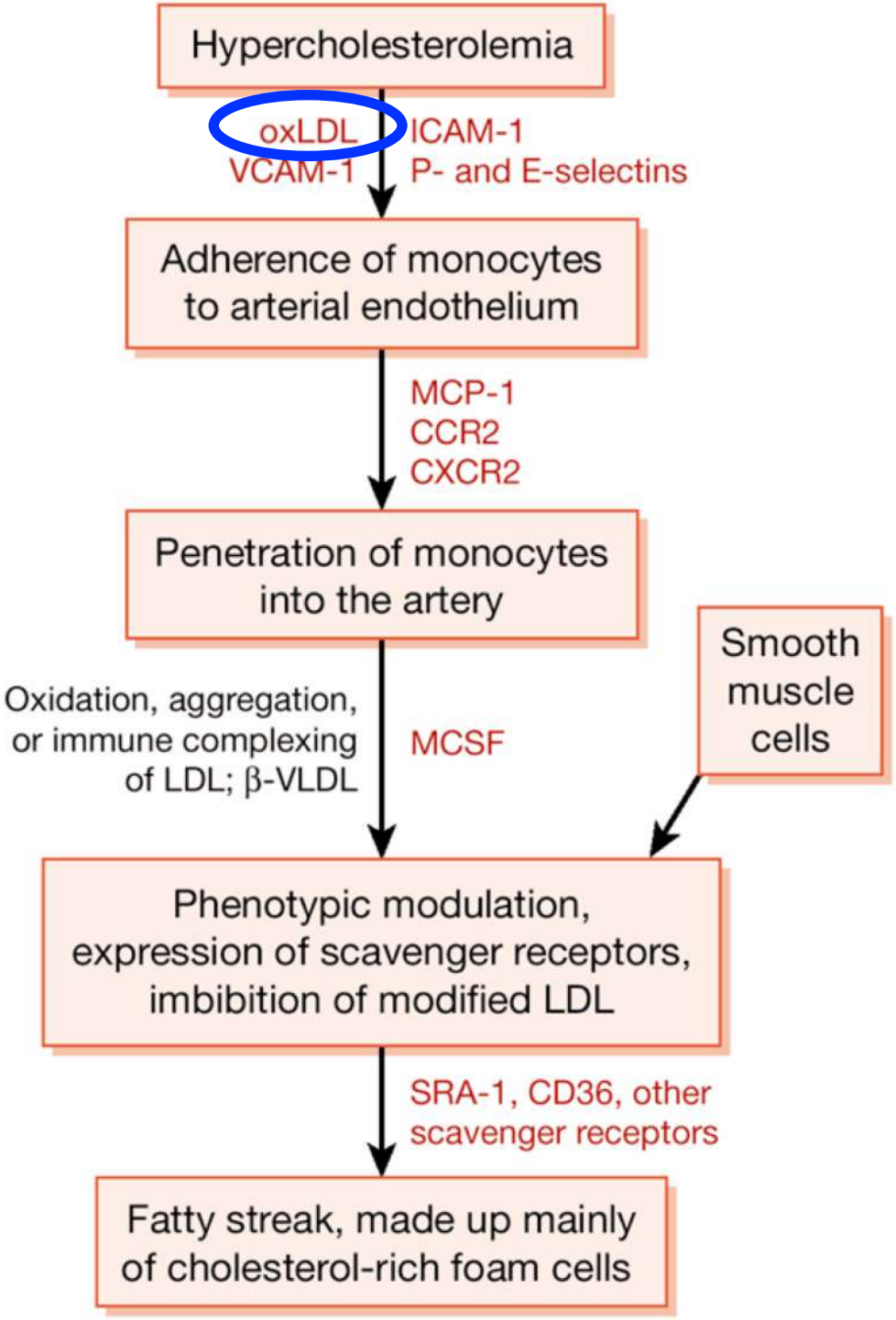
Souilhol C et al. Rev Cardiol. 2020 17:52-63.

Meccanismi di reclutamento dei monociti nell'intima dell'arteria e differenziamento in macrofagi



Circulating monocytes attach to endothelial cells by cell adhesion molecules that are induced in response to inflammatory signals. Selectins mediate low-affinity interactions that permit leukocyte rolling, whereas integrins mediate firm adhesion. Monocytes migrate through the endothelial layer into the intima, where they differentiate further into macrophages in response to locally produced factors such as monocyte colony-stimulating factor (M-CSF). This program of differentiation includes upregulation of scavenger receptor A (SR-A), CD36 and other receptors for oxLDL.

Scavenger receptors agiscono da PRR multifunzionali



Sequenza di eventi che genera le strie lipidiche

ICAM-1, intracellular adhesion molecule 1;

VCAM-1, vascular cell-adhesion molecule 1;

MCP-1, monocyte chemoattractant protein 1;

CCR2, CC chemokine receptor 2**;**

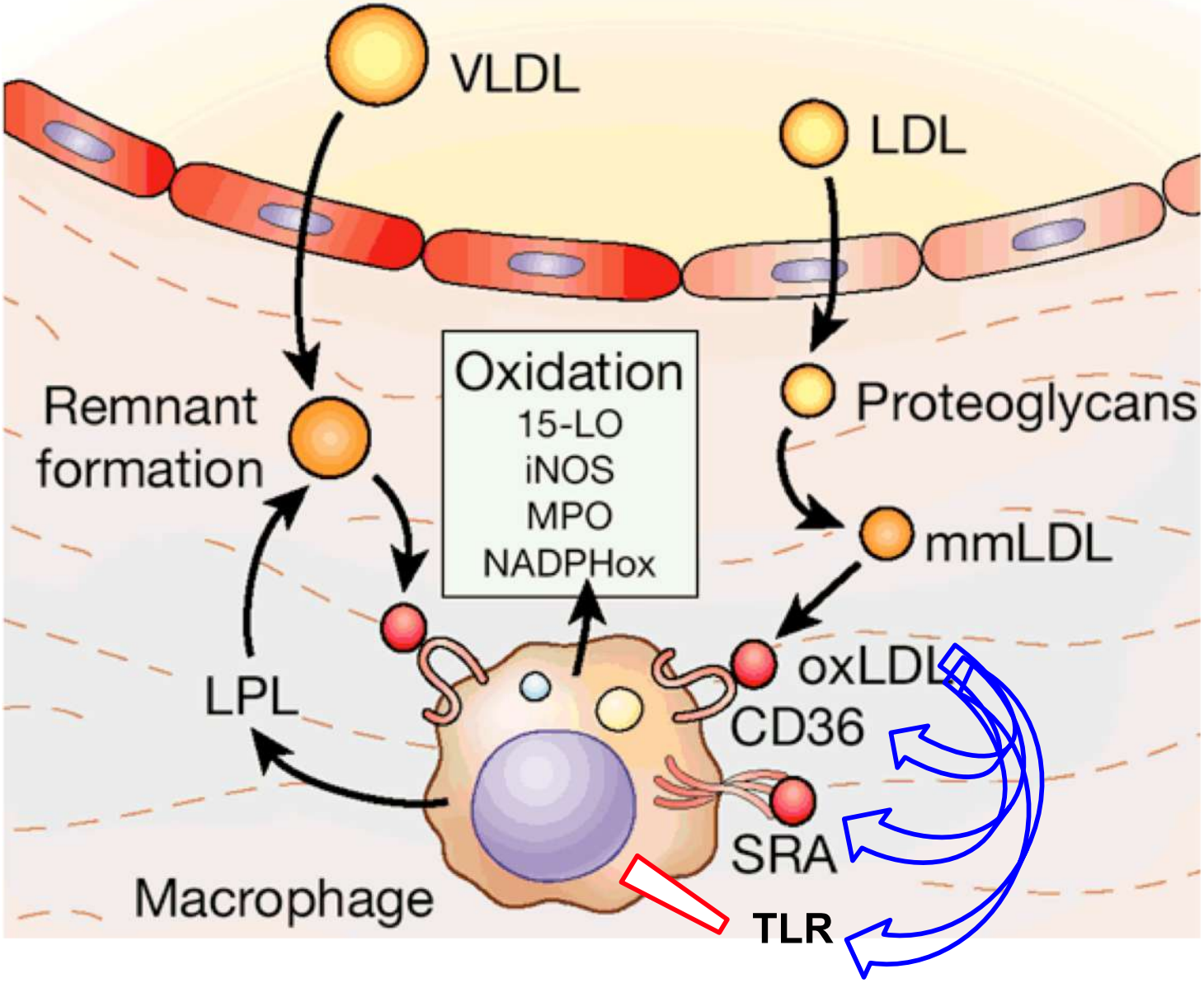
CXCR2, CX chemokine receptor 2 (IL8R)

VLDL, very-low-density lipoprotein;

MCSF, monocyte colony-stimulating factor.

Modificazione delle LDL e legame ai recettori spazzini e ai TLRs

Meccanismi che contribuiscono alla formazione delle cellule schiumose (foam cells)



LDL penetrates into the artery wall where it can adhere to **proteoglycans**. These interactions are thought to trap the LDL particles and increase their susceptibility to oxidation.

Enzymes contributing to LDL oxidation include lipoxygenases, MPO and iNOS. VLDL particles are subject to modification by LPL. The resulting remnant particles are also subject to trapping by proteoglycans, oxidative modification and uptake by macrophages. mmLDL, minimally modified LDL; SRA, scavenger receptor class A.

