

Predisposition to NAFLD by Maternal Western Diet Involves Loss of Reparative Macrophages and Antioxidant Activity in Non-obese Juvenile Non-human Primates.

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Purpose: Predisposition to juvenile non-alcoholic fatty liver disease (NAFLD) can be programmed in early life by maternal Western diet (WD), but the mechanisms are poorly understood. **Methods:** We studied livers from 3yo juvenile non-human primates exposed to maternal WD or Control (C) diet during pregnancy, switched post-weaning at 7 mo to either C or WD, yielding 4 groups: (C/C, WD/C, C/WD, WD/WD). **Results:** WD/C animals had unchanged body weight, adiposity, and liver fat. Second harmonic generation imaging and picrosirius red staining showed increased fibrillar collagen deposition in the liver periportal region, suggesting stellate cell activation. Single cell RNAseq of WD/C liver immune cells showed non-reparative macrophage (MØ) and dendritic cells, characterized by decreased pro-inflammatory and anti-inflammatory cytokine genes, decreased oxidative phosphorylation, and less M2 polarization. Bulk whole liver RNA-sequencing, TBARs analysis, and western blotting revealed increased oxidative stress, decreased SIRT3 and NRF2 antioxidant pathways, and impaired mitochondrial quality control. Postnatal WD (C/WD and WD/WD) drove liver MØ recruitment and ER stress response, which was not present in WD/C. Compared to all other groups, WD/WD livers had worsened TBARs, increased collagen deposition, and an RNA profile of increased collagen synthesis and inflammation. **Conclusions:** Our results suggest that maternal WD exposure remodels immune cell function and promotes early fibrosis by hindering oxidative stress resolution and by driving mitochondrial dysfunction, whereas postnatal WD promotes MØ recruitment and ER stress, accelerating inflammation and fibrosis when paired with maternal WD. These results support that maternal diet plays a critical role in driving juvenile NAFLD risk, even in the absence of obesity.