The vascular biology of atherosclerosis

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The 20th century witnessed a remarkable evolution in concepts concerning the pathogenesis of atherosclerosis

Atherosclerosis became epidemic as populations increasingly survived early mortality associated with communicable disease and malnutrition

atherosclerosis also displays heterogeneity in time, this has both chronic and acute manifestations

Few human disease have a longer '*incubation*' period than atherosclerosis , which begins to affect the arteries of many Americans in the second and third decades of life

- Many young Americans have abnormal thickening of the coronary arterial intima
- Despite this indolent time course and prolonged period of clinical inactivity the dreaded complications of atheroma- MI, UA , stroke- typically occurs suddenly and often without warning

STRUCTURE OF THE NORMAL ARTERY

- ***Cell Types Composing the Normal artery***
- endothelial cell(EC)
- Smooth muscle cell(SMC)
- ***Layers of the Normal Artery***
- Intima
- Tunica media
- Adventitia

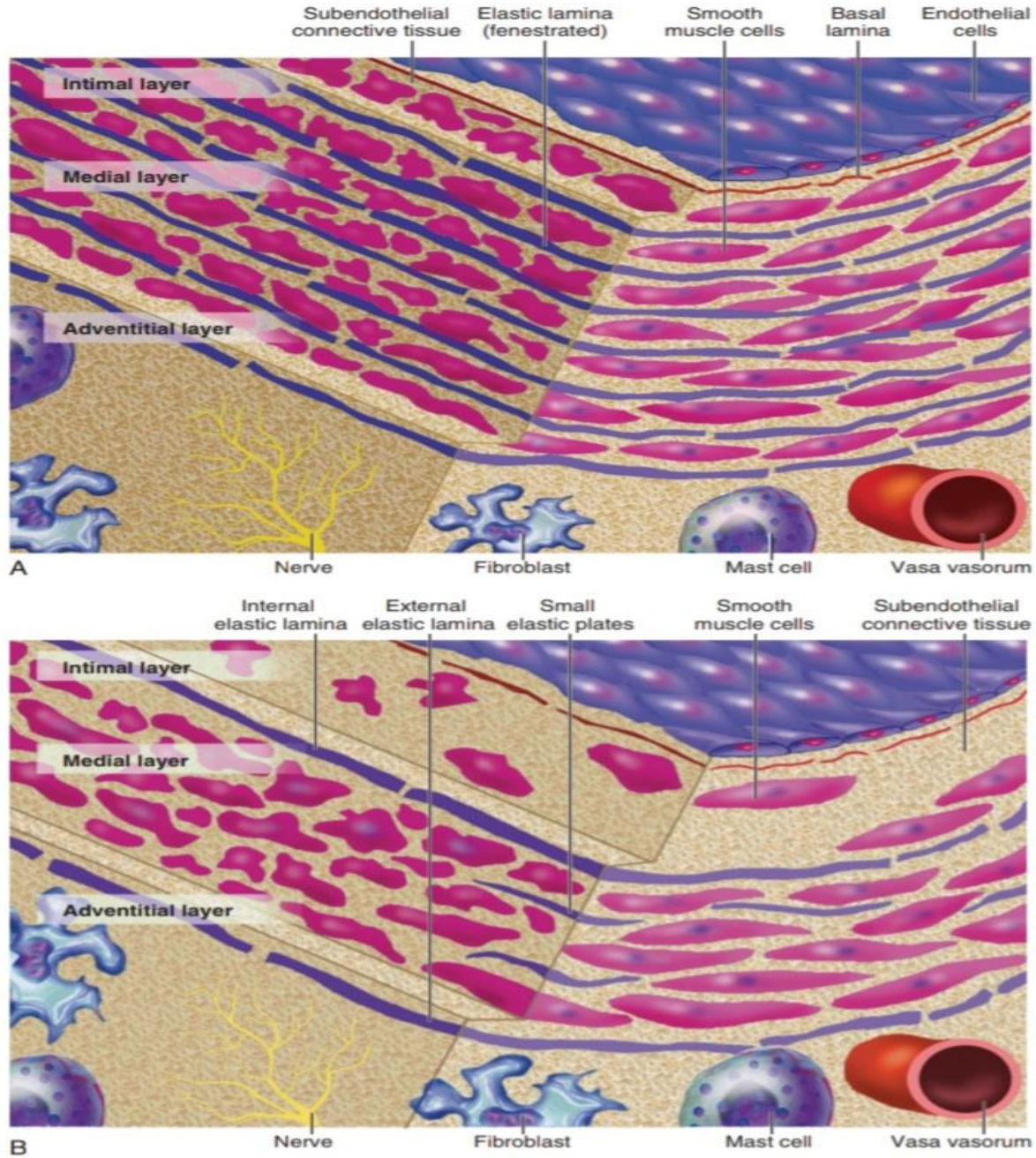


FIGURE 41-4 The structures of normal arteries. **A,** Elastic artery. Note the concentric laminae of elastic tissue that form sandwiches with successive layers of SMCs. Each level of the elastic arterial tree has a characteristic number of elastic laminae. **B,** Muscular artery. In the muscular artery, the SMCs are surrounded by a collagenous matrix but lack the concentric rings of the well-organized elastic tissue characteristic of larger arteries.

