Diet-induced (epigenetic) changes in bone marrow augment atherosclerosis

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Hypercholesterolemia induces leukocytosis, associated with altered proliferation of hematopoietic stem cells. In this study, we investigated the long-term hematopoietic changes induced by Western-type diet (WTD) exposure and the consequences for atherosclerotic plaque development. Here, bone marrow from LDL receptor knockout (LDLr KO) mice fed WTD (WTD-BM) or regular chow diet (Chow-BM) was transplanted into LDLr KO mice on chow.

At 17 weeks after transplantation, mice reconstituted with WTD-BM showed a significant 1.4-fold increase in aortic root plaque size \( (P=0.03) \) in absence of changes in serum cholesterol. Interestingly, the increased atherosclerosis susceptibility coincided with a larger \( (P<0.01) \) spleen size (Chow-BM: 0.27±0.02%, WTD-BM: 0.35±0.01% body weight).

FACS analysis showed a myriad of differences in spleen cells, with notable increases in T-cells (2.0-fold, \( P<0.05 \)) and macrophages (2.9-fold, \( P<0.01 \)). Furthermore, the percentage of macrophages expressing CD86 was highly induced (Chow-BM 16.9±1.6%, WTD-BM 30.9±2.5%, \( P<0.01 \)), indicating increased activation of splenic macrophages. Similarly, leukocytes in blood were increased (Chow-BM 5136±52 cells/µL, WTD-BM 7335±74 cells/µL, \( P<0.05 \)), associated with a relative increase \( (P<0.05) \) in F4/80\(^+\) monocytes (Chow-BM 14.5±2.5%, WTD-BM 30.3±5.8%). FACS analysis of the BM revealed no difference in the amount of Lin\(^{-}\)Sca1\(^+\)CD117\(^+\) hematopoietic stem cells. Hypermethylation of GpG regions in the gene encoding CD116 \( (P<0.05) \), a key regulator of myeloid cell survival and activation suggests that epigenetic changes might have contributed to the observed changes.

In conclusion, WTD challenge induces transplantable epigenetic changes in bone marrow, alterations in the hematopoietic system, and increased susceptibility to atherosclerosis.