Atherogenesis

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Atherogenesis

- The key initiating process in atherogenesis is the subendothelial retention of apolipoprotein B–containing lipoproteins.
- Local biological responses to these retained lipoproteins, including a chronic and maladaptive macrophage and T-cell– dominated inflammatory response, promote subsequent lesion development.
- The most effective therapy against atherothrombotic cardiovascular disease to date—low density lipoprotein–lowering drugs—is based on the principle that decreasing circulating apolipoprotein B lipoproteins decreases the probability that they will enter and be retained in the subendothelium.
- Ongoing improvements in this area include more aggressive lowering of low-density lipoprotein and other atherogenic lipoproteins in the plasma and initiation of low-density lipoprotein–lowering therapy at an earlier age in at-risk individuals.

Tabas I et al. Circulation. 2007;116:1832-1844

Atherogenesis

Basic Science for Clinicians

Subendothelial Lipoprotein Retention as the Initiating Process in Atherosclerosis

Update and Therapeutic Implications

Ira Tabas, MD, PhD; Kevin Jon Williams, MD; Jan Borén, MD, PhD

Abstract—The key initiating process in atherogenesis is the subendothelial retention of apolipoprotein B–containing lipoproteins. Local biological responses to these retained lipoproteins, including a chronic and maladaptive macrophage- and T-cell–dominated inflammatory response, promote subsequent lesion development. The most effective therapy against atherothrombotic cardiovascular disease to date—low density lipoprotein–lowering drugs—is based on the principle that decreasing circulating apolipoprotein B lipoproteins decreases the probability that they will enter and be retained in the subendothelium. Ongoing improvements in this area include more aggressive lowering of low-density lipoprotein and other atherogenic lipoproteins in the plasma and initiation of low-density lipoprotein–lowering therapy at an earlier age in at-risk individuals. Potential future therapeutic approaches include attempts to block the interaction of apolipoprotein B lipoproteins with the specific subendothelial matrix molecules that mediate retention and to interfere with accessory molecules within the arterial wall that promote retention such as lipoprotein lipase, secretory sphingomyelinase, and secretory phospholipase A_2. Although not the primary focus of this review, therapeutic strategies that target the proatherogenic responses to retained lipoproteins and that promote the removal of atherogenic components of retained lipoproteins also hold promise. The finding that certain human populations of individuals who maintain lifelong low plasma levels of apolipoprotein B lipoproteins have an ≈90% decreased risk of coronary artery disease gives hope that our further understanding of the pathogenesis of this leading killer could lead to its eradication.
(*Circulation*. 2007;116:1832-1844.)

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Response to Retention Model of Atherogenesis

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- Local biological responses to these retained lipoproteins, including a chronic and maladaptive macrophage and T-cell– dominated inflammatory response, promote subsequent lesion development.
- The most effective therapy against atherothrombotic cardiovascular disease to date—low density lipoprotein–lowering drugs—is based on the principle that decreasing circulating apolipoprotein B lipoproteins decreases the probability that they will enter and be retained in the subendothelium.
- Ongoing improvements in this area include more aggressive lowering of low-density lipoprotein and other atherogenic lipoproteins in the plasma and initiation of low-density lipoprotein–lowering therapy at an earlier age in at-risk individuals.

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Response to Retention Model of Atherogenesis

- Potential future therapeutic approaches include attempts to block the interaction of apolipoprotein B lipoproteins with the specific subendothelial matrix molecules that mediate retention and to interfere with accessory molecules within the arterial wall that promote retention such as lipoprotein lipase, secretory sphingomyelinase, and secretory phospholipase A2.
- Therapeutic strategies that target the proatherogenic responses to retained lipoproteins and that promote the removal of atherogenic components of retained lipoproteins also hold promise.
- The finding that certain human populations of individuals who maintain lifelong low plasma levels of apolipoprotein B lipoproteins have an 90% decreased risk of coronary artery disease gives hope that our further understanding of the pathogenesis of this leading killer could lead to its eradication.

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Response to Retention Model of Atherogenesis

- Biological responses to retained and subsequently modified lipoproteins, notably a chronic and maladaptive macrophage- and T-cell– dominated inflammatory response and changes in smooth muscle cell localization and phenotype, could explain virtually all of the features known to exist during the initiation and progression of atherosclerosis
- Retention is likely facilitated by accessory molecules like LpL, secretory sphingomyelinase (S-Smase), and sPLA2.
- These retained LPs become modified (eg, aggregated and oxidized), and elicit a series of biological responses that develop into a maladaptive inflammatory response. In particular, monocytes enter the subendothelium, differentiate into macrophages (Ms), and ingest the retained and modified LPs to become cholesterol-laden foam cells.
- Eventually, T cells, mast cells, and other inflammatory cells enter the lesions and, along with macrophages, contribute to the aforementioned maladaptive inflammatory response.