Meccanismi coinvolti nell'ossidazione delle LDL

Enzimatici

- Lipossigenasi
- Mieloperossidasi
- Sintasi inducibile dell'NO (iNOS)
- NADPH ossidasi

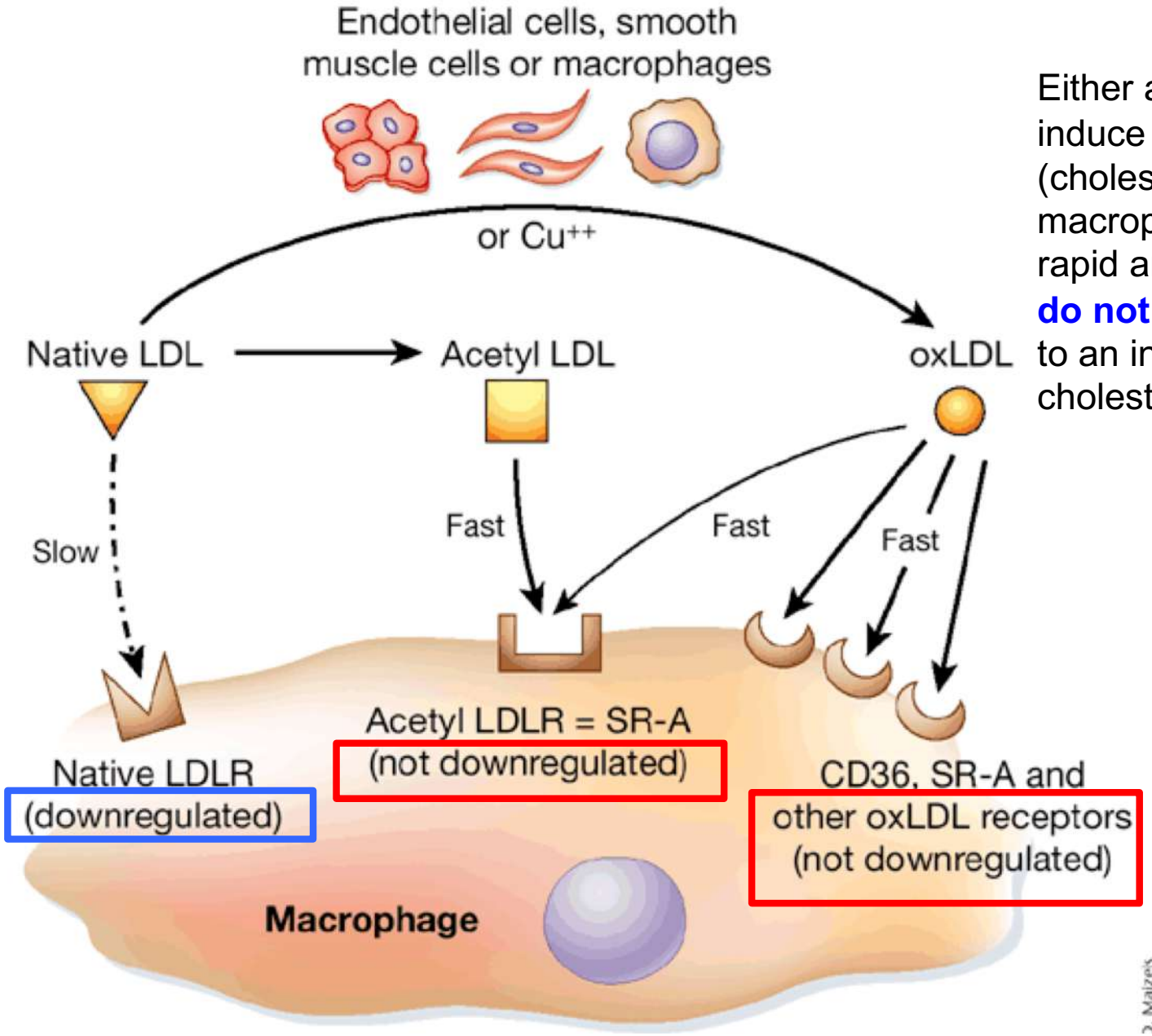
Specie reattive dell'ossigeno e dell'azoto

Functions of oxLDL and its products, oxidized phospholipids and oxysterols

Functions:

Mitogenic function on macrophages and smooth muscle cells
Chemotactic action on monocytes and T cells
Cytotoxic activity on endothelial cells
Induce monocyte binding to endothelial cells
Mimic effects of platelet-activating factor
Increase tissue factor activity
Increase expression of monocyte colony-stimulating factor and monocyte chemoattractant protein 1
Increase expression of vascular cell-adhesion molecule 1
Induce Fas-mediated apoptosis
Induce expression of interleukins 1 and 8
Inhibit nitric oxide release or function
Increase collagen synthesis in smooth muscle cells
Increase intracellular calcium
Activate nuclear factor-κB
Induce expression of type 1 metalloproteinase

Solo le LDL modificate possono indurre la formazione delle cellule schiumose



Either acetyl LDL or oxLDL can induce foam-cell formation (cholesterol accumulation in macrophages) because uptake is rapid and the **scavenger receptors do not downregulate** in response to an increase in cellular cholesterol.

Le LDL modificate sono immunogeniche e si comportano da "neoantigeni" o "self alterato"

Produzione di Ig

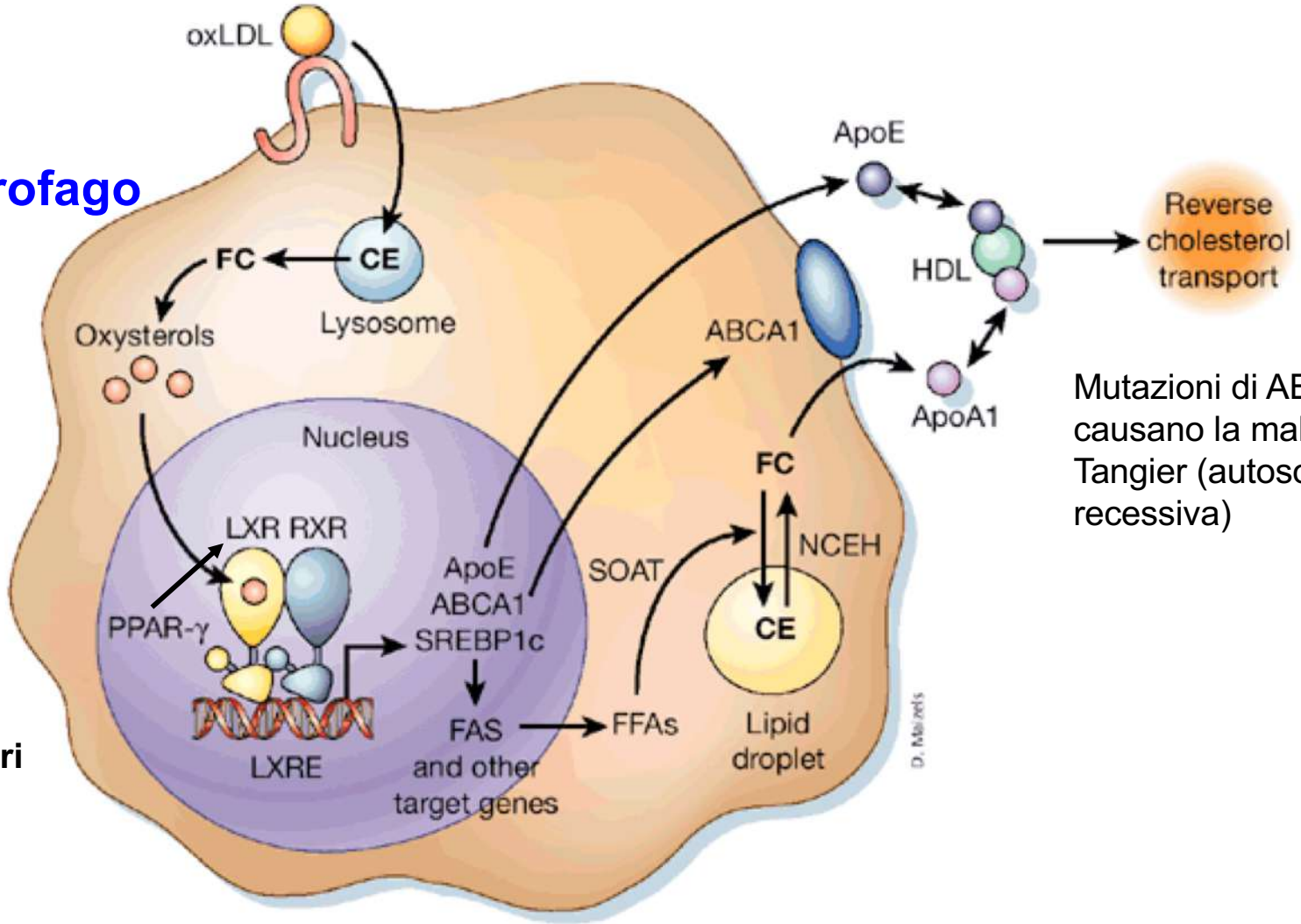
- Anti-LDL
- Anti-oxLDL
- Anti-ApoB
- Anti-PC

Cellula schiumosa da topo ipercolesterolemico

Modelli murini ipercolesterolemici
topi LDLR $^{-/-}$ oppure topi ApoE $^{-/-}$

Bright red cytoplasmic staining represents lipid droplets reflecting massive accumulation of cholesterol esters. Original magnification 314.