Atherosclerosis initiation

- The first step in human atherogenesis remain largely conjectural
- ***Extracellular lipid accumulation:*** On initiation of n atherogenic diet, typically rich in cholesterol and saturation fat, small lipoprotein particles accumulate in the intima
- Lipoprotein particles bound to the proteoglycan have increased susceptibility to the oxidative or other chemical modifications

Atherosclerosis initiation, cont.'s

- ***Leukocyte Recruitment and Retention***:
- Another hallmark of atherogenesis, *leukocyte recruitment* and accumulation, occurs early in lesion generation
- The normal EC generally resists adhesive interactions with leukocytes
- Very soon after initiations of hypercholesteremia ,leukocytes adhere to the endothelium and move between EC or penetrate through ECs (transcytosis) to inter the intima
- They begin to accumulate lipids and become *foam cells*

Atherosclerosis initiation, cont.'s

- ***Focality of Lesion Formation***
- The spatial heterogeneity of atherosclerosis is challenging to explain in mechanical terms
- Equal concentrations of blood borne risk factors such as lipoproteins bathe the endothelium throughout the vasculature
- It is difficult to envisage hoe injury resulting from inhalation of cigarette smoke could produce any local rather than global effect on arteries, yet stenosis caused by atheromas typically form focally
- Metacentric origin hypothesis of atherogenesis , positing that atheromas arise as benign leiomyoma of the artery wall

Atherosclerosis initiation, cont.'s

- The location of sites of lesion predication at proximal portions of arteries after branch points or bifurcations at flow dividers, suggest a hydrodynamic basis for early lesion development
- Arteries without many branches tend not develop atherosclerosis

Atherosclerosis initiation, cont.'s

- ***Intracellular Lipid Accumulation: Foam Cell formation***
- The monocyte, once recruited to the arterial intima, can imbibe lipid and become a foam cell or lipid-laden macrophage
- Scavenger receptors appear to mediate the excessive lipid uptake characteristic of foam cell formation
- Up to this point in the development of the nascent atheroma, the lesion consist primarily of lipid-engorged macrophages
- Complex features such as fibrosis , thrombosis, and calcification do not characterize the fatty streak, the precursor lesion of the complex atheroma
- Such fatty streaks can regress at least to some extent

EVOLUTION OF ATHEROMA

- ***Innate and Adaptive Immunity: Mechanism of Inflammation in Atherogenesis***
- The convergence of basic and clinical evidence has demonstrated a fundamental role for inflammation and immunity in atherogenesis
- The macrophage foam cells serve not only as reservoir for excess lipid but in establishes atherosclerotic lesion also furnish many pro inflammatory mediators
- This ensemble of inflammatory mediators can promote inflammation in the plaque and contribute to the progression of lesion
- The *innate immunity* describes this type of amplification of the inflammatory response that does not depend on antigenic stimulation

