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Mini-Review

The relationship between the naked mole-rat and hyaluronic acid, as mediated by its receptor CD44: A Mini-Review

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Abstract

The life expectancy of the naked mole-rat (Heterocephalus glaber) is longer than that of other rodents. In NMR cells, the hyaluronic acid concentration is at a higher level. The extracellular matrix's primary constituent is hyaluronic acid, and CD44 and RHMM are the receptors for hyaluronic acid in the cells. Hyaluronan synthases (HAS); HAS1, HAS2, and HAS3 are located in the plasma membrane and produce hyaluronic acid. Moreover, there are six types of hyaluronic degradation enzymes (Hyal-1, Hyal-2, Hyal-3, Hyal-4, and PH-20). Hyaluronic acid is known to have anti-cancerous effects and acts as a double-edged sword promoting cell senescence and protecting against cellular aging at the same time. NMR's lengthy lifespan may probably be due to the high molecular weight of hyaluronic acid. INK4 isoforms ($P16^{ink4a/b}$ and pALTINK4a/b) and $p27^{kip1}$ conferring on NMR a 2-way (early and regular respectively) defense mechanism make NMR more resistant to cancer cells than, humans and mice with only regular contact inhibition (regular ($p27^{kip1}$). This study, therefore, aims to examine the existing molecular interactions within the NMR-HA-CD44 axis and the ability to confer cancer resistance to mammalian cells through INK4 isoforms gene transfer using the CRISPR method. A lot of potential thus exists in studying these relationships and the prospects for answering the yet unknowns in this area.

Introduction

The naked mole rats (Heterocephalus glaber) had first been described over 150 years ago. Scientists have only recently begun to delve deeply into several aspects of extraordinary biological properties [1]. Naked Mole-Rat (NMRs) may live longer if they live in a setting that protects them from predators and bad weather conditions. Although it has adapted to subterranean living, the NMR metabolism has had to deal with various difficulties. A hypoxic environment is created because burrows are generally enclosed and gas exchanges via the soil are restricted (10-15 percent of oxygen) [2].

New swarm adaptive existence algorithms are being generated using the NMR approach. The natural pattern of matting mimicry is explained using the NMR method. Workers and breeders are the two categories of NMRs that show these patterns. The NMR algorithm is the result of studying the phenomenon of workers mating with the queen, where workers compete for the queen's affections. There is a new breeder for every sterile breeder, and the fittest worker is promoted to that position [3].

Furthermore, NMR lifespan is five times greater than what would be predicted allometrically for a 40 g rodent. The hyaluronan produced by the NMR has a very high molecular mass (vHMM-HA). While the polymer length of vHMM-exceptional hyaluronic acid (HA) appears to be significant for longer life, it is not clear whether this is the case [4]. Most diseases associated with old age do not affect the NMR, the longest-living rodent. A high dose of Irradiation (IR) is required to induce cellular senescence in NMR cells, and NMR fibroblasts were resistant to IR-induced apoptosis [5].

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According to Hadi, et al. NMR cells can be transformed by SV40LT (a large T antigen) and HRASG12V (an oncogene). Non-cell-autonomous processes underlie NMR cancer resistance, and they might be explained by a particular microenvironment or immune system in each individual. Whether hyaluronan's physical qualities contribute to cancer resistance remains to be explored [6].

NMR can live ten times longer than normal mice, and several scientists reported in 2013 that hyaluronic acid gives animals cancer resistance. Furthermore, naked mole-rat has abundant hyaluronic acid in their matrix, which will make their wrinkled skin elastic. The naked mole's matrix contains a high concentration of hyaluronic acid, and hyaluronic acid has also been linked to cancer treatment [7].

HA is not like other Glycosaminoglycans (GAGs). Unlike proteoglycan, HA is not synthesized as a single protein from the Golgi; Hyaluronan synthases (HAS), HAS1 and HAS2, and HAS3 are perfectly positioned on the plasma membrane's inner surface, where they produce HA. HAS1 and HAS2 are responsible for the manufacture of HA at high molecular weight, whereas HAS3 is responsible for the synthesis of low molecular weight HA [8]. Moreover, there are six types of hyaluronic degradation enzymes (Hyal-1, Hyal-2, Hyal-3, Hyal-4, and PH-20) [9]. Hyal1 and Hyal2 are the most well-known of these. The importance of HA chains of different molecular weights in the production of diverse cellular signals is well established. CD44 and RHAMM are the two HA receptors [8].

