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BITS AND BYTES

# Cancer resistance, high molecular weight hyaluronic acid, and longevity

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**Abstract** Longevity varies greatly among mammals. The naked mole rat is among the longest-lived rodents, having an average lifespan of 32 years, compared to the similarly-sized house mouse with lifespan of 4 years. The rate of cancer also varies widely among mammals and interestingly, the naked mole rat is essentially cancer-free (Gorbunova et al., Nat Rev Genet 15(531):540, 2014). A series of elegant studies (Tian et al. Nature 499:346–349, 2013) has revealed that this cancer resistance derives from the abundant production of high molecular weight hyaluronic acid. Remarkably, high molecular weight hyaluronic acid, which accumulates within the extracellular matrix, stimulates an intracellular pathway that induces expression of $p16^{ink4a}$ and suppresses oncogenic transformation.

**Keywords** Longevity · Cancer · Naked mole rat · Hyaluronic acid

The naked mole rat is the longest lived rodent species. It also possesses remarkably good health throughout its life. Cancer has never been observed in a naked mole rat in captivity (Gorbunova et al. 2014). The reason for this cancer resistance, which presumably contributes to longevity, is an intriguing question. Researchers at the University of Rochester from the laboratory of Vera Gorbunova and Andrei Seluanov have uncovered a surprising mechanism that may account, at least in part, for the cancer-free, long life span of the naked mole rat (Tian X et al. 2013). Their finding centers on a special form of hyaluronic acid (HA), which is an abundant component of the extracellular matrix of all mammals. HA is an unbranched carbohydrate polymer composed of repeating units of the disaccharide glucuronic acid/N-acetylglucosamine. It serves a variety of functions including tissue hydrodynamics, cell motility, wound healing, and immunity. HA is synthesized by three enzymes, hyaluronic acid synthesase (HAS) 1, 2, and 3, which produce chains of varying length ranging in size from approximately 0.5 to 3 MDa in humans, mouse, and guinea pig (which is phylogenetically closer to the naked mole rat than the mouse). A key finding is that naked mole rats produce high molecular weight HA (HMW-HA), ranging in size from 6 M to 12 MDa.

In a series of elegant experiments, the authors demonstrated that the production of HMW-HA resulted from substitution of two serines for two highly conserved asparagines in the active site of HAS2. Importantly, the production of HMW-HA was associated with reduced proliferation of cultured skin fibroblasts prior to reaching confluence. The investigators termed this property early contact inhibition (ECI), and previously implicated ECI as an anti-cancer mechanism in the naked mole rat (Seluanov A et al. 2009). While the mechanism(s) by which HMW-HA causes ECI remains unclear, it appears that HMW-HA acts as an extracellular signal that stimulates intracellular pathways leading to up-regulation of the cell cycle inhibitor $p16^{ink4a}$, which is required for ECI.

Relative to other species, the naked mole rat has abundant levels of total HA. This richness of HA was found to result from the combination of high levels of HAS2 expression coupled to low levels of hyaluronidases (HAase), the enzymes responsible for HA degradation. Naked mole rat fibroblasts are resistant to oncogenic transformation as measured by growth in soft agar. However, treatment of cultures with exogenous HAase, or knockdown of HAS2, was sufficient to cause transformation, indicating that HMW-HA confers resistance to oncogenesis. Finally, in a series of xenograft studies,

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the authors demonstrated that knockdown of HAS2 or overexpression of HAase was required for naked mole rat cells to produce tumors in mice.

Elucidation of the biochemistry of HMW-HA synthesis and the demonstration that HMW-HA imparts resistance to oncogenic transformation are noteworthy. HA is abundant and has been extensively studied. Its importance in extracellular matrix biology is well recognized. However, the discovery that a structural modification confers powerful anti-cancer activity comes as a surprise and raises many questions regarding not only the role of HA, but also other components of the extracellular matrix, in cancer biology and longevity.

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