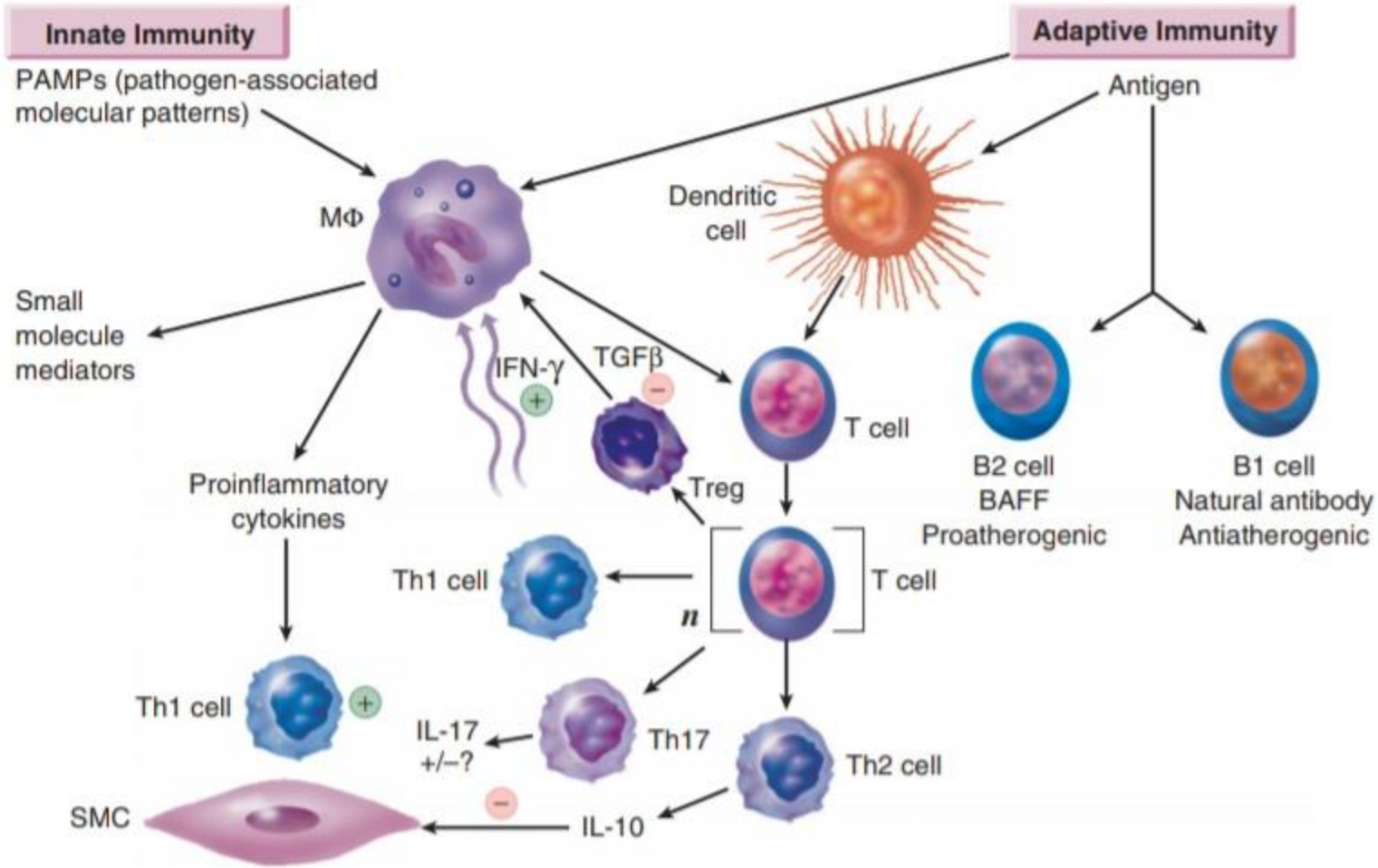


FIGURE 41-10 Innate and adaptive immunity in atherosclerosis. A diagram of the pathways of innate (*left*) and adaptive (*right*) immunity operating during atherogenesis. BAFF = B-cell activating factor; IFN-γ = interferon-γ; IL = interleukin; MΦ = macrophage; Th = T helper; TGF-β = transforming growth factor beta. *(After Hansson G, Libby P, Schoenbeck U, Yan ZQ: Innate and adaptive immunity in the pathogenesis of atherosclerosis. Circ Res 91:281, 2002.)*

Adaptive Immunity: Mechanism of Inflammation in Atherogenesis, cont.'s

- Evidence supports a prominent roll for antigen-specific or *adaptive immunity* in plaque progression
- Helper T cells(bearing CD4): Th1 & Th2
- Th1 elaborate proinflammatory cytokines : INF-gama , TNF-alfa…. Can lead to plaque destabilization and heightened thrombogenicity
- Th2 cytokines, such as IL10 can inhibit inflammation in the context of the atherogenesis
- Cytotoxic Tcells(bearing CD4) can promot cytolysis and apoptosis of the target cells(SMCs,Ecs,and macrophage
- The death of the all three cell types can occur in atherosclerotic lesion and may contribute to plaque progression and complication

Adaptive Immunity: Mechanism of Inflammation in Atherogenesis, cont.'s

- The roll of B cells and antibody in atherosclerosis remains incompletely explored
- B1 cells that produce natural antibodies, many of which recognize oxidatively modified LDL , can protect against experimental atherosclerosis
- B2 cells aggravate atherosclerosis in mice promoting proinflammatory cytokine production

