Role of Runx2 in Calcific Aortic Valve Disease: A T2DM Mouse Model with Greatly Increased Aortic Stenosis

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Calcific aortic valve disease (CAVD) is prevalent in elderly, especially those affected with type II diabetes mellitus (T2DM). To explore the mechanisms of CAVD, we developed an improved mouse model that had >75% incidence of hemodynamically significant aortic stenosis (AS) as determined by echocardiography. LDLr⁻/⁻ApoB¹⁰⁰/¹⁰⁰ mice fed a customized diabetogenic, procalcific diet¹ developed thickened aortic valve leaflets and calcification in both valve leaflets and hinge areas. In comparison to normal chow (NC) and “Western” diet fed LDLr⁻/⁻ApoB¹⁰⁰/¹⁰⁰ mice that had 38% and 50% AS rate respectively, T2DM mice with AS showed significantly impaired cardiac function as determined by reduced ejection fraction and fractional shortening. Histological analysis of the valve tissue showed widespread expression of the osteochondrogenic factor, Runx2 and/or Sox9 in valve leaflet and hinge area. Genetic fate mapping in T2DM LDLr⁻/⁻ mice with SM22-Cre and R26R-LacZ transgenic alleles showed that majority of cells in the thickened valve leaflets and hinges were β-galactosidase positive, identifying them as activated valve interstitial cells (aVICs) that once expressed SM22. These same aVICs also expressed the osteochondrogenic factors Sox9 and/or Runx2. Finally, removal of Runx2 from aVICs with SM22-Cre in T2DM LDLr⁻/⁻ mice resulted in significantly improved aortic valve function compared to NC LDLr⁻/⁻ mice. Functional improvement was also accompanied by a reduction in osteochondrogenic genes. To our knowledge, this is the highest rate of AS in a mouse model of CAVD to date. Our data are also the first to have definitively determined a role for aVICs and Runx2 in CAVD.

Reference List