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NAP1L2 Drives Mesenchymal Stem Cell Senescence and Suppresses Osteogenic Differentiation

Meilin Hu[1], Liangyu Xing[1], Li Zhang[1], Fan Liu[1], Sheng Wang[2], Ying Xie[2], Jingjing Wang[2], Hongmei Jiang[2], Jing Guo[2], Xin Li[2], Jingya Wang[2], Lei Sui[1], Changyi Li[1*], Dayong Liu[1*], Zhiqiang Liu[2*]

Meilin Hu
Tianjin Medical University School of Stomatology Doctoral degree candidate.
humeilin@tmu.edu.cn

Summary

Background and Objective: Senescence of bone marrow mesenchymal stem cells (BMSCs) impairs stemness and osteogenic differentiation. However, the role of NAP1L2 in regulating cell senescence and bone formation remains unclear.

Methods and Results: We screened the gene expression profiles of human BMSCs from young and old donors and identified that elevation of the nucleosome assembly protein 1-like 2 (NAP1L2) expression was correlated with BMSC senescence and impaired osteogenesis. Elevated NAP1L2 expression was observed in replicative cell senescence and induced cell senescence *in vitro*, and in age-related senescent human and mouse BMSCs *in vivo*, concomitant with significantly augmented chromatin accessibility detected by ATAC-seq. Loss and gain functions of NAP1L2 affected the activation of NF-κB pathway, the status of histone 3 lysine 14 acetylation (H3K14ac) , and chromatin accessibility on osteogenic genes in BMSCs. Mechanistic studies revealed that NAP1L2, a histone chaperone, recruited SIRT1 to deacetylate H3K14ac on promoters of osteogenic genes such as *Runx2, Sp7*, and *Bglap* and suppressed the osteogenic differentiation of BMSCs. Importantly, molecular docking analysis showed a possible bond between NAP1L2 and an anti-aging reagent, the nicotinamide mononucleotide (NMN), and indeed, administration of NMN alleviated senescent phenotypes of BMSCs. *In vivo* and clinical evidence from aging mice and patients with senile osteoporosis also confirmed that elevation of NAP1L2 expression was associated with suppressed osteoblastogenesis.

Acknowledgements: This work was supported by the National Natural Science Foundation of China(82071079).

Results

Figure 1 BMSCs from elderly donors manifest senescent phenotypes and suppressed osteogenic differentiation

