High fat diet modulates conventional dendritic cell development through Interferon regulatory factor 8

The incidence of obesity worldwide is rising. obesity is a risk factor for a metabolic syndromes like type 2 diabetes. Obesity induces chronic low-grade inflammation which disturbs many immune cells, especially within the myeloid cell compartment. Conventional dendritic cells cDCs can be categorized into two subsets cDC1 and cDC2 according to their phenotypic and functional properties. Despite recent studies showed that (cDC) contribute to inflammation state during obesity, the initial events altering the development and differentiation of cDCs from hematopoietic progenitors remain elusive.

To address this question, we use diet-induced obesity (DIO) model. We fed wildtype mice either high-fat diet or control diet for two to eight weeks. We observed that starting from three week high-fat diet challenge significantly reduces the number of bone marrow resident cDC1 but not cDC2.Also, cDC1 in HFD showed lower level of CD80 and KI67. In BM and Blood we find direct progenitor Pre-DC1 numbers and proliferation decrease. Recently it was shown that Interferon regulatory factor-8 (IRF8) is essential for the development and maintenance of cDC1. We find that in mice receiving high-fat diet bone marrow pre-cDC1 express lower amounts of IRF8 compared to mice fed with control diet. IRF8 signaling is controlled by interferon γ (IFNγ). To understand if IFNγ plays a role in bone marrow cDC1 development we used the IFNγ receptor knock out mice (IFNγR KO). Interestingly, we find that IFNGR KO mice display a similar reduction in cDC1.finally, the same observation of cDC1 reduction observed in spleen and Gonadal adipose tissue.

In conclusion, we show that HFD feeding modulates the development of cDC1 via regulation of IRF8, resulting in lower proliferative capacity and progenitor cell numbers in an IFNg dependent fashion. Therefore these data link the acute effects of HFD within the dendritic cell compartment with the establishment of chronic immune activation during metabolic syndrome.

Keywords : Dendritic cells, hematopoietic cells, nutrition
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