Novel evidence that ApoA-1 deficiency facilitates HSC mobilization and differentiation and halts HSC quiescence and self-renewal, in mice

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INTRODUCTION

Recent evidence suggests that osteoblastic bone marrow niche (BMN) is vital for the maintenance and self-renewal of hematopoietic stem cells (HSC). It has been recently proposed that cholesterol efflux pathways participate in HSC mobilization and that cholesterol-sensing pathways control the proliferation of HSC progenitors. Moreover, we have recently documented that HDL perturbations result in impaired osteoblastic function in mice. In the present study we aimed at investigating the role of ApoA-1, the cardinal regulator of HDL biosynthesis in the regulation of HSC quiescence-mobilization and consequently in hematologic malignancies.

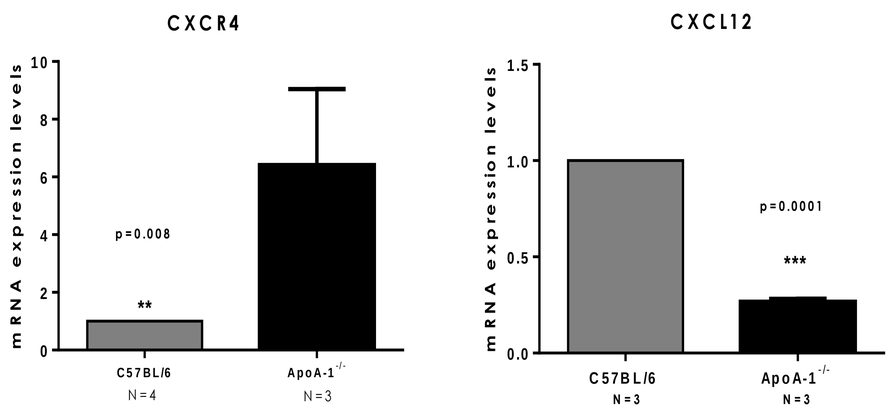
METHODS

Whole bone marrow cells (WBMCs) were isolated, from the femora of ApoA-1$^{-/-}$ (n=6) and wild-type (WT) (n=6) C57BL/6 mice and assessed for the expression of factors that are differentially expressed in the BM microenvironment and affect HSC fate. More specifically we tested the expression of the chemoattractant cytokine CLCX12, its receptor CXCR4, the Jagged-1/Notch (1,2) signaling cascade elements as well as N-cadherin and osteopontin, factors that promote HSC quiescence and self-renewal with qRT-PCR. Additionally, we assessed the expression of CXCR4 of HSC with flow cytometry.

RESULTS

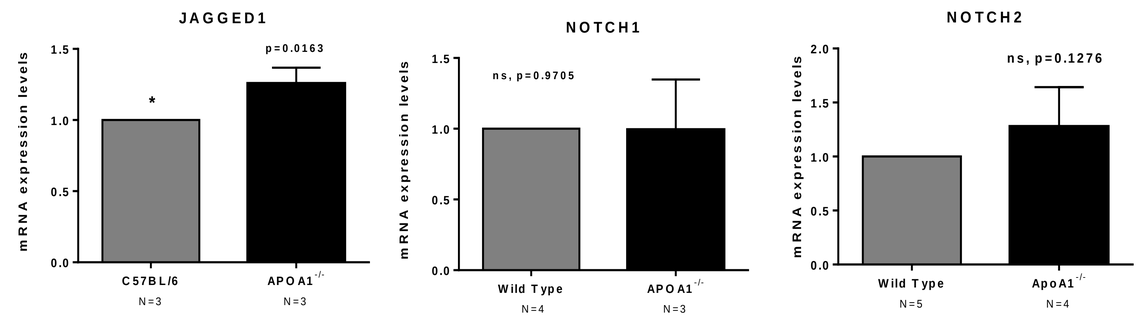
Real time PCR analysis of CXCR4 and CXCL12 in WBMCs devired from apoA-1$^{-/-}$ and C57BL/6 mice. **WBMCs obtained from apoA-1$^{-/-}$ mice (n=4) showed a significant increase (p =0.008) in CXCR4 expression and a significant decrease in CXCL12 expression (p=0.001), compared to WT mice (n=4) (Fig.1).**

