Research Article **IJOAR (2018) 1:13**

International Journal of Aging Research (ISSN:2637-3742)

Deciphering the longevity of the mole-rats

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ABSTRACT

A theoretical model of a nonlinear network that outlines the general aspects of mole-rat resistance to age-related diseases, such as cancer and the action of ROS was elaborated. According to our conjecture, it was shown that the protection is established because hyaluronic acid of high molecular mass forms a non-linear network of interactions. That network leads to self-organization away from the thermodynamical equilibrium, which appears through a “first order” phase transition as a supercritical bifurcation of Andronov-Hopf type. Finally, it is shown how the rate of entropy production is a Lyapunov function of the dynamics of the process.

Keywords:
mole-rat
hyaluronic acid
ROS
Biological phase transition
Entropy production rate as a Lyapunov function

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How to cite this article:
L. Triana, G. Cocho, R. Mansilla and J.M. Nieto-Villar. Deciphering the longevity of the mole-rats. International Journal of Aging Research, 2018, 1:13

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Website: http://escipub.com/

1. Introduction

Longevity and aging remain one of the most captivating and intriguing topics of human knowledge. Despite all the achievements in the biomedical sciences, the mechanism for aging processes is still very unknown.

Mole-rats represent an ideal model for the study of the aging process [1], as well as, to understand the so-called degenerative diseases such as cancer [2, 3]. As a fact, the journal Science named the naked mole-rat "Vertebrate of the Year" for 2013 [2].

The mole-rat is the longest known living rodent and is a unique model of successful aging that shows attenuated decreases in most physiological functions [4]. In addition to their longevity, mole rats show unusual resistance to cancer [1]. More than this, the mole rat can tolerate high levels of oxidative stress and have mechanisms to prevent age-related diseases, such as cancer, diabetes, and cardiovascular, brain, and liver diseases, as well as many infections [5, 6, 7].

The question that has puzzled the scientific community for decades is: Why does the human being, the mouse and the rat develop cancer, but the mole rats do not or rarely do it?

It is well known that there are multiple factors that influence the biology of cancer [8] and aging [9]. Therefore the mole rat is an appropriate animal model, because of the mechanisms they possess to reach a greater longevity, resistance to hypoxia and to cancer. These mechanisms could be taken as a reference for studies of human cancer and degenerative diseases [1, 2, 3].

The aim of this work is to show, through a simple theoretical model, the mechanism of resistance of the mole rat to age-related diseases such as cancer and the action of ROS. For this we establish as conjecture that: *Protection is established because hyaluronic acid of high molecular mass* (HA) *conforms a non-linear network of interactions that lead to self-organization outside the thermodynamical equilibrium*.

The paper is organized as follows: in Section 2 we propose a non-linear network model. Section 3 focuses on the analysis of the ordinary differential equations model derived from the previously proposed mechanism, including quantitative simulations and stability analysis. The development of a thermodynamic framework, based on the rate of entropy production is presented in Section 4. Finally, some comments and remarks are presented.

2. A nonlinear network model of mole-rat

Xiao Tian *et al.* [10] found that naked mole rat fibroblasts secrete high molecular weight hyaluronan (HA), which is five times larger than the human or the mouse. High molecular weight hyaluronan accumulates abundantly in mole rat tissues due to the decreased activity of degrading enzymes and a unique sequence of hyaluronan synthase 2 (HAS2). In addition, mole rat cells are more sensitive to signaling, since naked mole rat cells have a higher affinity than those of the mouse or the human cells.

It is well known that mole rats live in conditions of hypoxia [11] and that they tolerate extreme conditions such as anoxia [12]. During chronic hypoxia, high levels of reactive oxygen species, ROS, are induced, which may be associated with a normal physiological response to the imbalance in oxygen supply and demand or environmental stress [13]. The hypoxia inducible factor, HIF, is a transcription factor that regulates the cellular response to hypoxia and acts as a regulator of oxygen homeostasis [14]. The system of HIF transcription [14] and hypoxia are the major determinants in angiogenesis and regulate, for instance the processes of tumor invasion.

