Naked mole-rat resistance to senescence and cancer: Key constraints embodied by the histone H1.0 protein on chromatin dynamics

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Naked mole-rat resistance to senescence and cancer: Key constraints embodied by the histone H1.0 protein on chromatin dynamics

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Background: The naked mole-rat (*Heterocephalus glaber*) appears not to undergo senescence to any significant degree in late adulthood, and has almost negligible cancer incidence. These observations are explicated under the recently proposed hologenic theory of individuated multicellularity and a corollary theory of senescence. Both theories are grounded in considerations of thermodynamic constraints on histone post-translational modifications. Together, these theories underpin the formulation of an experimentally falsifiable hypothesis that may explain the remarkable resistance to both senescence and cancer displayed by the naked mole-rat.
Presentation of the hypothesis: Here, I propose that the constraints imposed on chromatin dynamics by the naked mole-rat's histone H1.0 protein—which in terminally differentiated cells constrains the post-translational modification of nucleosome core histones—are a necessary and sufficient condition for its resistance to both senescence and cancer.
Testing the hypothesis: I suggest two experiments for the direct testing of the proposed hypothesis. These experiments comprise, as test subjects, mutant naked mole-rats synthesizing a house mouse (*Mus musculus*)-like histone H1.0, and mutant house mice synthesizing a naked mole-rat-like histone H1.0. The prediction is that the constraints on chromatin dynamics embodied by the respective mutant histone H1.0 proteins will negate the otherwise significant resistance to both senescence and cancer of the naked mole-rats and, conversely, confer such resistance to the house mice.
Implications of the hypothesis: If this hypothesis is experimentally verified, it will provide empirical support for the hologenic theory of individuated multicellularity and the theory of senescence. The verification of this hypothesis implies that constraints on chromatin dynamics through naked mole-rat-like histone H1 proteins could confer significant resistance to both senescence and age-related cancer to otherwise senescence-prone and/or cancer-susceptible multicellular organisms, including humans.

Keywords: *Heterocephalus glaber*; histone H1; aging; ageing; replication-independent; linker histone; hologenic theory; oncogenesis; tumorigenesis; teleodynamics

BACKGROUND

The rodent species known as naked mole-rat (*Heterocephalus glaber*) has been reported to be very long-lived [1]. Moreover, the species is an exception to the age-dependent component of the Gompertz-Makeham empirical law of mortality, which positively correlates mortality rate with age after adulthood [2]. In other words, this species is not only very long-lived but also appears not to undergo any significant senescence process after reaching adulthood. The naked mole-rat also displays an almost negligible cancer incidence [3]—the only unambiguously diagnosed case in this species corresponds to a gastric neuroendocrine carcinoma [4]. However, it is not known why the naked mole-rat does not undergo senescence nor display significant cancer incidence.

The recently proposed hologenic theory of individuated multicellularity [5] and a theory of senescence derived from it [6] may shed some light onto the underpinnings of this senescence and cancer resistance. Both theories are grounded on thermodynamic constraints on histone post-translational modifications. Based on these two theoretical descriptions, I offer an experimentally falsifiable hypothesis that may explain the naked mole-rat's remarkable negligible-senescence and cancer-resistance traits in terms of chromatin dynamics. The plausibility of this hypothesis is here supported by three unambiguous proofs of concept. If verified, the hypothesis will be important for a better understanding of senescence and cancer processes in the naked mole-rat and other individuated multicellular species. The hypothesis may also inform biotechnological research and could ultimately be important for potential therapeutic or even prophylactic options for senescence-related health conditions in biomedicine.

PRESENTATION OF THE HYPOTHESIS

Theoretical considerations

Histone post-translational modifications (hPTMs), observable in nucleosome core particles (NCPs) nearby each transcription start site (TSS), can be understood as a physical medium with finite capacity to convey biologically meaningful information content. For instance, a fraction of this information content has been used to robustly predict transcript abundance levels from TSS-adjacent

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hPTM levels [7]. According to the hologenic theory of individuated multicellularity, two mutually independent constraints on hPTMs in each NCP respectively convey two types of critical yet mutually unrelated information contents necessary for transcriptional regulation at the multicellular-individual level [5]. Here, constraints are understood as local and level-of-scale specific thermodynamic boundary conditions.

The first information content is hologenic content, which is conveyed in constraints that depend on interactions between NCP histones and other proteins [5]; this content regulates (i.e., constrains) transcription, making it accurate for the needs of the multicellular individual (Fig. 1a, blue). The second is epigenetic information content, which is conveyed in constraints dependent on interactions between NCP histones and DNA [5]; this content regulates (i.e., constrains) transcription making it precise for said needs (Fig. 1b, orange).