Pathway cellulare per la regolazione dell'omeostasi del colesterolo

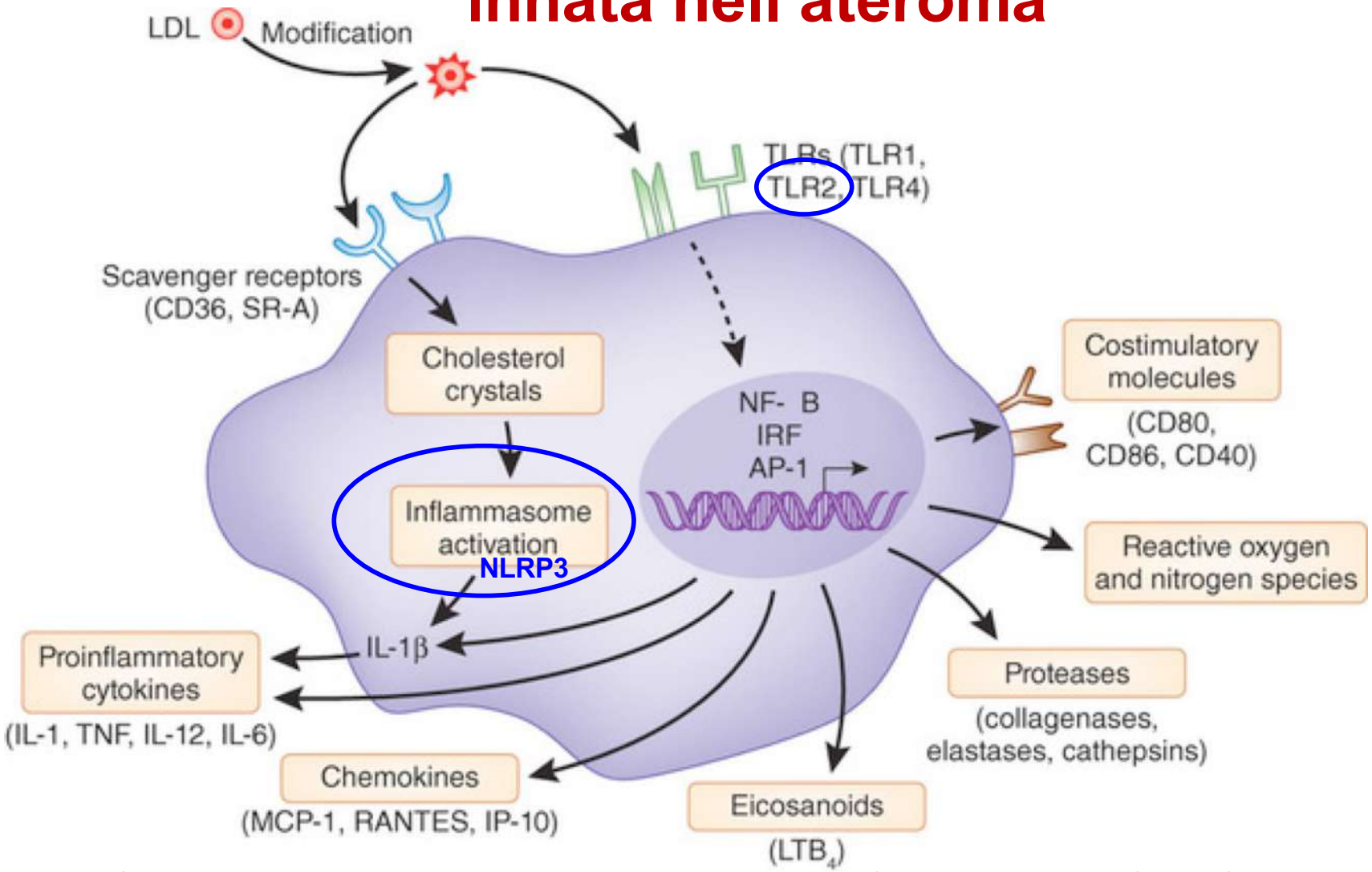


LXRα e β sono regolatori dell'omeostasi del colesterolo ma hanno anche effetti anti-infiammatori

Mutazioni di ABCA1 causano la malattia di Tangier (autosomica recessiva)

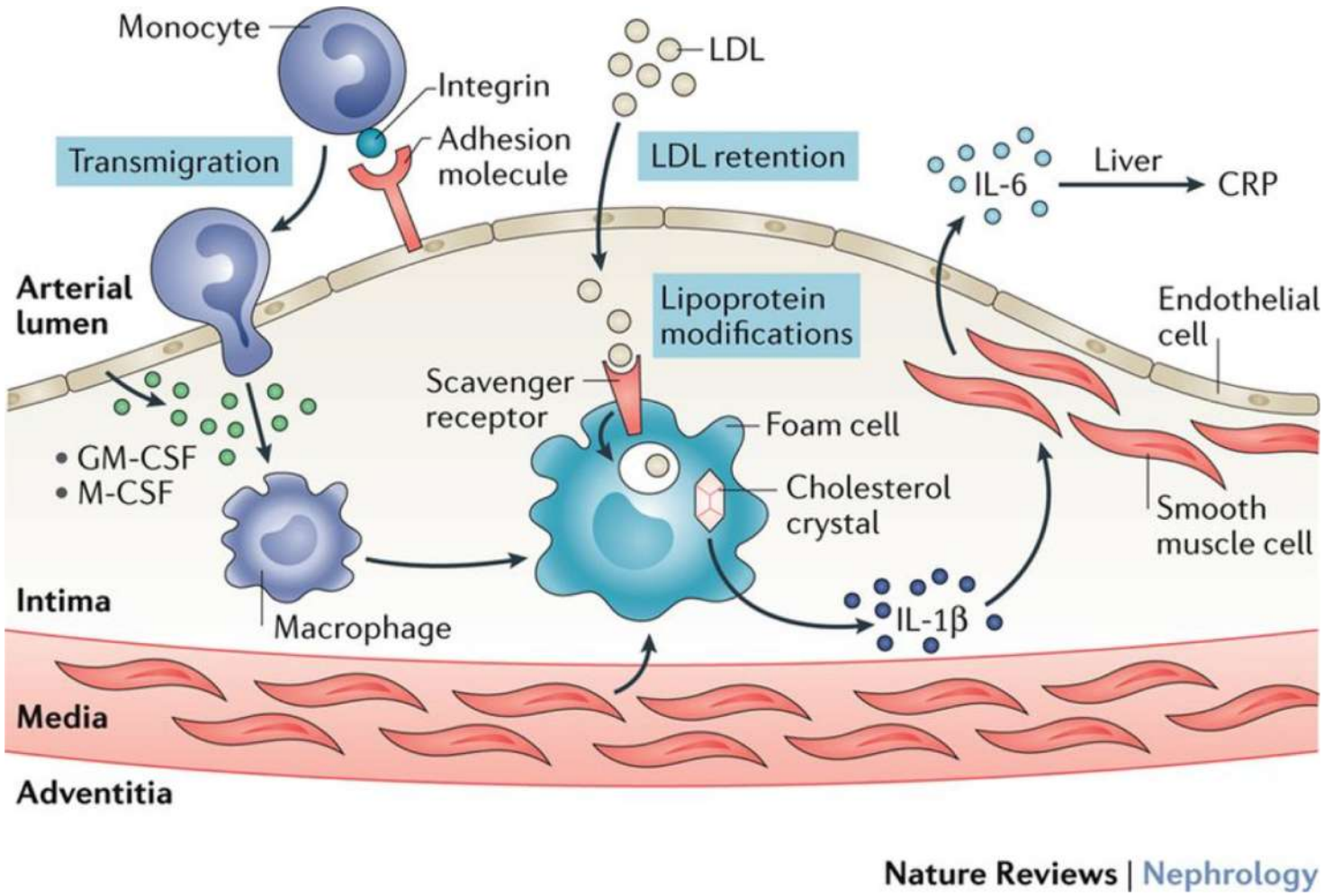
Oxysterols generated from free cholesterol (FC) activate LXR–RXR heterodimers, resulting in increased transcription of target genes. These genes include those encoding **ApoE** and **ABCA1**, which are linked to efflux of cholesterol to extracellular acceptors, and **fatty acid synthetase** (FAS), which leads to the synthesis of free fatty acids (FFAs) used for cholesterol esterification by SOAT. PPARs (peroxisome proliferator activated receptor) may promote cholesterol efflux by inducing LXR expression. CE, cholesterol ester; LXR, liver X receptor; RXR, retinoid X receptor; NCEH, neutral cholesterol ester hydrolase; **SREBP, sterol regulatory element-binding protein.**

Attivazione delle risposte dell'immunita' innata nell'ateroma



Macrophages, DCs and endothelial cells display a large repertoire of PRRs. Uptake of modified LDL particles such as oxLDL through scavenger receptors leads to the intracellular accumulation of cholesterol that can activate the inflammasome, leading to IL-1β secretion. Components of modified LDL can also ligate TLRs, triggering an intracellular signaling cascade that leads to the expression of a series of genes encoding proinflammatory molecules, including cytokines, chemokines, eicosanoids, proteinases, oxidases and costimulatory molecules. NF-κB, IRF and AP-1 are transcription factors