EVOLUTION OF ATHEROMA,CONT.'S

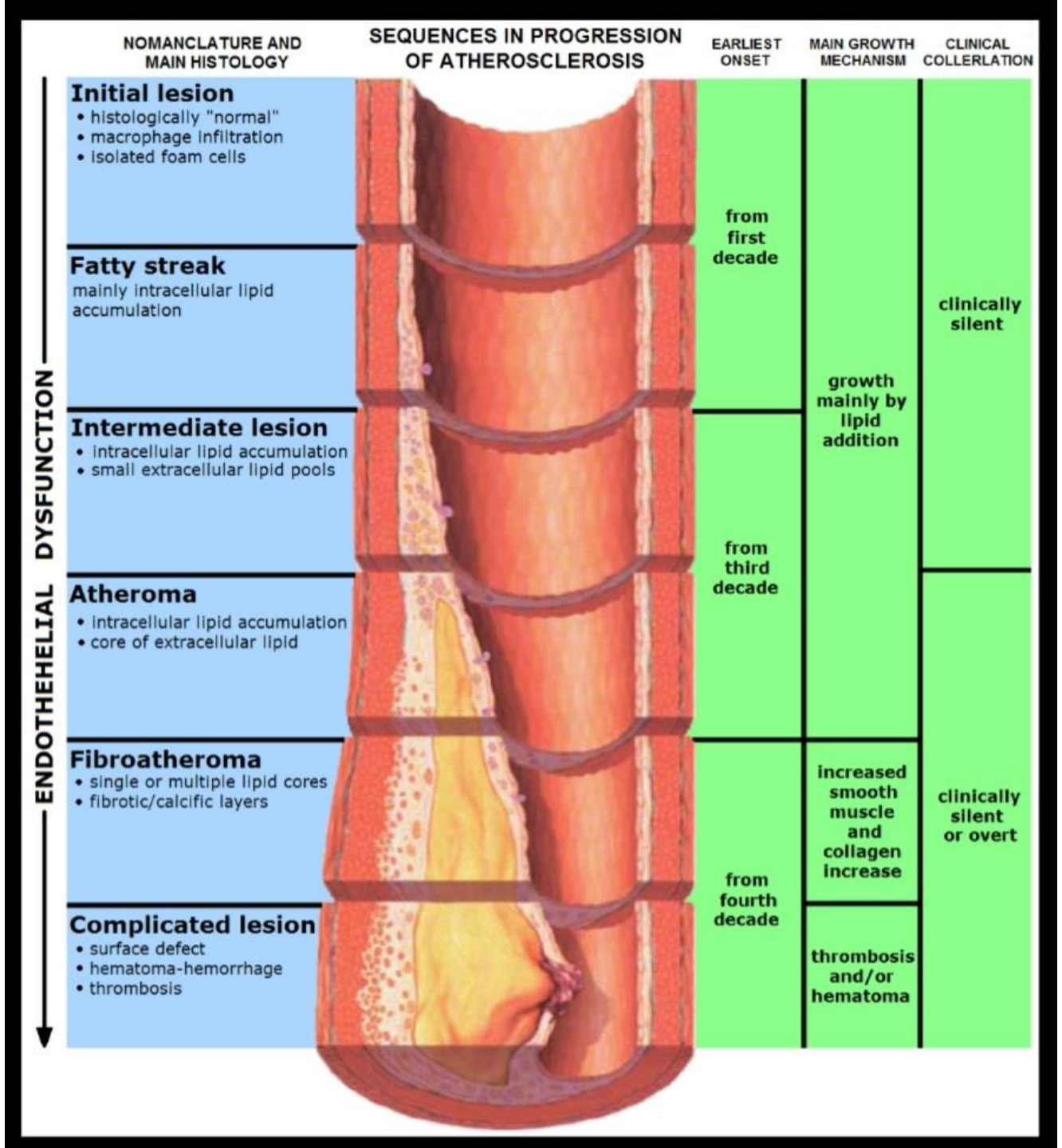
- ***Smooth Muscle Cell Migration and Proliferation***
- SMCs in the normal arterial tunica media differ considerably from those in the intima of the evolving atheroma
- Some SMCs probably arrive in the arterial intima early in life
- SMCs in the atherosclerotic intima appears to exhibit as less mature phenotype
- Recapitulate an embryonic phenotype
- Morphologically distinct from SMCs in normal medial layer

Smooth Muscle Cell Migration and Proliferation, cont'.s

- Replication of SMCs in the steady state appears uncommon in mature human atheroma
- Bursts of SMC may occur during the life history
- Episodes of plaque disruption with thrombosis may expose SMCs to potent mitogen
- Accumulation of SMCs during atherosclerosis and growth of the intima may not occur in continuous and linear manner

