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High-Fat Diet Induced Hematopoietic Stem Cell Dysfunction in Middle-Aged Mice: The role of Nox2 and Oxidative Stress

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Systemic oxidative stress is a characteristic of obesity related metabolic disorders associated with high cardiovascular disease susceptibility. Bone marrow-derived hematopoietic stem cells (BMSC) hold the hope for regeneration of diseased endothelium; however, the effect of oxidative stress on BMSC function remains unknown. Recently, a superoxide producing NADPH oxidase 2 (Nox2) has been found to be involved in obesity-related oxidative stress. In this study, we investigated BMSC function in mouse models of middle-age obesity. Age-matched littermates of C57BL/6J wild-type and Nox2 knockout mice (7 m old, n=15) were fed with high fat diet (HFD, 45% kcal fat, 20% kcal protein and 35% kcal carbohydrate) or normal chow diet (NCD, 12% kcal fat, 28% kcal protein and 60% kcal carbohydrate) for 16 weeks. BMSCs in hind limbs were isolated from mice at 11 months of age using ficoll-density centrifugation. Compared to NCD controls, the numbers of $CD133^+/VEGFR2^+$ endothelial progenitor cells (EPC) were significantly decreased (3.2%±0.3 NCD vs 0.8%±0.5 HFD; $p<0.05$, Students *t*-test) in HFD mice. Furthermore, there were significant increases (92±9.2%; $p<0.05$, Students *t*-test) in the levels of $O_2^{\cdot-}$ production by HFD BMSC, and this was accompanied with accelerated *ex vivo* cell proliferation (160±5.2%; $p<0.05$, Students *t*-test), cell cycle progression from G_1/G_0 phase to S phase, and importantly, HFD was associated with a 4-fold increase in inflammatory cell population ($CD45^+$) examined by FACS. Isolation of $CD133^+$ cells using magnetic beads showed a significant increase in HFD associated cell apoptosis (6.9±2.5% NCD vs 29.8±8.2% HFD; $p<0.05$; Students *t*-test) as examined by annexin-V flow cytometry. Moreover, the level of p53 expression in EPC was significantly increased with HFD treatment. However, all these changes were absent in BMSC isolated from Nox2 knockout mice fed with HFD. In conclusion, an obese environment activates Nox2 and oxidative stress damages BMSC function and reduces EPC population. Nox2 may present a potential therapeutic target for the prevention and treatment of obesity-related diseases.