Synopsis of Original Research Paper

Development of a new method to prevent skin aging using the longest-lived and aging-resistant rodent

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The naked mole-rat (NMR) is an African rodent that forms a eusocial colony in subterranean environments. The NMR shows an extraordinary longevity with a maximum lifespan of more than 37 years, although its body mass is similar to that of the laboratory mouse. The NMR also displays delayed aging phenotype and cancer resistance. Cellular senescence plays an important role in the aging and carcinogenesis processes, suggesting that NMRs may have species-specific mechanisms to prevent the accumulation of senescent cells. Here we show that upon induction of cellular senescence, NMR fibroblasts progressively activate cell death including apoptosis through activation of the INK4a-Retinoblastoma protein (RB) pathway in a mechanism we termed " INK4a-RB cell death". We show that INK4a-RB cell death is independent of p53 activity and not observed in mouse fibroblasts. NMR fibroblasts uniquely accumulate serotonin and are inherently vulnerable to hydrogen peroxide (H_2O_2). Upon activation of the INK4a-RB pathway, NMR fibroblasts increase monoamine oxidases (MAOs) levels, which oxidize monoamine including serotonin and produce H_2O_2, resulting in increased oxidative damage and activation of cell death. The INK4a-RB cell death may potentially contribute to the suppression of senescent cell accumulation in NMRs. Our findings provide novel insights into the mechanisms of delayed aging and cancer resistance in NMRs.