SMOOT MUSCLE CELL DURING ATHEROGENESIS

- SMCs replication and death my participate in complication of the atherosclerotic plaque
- Apoptosis of this cells may occur in response to inflammatory cytokines
- SMCs in the media of the arteries can arise from many sources(neuroectoderm , mesoderm….)
- The *heterogeneity of SMCs* may have direct clinical implications for understanding several common observation, such as *propensity* of certain arteries or region of the arteries to *develop atherosclerosis* or heightened response to injury(e.g. proximal LAD)


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

EVOLUTION OF ATHEROMA,CONT.'S

- ***Arterial Extracellular Matrix***
- ECM makes up much of the volume of advances atherosclerotic plaque
- The major ECM macromolecules include collagens(type I & III),proteoglycans….elastin fibers
- Arterial SMCs produce these ECM
- ECM secretion also depends on a balance
- ECM breakdown likely plays a role in arterial remodeling than accompanies lesion growth

- ***Arterial Extracellular Matrix***
- During the early life of atheromatous lesion , plaques grow outwardly
- This outwards growth of the intima leads to an increase in the caliber of the entire artery(*positive remodeling* , compensatory enlargement)
- *Luminal stenosis* tend to occur only after the plaque burden exceeds *approximately 40% of the cross-sectional area of the artery*

EVOLUTION OF ATHEROMA,CONT.'S

- ***Angiogenesis in Plaques***
- Atherosclerotic plaques develop their own microcirculation
- ***Plaque Mineralization***
- Plaques often develop areas of calcification as they evolve

COMPLICATIONS OF ATHEROSCHELEROSIS

- ***Arterial Stenosis and Clinical Implications***
- The plaques of the atherosclerotic process generally last many years, during which the affected person often have no symptoms
- Growth probably occurs discontinuously, with periods of relative quiescence punctuated by episodes of rapid progression

- ***Arterial Stenosis and Clinical Implications***
- In many cases of MI ,no history of previous stable angina heralds the acute event
- Acute coronary syndromes may result from thrombi that do not produce a critical stenosis
- This findings ***do not*** imply that ***small atheromas*** cause most MIs
- Culprit lesions of acute MI may be sizable but *may not produce* a critical luminal narrowing because of *compensatory enlargement*

COMPLICATIONS OF ATHEROSCHELEROSIS, CONT.'S

- ***Thrombosis and Atheroma Complication***
- Several major modes of plaque disruption provoke most coronary thrombi
- The first mechanism:
- accounting for about 2/3 of acute MI
- fracture of plaque's fibrous cap
- Another mode involves a superficial erosion of intima, accounting for a quarter or a third of acute MI

