Obesity-Induced Inflammation Cooperates with Loss of DNA Methyltransferase 3A to Develop Early-Onset of Leukemia

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Obesity is an increasing epidemic disease world-wide responsible for enhancing the risk for developing Type 2 diabetes mellitus (T2DM) as well as cancer. However, it is unclear if and how obesity contributes to the transformation of pre-leukemic stem and progenitors (pre-LHSC/Ps) into full-blown leukemia such as acute myeloid leukemia (AML) or severe form of myeloproliferative neoplasm (MPN). We hypothesized that obesity induced chronic inflammation might be responsible for clonal selection of pre-LHSC/Ps bearing pre-leukemic mutations such as DNA methyltransferase 3A (*DNMT3A)* and for promoting the progression of early-onset MPN towards severe forms of AML/leukemia. To test this hypothesis, we genetically crossed pre-leukemic *Dnmt3a*$^{+/-}$*;Mx-Cre*+ mice with leptin deficient obese (*Lep*$^{Ob/Ob}$) mice to obtain *Ob/Ob*;*Dnmt3a*$^{+/-}$*;Mx-Cre*+ compound mutant mice. Further, the *Dnmt3a* gene was deleted by giving the PolyIC and the deletion was confirmed through PCR. After 12 days of post-PolyIC the myeloid cells (neutrophils and monocytes) were expanded in *Ob/Ob*;*Dnmt3a*$^{+/-}$*;Mx-Cre*+ mice compared to *Dnmt3a*$^{+/-}$*;Mx-Cre*+*, Dnmt3a*$^{+/-}$*;Mx-Cre-, Ob/Ob* and *WT* mice. We have harvested and analyzed all these mice after 26 days of post-PolyIC. Interestingly, *Ob/Ob*;*Dnmt3a*$^{+/-}$*;Mx-Cre*+ mice showed increased BM cellularity, both the frequency of lineage negative, Sca-1+ and c-KIT+ (LSK) cells, short-term hematopoietic stem cells (ST-HSCs; LSK/CD48+/CD150-), granulocyte macrophage progenitor (GMPs; LSK/CD16+/CD34+), and reduction in LT-HSCs (LT-HSCs; LSK/CD48-/CD150+) compared to other groups. Flow cytometry analysis of PB, BM and spleen from *Ob/Ob*;*Dnmt3a*$^{+/-}$*;Mx-Cre*+ mice demonstrated a significant increase in the frequency of mature myeloid cells (Gr-1+/Mac-1+) and a profound reduction in B220+ B cells compared to other groups. Remarkably, these mice also showed splenomegaly, elevated heart size and early signs of AML blasts as reflected by the presence of c-KIT+/CD11b+ double positive cells in the BM, consistent with severe MPN/AML development. Taken together, these results demonstrate that obesity induced inflammation cooperates with pre-leukemic *Dnmt3a*$^{+/-}$ mutation to induce an early-onset of severe MPN/AML like disease.