Editorial

Atherosclerosis in Apolipoprotein E-knockout Mice as a Model of Human Disease

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Editorial

Cardiovascular disease was the top cause of death in the world in 2000 and 2012 according to the World Health Organization fact sheet [1]. In 2012, an estimated 56 million people died worldwide, with cardiovascular diseases responsible for 17.5 million of those deaths; this translates to 3 in every 10 fatalities. Ischemic heart disease alone killed 7.4 million people [1]. In Japan, vascular disease of the heart and of the brain are the 2nd and 4th most common cause of death, respectively, according to the 2012 annual report of the Ministry of Health, Labour and Welfare [2]. When considered together, they come close to malignant neoplasm as the most lethal disease of man. The primary etiologic lesion of cardiovascular disease is atherosclerosis, which causes vessel stenosis, embolus via thrombus formation, and ischemia of heart and brain.

Establishment and availability of a relevant atherosclerotic animal model is an extremely crucial tool in translational research to study and understand the disease process. A gene-targeted mouse model of atherosclerosis was created by the Jackson Laboratory in Bar Harbor, Maine, USA; C57BL/6J mice homozygous for the ApoE^{tm1Unc} mutation results in functional knockout of the anti-atherogenic apolipoprotein E (ApoE) gene involved in cholesterol metabolism [3,4]. This ApoE-knockout (ApoE-KO) mouse has been and remains to be the most popular animal model for atherosclerosis research because of its propensity to spontaneously develop hypercholesterolemia and atherosclerotic lesions that are similar to those found in humans [5,6].