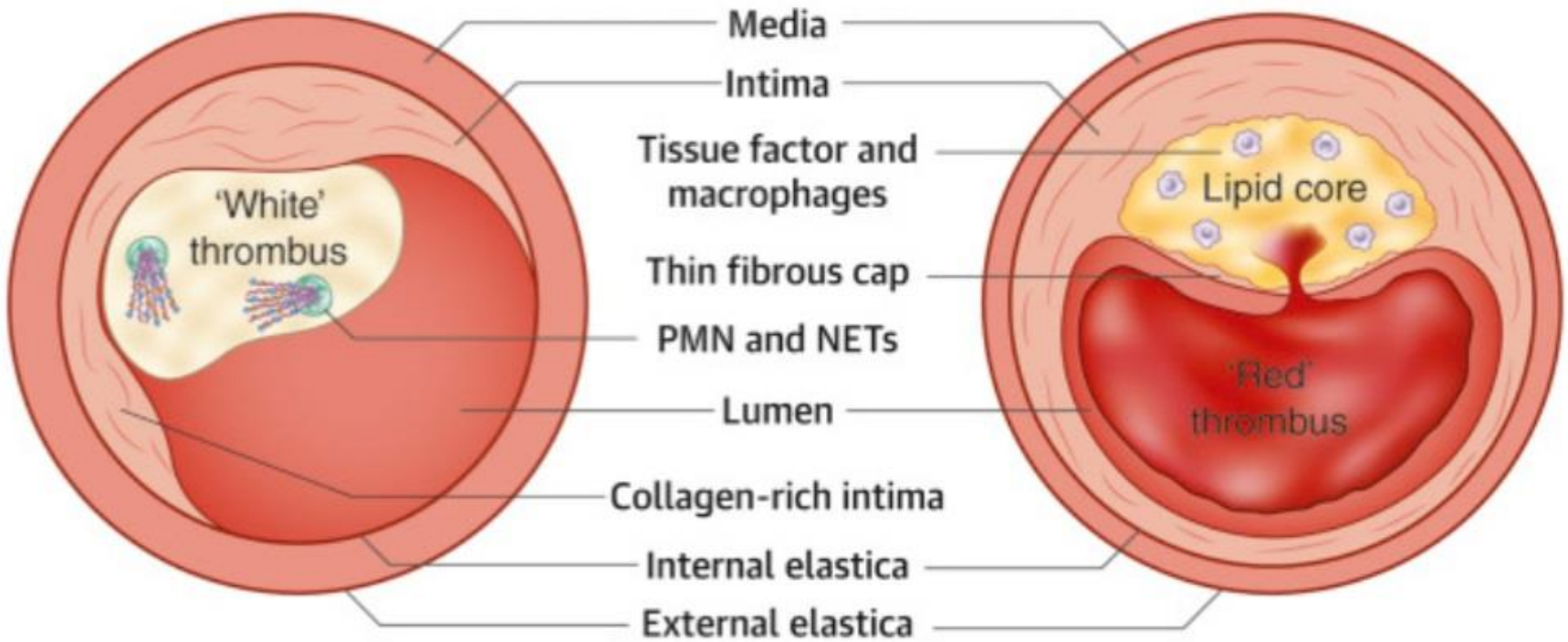
COMPLICATIONS OF ATHEROSCHELEROSIS, CONT.'S

- ***Plaque Rupture and Thrombosis***
- The rupture of the plaque's fibrous cap probably reflects an imbalance between the forces that impinge on the cap and the mechanical strength on the cap
- The metabolism of probably participates in regulating the propensity of the plaque rupture
- A relative lack of SMCs (may contribute to weakening of the fibrous cap and plaque rupture)also characterizes plaques that have caused fatal MI

- ***Plaque Rupture and Thrombosis***
- Plaques that fatally ruptured exhibit another microanatomic feature: prominent accumulation of macrophages with large lipid pool
- Apoptotic macrophages and SMCs can generate particulate tissue factor , a potential instigator of microvascular thrombosis after spontaneous or iatrogenic plaque disruption
- The success of ***lipid lowering therapy*** in reducing the incidence of acute MI or unstable angina in patients at risk may result from a reduced accumulation of lipid and a decrease inflammation and plaque thrombogenicity

- ***Thrombosis Caused by Superficial Erosion of plaque***
- The lesion that provoke superficial erosion appear quite distinct from those that cause plaque rupture

Coronary Artery Cross-Sections



Thrombosis due to erosion

- Fibrous cap thick and intact
- 'White' platelet-rich thrombus
- Collagen trigger
- Smooth muscle cells prominent
- Often sessile, non-occlusive thrombus
- Usually less remodeled outward
- NETs involved
- More frequent in non-STEMI?

Thrombosis due to rupture

- Thin fibrous cap with fissure
- 'Red' fibrin-rich thrombus
- Tissue factor trigger
- Macrophages prominent
- Often occlusive thrombus
- Usually expansively remodeled
- Less NET involvement?
- More frequently cause STEMI?

- ***Thrombosis and Healing in Progression of Atheroma***
- Most plaque disruption do not give rise to clinically apparent coronary events
- Repetitive cycles of plaque disruption, thrombosis, in situ and healing probably contribute to lesion evolutiuon and plaque growth
- Plaque disruptions with healing underlie many thrombi that cause sudden death

- ***Diffuse and Systemic Nature of Plaque Susceptibility to Rupture and Inflammation in Atherogenesis***
- *Vulnerable* or high risk plaque
- Current evidence , suggest that more than one such high risk plaque often resides in a given coronary tree
- The inflammation though to characterized the so -called vulnerable plaque appears widespread