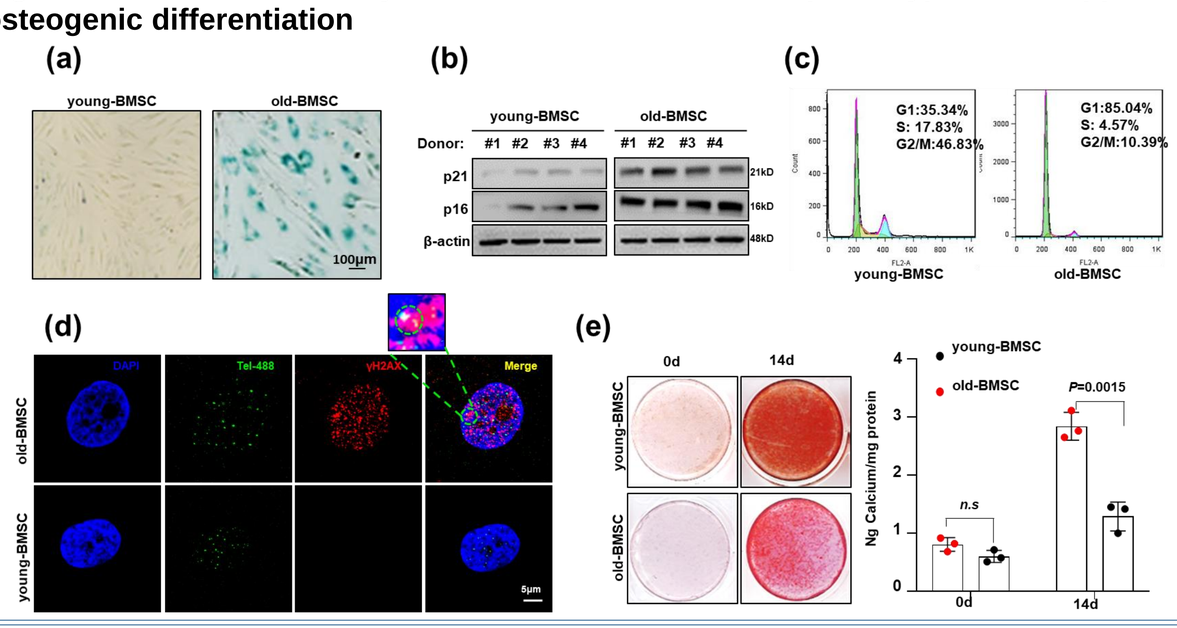


Figure 2 Highly expressed NAP1L2 is correlated with BMSCs senescence

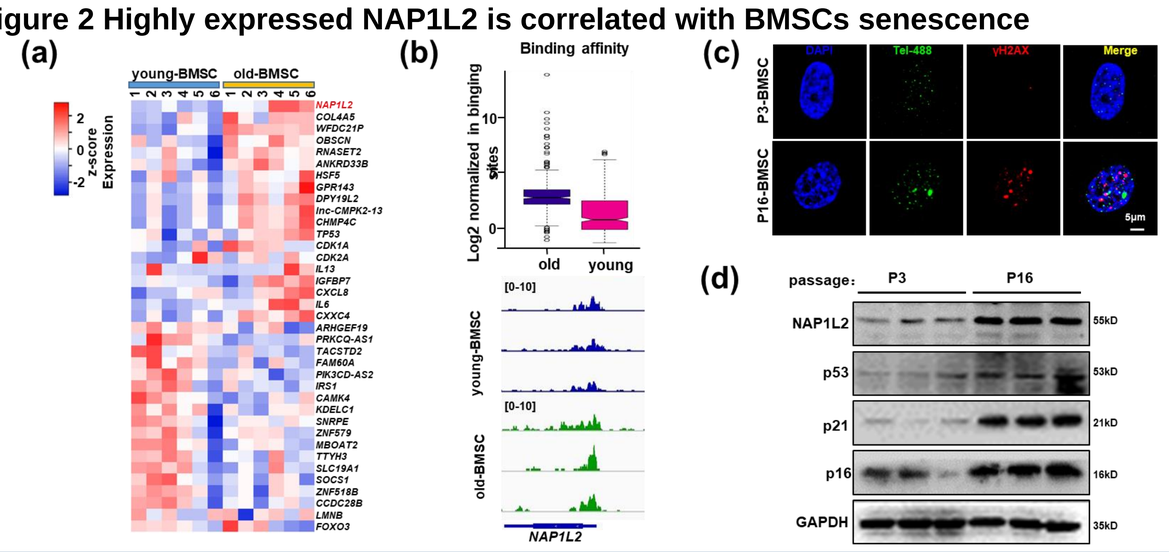


Figure 3 NAP1L2 expression is elevated in induced cellular senescence models and NMN and knockdown NAP1L2 alleviated cell senescence