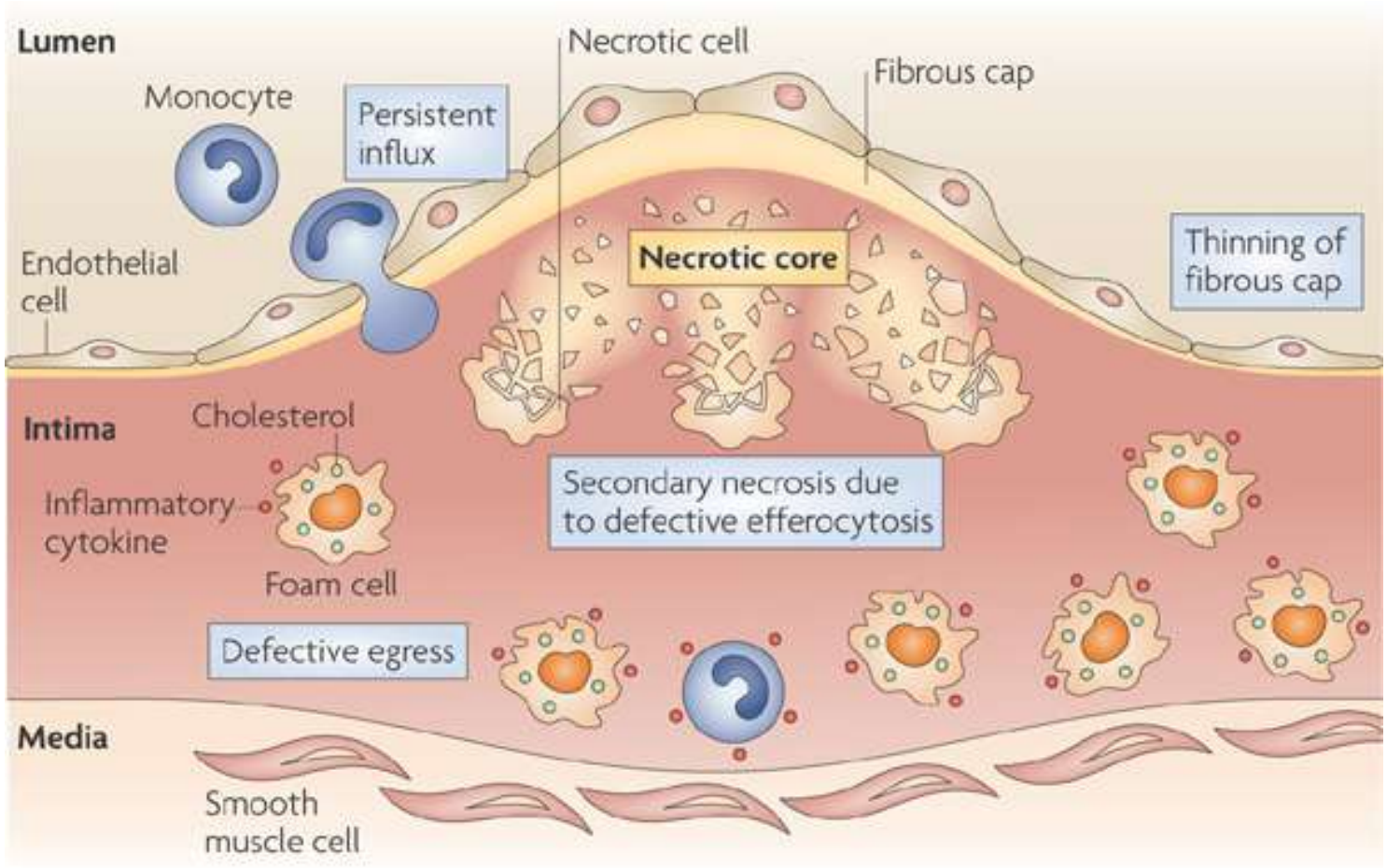
Innate immune responses in atherosclerosis



LDL retention initiates atherosclerosis development. Subendothelial accumulation of lipoproteins leads to upregulation of adhesion molecules on the endothelial surface and recruitment of monocytes to the forming lesion. Monocytes transmigrate into the subendothelial space and differentiate into macrophages in response to macrophage-colony stimulating factor (M-CSF) and granulocyte–macrophage colony stimulating factor (GM-CSF) produced by endothelial cells. **Smooth muscle cells can also transdifferentiate into macrophage-like cells**.

Scavenger-receptor-mediated uptake of lipoproteins by macrophages leads to the formation of foam cells. Cholesterol crystals form in these cells and activate the NACHT, LRR and PYD domains-containing protein 3 inflammasome, resulting in release of IL-1β, which stimulates smooth muscle cells to produce IL-6. Both IL-1β and IL-6 exert proinflammatory effects. In addition, circulating IL-6 might signal to the liver to produce C-reactive protein (**CRP**). The levels of this biomarker are increased in patients with atherosclerotic cardiovascular disease.

Meccanismi difettivi nella placca



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Inflammatory cells, including lipid-laden macrophage foam cells, accumulate in the intima owing to the persistent influx of new cells, particularly monocytes, and defective egress of the resident cells. Moreover, apoptotic macrophages are not efficiently cleared by efferocytosis and so they undergo secondary necrosis. This process contributes to the formation of the necrotic core, which promotes plaque disruption, particularly thinning of the fibrous cap. If the process continues, the fibrous cap breaches, leading to lumenal thrombosis and arterial occlusion.

Inflammation versus resolution

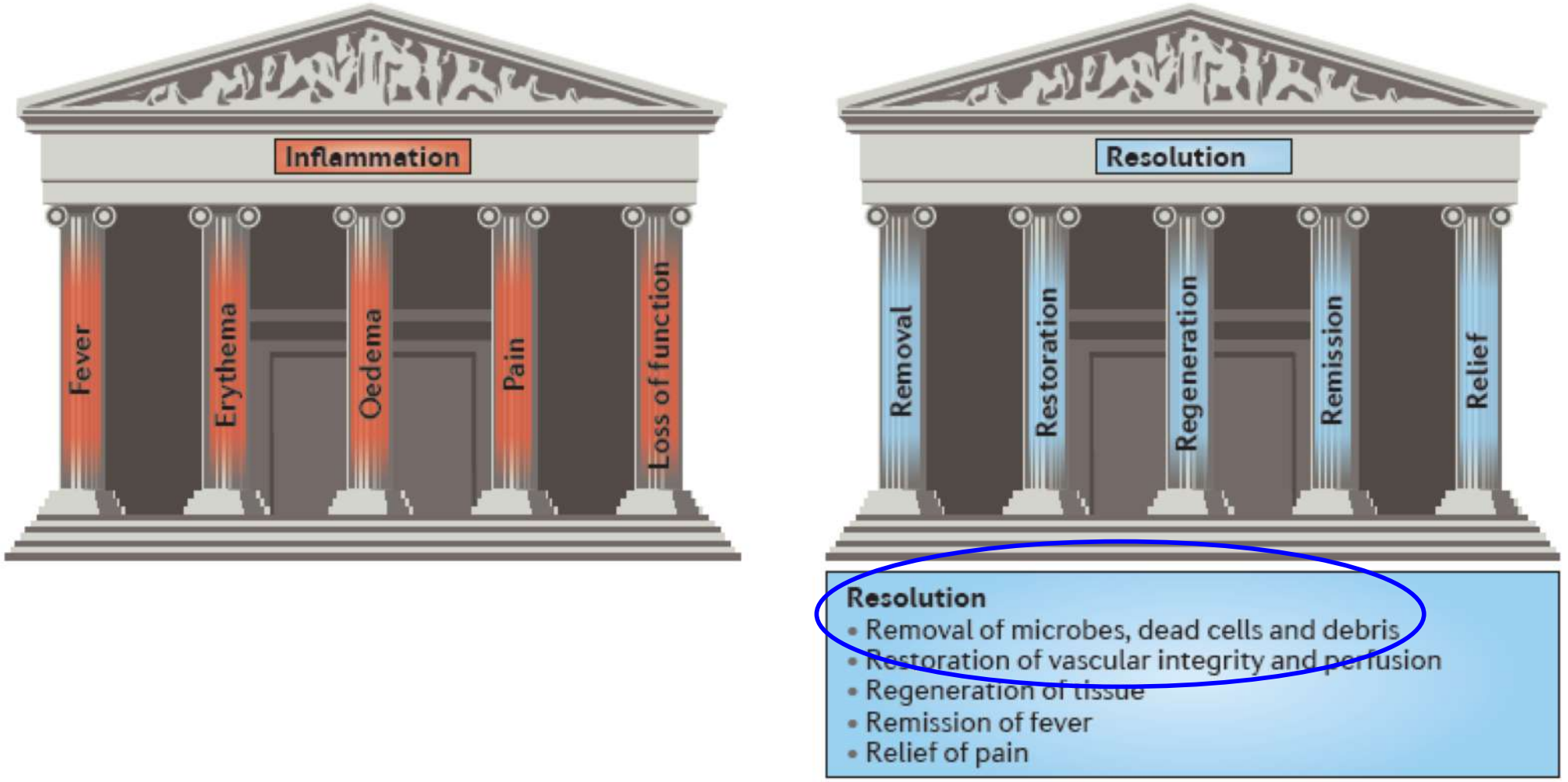
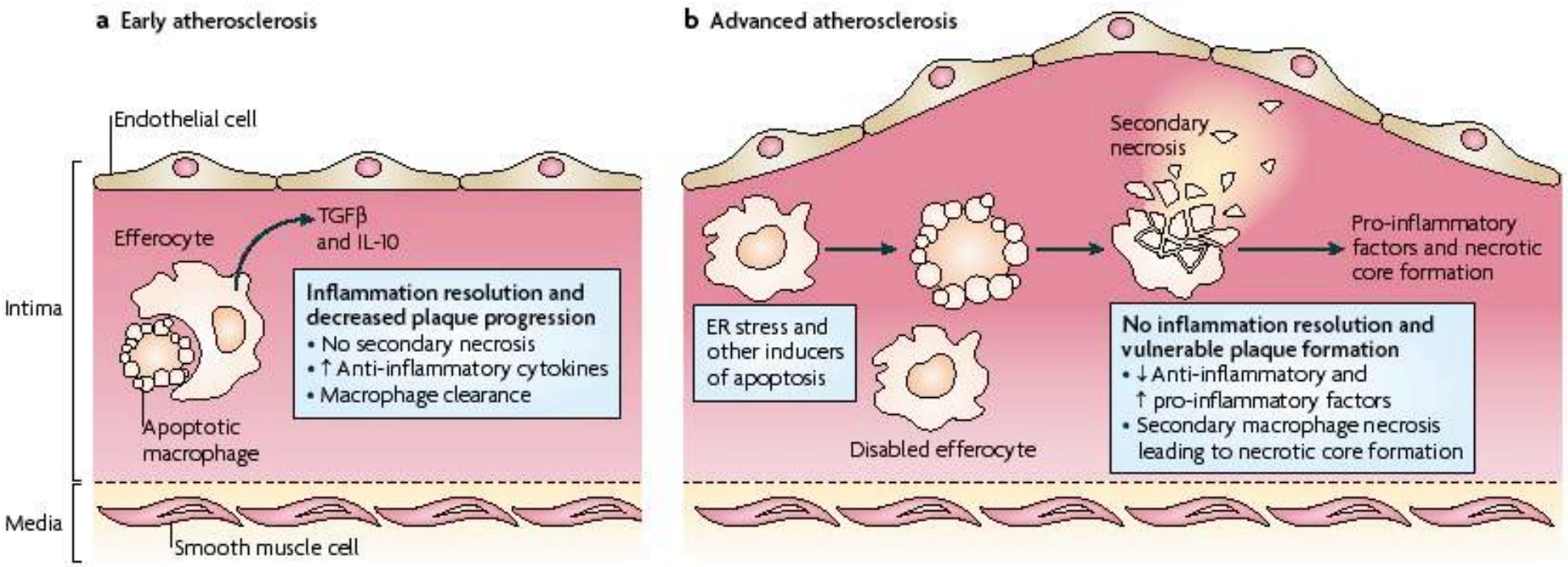


