**EZH2-Driven Epigenetic Mechanisms in Foam Cell Formation: Insights into Diabetic Atherosclerosis.**

**Background.** Myeloid cells, including macrophages, play a critical role in atherosclerosis. The deficiency of a histone methyltransferase, Enhancer of Zest Homolog-2 (EZH2) has recently been shown to reduce foam cell formation, a key feature of atherosclerosis. However, the role of EZH2 in foam cell formation in diabetic atherosclerosis, specifically in macrophages of diabetic patients, is not known.

**Methods.** Diabetes was induced inAtheroprone ApoE knockout mice using streptozotocin. After 5-weeks of diabetes, mice were treated with EZH2 inhibitor, GSK-126 (50mg/kg-BW, daily) for 5-weeks. A myeloid-specific EZH2 knockout (KO) mouse model was generated (LysM-Cre+ x EZH2fl/fl) and bone marrow-derived macrophages (BMDMs) from EZH2 KO and wildtype mice were cultured either in high glucose (HG) or serum derived from diabetic mice + fluorescently labelled ox-LDL. Additionally, BMDMs isolated from C57BL/6 mice were stimulated with HG + ox-LDL ± GSK-126.CD14+ monocytes isolated from coronary artery disease patients ± diabetes were differentiated into macrophages and cultured in the presence of ox-LDL and media containing patients' serum ± GSK-126.

**Results.** En-face Sudan-IV staining analysis of aorta showed 43% reduced plaque area in diabetic mice treated with GSK-126, compared to vehicle-treated mice. BMDMs from myeloid-specific EZH2 KO mice exhibited a marked reduction (48%) in ox-LDL uptake under diabetic conditions including HG and serum from diabetic mice. BMDM from C57BL/6 mice exposed to HG + ox-LDL, resulted in reduced foam cell formation in the presence of GSK-126. Patients' derived macrophages, stimulated with serum of diabetic patients showed increased ox-LDL uptake and GSK-126 treatment significantly reduced it.

**Conclusion.** Our study demonstrated that EZH2 inhibition with GSK-126 blocked ox-LDL uptake by patients derived macrophages, resulting in reduced foam cell formation. This highlighted the translational potential of GSK-126 as a new treatment for diabetes-associated atherosclerosis.