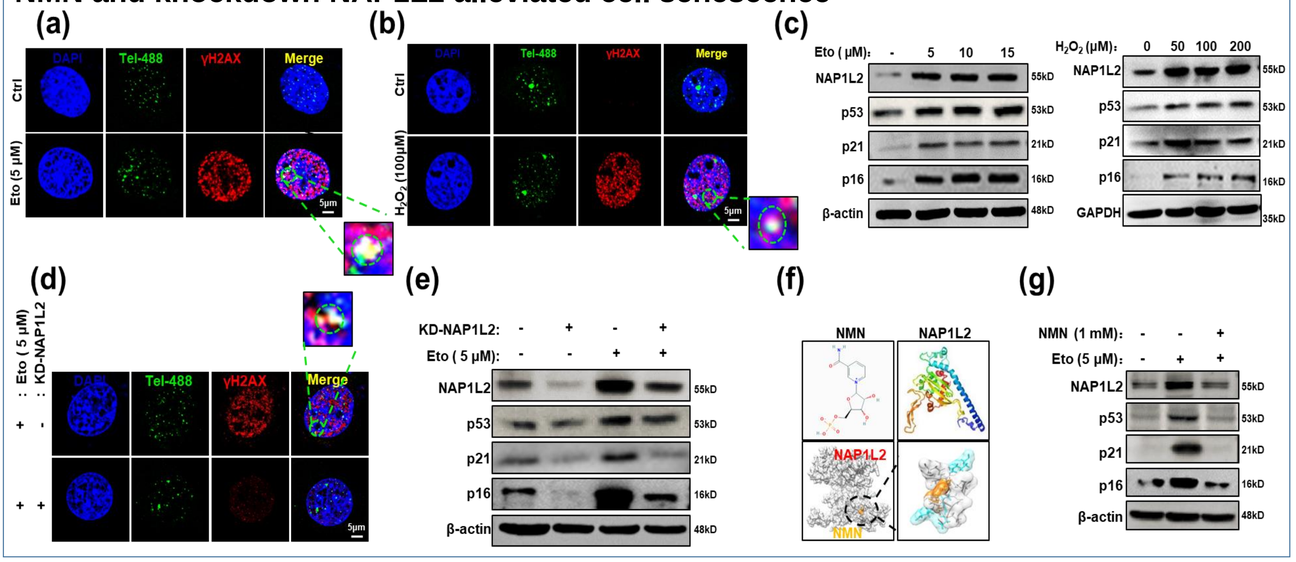


Figure 4 Manipulation of NAP1L2 alters cellular senescence progression through NF-κB signaling pathway

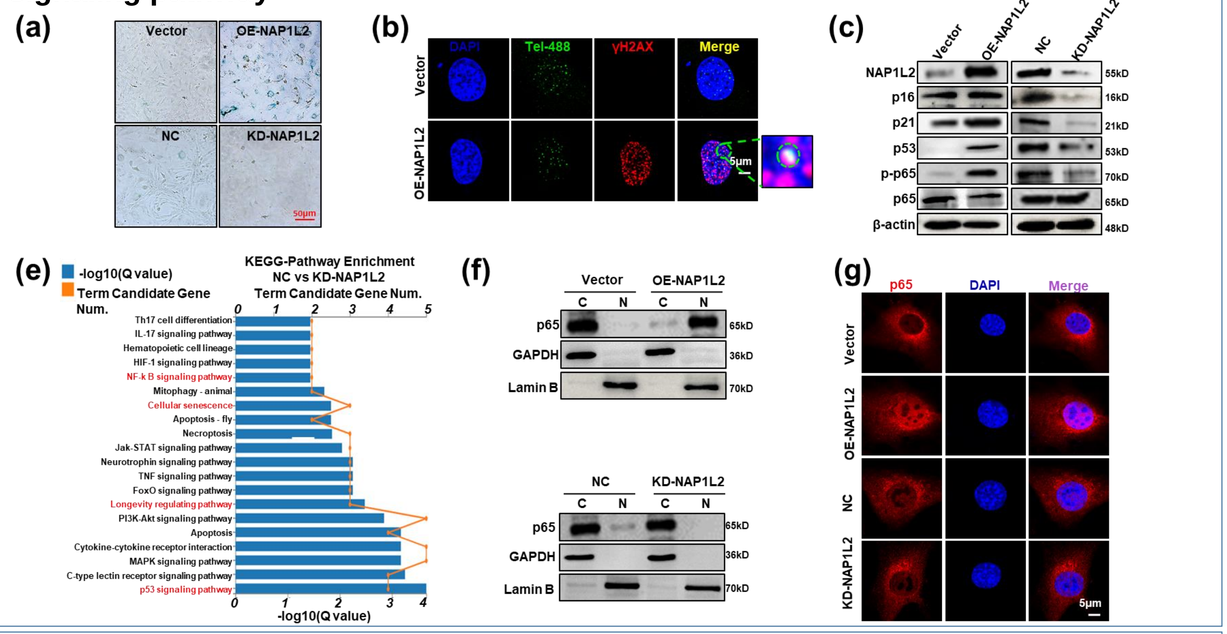


Figure 5 NAP1L2 recruits SIRT1 to deacetylate H3K14ac on promoters of osteogenic genes and suppresses osteogenesis

