Long noncoding RNA MAGI2-AS3 regulates the H2O2 level and cell senescence via HSPA8

Yingmin Zhang, Xinhua Qiao, Lihui Liu, Wensheng Han, Qinghua Liu, Yuanyuan Wang, Ting Xie, Yiheng Tang, Tiepeng Wang, Jiao Meng, Aojun Ye, Shunmin He, Runsheng Chen, Chang Chen
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1. 簡述論文的概要和重大發現

氧化還原的調節會參與基礎的細胞過程，例如細胞生長與死亡、細胞分化與衰老等，並且許多疾病和病理過程，包括糖尿病、關節炎、骨質疏鬆症、白內障和腫瘤發生都是因為氧化還原不平衡而引起的，而 H2O2 是一種 ROS，當細胞中有過多的 ROS 可能會對細胞造成損害。

MAGI2-AS3 是一條 long noncoding RNA，再這個研究中，作者發現 MAGI2-AS3 的下調通過抑制 HSPA8 的蛋白酶體降解來穩定 HSPA8 蛋白水平，從而降低了過氧化氫 (H2O2) 的含量，並且 lncRNA MAGI2-AS3 的下調也會通過穩定 HSPA8 蛋白水平延遲細胞衰老，此外，作者也發現 MAGI2-AS3 knock down 抑制細胞衰老的潛在分子機制是通過抑制 ROS/MAP2K6/p38 signaling pathway 介導的，從而確定了潛在的抗衰老應用。

2. 對論文內容的提問

在基因功能分析顯示有 8 個基因與衰老有關，對於 MAGI2-AS3 sh-1 有下調 mRNA level 的基因有兩個，選擇 MAP2K6 的原因為何?

最後 Overexpression MAP2K6 kinase，MAP2K6 是一個 kinase，在體內可能會有很多影響，為何不是使用下游的 p38 做實驗？

3. 論文的缺點與評論

lncRNA MAGI2-AS3 的 downregulation 降低了 superoxide level 並延遲了細胞衰老，為抑制細胞衰老提供了潛在的靶點。

而由於 MAGI2-AS3 在人類和其他靈長類動物（如恒河猴）中特異性表達，而在小鼠中沒有 homolog，因此未來需要在靈長類動物中研究 MAGI2-AS3 knockdown 對 superoxide downregulation 和抗衰老的影響，重要的是要驗證從 replicative 的衰老細胞到人類中得出的結論。

未來也可以進一步研究其他衰老相關基因與 MAGI2-AS3 的關係，使 lncRNA 在降低 H2O2、ROS 方面以及延遲細胞衰老方面的了解能夠更深入。

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ABSTRACT

The redox homeostasis system regulates many biological processes, intracellular antioxidant production and redox signaling. However, long noncoding RNAs (lncRNAs) involved in redox regulation have rarely been reported. Herein, we reported that downregulation of MAGI2-AS3 decreased the superoxide level in Human fibroblasts (Fbs), a replicative aging model, as detected by the fluorescent probes dihydroethidium (DHE) and MitoSOX™ Red. RNA pulldown combined with mass spectrometry showed that HSPA8 is a novel interacting protein of MAGI2-AS3, which was further confirmed by photoactivatable ribonucleoside–enhanced crosslinking and immunoprecipitation (PAR-CLIP). Downregulation of MAGI2-AS3 decreased the hydrogen peroxide (H_2O_2) content by stabilizing the HSPA8 protein level via inhibiting the protesome degradation of HSPA8. Further evidence showed that MAGI2-AS3 interacted with the C-terminal domain (CTD) of HSPA8. Downregulation of MAGI2-AS3 delayed cell senescence, while this antiaging effect was abolished by HSPA8 knockdown. The underlying molecular mechanism by which MAGI2-AS3 knockdown inhibited cell senescence was mediated via suppression of the ROS/MAP2K6/p38 signaling pathway. Taken together, these findings revealed that downregulation of lncRNA MAGI2-AS3 decreased the H_2O_2 content and delayed cell senescence by stabilizing the HSPA8 protein level, identifying a potential antiaging application.

1. Introduction

Redox-regulated events are fundamental for cellular processes, such as cell growth and death, cell differentiation and senescence and so on. Many diseases and pathological processes, including diabetes, arthritis, osteoporosis, cataracts and tumorigenesis, are caused by a redox imbalance [1–6]; therefore, research on redox regulation is very important. With global aging, health management based on the redox theory of aging has begun to provide potential strategies to prevent disease progression [7]. Cellular redox levels are widely reported to be regulated by proteins and genes [8], but only ~2% of the human genome encodes proteins and a large amount of our DNA produces thousands of uncharacterized RNAs [9]. In recent years, noncoding RNAs (ncRNAs) have received wide appreciation; among these transcripts, long noncoding RNAs (lncRNAs) are noncoding transcripts that are transcribed by RNA polymerase II; frequently 5' capped, spliced and polyadenylated and longer than 200 nucleotides [10].

LncRNAs participate in biological processes via various mechanisms, including affecting gene expression and epigenetics. However, there are only a few reports about redox regulation by lncRNAs. Downregulation of the lncRNA LINC00963 was found to suppress oxidative stress in chronic renal failure (CRF) by elevating the enzymatic activity of

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