The theory of senescence describes senescence as a developmental byproduct in which hologenic information capacity in hPTMs is increasingly gained in each NCP and throughout development at the expense of capacity for epigenetic information [6]. This uninterrupted process creates a hologenic/epigenetic information imbalance after adulthood in terms of accuracy versus precision in transcriptional regulation. To illustrate this without loss of generality, let *geneG* be any given gene, let X be a random variable representing the *geneG* transcript abundance in a cell within any given cell type (CT), and let x_f be the mean *geneG* transcript abundance level that is functional for the multicellular individual in any given condition. The hologenic/epigenetic information imbalance over-regulates transcription in terms of accuracy (i.e., closeness of the mean μ_X to x_f) gained at the increasing expense of precision (i.e., closeness of the X values to their own mean μ_X) up to the point of dysfunctionality for the multicellular individual [6] (see schematic probability density function (PDF) in Fig. 1a).

The theory of senescence also describes age-related cancer to be a result of a poorly tuned yet strong enough "pushback" by the multicellular individual at the chromatin level against its own senescence process, thereby dysregulating transcription. For each TSS within a given cell type, this pushback occurs in terms of precision gained at the increasing expense of accuracy, up to the point of dysfunctionality for the multicellular individual [6] (see schematic PDF in Fig. 1b).

Empirical considerations

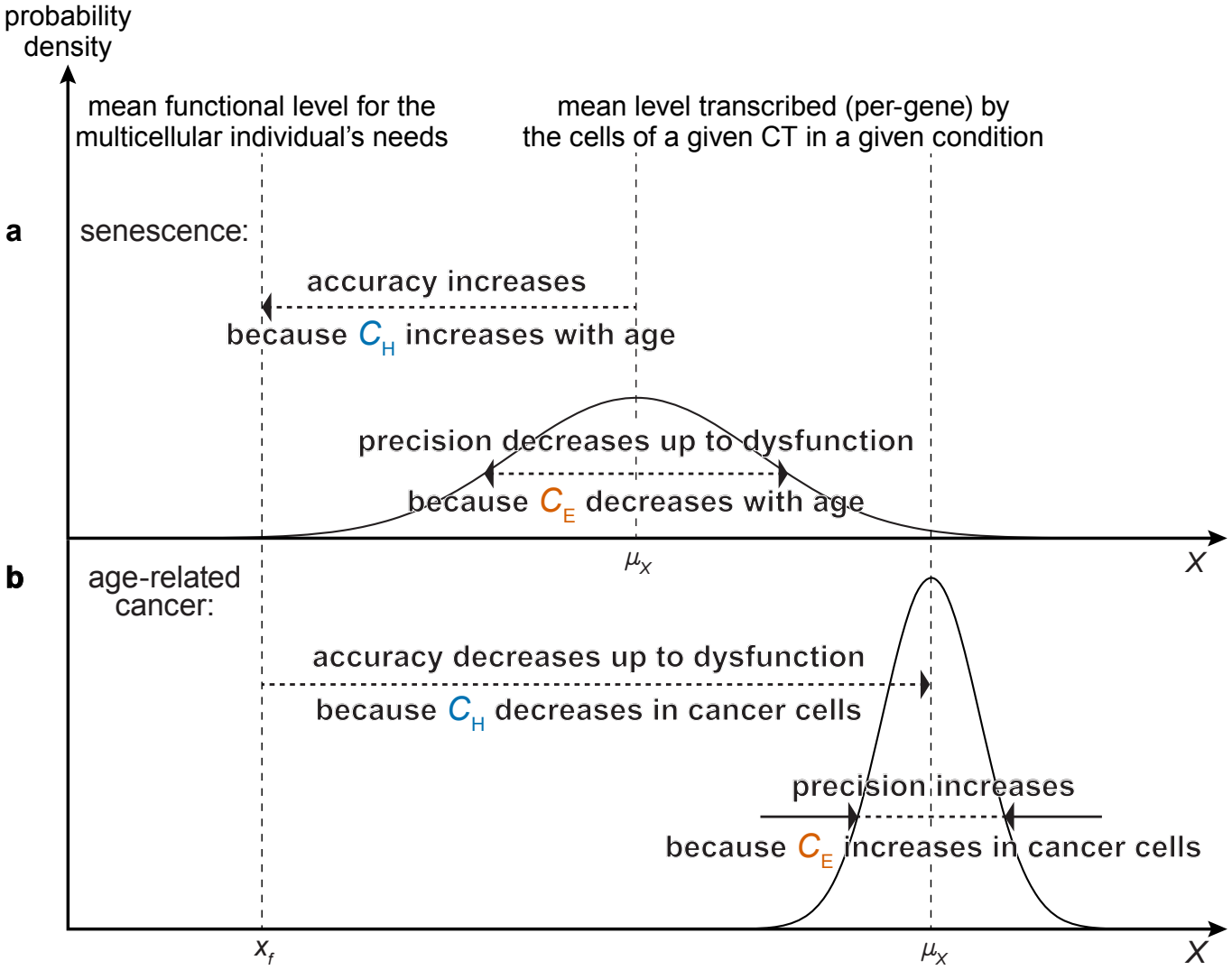
In the described two theories, histones and their post-translational modifications embody critical constraints on chromatin dynamics for development-related processes, such as senescence and age-related cancer. In particular, constraints on chromatin dynamics in age-related cancer can be understood as a poorly tuned yet strong enough "pushback" against senescence as mentioned previously [6]. One particular histone family, namely the histone H1 (also known as the "linker" histone) family, could explain the particular traits of the naked mole-rat in terms of chromatin dynamics because (i) histone H1 is less evolutionarily conserved and much more variable in size and sequence than the core histone families (H2A, H2B, H3 and H4) [9] and (ii) histone H1 constrains the accessibility of critical histone-modifying enzymes and chromatin remodeling factors to the NCP [10, 11].