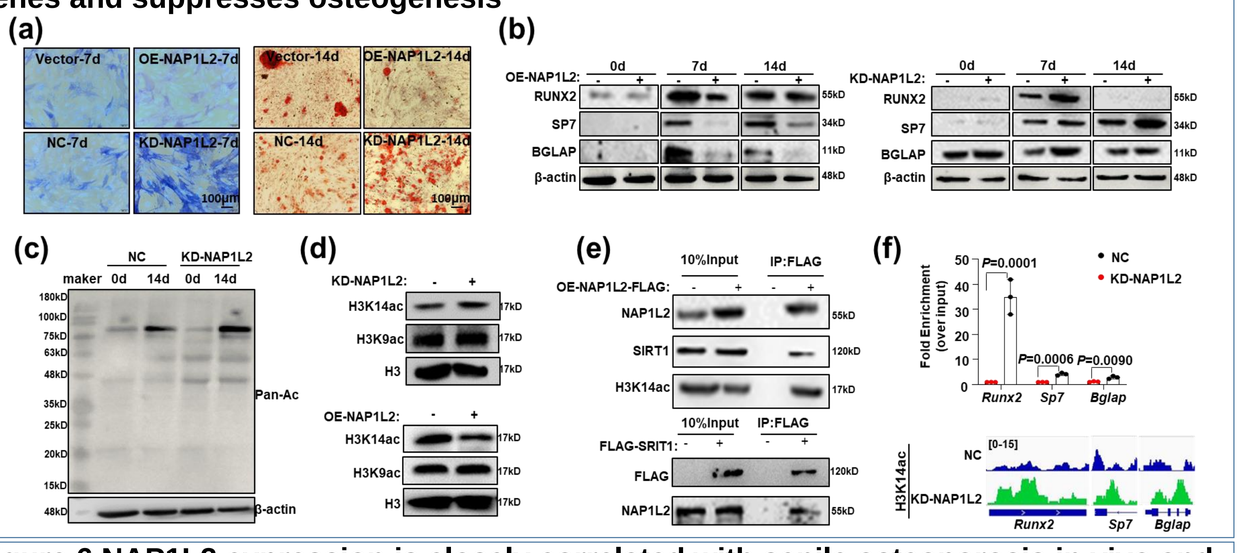


Figure 6 NAP1L2 expression is closely correlated with senile osteoporosis in vivo and in clinic

