REVIEW ARTICLE

Atherosclerosis in 2012: what is new?

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KEY WORDS

atherosclerosis, hemostatic system, translational medicine

ABSTRACT

Recently, two important issues concerning atherogensis have been raised: first – the role of hemostasis in the progression of atherosclerosis, and second – how the results of experimental animal studies can be translated into humans. There is no direct clinical evidence for the role of the coagulation system in the progression of atherosclerosis, but ample experimental data indicate that platelets and coagulation factors have an important role in the progression of both atherosclerosis and thromboembolism. A new scientific approach is thus needed to assess the actual effect of the hemostatic system on molecular and cellular responses in the vasculature. Although experimental studies helped to unravel numerous factors underlying the pathophysiology of atherosclerosis, there is still a significant gap in the translation of the experimental results to the clinic, and this gap needs to bridged to achieve reliable data from scientific research. Direct translation of the results from mouse studies to human is problematic. Clinical trials should be used more often as an early scientific probe, not just as a pathway to the commercialization of pharmaceuticals or for evaluating comparative efficacy of the agents in clinical use.

Introduction In 2008, the *Polish Archives of Internal Medicine* published my review: "New insights into immunological aspects of atherosclerosis".[1] Since the publication, several important issues concerning atherogenesis have been raised, particularly the role of the hemostatic system in the progression of atherosclerosis and the translation of the experimental animal findings into humans.

Role of the hemostatic system The available data indicate that both platelets and coagulation system play an important role in the pathogenesis of atherosclerosis. However, in numerous clinical trials neither antiplatelet or anticoagulant drugs affected the progression of atherosclerosis. Despite these results, it can be assumed that the hemostatic system has a strong effect on the vascular wall and thus may contribute to the development of atherosclerotic plaque.[2]

Platelets – the cellular interface between hemostasis and atherosclerosis Based on several studies, platelets play a significant role in experimental models of atherogenesis.[3] They are a common element of hemostasis, innate immunity, and inflammation in atherosclerosis. Endothelium dysfunction leads to expression of selectins. Adherent platelets secrete proatherogenic mediators. Platelets can bind with monocytes, neutrophils, dendritic cells, and progenitor cells.[4,5]

Coagulation system during atherosclerotic plaque progression A local synthesis of functionally active coagulation proteins within human atherosclerotic plaques has been observed.[6] In early atherosclerotic lesions, there is also an increased activity of thrombin generation. The same occurs in experimental models.[7] Paradoxically, a clinical study on patients with carotid-artery stenosis proved that plaques with more fibrous structure, compared with those abundant in lipids, are associated with increased thrombin generation.[8] Local thrombin generation can turn into a vicious cycle, which contributes to the formation of intraplaque thrombi.[9]

Future perspectives In atherogenesis, there is a cross-talk between hemostasis and inflammation. Several experimental studies showed that hemostasis is linked with atherogenesis. But what about clinical data?

Nowadays, there is a consensus that plaque microruptures, followed by subclinical thrombosis, play a pivotal role in plaque growth.[10] Several studies proved that most of coronary thrombi received from patients who died suddenly from cardiovascular causes were in later stages

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of maturation. This can suggest that thrombi may appear long before a rupture.[9]

Antithrombotic therapy and antiplatelet or anticoagulant drugs play a crucial role in the prevention of atherothrombosis.[11] Antiplatelet therapy is particularly important in secondary prevention.[12] For example, the use of aspirin is associated with a 30% reduction in the risk of myocardial infarction.[13] The effect of aspirin may be also associated with its anti-inflammatory action.[14] Anti-inflammatory and antiatherogenic effects have also been proved for other antiplatelet drugs, such as thienopyridines.[15] However, clinical trials with antiplatelet drugs did not confirm their antiatherogenic effects.[16]

The introduction of direct inhibitors of factor Xa and thrombin[17] (small molecules that can enter the vessel wall) provides another opportunity to prove their potential beneficial effect on plaque formation in humans. However, it may not be straightforward because both thrombin inhibition[18] and prothrombotic state[7] have been suggested as promoters of plaque stability in experimental atherosclerosis.

To sum up, it is particularly important nowadays to collect more data on the phenotyping of lesions. Moreover, most clinical studies focus on the mortality outcome, while only few investigate plaque progression. This should change. Also, the development of high-resolution magnetic resonance imaging for plaque assessment could be helpful and might improve vessel-wall phenotyping.

How experimental animal findings can be translated into humans There is still a wide gap between the experimental findings and human atherosclerosis. We can no longer assume that the results from cultured cells or mice closely correspond to humans. Experimental research has definitely helped to discover numerous factors underlying the pathophysiology of atherosclerosis, but it is still unclear how to translate these findings to the clinic.[19]

Oxidation and human atherogenesis Experimental results have long shown that oxidized low-density lipoprotein (oxLDL) promotes atherosclerosis.[20] However, there is limited direct evidence to confirm that oxLDL participate in human atherosclerosis. Moreover, in vitro preparations of oxLDL (by transition metal chemistry) vary by day, donor, and laboratory. Also, clinical trials have already shown that antioxidant vitamins do not reduce cardiovascular events.[21-23]

It has been observed that phospholipases may generate toxic or proinflammatory agents from oxidized phospholipids bound to oxLDL.[24] Thus, the real in vivo importance of oxLDL in humans remains speculative.