Chronic hypoxia inevitably leads to an increase in glucose uptake and the accumulation of its metabolites; consequently, hyaluronic acid will be degraded by some hyaluronidases (HYAL1-6) or by ROS in fragments of different sizes [15]. These low molecular weight hyaluronic acid fragments serve as tissue repair signals, including signals of cell proliferation, cell survival and angiogenesis, which lead to the initial proliferation of the underlying cells [16].

It is well known that the mole rat can tolerate high levels of oxidative stress [17] and exhibits a high resistance to cancer [18, 5] due to its capacity in the production of high molecular weight hyaluronic acid [10]. In fact, it has been found that ROS levels in moles are lower compared to rats [19].

Based on what was discussed above, an integrated framework according to the network structure shown in Figure 1 is proposed.

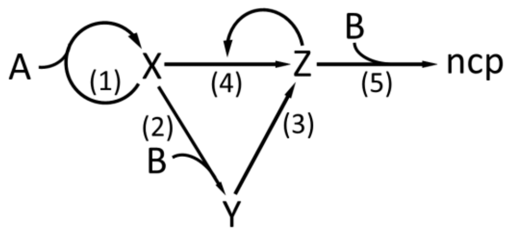

Fig. 1. The nonlinear network model of mole-rat

In the model, A represent the oxygen concentration, B, the high molecular weight hyaluronan (HA) concentration, which is taking as the control parameter, x are the concentration of ROS spices, y are the concentrations of the low molecular weight HA, z are the populations of the cancer cells and ncp represent the concentration of the non-cancer products.

Step 1 is related to the auto-catalytic formation of reactive ROS oxygen species, (x) because chronic hypoxia induces high level of ROS [13]. Step 2 shows the degradation of the hyaluronic acid by ROS in fragments of different sizes (y) [15]. Step 3 shows the formation of tumor cells (z) from fragments of different sizes of hyaluronic acid [16]. Step 4 shows the spread of the tumor promoted by the action of ROS [20]. Finally, step 5, outlines the protective action of high molecular weight of hyaluronic acid (B) [11]. Considering that the high molecular weight accumulates abundantly in mole-rat tissues [11] we take as the control parameter.

The constants for the model proposed (see Fig. 1) were chosen empirically trying to have a greater generality and simplicity as possible, so we have: $k_1 = 4.7$ ml/(mmol s), $k_2 = 1$ ml/(mmol s), $k_3 = 1\ \mathrm{s}^{-1}$, $k_4 = 1$ ml/(mmol s), $k_5 = 2$ ml/(mmol s).

3. Mathematical model, stability analysis and numerical simulations

Mathematical models represent an adequate way to formalize knowledge of living systems obtained through a Systems Biology approach [21, 22]. These types of models make possible the description of important regularities and are useful to provide effective guidelines for the development of therapies, drugs and clinical decision making.

The network model (Fig. 1) we propose is a qualitative representation of the action of high molecular weight hyaluronan (HA) concentration. We use the mathematical methods of chemical kinetics to reduce the network to a system of ordinary differential equations such as

$$\frac{dx}{dt} = 4.7xA - xz - x\mathrm{B}$$
$$\frac{dy}{dt} = x\mathrm{B} - y$$
$$\frac{dz}{dt} = y - 2z\mathrm{B}$$

(3.1)

Quantitative value for each constant has been empirically obtained. Fixed points, stability and bifurcations analysis were calculated using the standard procedure [23,24,25]. Control parameters were represented by the high molecular weight HA accumulates abundantly in mole-rat tissues [11]. The corresponding stationary state is:

$$x_{ss} = \tfrac{47}{5}A - 2\mathrm{B},\ y_{ss} = \tfrac{47}{5}A\mathrm{B} - 2\mathrm{B}^2,\ z_{ss} = \tfrac{47}{10}A - \mathrm{B}$$

(3.2)

The characteristic equation as a function of the eigenvalues λ is

$$\lambda^3+(2B+1)\lambda^2+2B\lambda-B\left(2B-\tfrac{47}{5}A\right)$$

(3.3)

and we find that the periodic oscillations occur product of a supercritical Andronov-Hopf bifurcation [23], where the critical value of the control parameter is obtained from the following equation:

$$B_c=1.5667A-0.33333$$

(3.4)

For hypoxia condition, $A=1$, is obtained that: $B_c=1.2334$. For simulating network model, COPASI v. 4.6.32 software was used. In Fig. 2 is shown the dynamic behavior for the system (3.1).