Figure 1 | **Cardinal signs of inflammation and its resolution.** Tissue- and organism-level responses to inflammation have been well recognized for centuries and can be summarized as the 'five pillars of inflammation'; namely, *calor* (fever), *rubor* (redness), *tumor* (swelling and oedema), *dolor* (pain) and *functio laesa* (loss of function). With the recognition that the resolution of inflammation is an active process, recent research has identified molecular and cellular processes that promote catabasis. These can be summarized as the 'five pillars of resolution'; that is, removal of microorganisms, dead cells and debris, restoration of vascular integrity and perfusion, tissue regeneration, remission of fever and relief from inflammatory pain.

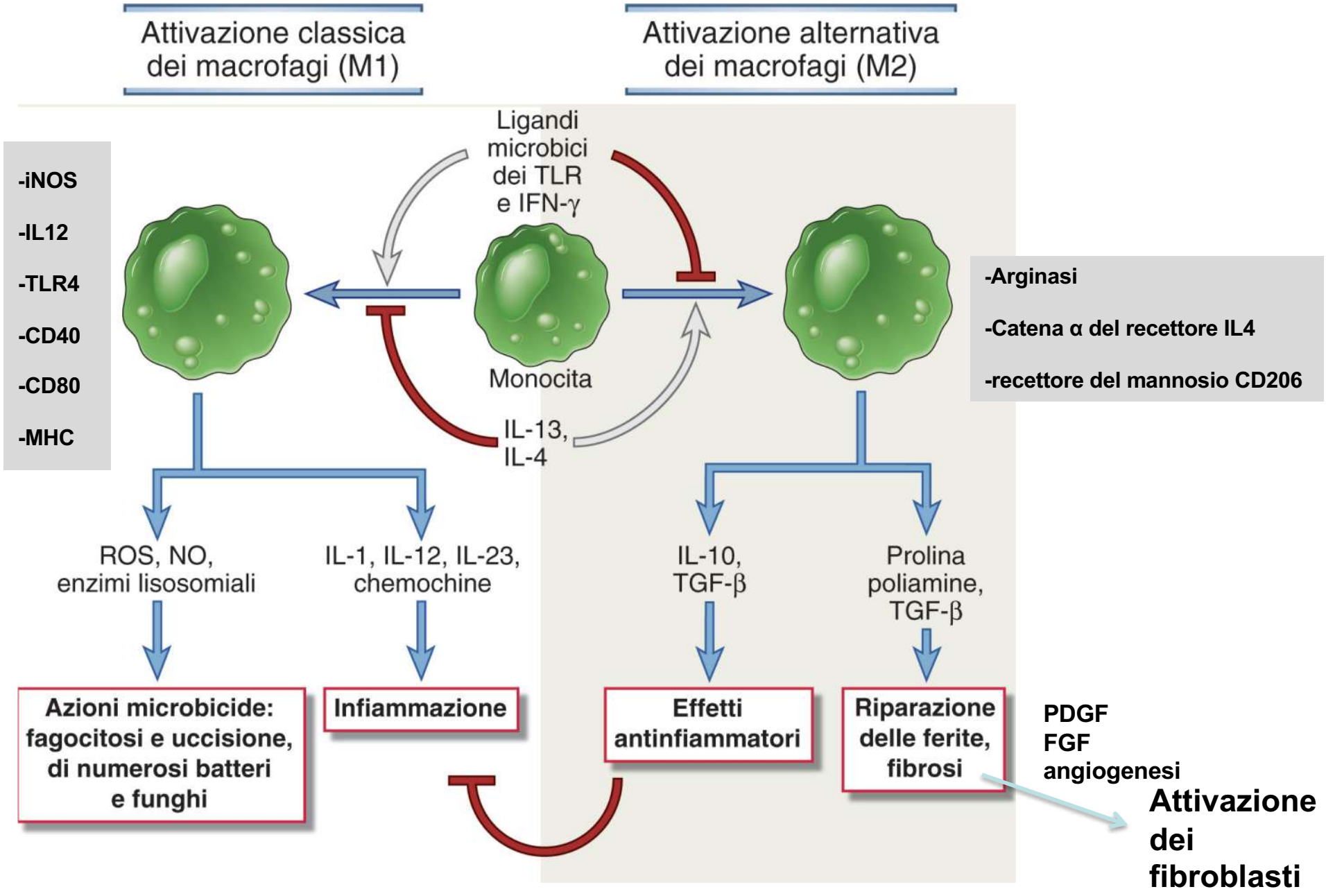
Differenze nell'efferocitosi e nella risoluzione dell'infiammazione nella placca neo-formata e nella placca allo stadio avanzato