The globular domain of the histone H1 protein folds into a major structural motif known as a "winged" helix-turn-helix (wHTH) [9], in the form of α_1-β_1-α_2-α_3-β_2-β_3 [12], where the α_i motifs are alpha helices and the β_j motifs are beta sheets. The α_3 motif within the wHTH is critical for the histone H1 binding affinity to the NCP [13–16].

All known variants of the histone H1 are encoded by paralog gene families [17]. In particular, the two variants relevant for the proposed hypothesis—i.e., with "linker" histone function critical for the adult body or soma—are (i) "replication independent" variants (i.e., they are synthesized throughout the cell cycle) and (ii) synthesized chiefly by somatic cells. For all metazoans the common variant is H1.0 (H1 histone family, member 0; also known as H1°, H1(0), H5, H1δ, or RI H1) and within metazoans, vertebrates add a second variant H1x (H1 histone family, member X; also known as H1.10) [12, 18]. Whereas H1x histones are highly expressed in human neuroendocrine cells and tumors [19], H1.0 histones accumulate in terminally differentiated mammalian cells [20, 21], accounting for ≈80% of all H1 transcripts [22].

Statement of the hyphotesis

Here, I hypothesize that the constraints posed by the naked mole-rat's histone H1.0 protein on chromatin dynamics in terminally differentiated cells are a necessary and sufficient condition for its resistance to both senescence and cancer. This causal relationship can be explained in that the naked mole-rat histone H1.0 confers particular stabilization to the histone H1.0-NCP binding affinity in terminally differentiated cells. This stabilization is critical to counteract the otherwise increasing hologenic/epigenetic information imbalance after adulthood that has been proposed as the fundamental cause of senescence [6] (see Fig. 1a and the subsection entitled Making sense out of the results).



key properties	accuracy := closeness of μ_X to x_f precision := closeness of the X values to μ_X
variables & measures	X := per-gene, per-CT transcript abundance level in a cell C_T := total correlation of TSS-adjacent hPTMs in bits C_H := total correlation of TSS-adjacent hPTMs (given X) in bits C_E := total correlation of TSS-adjacent hPTMs and X in bits $C_T = C_H + C_E \approx$ constant with age (ref. [6])
theoretical interpretation	$C_H \Rightarrow$ capacity for hologenic information in TSS-adjacent hPTMs $C_E \Rightarrow$ capacity for epigenetic information in TSS-adjacent hPTMs

Fig. 1. Schematic PDFs representing the theory of senescence as an imbalance of hologenic (blue) and epigenetic (orange) information in hPTMs [6]. (a) Senescence is a developmental byproduct caused by a substantial information imbalance in chromatin—in which transcription becomes increasingly over-regulated after the multicellular individual reaches adulthood, in terms of gaining accuracy at the increasing expense of precision—up to the point of dysfunctionality for the multicellular individual. **(b)** Age-related cancer is the result of a poorly tuned yet strong enough "pushback" by the multicellular individual against its own senescence process—making transcription dysregulated by gaining precision at the increasing expense of accuracy—up to the point of dysfunctionality for the multicellular individual. Constraints on hPTMs can be quantified in bits using the Shannonian measures known as total correlation $C(Y_1, \ldots, Y_n)$ and conditional total correlation $C(Y_1, \ldots, Y_n | X{=}x)$ [8], where $\{Y_1, \ldots, Y_n\}$ are random variables representing TSS-adjacent hTPM levels in the NCP and X is a random variable representing the per-gene, per-cell-type transcript abundance level in a cell.