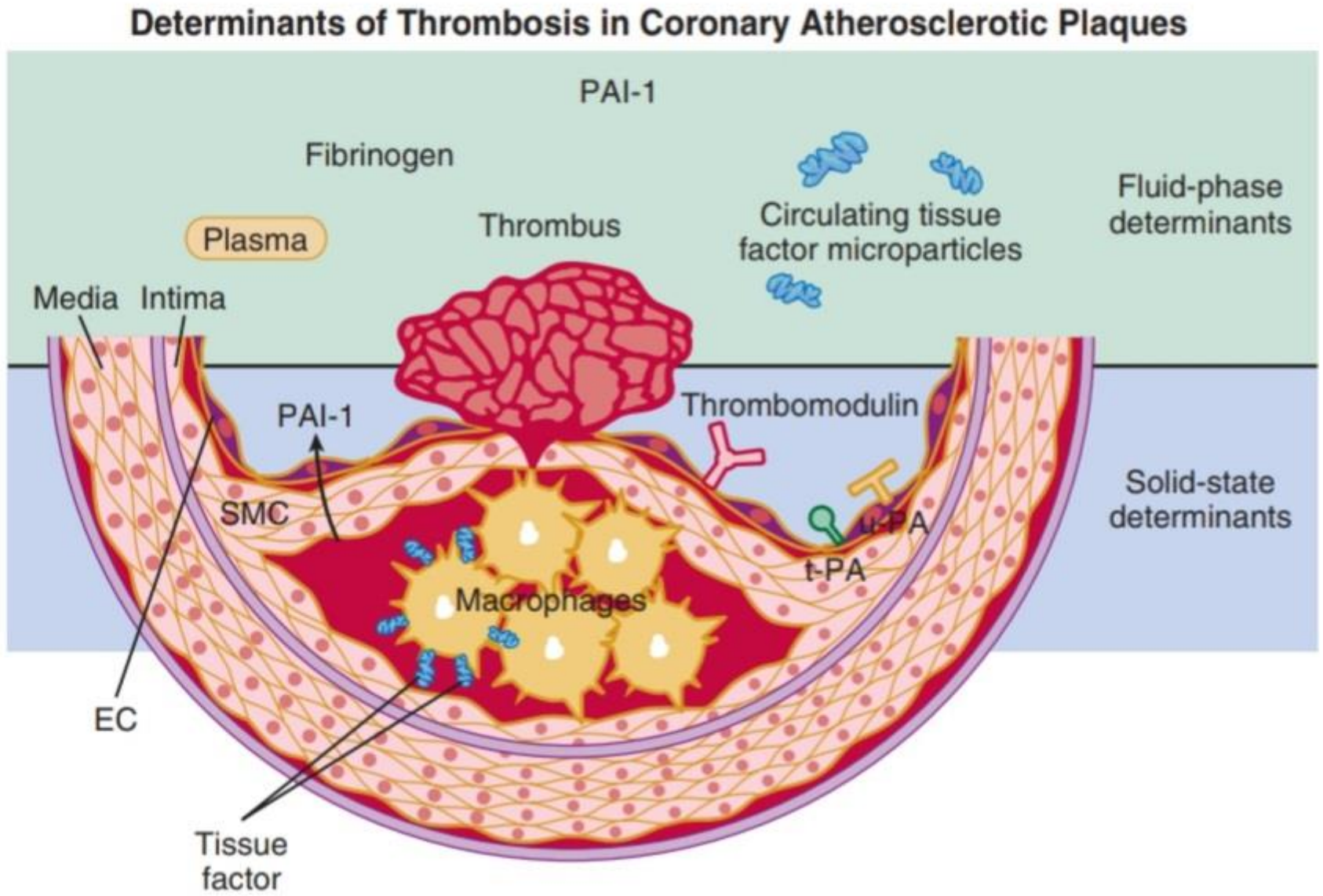
- ***Diffuse and Systemic Nature of Plaque Susceptibility to Rupture and Inflammation in Atherogenesis***
- Several concordant lines of evidence support the systemic and diffuse nature of inflammation associated with ACS

Combination of imaging studies and investigations using inflammatory markers support the diffuse and systemic nature of instability of atheromas in individuals with or at risk for ACS

- ***Diffuse and Systemic Nature of Plaque Susceptibility to Rupture and Inflammation in Atherogenesis***
- Thrombosis depends on not only on the "*solid state*" of the plaque that may rupture of or erode to trigger thrombosis but also on the "fluid phase" of blood that determines the consequences of given plaque disruption

The amount of tissue factor in the lipid core of plaque (the solid state) can control the degree of clot formation that will ensue after disruption

The degree of fibrinogen in the fluid phase of blood can influence weather plaque disruption will cause an occlusive thrombus that can precipitate an acute STEMI or yield merly a small mural thrombosis


Determinants of Thrombosis in Coronary Atherosclerotic Plaques
PAI-1
Fibrinogen
Plasma
Thrombus
Circulating tissue factor microparticles
Fluid-phase determinants
Media
Intima
PAI-1
Thrombomodulin
SMC
u-PA
t-PA
Macrophages
Solid-state determinants
EC
Tissue factor

CLINICAL MANIFESTATIONS OF STEMI

Clinical features

- Up to one third of patients with STEMI have an identifiable precipating trigger or prodromal symptoms
- Unusually heavy exercise (particularly in fatigued or habitually inactive patients),emotional stress and acute illness are the most frequent triggers
- Such infarctions could result from marked increase in myocardial oxygen consumption in the presence of severe coronary arterial narrowing (a type 2 MI)or the acute hemodynamic stress on a fragile plaque from a catecholamine or blood pressure surge

PREDISPOSING FACTOR

- Accelerating angina or resting angina , two patterns of unstable angina, may culminate in STEMI