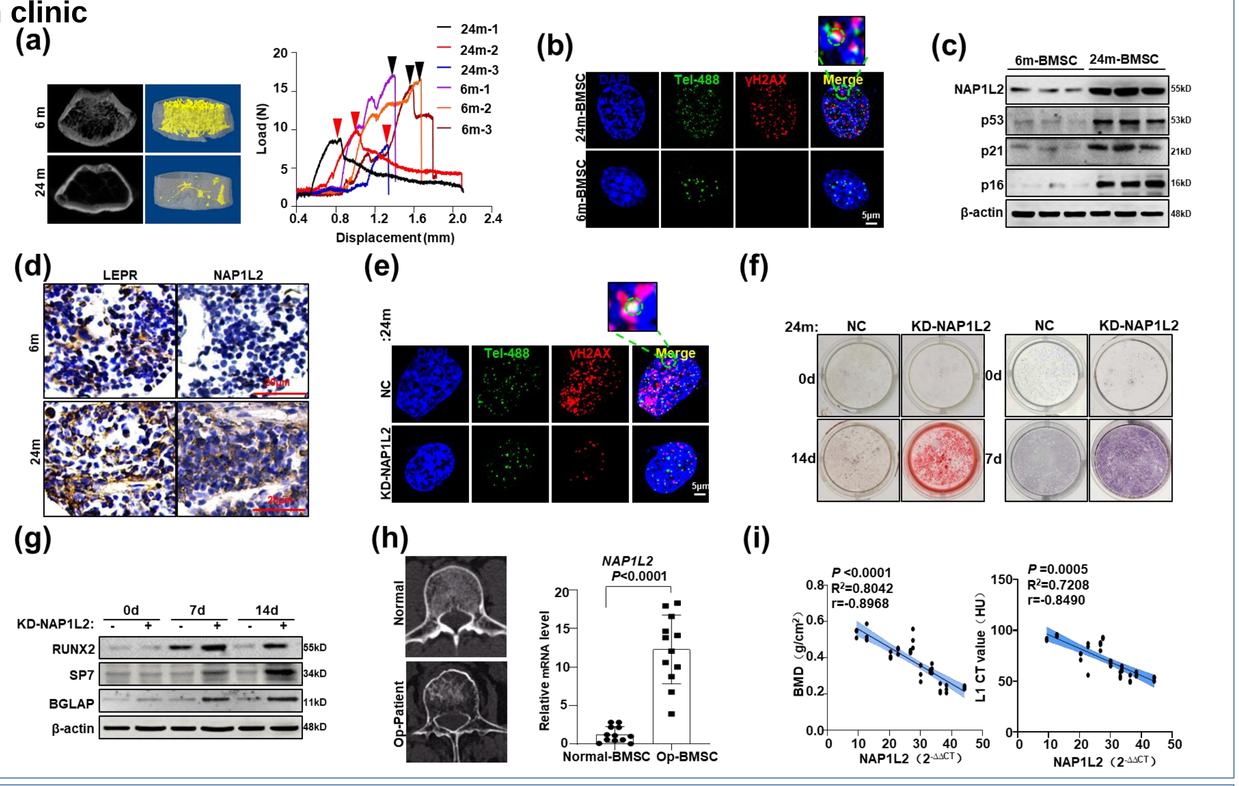
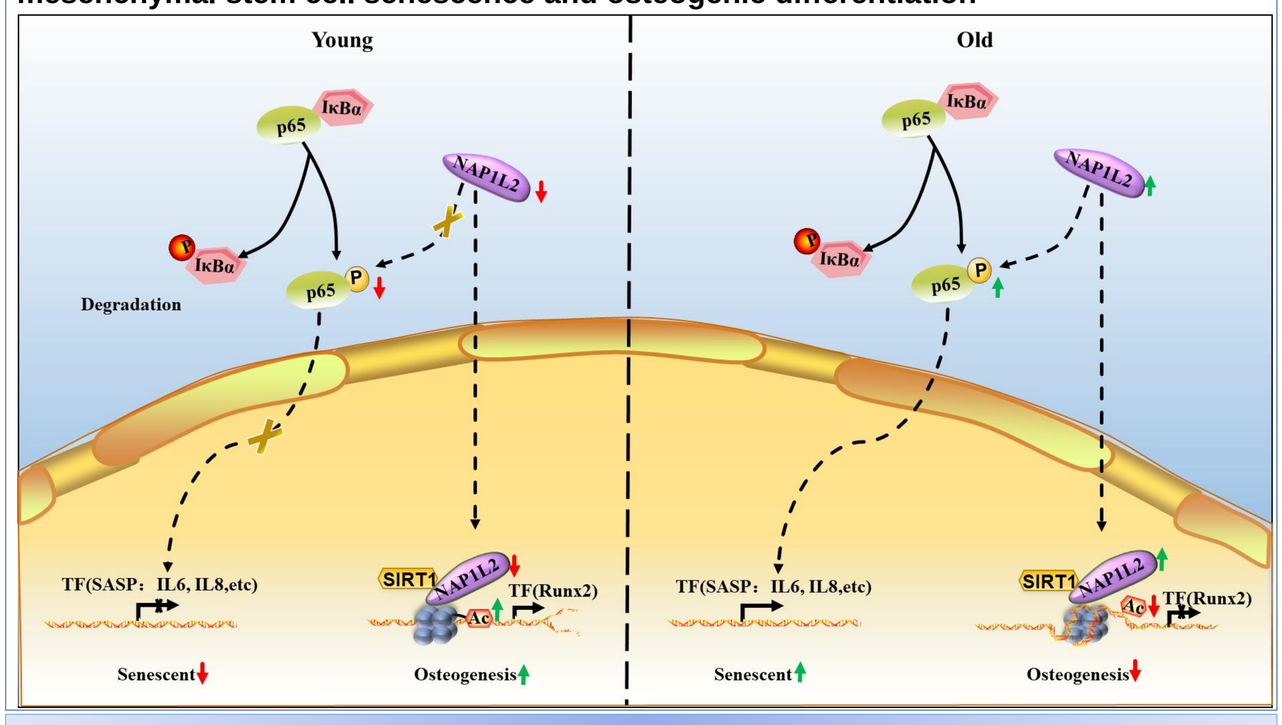


Figure 7 Proposed schematic diagram for mechanisms of NAP1L2 regulating mesenchymal stem cell senescence and osteogenic differentiation



Conclusion

NAP1L2 serves as an important regulator of both the senescence and osteogenic differentiation of BMSCs through inhibition of NF-κB signaling and recruitment of SIRT1 to deacetylate the H3K14ac level on promoters of osteogenic genes. thus providing a theoretical basis for the management of aging-related diseases.