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(a) Abstract

The naked mole rat (NMR) is the longest-lived rodent, resistant to multiple age-related diseases including neurodegeneration. However, the mechanisms underlying the NMR's resistance to neurodegenerative diseases remain elusive. Here, we isolated oligodendrocyte progenitor cells (OPCs) from NMRs and compared their transcriptome with that of other mammals. Extracellular matrix (ECM) genes best distinguish OPCs of long- and short-lived species. Notably, expression levels of CD44, an ECM-binding protein that has been suggested to contribute to NMR longevity by mediating the effect of hyaluronan (HA)[1], are not only high in OPCs of long-lived species but also positively correlate with longevity in multiple cell types/tissues. Moreover, CD44 promoted ATF6 target gene expressions and enhanced endoplasmic reticulum (ER) stress resistance in both NMR and human cells. CD44 localized to the ER and associated with ER proteins including those related to the ATF6 pathway. CD44 substantially modified ER proteome, changed the properties of the ER membrane, promoted ER-to-Golgi transport of ATF6, and conferred ER stress resistance in a manner dependent on IRE1, PERK, and ATF6. Considering that UPR plays a crucial role in lifespan regulation in yeast, worm, and fly[2-3] and that pharmacological activation of ATF6 protects various tissues from ischemia-reperfusion injury in the mouse[4], our results suggest that CD44 regulate longevity not only by mediating HA signals at the plasma membrane but also by enhancing basal ATF6 activity and ER stress resistance through its function in the ER[5].

References

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