Invited commentary

Embryonic cell origin defines functional role of Lrp5

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The low-density lipoprotein-related receptor 5 and 6 (Lrp5 and Lrp6) genes were cloned in 1998 based on their homology with the low-density lipoprotein receptor (LDLR) [1–4]. Variants in either LRP5 or LRP6 proteins have caused a number of disease processes in the field of bone [5,6], and have been associated with cardiovascular disease [4,7–9]. In the previous issue of Atherosclerosis, the authors confirm the novel finding that Lrp5 plays an atheroprotective role in the vascular aorta. In the wildtype (WT) versus the Lrp5−/− mice there are larger atheromatous lesions in the Lrp5−/− mice as compared to WT littermates, with an upregulation of the LDLR family members including VLDR, Lrp6 and Lrp2. The mechanism postulated by the authors implicates higher plasma cholesterol levels in the Lrp5−/− mice as compared to the WT littermates as the driving factor for the significant increase in atheroma in the thoracic aorta. The production of mice lacking Lrp5 revealed that Lrp5 deficiency led to increased plasma cholesterol levels in mice fed a high-fat diet, secondary to decreased hepatic clearance of chylomicron remnants and also marked impaired glucose tolerance [7]. Lrp6 also regulates bone, but has been found to have a low bone mass effect in patients in which a putative partial loss-of-function mutation in Lrp6 was identified to lead to early cardiovascular-related death associated with increased plasma LDL, triglycerides, hypertension, diabetes and osteoporosis [11]. This background studies are the foundation for the results in the novel study by Borell-Pages et al., implicating the role of Lrp6, CLDR and Lrp2 in lipid metabolism and progression of aorta atherosclerosis [10].

Previous studies testing experimental hypercholesterolemia in mouse and rabbit models demonstrated an upregulation of Lrp5 receptor expression and activation of cell proliferation and extracellular matrix production critical in bone formation in the aortic valve in vivo and ex vivo [8,9,12]. Specificity for the role of Lrp5 in aortic valve calcification was tested in the previous study using a high cholesterol diet in the Lrp5 null mice, which demonstrated opposite results in the aortic valve: no evidence of atherosclerosis or valve calcification [13].

The Lrp5 pathway also regulates bone formation in different diseases of bone [5,14]. The discovery that the Lrp5 receptor carries the gain of function [14] and loss of function [5] mutations in the development of bone diseases, resulted in a number of studies which have shown that activation of the canonical Wnt pathway is important in osteoblastogenesis [7,15–17]. Three studies to date have confirmed the regulation of the Lrp5/Wnt pathway for cardiovascular calcification in vivo and ex vivo [8,9,12]. In this pathway, Wnt proteins bind to receptors composed of a frizzled protein and either of the low-density lipoprotein receptor-related proteins Lrp5 or Lrp6. Signaling via Disheveled and/or Axin then results in inactivation of a multiprotein complex including Axin, adenomatous polyposis coli (APC), and glycogen synthase kinase-3β that normally renders β-catenin unstable. By inhibiting this complex, Wnt signals lead to accumulation of β-catenin in the cytosol and its entry into the nucleus. Once in the nucleus, β-catenin binds to proteins of the T-cell factor/lymphoid enhancer factor-1 family and modulates the expression of several target genes which include Cyclin D, Cbfα1, and Sox9. Bone and cartilage are major tissues in the vertebrate skeletal system, which is primarily composed of three cell types: osteoblasts, chondrocytes, and osteoclasts. In the developing embryo, osteoblast and chondrocytes both differentiate from common mesenchymal progenitors in situ, where as osteoclasts are of hematopoietic origin and brought in later by invading blood vessels. Osteoblast differentiation and maturation lead to bone formation controlled by two distinct mechanisms: intramembranous and endochondral ossification, both starting from mesenchymal condensations.

The role of lipid signaling of the Lrp5 receptor has been defined in experimental in vitro and in vivo lipid models of
vascular atherosclerosis. Lrp5, which binds apoE-containing lipoproteins in vitro, is widely expressed in many tissues including hepatocytes, adrenal gland and pancreas [4]. The production of mice lacking Lrp5 revealed that Lrp5 deficiency led to increased plasma cholesterol levels in mice fed a high-fat diet, secondary to decreased hepatic clearance of chylomicron remnants, and also marked impaired glucose tolerance [7]. The Lrp5 deficient islets also demonstrated a reduction of intracellular ATP and Calcium in response to glucose, thereby decreasing glucose induced insulin secretion [7]. Furthermore, experimental hypercholesterolemia is associated with the increase in Lrp5 receptor expression and activation of cell proliferation and extracellular matrix production critical in bone formation [8]. These studies provide evidence that lipoprotein metabolism is regulated by the fifth family member of the LDL co-receptor family Lrp5 in these knockout mouse studies.

Embryonically, Wnt proteins bind to receptors composed of a frizzled protein and either of the low-density lipoprotein receptor-related proteins Lrp5 or Lrp6. In the developing embryo, osteoblast and chondrocytes, both differentiate from common mesenchymal progenitors, and neural crest cells. The role of Wnt and Lrp5 coreceptors in embryogenesis, have been the most detailed studies in the field to date [18]. Studies have demonstrated that the neural crest cells are specific to the aortic valve [18] and mesodermal cells are specific to the descending aorta [19]. Furthermore, a recent study in the proximal ascending aorta where neural crest cells reside, versus the descending aorta, indicate proximal aorta calcifies at an accelerated rate than the descending aorta in the presence of hyperphosphatemia [20].

Fig. 1 demonstrates the role of hypercholesterolemia and the role of the Lrp5 receptor in the aortic valve and the aorta. The embryonic cell origin may provide another clue for why the hypercholesterolemic Lrp5 null mouse develops excessive atherosclerosis in the aorta that has mesodermal derived cells [10], but does not develop calcifying lesion in the aortic valve [13]. The novel finding by Borrell-Pages et al. [10], in this issue of Atherosclerosis that Lrp5 plays an atheroprotective role in the vascular aorta, is unique in the field and will help to further define the complex role of Lrp5 co-receptors in the field of embryogenesis, atherosclerosis, cell differentiation and bone biology.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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