Translation from mice to humans The discovery of almost all cell types involved in innate and adaptive immunity in human plaques supports a possibility that the immune system participates in the pathophysiology of atherosclerosis.[25] Experimental studies showed that T helper 1 (Th1) cells play a pivotal role in proatherogenic actions in apoE-knockout mice. There are 2 most important autoantigens: LDL and heat-shock protein 60.[26,27] Recently, it has been observed that immune response to LDL specifically targets components of the native LDL rather than oxLDL.[28] Anti-inflammatory cytokines, such as interleukin (IL)-10 and transforming growth factor-β, inhibit the process of atherogenesis. These cytokines are produced by regulatory T (T_{reg}) cells.[29] Interestingly, a number of studies proved a proatherogenic role of IL-17.[30]

Direct translation from animal to human studies is difficult. Atherosclerotic mice have high cholesterol levels that cannot be compared with those in hypercholesterolemic patients.[31] The mouse immune system is substantially different from that in humans. For example, humans lack Th1 and Th2 polarization that is observed in mice. FOXP3 expression is a useful marker of T_{reg} cells in mice, but not in humans.[32]

In polarization of macrophages, the markers of classical (M_1) vs. alternative (M_2) activation patterns in mice differ from those in humans.[33] Therefore, the findings in mice should stimulate clinical studies. And vice versa, identification of a putative disease-promoting molecule in human lesions should end in animal studies.

Inflammation in atherosclerosis at the crossroads Atherosclerosis is an inflammatory disease.[34,35] Testing the inflammatory hypothesis of atherosclerosis in humans will require a series of randomized, placebo-controlled trials. These trials should evaluate proven anti-inflammatory agents as cardiovascular therapeutic agents. The Cardiovascular Inflammation Reduction Trial and the Canakinumab Anti-inflammatory Thrombosis Outcomes Study are the examples of such studies.

Animal experiments vs. human disease How can we bridge the gap between experimental advances and clinical practice? Mice research proved to be indispensable in the studies of atherosclerotic mechanisms; however, we have to remember about their limitations. It happens too often that pharmaceutical companies adopt targets on the basis of the results from experimental animal studies, which they are too willing to accept without any criticism. However, we have to remember that mouse is not a human. To give an example, atherosclerotic lesions in genetically modified mice rarely develop plaque disruption with thrombosis, while it is a typical mechanism complicating human atherosclerosis. Moreover, mouse studies focus mostly on the aorta and proximal great vessels, while the most important vessels in humans from the clinical point of view are the coronary, carotid, and cerebral arteries. Moreover, the structure and hydrodynamics of these

smaller muscular arteries in humans differ from the large elastic arteries analyzed in mouse studies. Studies on mice should definitely be continued but the results should be carefully interpreted when extrapolated to human disease.[19]

Clinical trials as a laboratory for discovery The solution of the above problem is to use clinical trials more often as an early scientific probe.[36,37] Therefore, clinical trials constitute the ultimate translational tool.[38] The major limitation to the translation of biological advances to atherosclerosis treatment is the increasing cost of clinical trials. Costs have diverted investments of the pharmaceutical industry, reducing the discovery effort. Models for the public support of trials to test crucial hypotheses and improvements in trial designs to make them less costly should help overcome these barriers.

Summary There has been enormous experimental progress in the understanding of atherogenesis and its mechanisms. However, sustained effort is required to fully understand the experimental data in reference to humans and future application of drugs. Well-designed clinical trials should bridge the gap between experimental research and human disease.

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ARTYKUŁ POGLĄDOWY

Miażdżyca w roku 2012 – co nowego?

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SŁOWA KLUCZOWE

medycyna translacyjna, miażdżyca, układ krzepnięcia

STRESZCZENIE

W ostatnim czasie podniesiono dwie istotne kwestie dotyczące aterogenezy: po pierwsze – rolę hemostazy w rozwoju miażdżycy i po drugie – jak wyniki badań eksperymentalnych na zwierzętach można odnieść do człowieka. Nie ma bezpośrednich dowodów z badań klinicznych na rolę układu krzepnięcia w rozwoju miażdżycy, jednak wiele danych z badań eksperymentalnych wskazuje na istotną rolę płytek krwi oraz czynników krzepnięcia w rozwoju zarówno miażdżycy, jak i choroby zakrzepowo-zatorowej. Potrzebne jest zatem nowe podejście naukowe w celu określenia rzeczywistego wpływu układu hemostazy u człowieka na odpowiedzi molekularne i komórkowe w układzie naczyniowym. Chociaż badania eksperymentalne pomogły w odkryciu wielu ważnych czynników patofizjologii miażdżycy, wciąż istnieje istotna luka w translacji do kliniki danych eksperymentalnych, którą należy wypełnić, aby uzyskać wiarygodne dane z badań naukowych. Bezpośrednia translacja na człowieka wyników badań eksperymentalnych prowadzonych na myszach jest problematyczna. Badania kliniczne powinny być częściej wykorzystywane jako wczesna „sonda" naukowa, a nie tylko jako droga do wprowadzenia na rynek nowych leków lub oceny porównawczej skuteczności stosowanych już leków.

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