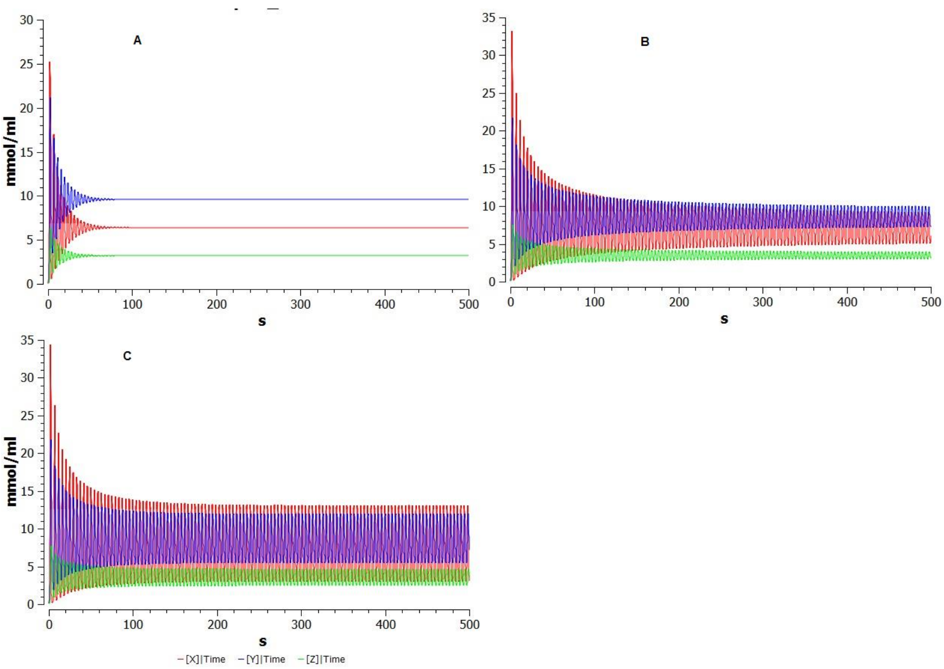

Fig. 2. Time series of the proposed model (see Fig.1) for different values of the control parameter B: a. $B>B_c=1.5$, b. $B<B_c=1.23$, c. $B<B_c=1.2$; x (red), y (blue); z (green).

As observed, for the value of $B>B_c=1.5$ (see Fig.2a) a stationary stable state appears, which guarantees low levels of ROS (x) and the tumor cells (z). For values of $B<B_c=1.23$ (see Fig.2b) due to the supercritical Andronov-Hopf bifurcation appear periodic oscillations and the same phenomenology observed in Fig.2a is here maintained.

This dynamic behavior leads to self-organization outside the thermodynamic equilibrium. At macroscopic scales, the self-organization and the complexity exhibited by dynamic systems are manifested through oscillations in time and / or space. In biological systems, these oscillations are usual [26], and they do not only guarantee robustness [27], but also allow the system to perform various functions, including control and regulation.

In Fig.2c, it is observed that a small decrease in the concentration of B ($B<B_c=1.2$), leads to an increase in the concentration of ROS species (x), which suggests that the robustness of the action of HA not only comes given that there is a critical concentration B_c of HA that guarantees self-organization, but also that there must be a fine regulation of it.