The hyaluronan produced by the NMR has a very High Molecular Mass (vHMM-HA). Cell death is prevented in NMR cells as well as mouse and human cells due to stress-induced cell-cycle arrest and cell death. The cytoprotective effect of HA is dependent on CD44, the major HA-receptor. There is a direct correlation between cell stress resistance and the ability of CD44 proteins to interact with each other and decrease p53. According to Takasugi, et al. vHMM may be useful in improving cellular stress resistance against age-related diseases [10] Figure 1.

A Cluster Differentiation-44 (CD44) is a ubiquitously present glycoprotein on the surface of mammalian cells that plays a significant role in several biological functions. The receptor is over-expressed in a variety of solid tumors, such as pancreatic, breast, and lung cancer [8,11]. In addition, Hyaluronan, a glycosaminoglycan, abundant in the tumor microenvironment, is a key player in many processes associated with cancer. Moreover, the Naked Mole-Rat (NMR) is a subterranean rodent that has gained significant attention from the biomedical research community in recent years as molecular mechanisms underlying its unusual biology started to be unraveled. However, the review of the relationship between the naked mole-rat and hyaluronic acid has been rarely reported. Therefore, this mini-review is interesting.

Interestingly, NMR with the two distinct genes; INK4 isoforms ($P16^{ink4a/b}$ and pALTINK4a/b) [12] and $p27^{kip1}$ [13], has a 2-tier contact inhibition mechanism of early ($P16^{ink4}$ and isoforms,) and regular ($p27^{kip1}$) contact inhibition respectively [4], making it more cancer-resistant than humans and mouse cells, with the regular contact inhibition (regular ($p27^{kip1}$)) and extremely low p16 gene expression [4,13].

Using the CRISPR genome editing methodology and other molecular biology techniques, this study aims therefore to investigate and decipher the fundamental mechanisms of NMR-CD44- vHMM-HA crosstalk relationships and its possible application (including p16 gene introduction into the human cancer genome) to treat human cancer, cellular aging and other neurodegenerative conditions.

The NMR as a model organism for human health and quality of life could be beneficial because it is an unusually long-lived and healthy rodent that shows no signs of aging. Due to its slower aging and age-related disorders, this species may disclose unique, possibly causative natural processes. Having this information will enable the development of therapies aimed at activating mechanisms that will delay human aging, prevent degenerative disease, and cancer, and raise the standard of living in old age [14,15].

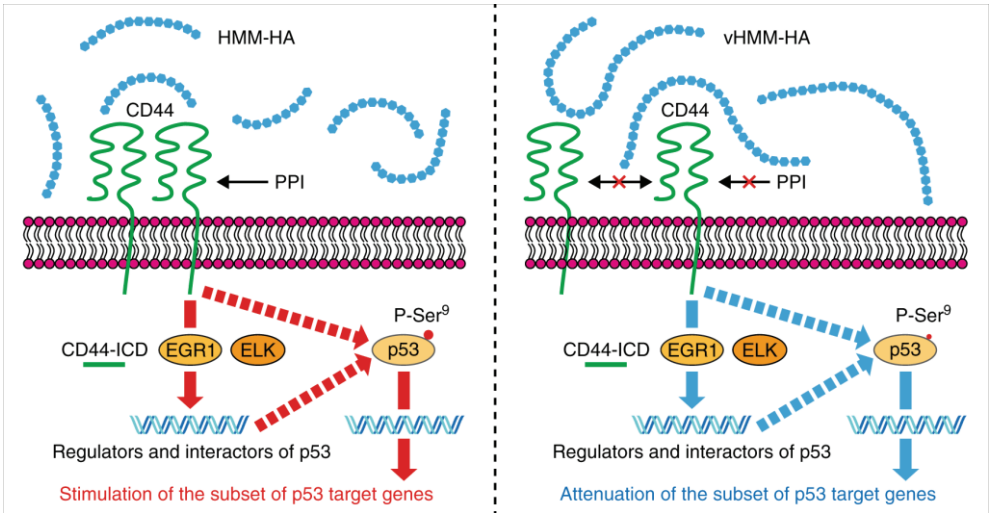

Figure 1: NMR-CD44- vHMM-HA crosstalk relationships [4].

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Conclusion and future scope

NMR's breeding mechanism is similar to the honeybee, its longest life span of all the rodents and burrowing lifestyle have caused its genes to be modified for excellent adaptations, making NMR a good model for studying human health and quality of life. Among them are the extraordinarily high cellular high molecular weight hyaluronic acid and 2-tier contact inhibition systems, conferring cancer resistance. We think that exploring these 2 mechanisms in other mammalian cells may aid in the treatment of not only cancer but aging and other neurodegenerative diseases.

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