INTRODUCTION

Atherosclerosis is an inflammatory vascular disease (1) of increasing incidence in the developed countries. Mouse has become an excellent experimental model of atherosclerosis (2) since 1992, when apolipoprotein E (apoE) - knockout mice were developed (3-5).

Since inflammation plays an important role in atherogenesis, during recent years it has become apparent that the 5-lipoxygenase (5-LO) pathway may take significant part in modifying the pathogenesis of atherosclerosis. Indeed, it has been recently demonstrated that the 5-LO substantially contribute to atherosclerosis in both mouse models and humans. However, animal models potentially bear the risk of compensatory mechanisms, due to genetic modification of the target gene that render the results difficult to interpret. Another caveat is species differences between mice and humans. 5-LO expression in intimal atherosclerotic lesions varies between mice and humans; also, 5-LO and 12/15-LO appear to be differentially regulated in inflammatory cells of mice. Moreover, atherogenesis in mice differs in several facets from the human pathology. Thus, T cells, whose presence in all stages of atherosclerotic lesions is acknowledged, are underrepresented in murine models of atherosclerosis. 5-LO/LT pathway shows important disparities between murine and human atherosclerosis. Advanced human plaques show differences in 5-LO expression compared with mouse lesions. Taken together, in advanced human atherosclerosis, a role for 5-LO is likely, which is distinct from its role in early atherogenesis. This presence of the 5-LO/LT pathway in advanced lesions is not found in mouse models, which might be due to: (i) rapid progression of atheroma growth in mice vs. slower, often interrupted progression in humans; (ii) advanced human plaques display a higher degree of instability and risk to rupture than murine plaques; (iii) temporal dissociation in the Th1/Th2 "balance" at distinct lesion stages between mice and humans.

Key words: apoE-knockout mice, atherosclerosis, leukotrienes, 5-lipoxygenase, coronary vascular disease
limonoids within certain compartments of plasma membrane. The role of FLAP in atherosclerosis was additionally confirmed in humans by Helgadottir et al. (27) who showed that genetic polymorphisms of FLAP are associated with myocardial infarction and stroke by increasing leukotriene production and inflammation in the arterial wall.

The 5-LO is abundantly expressed in atherosclerotic lesions of apoE- and LDLR deficient mice, appearing to co-localize with a subset of macrophages but not with all macrophage-staining regions. Indeed, the results of our studies showed that the inhibition of FLAP by MK-886 or BAYx1005 can significantly prevent the development of atherosclerosis in gene-targeted apoE/LDLR-DKO mice (28, 29). Moreover, this study showed that cysteinyl leukotriene receptor blocker montelukast decreases atherosclerosis in apoE/LDLR-double knockout mice (30). These results derived also from our numerous studies, concerned with atherosclerotic mice (31-35). The findings of the study concerning MK-886 were confirmed by Back et al. on their model of transgenic apoE-/- mice with the dominant-negative transforming growth factor β type II receptor, which displays aggravated atherosclerosis (36).

Surprisingly, Colin D. Funk's research team questioned the hypothesis concerning leukotrienes, 5-LO and their role in atherogenesis in gene-targeted mice, stating that in mouse plaques there is no 5-LO overexpression detectable (37). Finally, in a recently published article (38), they have tried to explain the whole complicated phenomenon.

