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POSTER ABSTRACTS

301.VASCULATURE, ENDOTHELIUM, THROMBOSIS AND PLATELETS: BASIC AND TRANSLATIONAL

Obesity-Induced Platelet Mitofusin-1 Expression Causes Vascular Dysfunction

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Background: The growing epidemic of obesity is strongly linked to cardiovascular disease (CVD). Obesity leads to endothelial dysfunction, an instigating event that drives vascular injury and subsequent CVD, but the mechanisms by which obesity causes endothelial dysfunction remain unclear. Platelets circulate proximal to the endothelium and are traditionally thought to contribute to obesity-associated vasculopathy through thrombotic activation. However, platelets are metabolically active and release vaso-modulatory molecules into their environment and the role of these functions have not been examined in the context of obesity-induced vasculopathy. We previously showed that alterations in platelet mitochondrial function regulate platelet degranulation. Further, it has been reported that thrombospondin 1 (TSP1), a platelet factor that propagates endothelial dysfunction, is elevated in the plasma of obese humans. **We hypothesized that obesity/weight gain modulates platelet mitochondrial function, which stimulates the release of TSP1 from platelets to propagate vascular dysfunction.**
Methods: Platelets were isolated from lean and obese humans and mitochondrial structure and function measured. To induce diet-induced obesity wildtype (WT) mice were fed with a high fat diet (HFD, 60 kcal% fat) for 10 weeks, and low fat diet (LFD, 10 kcal% fat)- fed WT mice were used as controls. Platelets and plasma from the mice were screened for mitochondrial proteins and plasma TSP-1 was measured by ELISA. A murine model with platelet-specific deletion of mitofusin-1 (MFN1; pltMFN1KO mice), a mitochondrial GTP-ase that increases mitochondrial function was generated and fed either HFD or LFD for 4-10 weeks. Further, endothelial-dependent- and independent- vascular relaxation was measured in both groups by stimulating aortic rings with acetylcholine (Ach) or sodium nitroprusside (SNP) using wire myography. Additionally, platelet-specific TSP1 knockout (plt-TSP1KO) mice were generated and fed with HFD for 10 weeks and measured plasma TSP1 levels.
Results: Platelets from obese subjects showed increased levels of MFN1 compared to lean subjects. WT mice fed with HFD had increased platelet MFN1 and plasma TSP1 levels compared to LFD-fed WT mice. Platelet-specific deletion of MFN1 in mice resulted in reduced plasma TSP1 levels compared to control PF4-cre mice after HFD challenge. We found that HFD caused impaired Ach-stimulated vasorelaxation (indicative of endothelial dysfunction) in control PF4-cre mice, and this effect was attenuated in pltMFN1KO mice. Further, we found that HFD-induced increases in plasma TSP1 levels were attenuated in plt-TSP1KO mice, indicating platelets are the major source of TSP1 in HFD induced obesity model.
Conclusion: These data demonstrate that obesity/weight gain induces platelet MFN1 expression, which drives TSP1 release from platelets to propagate vascular dysfunction. Our findings elucidate a novel platelet-centric mechanism underlying obesity-associated vasculopathy and have implications for the targeting of non-thrombotic platelet function as a therapeutic strategy for obesity-induced vasculopathy.

Disclosures No relevant conflicts of interest to declare.

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