Fig.1



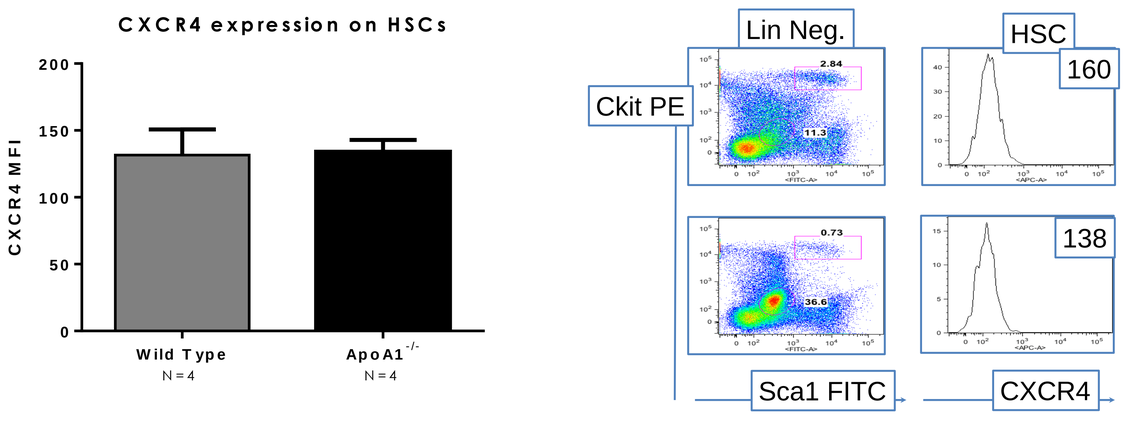
Real time PCR analysis of the Jagged-1/Notch (1,2) signaling cascade elements in WBMCs devired from apoA-1$^{-/-}$ and C57BL/6 mice. **Jagged-1 mRNA levels from WBMCs were significantly increased in apoA-1$^{-/-}$ mice (p=0.0163), compared to C57BL/6 WT mice. In contrast, Notch 1 (p=0.9705) and Notch 2 (p=0.1276) mRNA levels from bone marrow cells showed no significant differences between both study groups of animals (Fig.3).**

Fig.3



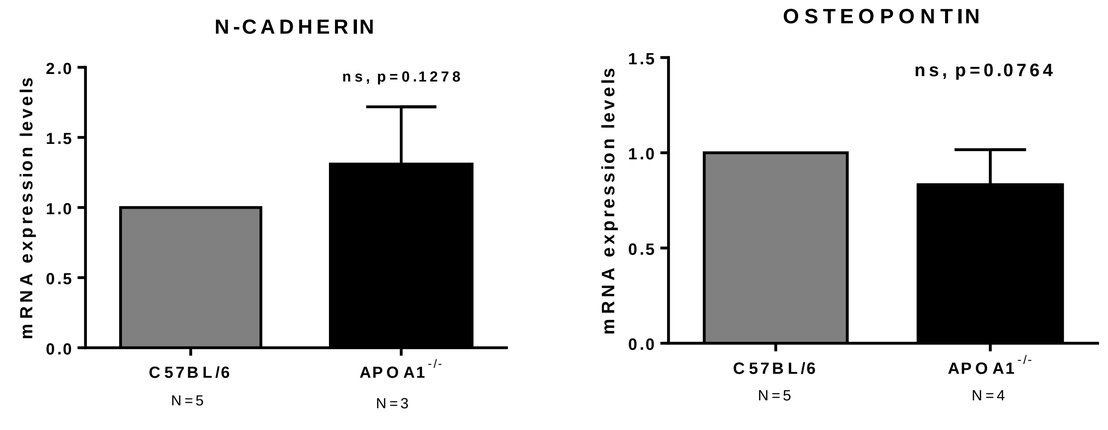
Flow Cytometric analysis of CXCR4 in HSCs derived from apoA-1$^{-/-}$ and C57BL/6 mice. **The evaluation of CXCR4 protein expression levels on HSCs obtained from apoA-1$^{-/-}$ revealed no significant differences compared to C57BL/6 mice (Fig.2).**

Fig.2



Real time PCR analysis of N-cadherin and Osteopontin in WBMCs devired from apoA-1$^{-/-}$ and C57BL/6 mice. **N-cadherin mRNA levels from WBMCs revealed no significant differences between both study groups of animals (p=0.1278). Osteopontin mRNA from bone marrow cells showed a trend to decreased expression in apoA-1$^{-/-}$ mice in contrast to WT mice (p=0.0764) (Fig.4).**

Fig.4



CONCLUDING REMARKS

SUMMARY OF RESULTS:

1.The expression of CLCX12 was significantly reduced, while the expression CXCR4 was greatly augmented (possibly via feedback cell reaction-mechanism) in the WBMCs of the ApoA-I$^{-/-}$ compared to the WT mice.

2.WBMCs from ApoA-I$^{-/-}$ mice displayed strongly increased mRNA levels of Jagged-1 compared to the WT mice.

3.Osteopontin mRNA expression levels were decreased in apoA-1$^{-/-}$ mice in contrast to the WT mice.

4.Flow cytometry revealed no significant differences in CXCR4 expression on HSCs of both study groups.

CONCLUSIONS:

The present study suggests for the first time that ApoA-I deficiency (and thus impaired HDL) halts HSC maintenance and quiescence, whereas it promotes HSC differentiation suggesting that it may be involved in the pathobiology of hematologic malignancies and possibly bone metastases.

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There is no conflict of interest to declare.

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