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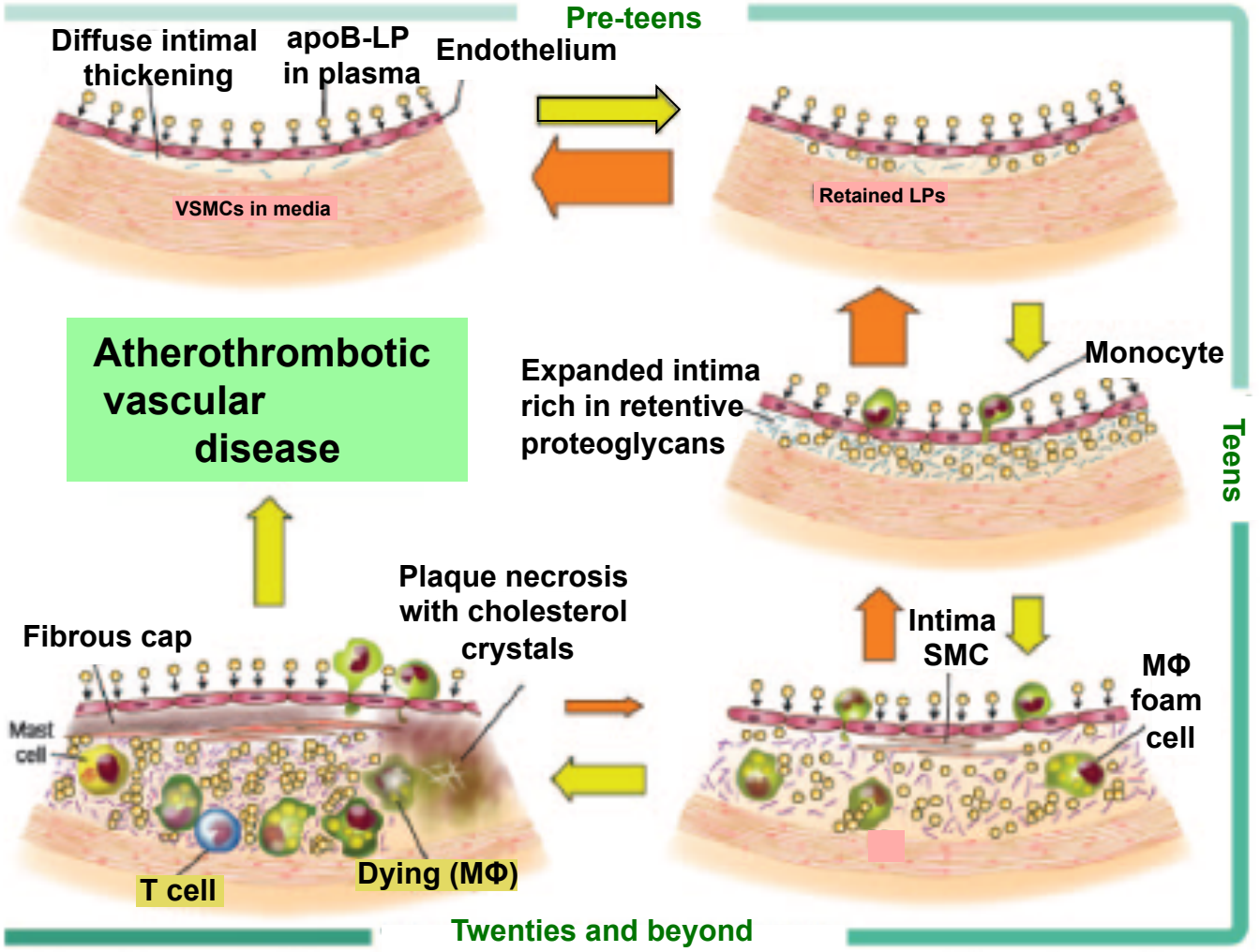
Response to retention Model of Atherogenesis

- Pre-lesional susceptible area of the arterial wall and diffuse intimal thickening
- Early lipoprotein retention



Early responses to LP retention, e.g. monocyte entry

Lowering apoB lipoproteins and decreasing risk factors will readily promote removal of atherogenic components and prevent further responses and future disease

- Advanced responses to LP retention, including maladaptive inflammation
- LP retention continues to accelerate
- Continued response to LP retention, e.g. foam cell formation and SMC migration

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Response to Retention Model of Atherogenesis

- Smooth muscle cells (SMCs) migrate into the intima and promote formation of a collagenous fibrous cap, probably representing a scar-like response to wall off the lesion.
- However, as the lesion progresses, macrophages die and eventually give rise to areas of necrosis filled with extracellular debris, cholesterol crystals, proteases, and procoagulant/thrombotic material.
- These advanced plaques can lead to fibrous cap thinning, plaque rupture or erosion, and acute thrombotic vascular events such as myocardial infarction and stoke.