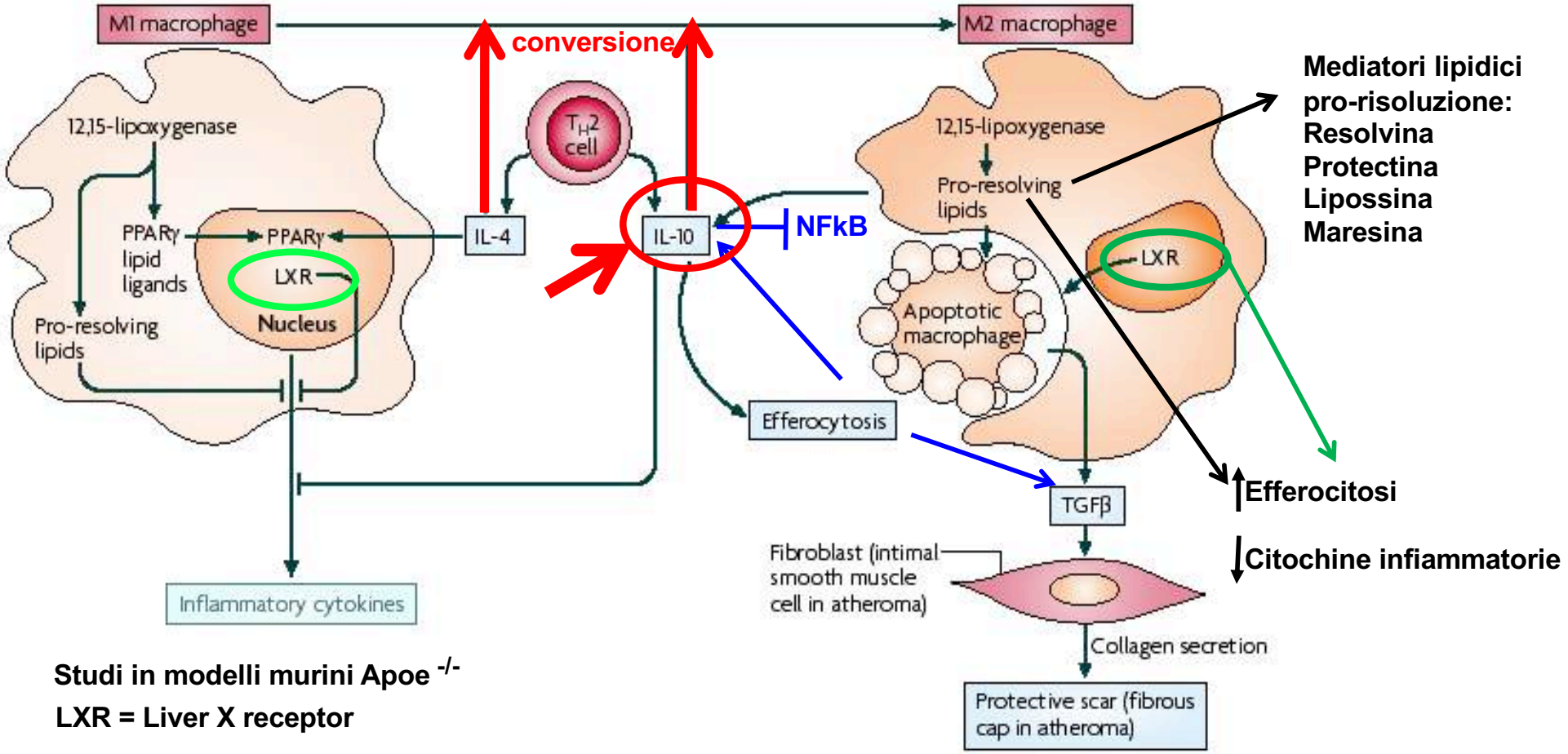
a | In early atherosclerotic lesions, efferocytosis is efficient, leading to rapid clearing of apoptotic macrophages. This process prevents secondary necrosis, elicits the production of anti-inflammatory cytokines and clears macrophages from the lesions. The result of this inflammation resolution process is decreased plaque progression.

b | In advanced lesions, efferocytes do not function properly and thus apoptotic macrophages, which arise in part from endoplasmic reticulum (ER) stress-induced apoptosis, become secondarily necrotic. The necrotic material is a stimulus for inflammation, and the normal anti-inflammatory signalling associated with efferocytosis does not occur. Moreover, an important mechanism for ridding the lesion of inflammatory macrophages is lost. Thus, inflammation resolution fails to occur normally, and necrotic macrophages coalesce into necrotic cores. These features define plaques that are vulnerable to rupture, which in turn can trigger acute lumenal thrombosis and arterial occlusion. IL-10, interleukin-10; TGFβ, transforming growth factor-β.

Attivazione dei macrofagi: classica o alternativa



Mediatori che potrebbero indurre risoluzione dell'infiammazione nel processo aterogenico

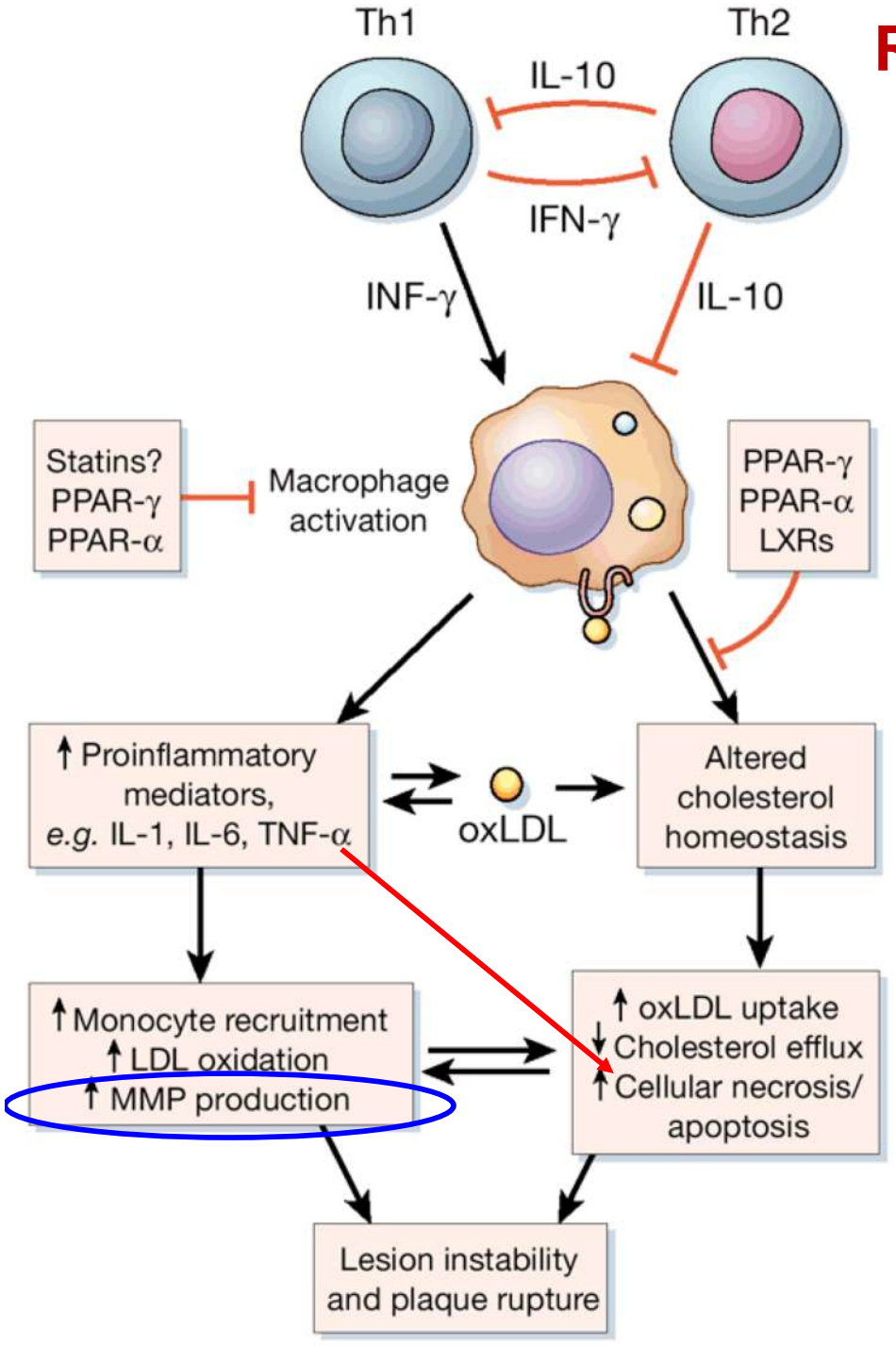


Studi in modelli murini Apoe $^{-/-}$

LXR = Liver X receptor

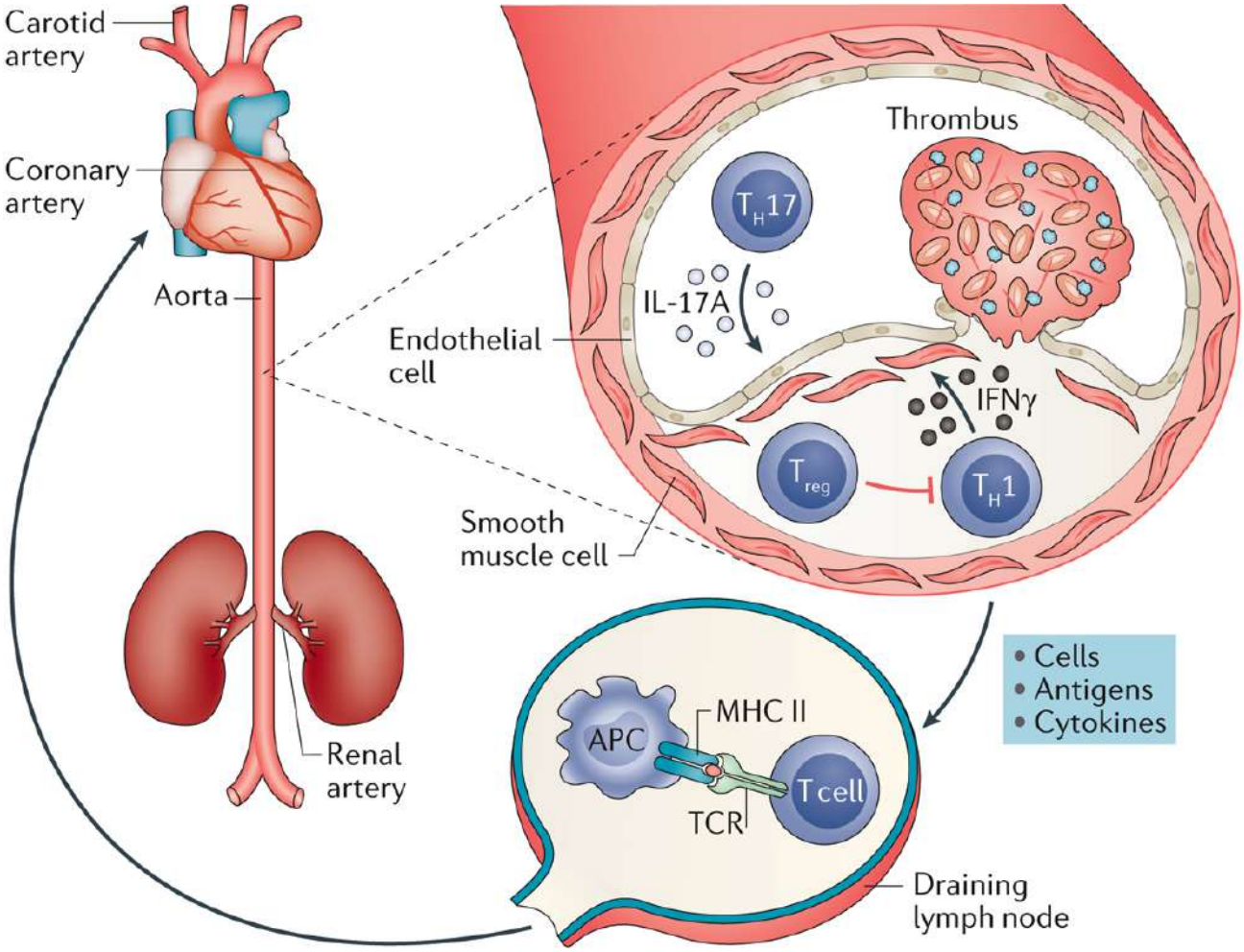
Figure 2 | **Examples of integration of inflammation resolution by resolution mediators.** Interleukin-10 (IL-10), which is secreted by T helper 2 (T_H2) cells and by efferocytes during apoptotic cell clearance, blocks inflammatory responses in classically activated M1 macrophages, stimulates the conversion of M1 macrophages to alternatively activated M2 macrophages and enhances efferocytosis itself. T_H2 cells also secrete IL-4, which (similarly to IL-10) promotes M2 macrophage formation. IL-4 also induces the transcription factor peroxisome proliferator-activated receptor-γ (PPARγ), which suppresses inflammation in macrophages. Moreover, lipid ligand activators of PPARγ are synthesized through the action of 12,15-lipoxygenase, which also leads to the synthesis of pro-resolving lipids, including lipoxins, resolvins and protectins. These lipid mediators suppress inflammatory cytokine production and stimulate efferocytosis. Activation of another family of transcription factors, the liver X receptors (LXRs), links two key features of inflammation resolution: suppression of inflammatory cytokine production and enhancement of efferocytosis. Successful efferocytosis leads to the production of transforming growth factor-β (TGFβ), which stimulates formation of scar tissue in wound healing during inflammation resolution and the protective fibrous cap in atheroma.

