



CANCER *and* LONGEVITY ANSWERS

*Naked Mole Rats,
Exercise &
EMODs (ROS)*

Prof Randolph M. Howes MD, PhD

Cancer And Longevity Answers Naked Mole Rats Exercise And Emods

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Cancer And Longevity Answers Naked Mole Rats Exercise And Emods:

Cancer and Longevity Answers Phd Prof Randolph M Howes MD, Prof Randolph M. Howes, 2015-06-04 Decades of research resulted in my appreciation of the many benefits of exercise in reducing the risks of acquiring a wide spectrum of common diseases and in an incredible rodent known as the naked mole rat NMR or the sand puppy The NMR has the highest level of oxidative stress of all rodents and it lives eight times as long as other rodents with a superb healthspan and it has never had a case of cancer reported in this species ever What does the naked mole rat and exercise have in common that could revolutionize our thinking about oxygen electronically modified oxygen derivatives EMODs and oxidative metabolism Are oxygen free radicals or reactive oxygen species the cellular assassins they have been portrayed to be Or could they be the secret weapon of the NMR which keeps it in good health for so long Is there a commonality between the NMR and the effects of increased oxygen consumption and so called oxidative stress associated with exercise Can the unique salutary benefits of exercise and unique EMOD qualities be applied to man such that our healthspan is dramatically extended as well as our lifespan The hallmark of exercise is a 10 20% increase in oxygen consumption which is rapidly metabolically converted to electronically modified oxygen derivatives EMODs EMODs formerly confusingly called reactive oxygen species ROS Can excessive levels of supplemental antioxidants and antioxidant vitamins block or interfere with the benefits of exercise Is exercise deficiency disease equivalent to an EMOD insufficiency disease EMOD and exercise insufficiency allows diseases to manifest themselves such as cancer heart disease strokes and arthritis I believe that oxygen metabolomics appear to be the basis of the good health and longevity seen in the NMR and in the benefits associated with exercise Oxygen and its EMOD progeny is the point of convergence for exercise and the naked mole rat as it relates to healthspan and lifespan

Identification of Longevity and Cancer Resistance Mechanisms in Long-lived Rodent Species Xiao Tian, 2016 Aging is a universal biological process and the majority of age associated diseases remain unsolved especially cancer However aging proceeds at different rates between mammals which results in a huge diversity of lifespans In the case of rodent species maximum lifespans range from 4 years to 32 years Strikingly rodents also exhibit differential tumor susceptibility Cancer incidence in some mouse strains reaches 95% In contrast naked mole rats *Heterocephalus glaber* and blind mole rats *Nannospalax* sp are extremely cancer resistant This thesis describes the results of several studies aiming to identify the molecular mechanisms responsible for longevity and tumor resistance in long lived rodent species The first two studies compared the efficiencies of several DNA repair mechanisms which are critical to maintain genomic stability The next two studies focused on the longest lived rodent the naked mole rat and identified the production of high molecular mass hyaluronan HMM HA as the responsible mechanism for its cancer resistance In addition to the tumor suppression function HMM HA synthesis inhibits mammalian target of rapamycin mTOR which potentially contributes to naked mole rats exceptional longevity Genomic instability is a critical hallmark of aging Genomic DNA relies on DNA repair mechanisms to

maintain its integrity. We therefore investigated the impact of different DNA repair pathways on the evolution of diverse lifespans. Nucleotide excision repair (NER) is responsible for removal of lesions that distort DNA helical structure such as thymine dimers and 6-4 photoproducts produced by UV exposure. Contradictory results were previously published on the contribution of nucleotide excision repair (NER) in the evolution of longevity. In the present study we did not find a significant correlation between NER efficiency and maximum lifespan in 19 rodent species. However our study revealed that solar UV acts as the major selection pressure in the evolution of NER as there is a strong positive correlation between NER efficiency and the level of UV exposure. DNA double strand break (DSB) repair is a critical genome maintenance mechanism as it protects against the most deleterious type of DNA damage. We identified a strong positive correlation between DSB repair efficiency and maximum lifespan of a species. Additionally we identified Sirtuin 6 (SIRT6) as a key factor contributing to more efficient DSB repair in long lived species. By comparing SIRT6 in representative short and long lived rodents (mouse and beaver) we identified the amino acid substitutions that are responsible for their dramatically different DSB repair activities. Based on our results we propose that modulating SIRT6 activity is a potential strategy in maintaining efficient DSB repair and genomic stability in aged organisms. The longest living rodent, the naked mole rat, exhibits negligible senescence with advancing age and is highly resistant to neoplasia. In contrast short lived mice are highly susceptible to cancer. We identified Hyaluronan (HMM HA) as a potent anti cancer mechanism in naked mole rats. Removing HMM HA renders naked mole rat cells susceptible to oncogenic transformation. Despite the discovery of HMM HA as a major contributor to naked mole rats' cancer resistance, the anti aging mechanisms in naked mole rats remained largely a mystery. Our recent study suggests that HMM HA production is not only an anti cancer mechanism but modulates a critical longevity regulator, mammalian target of rapamycin (mTOR). Overexpression of HMM HA in mouse or human cells inhibits mTOR signaling pathway. Mechanistically AMP activated protein kinase (AMPK) is the mediator that inhibits mTOR activity. mTOR activity in naked mole rat cells is repressed by the potent HMM HA synthesis as inhibiting hyaluronan synthase 2 (HAS2) activates mTOR. Considering the critical role of mTOR in interventions that extend lifespan which include rapamycin, dietary restriction and exercise we propose that HA synthesis by repressing mTOR activity contributes to the exceptional longevity of naked mole rats. In summary my work has identified a set of mechanisms responsible for longevity and cancer resistance in long lived rodent species. This knowledge opens new avenues for developing treatments of age related diseases in humans.

Pages vi-viii **Prolonged Longevity in Naked Mole-rats**

Angela Lee, 2007 Cancer Resistance in the Naked Mole Rat Patrick Heckman, 2014

Decoding **Cancer And Longevity Answers Naked Mole Rats Exercise And Emods**: Revealing the Captivating Potential of Verbal Expression

In a time characterized by interconnectedness and an insatiable thirst for knowledge, the captivating potential of verbal expression has emerged as a formidable force. Its power to evoke sentiments, stimulate introspection, and incite profound transformations is genuinely awe-inspiring. Within the pages of "**Cancer And Longevity Answers Naked Mole Rats Exercise And Emods**," a mesmerizing literary creation penned by way of a celebrated wordsmith, readers embark on an enlightening odyssey, unraveling the intricate significance of language and its enduring impact on our lives. In this appraisal, we shall explore the book's central themes, evaluate its distinctive writing style, and gauge its pervasive influence on the hearts and minds of its readership.

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