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Response to Retention Model of Atherogenesis

- The earliest stages are the most easily reversible by lowering plasma apoB LPs, and clinical studies have shown tremendous benefit from risk factor reduction at this stage of life.
- Moreover, future, complementary therapies directed at interfering with LP retention are likely to be most feasible in the earliest stages, because the later stages involve more complex mechanisms of LP retention.
- The complexity of advanced lesions, including accelerated LP retention, renders them less readily reversible. Nonetheless, clinical trials have clearly demonstrated that risk factor reduction at this stage, particularly lowering of plasma apoB LPs, can have substantial benefit in terms of primary and secondary prevention of vascular disease.
- This benefit undoubtedly arises from the eventual removal of atherogenic components of retained LPs and from regression of lesional elements, including inflammatory cells.

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Response to Retention Model of Atherogenesis

- What makes the emphasis on retained lipoproteins as the key initiating step in atherogenesis so crucial?
- The answer lies in the concept that understanding the root cause of a disease provides the foundation for the most effective therapy.
- By way of analogy, tuberculosis is a disease that has a strong inflammatory component that, like the maladaptive inflammatory response in atherosclerosis, is associated with influx and then persistence of macrophages and T cells, high levels of inflammatory cytokines, elevated plasma levels of C-reactive protein, and endothelial cell changes.

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Response to Retention Model of Atherogenesis

- The treatment for this "inflammatory" disease is, of course, the elimination of the root cause—*Mycobacterium tuberculosis—through the use of antibiotics.*
- Likewise, the most successful therapy for atherothrombotic vascular disease in humans—lowering plasma LDL concentrations—attacks the root cause of atherogenesis, which is **subendothelial apoB lipoprotein retention**.

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Response to Retention Model of Atherogenesis

- First, a snapshot of the critical juncture between lipoprotein retention and the earliest responses to retention supports the notion that inflammation is a consequence of apoB lipoprotein retention, not a de novo initiating factor.
- The Response-to-Retention model directly supports the concept of “lower is better.”
- However, lowering circulating apoB lipoproteins may have other beneficial effects in addition to decreasing the probability of arterial wall lipoprotein retention such as improving endothelial function and promoting the exit of macrophages from lesions.

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Response to Retention Model of Atherogenesis

- Other possible determinants of lipoprotein retention within the arterial wall include lipoprotein size, other lipoprotein properties (eg, electrical charge and cholesterol enrichment), and endothelial permeability.
- The influence of these determinants on lipoprotein retention and atherosclerotic disease in humans is much less certain than plasma lipoprotein concentration and the onset and duration of lipoprotein elevation.

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Response to Retention Model of Atherogenesis

- Although the entry of chylomicron remnant lipoproteins may not be as great as that of smaller LDL particles, the fact that they deliver 40 times more cholesterol per particle after retention can explain their atherogenicity.
- Whether variations in the size of LDL itself can affect permeation is not known.
  - Although so-called small, dense LDL may be more atherogenic than larger LDL, it is probably unlikely that the mechanism arises from size-related effects on endothelial permeability.
  - Rather, the presence of small, dense LDL is associated with increased lipoprotein binding to arterial proteoglycans in vitro, and conversion of apoB lipoproteins into a small, dense form by treatment with phospholipase A2 in vitro increases their affinity to proteoglycans

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Response to Retention Model of Atherogenesis

- Despite the complexity of advanced atherosclerosis, a clear root cause exists—subendothelial retention of apo-B containing lipoproteins—that has been and should continue to be a major focus of interventions to combat atherothrombotic vascular disease. The unequivocal success of LDL-lowering therapy is a testimony to this overall concept, as is the emerging discussion on how early such therapy should be instituted in at-risk young individuals.
- In this sense, a critically important goal remains the continued development of drugs that complement the LDL-lowing actions of statins, like cholesterol absorption inhibitors, which are in current clinical use, and inhibitors of PCSK9, apoB transcription, and apoB lipoprotein secretion.

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