IVUS, and Angiographic Imaging of Peripheral and Coronary Arteries in ExeGen LDLR Miniswine after Angioplasty Balloon Injury: Correlations with Gross- and Histopathological Assessments

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Introduction

Targeted disruption of the endogenous LDL receptor leads to hyperlipidemia and a propensity to accelerate development of both peripheral and coronary artery disease. With the concomitant feeding of a high-fat diet (simulating a “Western diet”), animals expressing either the homozygous or heterozygous LDL receptor knockout phenotype have been shown to develop atherosclerosis and lesions similar to human atherosclerotic plaque. In this initial feasibility study, we attempted to further accelerate the rate at which lesions formed by interventionally injuring selected sites in the peripheral arteries by balloon angioplasty with overstretch in the range of 15–30%. Follow-up angiography and IVUS measurements were performed ~30 days post-injury and the animals were allowed to survive for an additional 30 days. Several sites were evaluated grossly and selected lesions were investigated histologically and scored for lesion severity.

Methods

Four ExeGen LDLR miniswine (2 LDLr−/− and 2 LDLr+/−) were acquired from Exemplar Genetics and were fed a western-style high-fat diet for ~20 weeks. Three of the four animals were subjected to peripheral artery injury and then survived for ~60 days while maintaining the high-fat diet. Immediately prior to termination, selected injured arterial sites and normal arteries (both coronary and peripheral) were evaluated by intravascular ultrasound (IVUS), and quantitative vascular angiography (QVA). At necropsy, selected sites in the peripheral and coronary circulation were evaluated grossly for evidence of atheroma and more delineated atherosclerotic lesions. An early death animal (LDLr−/−) was also grossly and histologically assessed for spontaneous lesion formation.

Results

Table 1: Serum total cholesterol levels for study animals (mg/dL)

<table>
<thead>
<tr>
<th>LDLr−/−</th>
<th>LDLr+/−</th>
<th>LDLr+/+</th>
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<td>353</td>
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Figure 5. 13P0973 ILI 35 days post injury (10% overstretched drag followed by 30% overstretched).

VIUS Image of Stenosis

Score: 35% stenosis.

Figure 6. 13P0975 ILI - 28 days post injury (10% overstretched drag followed by 30% overstretched).

Score: ~ 55% stenosis.

Histopathology of Peripheral Lesions

Summary

The phenotypic hypercholesterolemia in coordination with a western-style high-fat diet in the LDL deficient animals appears to be associated with a baseline level of spontaneous atheroma and atherosclerotic lesions, especially at sites of turbulent flow (i.e., coronary ostia, iliac-femoral arterial tree ostia) leading to atheroma propagation. In addition, the ability to induce atherosclerotic lesions in targeted sites in the iliac-femoral tree after balloon-mediated injury suggests that these are valuable models for investigation of treatment modalities for coronary and peripheral artery disease. Overall this preliminary investigation indicated that there is an association between vessel injury and increased lesion extent and complexity. In addition, the combination of QVA and IVUS can be a powerful minimally-invasive tool for early detection of stenosis and lesion formation without the need for termination and histological confirmation.

Figure 7 (a,b,c). 13P0973 Right Internal Femoral ~60 days post injury (a, H&E stain; b, trichrome stain). This primary lesion is composed of neo-intimal growth with minimal lipid deposition.

Figure 8 (a,b,c). 13P0972 Left External Femoral ~60 days post injury (a, H&E stain; b, trichrome stain; c, pentachrome). This primary lesion is composed of neo-intimal growth with involvement of foam cells and macrophages.