Non cardiac surgical procedures may also precedes STEMI

Reduced myocardial perfusion secondary to hypotension(hemorrhagic or septic shock)

Increased myocardial oxygen demands caused by AS, fever, tachycardia, and agitation can contribute to necrosis

Other factors that contribute to predispose to STEMI includes respiratory infections, hypoxemia from any cause, pulmonary embolism, hypoglycemia, administration of ergot preparations, cocaine use, sympathomimetic,

Circadian predisposity

- The time onset of STEMI has pronounced circadian periodicity
- Peak incidence of the event in the morning
- Circadian rhythm affect many physiologic and biochemical variables; plasma catecholamine's and cortisol and platelet agreeability increase in early morning hours
- Patients receiving beta –blocking agents and Aspirin do not exhibit this characteristic circadian peak before the development of STEMI,consistent with precipitation by sympathetic stimuli or paletlet activation
- The concept of “triggering “a STEMI is a complex and involve the superimposition of multiple factors, such as the time of day,season, and the stress of natural disasters

Prodromal symptoms

- The patients history remains crucial to stablishing a diagnosis of STEMI
- Chest discomfort resembling classic angina pectoris usually characterized the prodrome, it occur at rest or with less activity than usual
- The symptoms are not disturbing enough to induce patients to seek immediate medical treatment
- A feeling of general malaise or frank exhaustion frequently accompanies other symptoms preceding STEMI

history

- Pain in patients with STEMI varies in intensity
- The pain is prolonged (it generally last more than 30minutes, and frequently for several hours if there is no reperfusion)
- In some patients pain from STEMI may begins in the epigastrium and simulate a variety of abdominal disorders, which often causes STEMI to be misdiagnosed as "indigestion”
- In patients with preexisting angina pectoris, the pain of infarction generally resembles that of angina with respect to location , but it is normally more severe , last longer, and is not relied by rest or nitroglycerin
-

- Both angina pectoris and STEMI pain likely arise from nerve endings in ischemic or injured ,but nor necrotic myocardium
- The pain often disappears suddenly and completely following restoration of blood flow to the infract territory
- Recurrent pain after initial reperfusion should promote immediate evaluation for acute re-occlusion of culprit lesion
- The recognition that pain implies ischemia and not infarction high lighten the importance of target anti- ischemic therapy and immediate reperfusion to relief the ischemia , for which the pain is a marker

Atypical features

- Heart failure(i.e., dyspnea without pain beginning de novo or worsening of established failure)
- Classic angina pectoris without a particularly severe or prolonged episode
- Atypical location of pain
- CNS manifestations resembling those of stroke secondary to sharp reduction in cardiac output in patients with cerebral atherosclerosis
- apprehension and nervousness
- Sudden mania or psychosis
- Syncope
- Overwhelming weakness
- Acute indigestion
- Peripheral embolization
- Although women may more likely present with ”atypical” features of STEMI than men, recent evidence suggests fewer differences between sexes than previous thought

Physical examination

- Patients suffering from STEMI often appear anxious and in considerable distress
- Heat rate can vary from marked bradycardia to rapid regular or irregular tachycardia, depending on the underlying rhythm and degree of LV failure
- Typically the pulse is rapid and regular initially(sinus tachycardia at 100to 110 beats/min)and slows as the patients pain and anxiety are relleived
- Tachycardia at presentation is associated with higher risk for fatal complications of MI

Blood pressure

- Many patients with uncomplicated STEMI are normotensive
- In previously normotensive patients a hypertensive response is occasionally seen during the first few hours(adrenergic discharge secondary to pain, anxiety and agitation…)
- Previously hypertensive patients may become normotensive without treatment after STEMI(many of them eventually regain their elevated BP levels , generally after 3-6 months)

Blood pressure , cont.'s

- Cardiogenic shock: SBP<90 mmHg and evidence of end organ hypo perfusion
- Some patients with inferior STEMI and activation of Bezold-Jarisch reflex may transiently have SBP<90mmHg(may resolve spontaneously , IV atropine, Trendelenburg position)
- Evidence of autonomic hyperactivity is common and varies in type with the location of the infarction

- Fever a non specific response to tissue necrosis
- develop most often in extensive STEMI, within 24-48 hours
- Body temperature often begin to rise within 4-8 hours
- Usually resolves by the fifth or fourth day after MI

- Heart sounds
- Friction rub
- Murmurs
- Neuropsychiatric finding

LABORATORY FINDINGS

- Serum and plasma levels of cardiac damage
- CRP
- Naturistic peptides
- Serum lipids
- Hematologic finding

Thanks for your attention