Macroscopic findings of the atherosclerotic lesions developed by ApoE-KO mice are presented in (Figure 1). Atherosclerotic lesions are seen in aortic arch and in the bifurcations of the descending aorta (Figure 1). Histopathological findings of the atherosclerotic lesions are shown in (Figure 2). These lesions were classified into 3 categories: i) Early, ii) Progressive and iii) Combined. Early lesions show fatty streaks which involve foamy cell accumulations (Figure 2A & 2B). Progressive lesions are composed of foamy cell accumulations, a
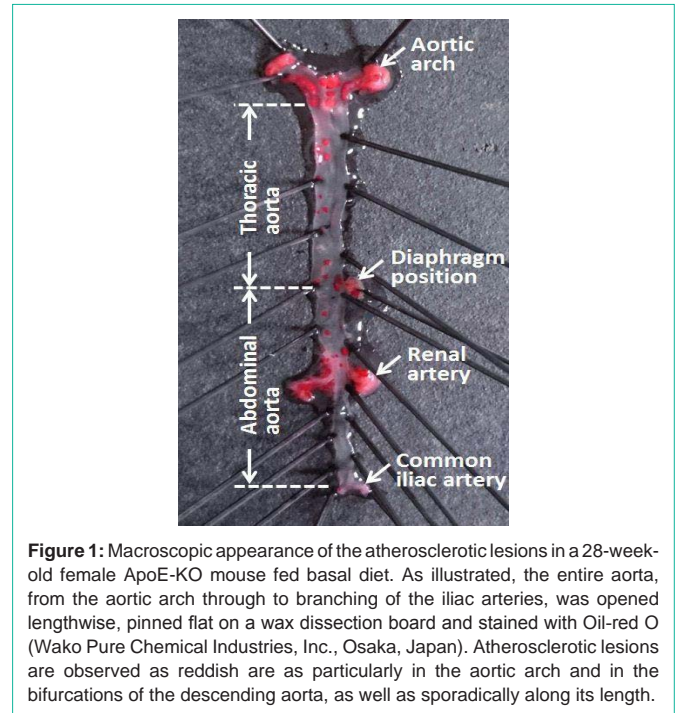
Figure 1: Macroscopic appearance of the atherosclerotic lesions in a 28-week-old female ApoE-KO mouse fed basal diet. As illustrated, the entire aorta, from the aortic arch through to branching of the iliac arteries, was opened lengthwise, pinned flat on a wax dissection board and stained with Oil-red O (Wako Pure Chemical Industries, Inc., Osaka, Japan). Atherosclerotic lesions are observed as reddish are as particularly in the aortic arch and in the bifurcations of the descending aorta, as well as sporadically along its length.
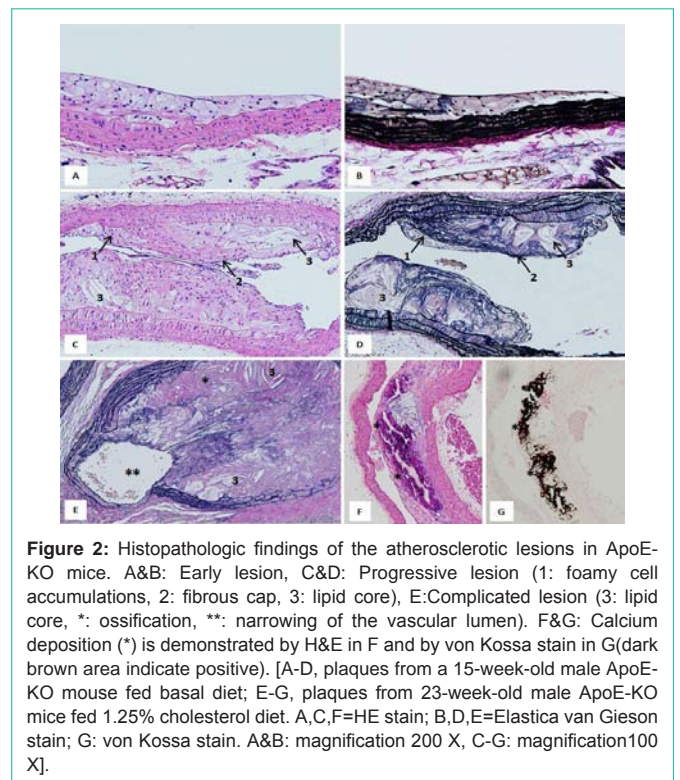
Figure 2: Histopathologic findings of the atherosclerotic lesions in ApoE-KO mice. A&B: Early lesion, C&D: Progressive lesion (1: foamy cell accumulations, 2: fibrous cap, 3: lipid core), E:Complicated lesion (3: lipid core, *: ossification, **: narrowing of the vascular lumen). F&G: Calcium deposition (*) is demonstrated by H&E in F and by von Kossa stain in G(dark brown area indicate positive). [A-D, plaques from a 15-week-old male ApoE-KO mouse fed basal diet; E-G, plaques from 23-week-old male ApoE-KO mice fed 1.25% cholesterol diet. A,C,F=HE stain; B,D,E=Elastica van Gieson stain; G: von Kossa stain. A&B: magnification 200 X, C-G: magnification100 X].

fibrous cap and lipid cores (Figure 2C & 2D). Complicated lesions are characterized by accompanying ossification and/or occlusion of the lumen (Figure 2E-2G).

Despite the overall similarities of lesions, there are 2 notable differences between mouse and human disease. One is that, even on a long-term high-fat diet, cardiovascular infarction does not present in mice as it does in humans. Although severe atherosclerotic lesions are seen in the aortas of ApoE-KO mice it is not accompanied by arterio scleros is in the cardiac coronary arteries [5]. The second is that while the majority of studies on human atherosclerosis report less disease in pre-menopausal women than in adult men, post-menopausal women have an equal risk of developing cardiovascular disease [6,7], suggesting a protective effect of estrogen. In ApoE-KO mice, however, differences in incidence by sex are more equivocal; some studies report males have less plaque development than females [8,9] while other studies report no clear sex differences [5,10]. Nevertheless, since the atherosclerotic lesions in ApoE-KO mice are so strikingly analogous to atherosclerotic lesions in humans in their molecular expression as well as in their histopathological progression, the ApoE-KO mouse is currently considered the most relevant model for translational studies of atherosclerosis [5,6,11].

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