Ruolo dei linfociti Th1 e Th2 nello sviluppo dell'aterosclerosi



Th1 cytokines such as IFNγ promote macrophage activation, leading to enhanced production of inflammatory mediators. These factors promote further entry of monocytes, increase expression of gene products linked to LDL oxidation, and increase the production of matrix metalloproteinases (MMPs) that weaken the fibrous cap. IFNγ inhibits expression of ABCA1 and, in concert with other inflammatory mediators such as tumor necrosis factor- α (TNFα), promotes cell death and formation of the necrotic core. These processes act to stimulate lesion growth and increase susceptibility to plaque rupture. Proinflammatory responses to Th1-derived mediators are counteracted by Th2 cytokines, such as IL-10. Oxidized LDL stimulates further inflammatory responses and disordered cholesterol homeostasis. LXR agonists stimulate increased cholesterol efflux, whereas PPAR-α and PPAR-γ agonists inhibit inflammatory responses and stimulate LXR- expression.

Adaptive immunity in atherosclerosis

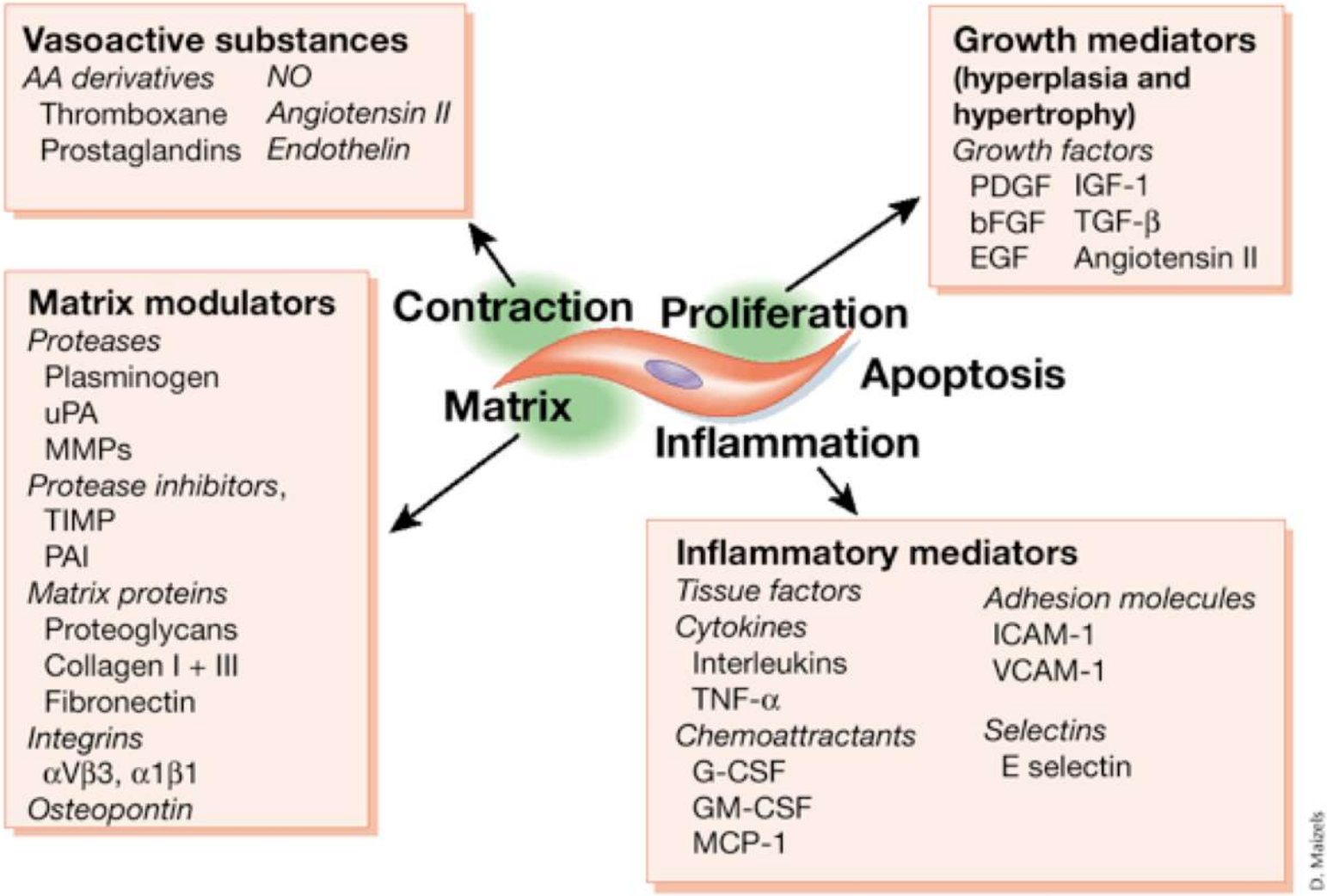


Gisterå, A. & Hansson, G. K. (2017) The immunology of atherosclerosis *Nat. Rev. Nephrol.*

Manifestations of atherosclerotic disease arise when plaques undergo rupture or superficial erosion. Stroke might be a consequence of these thrombotic events in a carotid artery, and myocardial infarction a consequence of thrombosis in a coronary artery. Compromised blood flow in a renal artery owing to a large plaque might result in secondary hypertension. Adaptive immunity has a crucial role in plaque formation, stability and rupture. T helper type 17 (T_H17) cells secrete IL-17A, which promotes plaque stability by enhancing collagen deposition by smooth muscle cells, leading to increased cap formation. T_H1 cells produce interferon-γ (IFNγ), which promotes macrophage activation and inflammation, and also counteracts cap formation by enhancing collagen degradation and inhibiting smooth muscle cell proliferation. These effects lead to vulnerable plaques that can rupture and cause thrombotic events. Regulatory T (T_{reg}) cells control the proinflammatory actions of other T_H cell subsets and limit T_H1 cell responses in the plaque.

