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ARTICLE OPEN

NUP62 alleviates senescence and promotes the stemness of human dental pulp stem cells via NSD2-dependent epigenetic reprogramming

Xiping Wang[1], Li Wang[1], Linxi Zhou[2], Lu Chen[3], Jiayi Shi[1], Jing Ge[3], Sha Tian[4], Zihan Yang[1], Yuqiong Zhou[3], Qihao Yu[1], Jiacheng Jin[5], Chen Ding[4], Yihuai Pan[1,6]✉ and Duohong Zou[1,3]✉

Stem cells play a crucial role in maintaining tissue regenerative capacity and homeostasis. However, mechanisms associated with stem cell senescence require further investigation. In this study, we conducted a proteomic analysis of human dental pulp stem cells (HDPSCs) obtained from individuals of various ages. Our findings showed that the expression of NUP62 was decreased in aged HDPSCs. We discovered that NUP62 alleviated senescence-associated phenotypes and enhanced differentiation potential both in vitro and in vivo. Conversely, the knocking down of NUP62 expression aggravated the senescence-associated phenotypes and impaired the proliferation and migration capacity of HDPSCs. Through RNA-sequence and decoding the epigenomic landscapes remodeled induced by NUP62 overexpression, we found that NUP62 helps alleviate senescence in HDPSCs by enhancing the nuclear transport of the transcription factor E2F1. This, in turn, stimulates the transcription of the epigenetic enzyme NSD2. Finally, the overexpression of NUP62 influences the H3K36me2 and H3K36me3 modifications of anti-aging genes (HMGA1, HMGA2, and SIRT6). Our results demonstrated that NUP62 regulates the fate of HDPSCs via NSD2-dependent epigenetic reprogramming.

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INTRODUCTION

The life expectancy of humans has steadily increased over the past century, resulting in an increased prevalence of age-related diseases, such as neurodegenerative diseases, diabetes mellitus, osteoporosis, and osteoarthritis.[1] Age-related diseases not only influence the quality of life for older individuals but also impose a significant financial burden on society. Recent studies on aging have focused on elucidating common features, such as telomere dysfunction, genomic instability, epigenetic alterations, impaired autophagy, cellular senescence, and stem cell exhaustion that influence the process of aging.[2,3] Understanding the aging process will help to identify appropriate therapeutic strategies for delaying or preventing age-related disease progression.

Stem cells play a critical role in maintaining of tissue regenerative capacity and homeostasis.[4,5] Adult stem cell aging and exhaustion play a significant role in the overall aging of adult organisms.[3] Human dental pulp stem cells (HDPSCs), which originate from the ectomesenchyme of the cranial neural crest,[6–8] are a specific type of adult stem cells. HDPSCs preserve their regenerative capacity in adult teeth and contribute to the maintenance of homeostasis in dental stromal tissue.[9] HDPSCs, which are isolated from permanent teeth, are readily accessible Mesenchymal Stem Cells (MSCs) that can meet the needs of recipients of various ages. Additionally, HDPSCs demonstrate an age-dependent decrease in proliferation and multilineage differentiation.[10–12] This characteristic makes them a reliable model for studying mechanisms associated with senescence. It has been previously demonstrated that the downregulation of ROR2 accelerated the senescence of DPSCs through the activation of the MSX2/NSUN2/p21 axis.[13] Yang R.L. et al. reported that serine metabolism regulates the senescence of DPSCs by influencing DNA methylation of p16.[10] Furthermore, mettl3-mediated m^{6}A modification influenced the cell cycle progression of DPSCs.[14] The molecular mechanism underlying DPSC senescence requires further investigation.

Nuclear pore complexes (NPCs), comprised of approximately 30 nucleoporin proteins (Nups),[15] not only mediate nucleocytoplasmic transport but also play a crucial role in genome organization and cellular homeostasis.[16–18] Interestingly, the dysfunction of NPCs and abnormalities in specific nucleoporins have been associated with age-related diseases.[19–21] This suggests that the composition and function of NPCs may play a significant role in the aging process. NPCs regulate gene expression by actively participating in the selective import of transcription factors, as well as chromatin remodeling and histone modification.[22] NUP62, located in the central avenue of NPC, plays a vital role in

[1]School and Hospital of Stomatology, Wenzhou Medical University, Wenzhou, China; [2]Department of Orthodontics, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology, Shanghai, China; [3]Department of Oral Surgery, Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology and Shanghai Research Institute of Stomatology, Shanghai, China; [4]State Key Laboratory of Genetic Engineering, School of Life Sciences, Human Phenome Institute, Fudan University, Shanghai, China; [5]Touro College of Dental Medicine, New York Medical College, New York, USA and [6]Department of Endodontics, School and Hospital of Stomatology, Wenzhou Medical University, Wenzhou, China
Correspondence: Yihuai Pan (yihuaipan@wmu.edu.cn) or Duohong Zou (zouduohongyy@163.com)
These authors contributed equally: Xiping Wang, Li Wang.

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