LIMITATIONS OF ANIMAL MODELS

Animal models potentially bear the risk of compensatory mechanisms due to genetic modification of the target gene that render the results difficult to interpret. Another caveat is species differences between mice and humans. For instance, 5-LO expression in normal atherosclerotic lesions varies between mice and humans; also, 5-LO and 12/15-LO appear to be differentially regulated in inflammatory cells of mice and humans with the murine 12/15-LO producing mainly 12-HPETE, while its human counterpart primarily synthesizes 15-HPETE. Notably, both products may have opposing effects in inflammation (39). Moreover, atherogenesis in mice differs in several facets from the human pathology. Thus, T cells, whose presence in all stages of atherosclerosis is acknowledged, are underrepresented in murine models of atherosclerosis (40, 41). Despite these shortcomings, animal models afford an invaluable means to study the effects of directed genetic overexpression, deletion or inhibition of FLAP by MK-886 or BAYx1005 can significantly prevent the development of atherosclerosis in mice and humans. 'Engineered' murine atherosclerosis is accelerated and develops within months, whereas human atherosclerosis progresses over decades. Some studies indicate roles for 5-LO in the early/acute stages of atherosclerosis in mice and humans, but only in the advanced stage of the human pathology. Other components of the 5-LO pathway are increasingly expressed in advanced human atherosclerosis.

CONCLUSIONS

Taken together, in advanced human atherosclerosis, a role for 5-LO is likely, which is distinct from its role in early atherogenesis. This presence of the 5-LO/LT pathway in advanced lesions is not found in mouse models, which might be due to: (i) rapid progression of atheroma growth in mice vs. slower, often interrupted progression in humans (i.e., initial fatty streaks might remain dormant for many years in humans, until certain factors promote the progression of some lesions into an advanced state) (43, 44); (ii) advanced human plaques display a higher degree of instability and risk to rupture than murine plaques; (iii) temporal dissociation in the Th1/Th2 'balance' at distinct lesion stages between mice and humans (45-47).

About participation of the 5-LO pathway in the development and progression of atherosclerosis in mice and humans, 'Engineered' murine atherosclerosis is accelerated and develops within months, whereas human atherosclerosis progresses over decades. Some studies indicate roles for 5-LO in the early/acute stages of atherosclerosis in mice and humans, but only in the advanced stage of the human pathology. Other components of the 5-LO pathway are increasingly expressed in advanced human atherosclerosis.

FUTURE DIRECTIONS

During the last few years there has been a resurgent focus on the 5-LO/LT pathway as a potential target in coronary vascular disease (CVD). The complexity of the 5-LO/LT pathway participation in mechanisms contributing to CVD is evident based on the many studies (38). Limitations of these studies often result from the 'snapshot' punctual nature of analysing a single time point in CVD pathogenesis that makes it difficult to gain systematic insight into 5-LO-driven or -independent processes.

Murine and human CVD etiology differ with respect to the 5-LO/LT pathway, and even within murine studies, the nature of the applied model (for atherosclerosis, abdominal aortic aneurysm (AAA), or ischemia/reperfusion injury) influences the conclusions. Whereas a role for 5-LO-derived LTs in early stages of murine and human atherosclerosis, AAA, and reperfusion injury is cogent based on their effects in chemotaxis and induction of pro-inflammatory responses, the 5-LO pathway appears to play a distinct role in advanced human atherosclerosis, but not in advanced murine disease.

Targeting specific leukotriene G protein-coupled receptors rather than upstream targets involved in LT synthesis may be a superior strategy for future CVD therapeutic interventions, based on extensive past experience with other pathways (e.g., via angiotensin II and adrenergic receptors), although this remains to be determined.

Conditional knockouts and comprehensive translational studies should serve better than the traditional, simplistic 'one model' approach to understand the complex effects exerted by 5-LO products. Understanding the cytokine milieu during distinct stages of CVD progression will be crucial to elucidate how the expression of members of the 5-LO/LT pathway is regulated. There is little doubt that 5-LO plays important roles in many facets of CVD, but the challenge for future studies will be to clearly dissect these activities in a temporal and cell- and tissue-
specify context in order to provide a solid basis for potential therapeutic interventions.

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REFERENCES

43. Libby P. Atherosclerosis: disease biology affecting the coronary vasculature. Am J Cardiol 2006; 98: 3Q-9Q.
44. Libby P, Sasiela W. Plaque stabilization: can we turn theory into evidence? Am J Cardiol 2006; 98: 26P-33P.

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