4. Thermodynamics framework

As we know from thermodynamics irreversible processes [28] for a chemical reaction the entropy production can be evaluated as:

$$S_i^{\circ}=\frac{A}{T}\xi^{\circ} \qquad (4.1)$$

where A, according to De Donder and Van Rysselberghe [29], represents the affinity and the term ξ° is the reaction rate. The formula (4.1) could be rewritten [30] for the *k*-th reaction as

$$S^{\circ}_{i/k} = \left(\xi^{\circ}_{f(k)} - \xi^{\circ}_{b(k)}\right) \ln \frac{\xi^{\circ}_{f(k)}}{\xi^{\circ}_{b(k)}} \qquad (4.2)$$

Where $\xi^{\circ}_{f(k)}, \xi^{\circ}_{b(k)}$ are the forward and backward reaction rates respectively. The whole entropy production rate $S^{\circ}_{i/T}$ for the network model (Fig.1) can be evaluated as

$$S^{\circ}_{i/T} = \sum_k S^{\circ}_{i/k} \qquad (4.3)$$

In a previous work [31] we have shown that the rate of entropy production is a Lyapunov function, in fact we extended this formalism to the development of cancer [32, 33, 34, 35, 36, 37]. Thus, we have the entropy production per unit time meets the necessary and sufficient conditions for Lyapunov function [30], such that

$$S^{\circ}_{i} = f\,(\Omega) > 0 \qquad (4.4)$$

where Ω is the vector of control parameters. The Eulerian derivative (4.4) must hold:

$$\frac{dS^{\circ}_{i}}{dt} = \frac{\partial S^{\circ}_{i}}{\partial \Omega}\frac{d\Omega}{dt} \leq 0; \qquad (4.5)$$

where Ω $(\Omega \equiv B)$ is related with concentration of high molecular weight hyaluronan. Taking into account (4.2) and (4.3), we can write the whole entropy production rate $S^{\circ}_{i/T}$ for the network model (Fig.1) as a function of control parameter B as

$$S^{\circ}_{i/T} = 4.0525B - (0.3B - 1.1 \times 10^{-5} \ln \frac{1}{B} + 8.4633 \qquad (4.6)$$

Then it fulfills that

$$\frac{\partial\left(S^{\circ}_{i/T}\right)}{\partial B} = 4.3525 - \frac{1.1\times 10^{-5}}{B} - 0.3 \ln \frac{1}{B} > 0 \qquad (4.7)$$

As the control parameter B is a concentration of high molecular weight hyaluronan a reactant, such as: $\frac{dB}{dt} < 0$, then it fulfills that: $\frac{dS^{\circ}_{i}}{dt} \leq 0$, that allows us to affirm that the rate of entropy production is a Lyapunov function.

5. Conclusions and remarks

The network model proposed for the mole rat generalizes, at least qualitatively, the main characteristics of the regulatory action of high molecular weight hyaluronic acid, as well as the resistance of age-related diseases such as cancer and the action of ROS.

In summary, in this paper we arrive at the following theoretical conclusions:

- It was shown, according to our conjecture, that the protection that the moles rats have is established because the high molecular weight hyaluronan conforms to the nonlinear network of interactions that lead to self-organization far from thermodynamical equilibrium and behaves according to the rules of a "first order" phase transition through a supercritical bifurcation of Andronov-Hopf type. In other words, oscillations grant high robustness and complexity.
- There must be a critical concentration of the high molecular weight of hyaluronic acid, such that it guarantees the self-organization and a fine regulation of the process.
- With the hyaluronic acid as the control parameter of the system, it was shown that the rate of entropy production is a Lyapunov function. That is, it provides the directionality of the process

We hope that the current theoretical framework will provide a better understanding of aging processes and cancer and will contribute to improving the duration of human health, longevity, as well as the search for optimal pathways for future treatments.

Acknowledgements

Prof. Dr. A. Alzola in memoriam. We would like to thank Prof. Dr. Jacques Rieumont for support and encouragement for this research. One of the authors (JMNV) thanks the CEIICH and the Institute of Physics of the UNAM Mexico for the warm hospitality and the financial support by DGAPA/DF A/2210/2017. Also, we appreciate the financial support provided by Dr. Gregory Gaiser, CEO of Complete Pharmaceutics.

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