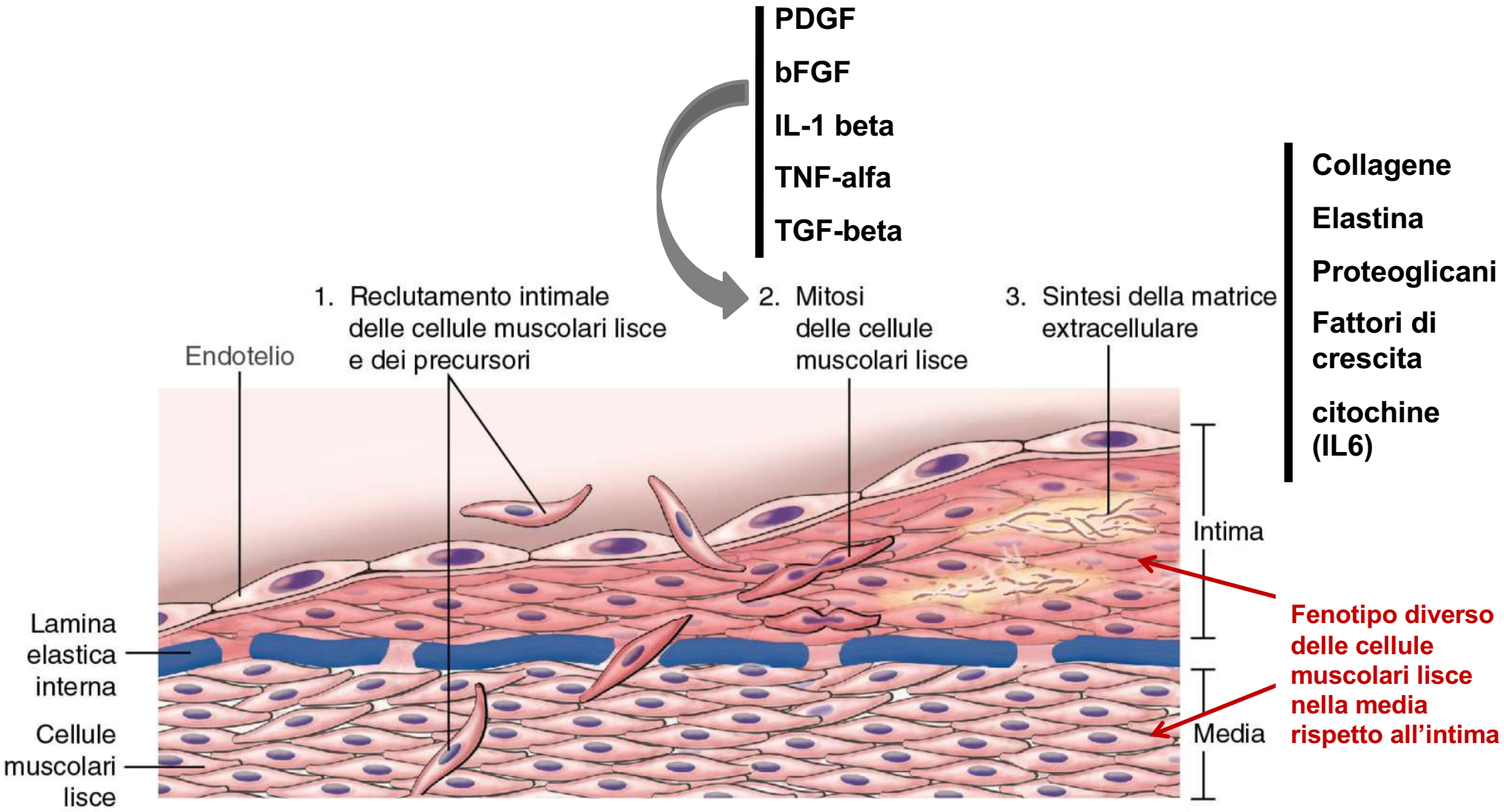
Lipid-laden foam cells in plaques have reduced migratory capacity, but other immune cells can potentially migrate to draining lymph nodes in which important immune interactions occur. The aorta-draining lymph node is an important site in which plaque-derived antigens can be presented by antigen presenting cells (APCs) to a large repertoire of T cells. When a T_H cell becomes activated it differentiates into one of the effector T cell subtypes, depending on the local cytokine milieu, which is in part dictated by cytokines drained from the plaque. Effector T cells recirculate in the blood and migrate to inflammatory sites, such as the atherosclerotic lesion. Local presentation of antigens in atherosclerotic plaques can reactivate T cells, leading to further differentiation.

Cellule muscolari lisce nell'ateroma



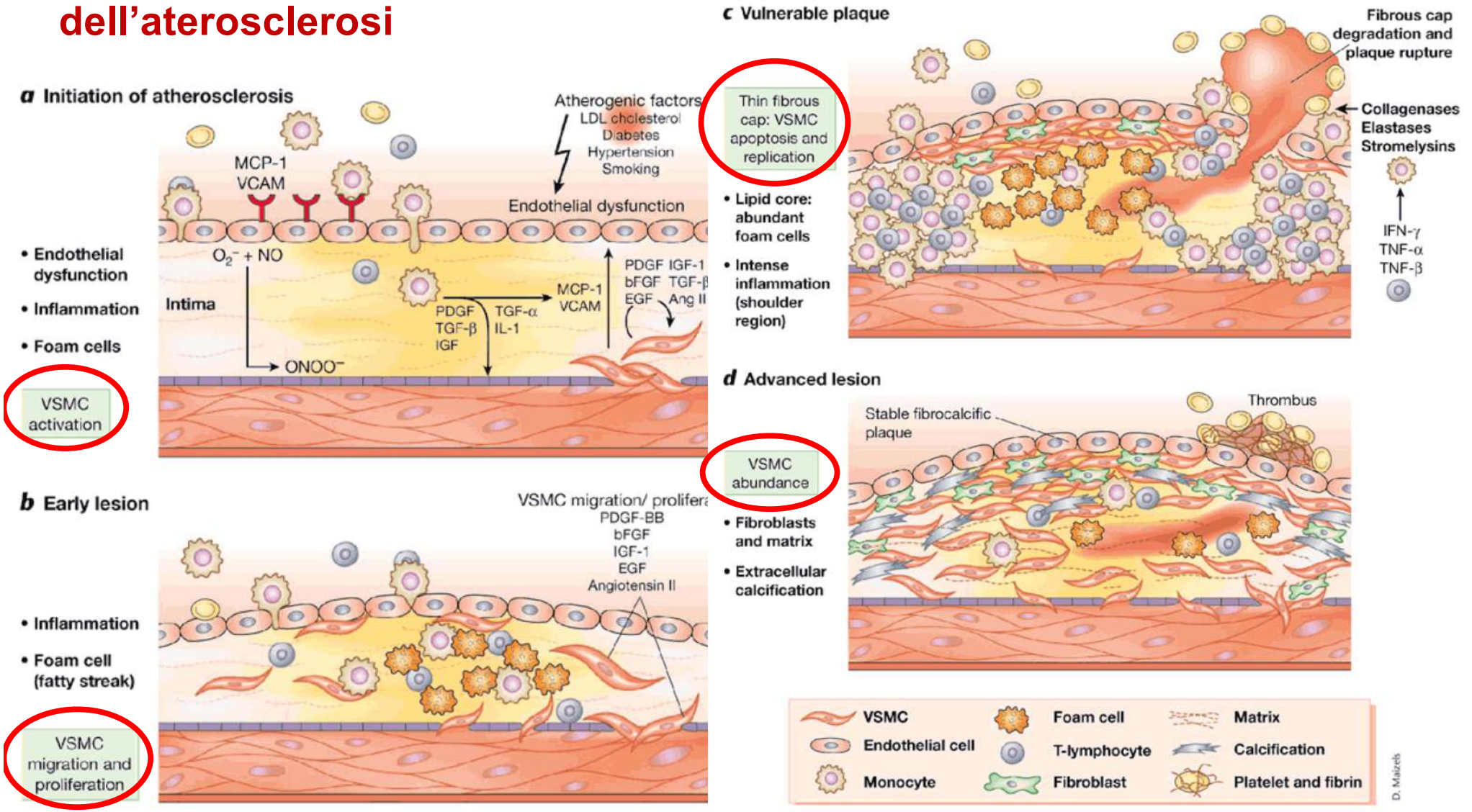
VSMCs mediate proliferation, inflammation, matrix alterations and contraction.
Many of the mediators have multiple functions. For example, angiotensin is a vasoconstrictor, but also stimulates proliferation and inflammation. The list here of mediators secreted by VSMCs is not complete. AA, arachidonic acid; TNF, tumor necrosis factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–monocyte colony-stimulating factor; MCP, monocyte chemoattractant protein; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; IGF, insulin-like growth factor; TGF, transforming growth factor; uPA, urokinase-type plasminogen activator; MMPs, matrix metalloproteinases; TIMP, tissue inhibitor of metalloproteinases; PAI, plasminogen activator inhibitor.

Ruolo delle cellule muscolari lisce nella formazione placca fibrosa



Patogenesi dell'ispessimento intimale che evidenzia la migrazione intimale e la proliferazione delle cellule muscolari lisce e la produzione di proteine della matrice extracellulare ed altri fattori

La funzione delle cellule muscolari lisce durante gli stadi progressivi dell'aterosclerosi



Cardiovascular risk factors alter the vascular endothelium (EC), which triggers a cascade of events, including the recruitment of leukocytes. Cytokines and growth factors are released by inflammatory cells and vascular cells, generating a highly mitogenic milieu. VSMCs migrate, proliferate and synthesize extracellular matrix components on the luminal side of the vessel wall, forming the fibrous cap of the atherosclerotic lesion. Inflammatory mediators ultimately induce thinning of the fibrous cap by expression of proteases, rendering the plaque weak and susceptible to rupture and thrombus formation. In advanced disease, fibroblasts and VSMCs with extracellular calcification give rise to fibrocalcific lesions. LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; VCAM, vascular cell adhesion molecule; PDGF-BB, platelet-derived growth factor (BB, -chain homodimer); TNF, tumor necrosis factor; TGF, transforming growth factor; IL, interleukin 1; IGF, insulin-like growth factor; bFGF, basic fibroblast growth factor; Ang II, angiotensin II; EGF, epidermal growth factor; IFN, interferon.

Evolution and stabilization of 'vulnerable' atherosclerotic plaques