The number of lipoprotein(a) kringle IV-type 2 repeats is associated with the osteogenic profile of aortic valvular interstitial cells induced by plasma from patients with calcific aortic stenosis

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Background: Considerable progresses have been made in the invasive treatment of calcific aortic stenosis (AS), but there is still no pharmacological treatment available because the exact mechanism leading to the initiation of valvular calcification remains unknown. An increasing number of evidences, including large-scale genetic studies, have linked Lipoprotein(a) (Lp(a)) to AS but its pathogenic role in the osteoblastic transition of valvular interstitial cells (VIC) has remained undeciphered.

Objective: We sought to study the mechanistic link between the transition of VICs towards an osteoblastic phenotype leading to intraleaflet calcium deposition and the type of Lp(a) isoform, defined by the number of kringle IV-type 2 (KIV 2) repeats, in the plasma of patients with AS compared with healthy controls.

Methods: VICs isolated from healthy aortic valves were cultured in the presence of plasma samples deriving from 100 patients with severe AS included in the prospective cohort GENERAC and 50 matched control patients exempt from any aortic valve disease. We evaluated the number of Lp(a) KIV 2 repeats of each plasma preparation by liquid chromatography-mass spectrometry. The phenotypic changes of VICs towards an osteoblastic phenotype were assessed by immunofluorescence microscopy (osteocalcin expression) and Alizarin red staining (calcium deposition).

Results: Incubation of VICs with the plasma of AS patients triggered their transformation towards an osteoblastic phenotype, evidenced by the production of osteocalcin, and calcium deposition. There was no association between the plasma levels of Lp(a) and the extent of calcium deposition in the study population. However, a negative and significant correlation was found between calcium deposition and the number of KIV-2 repeats in the Lp(a) of the different plasma preparations (r=-0.20, p=0.038). A direct, causal role of Lp(a) isoforms containing a low number of KIV-2 repeats (5 to 6) in the transition of VICs towards an osteoblastic phenotype was supported by experiments performed with preparations of these isoforms, isolated from the plasma of blood donors.

Conclusion: A low number of KIV–2 repeats in plasma Lp(a) triggers the acquisition of an osteoblastic phenotype by VICs. The isoform, rather than the concentration of Lp(a) may play a pathogenic role in AS. Determining the number of KIV-2 repeats in the Lp(a) of patients may allow to identify subgroups of patients with an increased risk of developing AS.
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