Proofs of concept

The following three proofs of concept are meant to support the plausibility of the hypothesis but in no way should be regarded as evidence for it. The proofs consist of an independent proof #1 plus its derived proofs #2 and #3, all obtained by surveying publicly available histone H1 protein sequences:

1. If the hypothesis presented here is correct, the differential constraints embodied by the naked mole-rat histone H1.0 protein should be accounted for by at least one differential amino acid residue in the sequence of that histone protein. In other words, at least one amino acid residue in the naked mole-rat histone H1.0 protein should be non-conserved with respect to a highly conserved residue (at the same homologous site) in vertebrate species both closely or distantly related to the naked mole-rat. A multiple alignment of the histone H1.0 reference protein sequences from the naked mole-rat (*Heterocephalus glaber*), Damaraland mole-rat (*Fukomys damarensis*), Norwegian rat (*Rattus norvegicus*), house mouse (*Mus musculus*), human (*Homo sapiens*), Western painted turtle (*Chrysemys picta bellii*), and the African clawed frog (*Xenopus laevis*) reveals that three of such expected sites exist (sites S_1, S_2, and S_3; see Additional file 1). Notably, one of these sites (S_2) is occupied in the naked mole-rat by a non-conserved arginine (R) residue, which is located in the critical α_3-motif sequence (relative position #12 in Fig. 2a). The arginine residue is also proximal to a highly-conserved lysine (K) residue (relative position #10 in Fig. 2a). This highly conserved lysine residue is already known to undergo a post-translational acetylation in the fruit fly *Drosophila melanogaster* [23, Table S1]. Importantly, lysine acetylation neutralizes the otherwise positive electrostatic charge of this residue and also impairs its ability to form hydrogen bonds [24] thereby decreasing its binding affinity to the negatively-charged DNA [24, 25].

2. The Cnidaria phylum is interesting for the concept-proofing of the hypothesis because some member species, such as the freshwater polyp (*Hydra vulgaris*), have also been found to display negligible senescence [26]. Nematoda (roundworms) is another interesting phylum because adult lifespan varies up to more than 300-fold among some of its known member species [27, 28]. Expanding the explanatory scope of the hypothesis to these phyla and given the proof of concept #1, it is expected that only in their long-lived member species—such as the cnidarian *Hydra vulgaris* and the disease-causing nematodes *Onchocerca volvulus* (onchocerciasis [29]), *Brugia malayi* (lymphatic filariasis [30]), and *Loa loa* (loiasis [31])—differential constraints on chromatin dynamics entail a conserved arginine (R) residue in the respective histone H1.0 α_3-motif sequences. Remarkably, their α_3-motif sequence alignment reveals an arginine residue conserved only in the long-lived species (Fig. 2b). Moreover, this conserved arginine residue is located in a strikingly similar relative position (#11 in Fig. 2b) to that of the non-conserved arginine residue found in the α_3-motif sequence of the naked mole-rat histone H1.0 protein (relative position #12 in Fig. 2a).

3. In terms of a "negative-control" proof of concept, it is worth noting that the naked mole-rat appears to be somewhat susceptible to cancer onset in neuroendocrine cells [4]. This finding implies that the hypothesized cancer protection conferred to the other cell types by the constraints embodied by the naked mole-rat histone H1.0 protein are either absent or counteracted in neuroendocrine cells. As mentioned previously, the histone H1x protein is highly expressed in human neuroendocrine tumor cells and, importantly, more expressed than the histone H1.0 protein [19]. Given these facts and the proof of concept #1, it is then to be expected that the naked mole-rat histone H1x α_3-motif sequence does not display any non-conserved residues, let alone a non-conserved arginine (R) residue. A multiple sequence alignment of the naked mole-rat's histone H1x protein against those of other closely or distantly related vertebrates shows just that (Fig. 2c).

TESTING THE HYPOTHESIS

To test the hypothesis directly, the naked mole-rat's histone H1.0 α_3-helix subsequence in comparison to those of other closely or distantly related vertebrate species suggests the following two experiments, each with a prediction of its outcome:

1. The constraints on chromatin dynamics embodied by a mutant histone H1.0 protein, as specified by the NCBI protein ID XP_004838566.1 with the site-directed amino acid substitution R75L, will nullify in the mutant naked mole-rats their otherwise significant resistance to both senescence and cancer.

2. The constraints on chromatin dynamics embodied by a mutant histone H1.0 protein, as specified by the NCBI protein ID NP_032223.2 with the site-directed amino acid substitution L75R, will confer to mutant house mice significant resistance to both senescence and cancer.

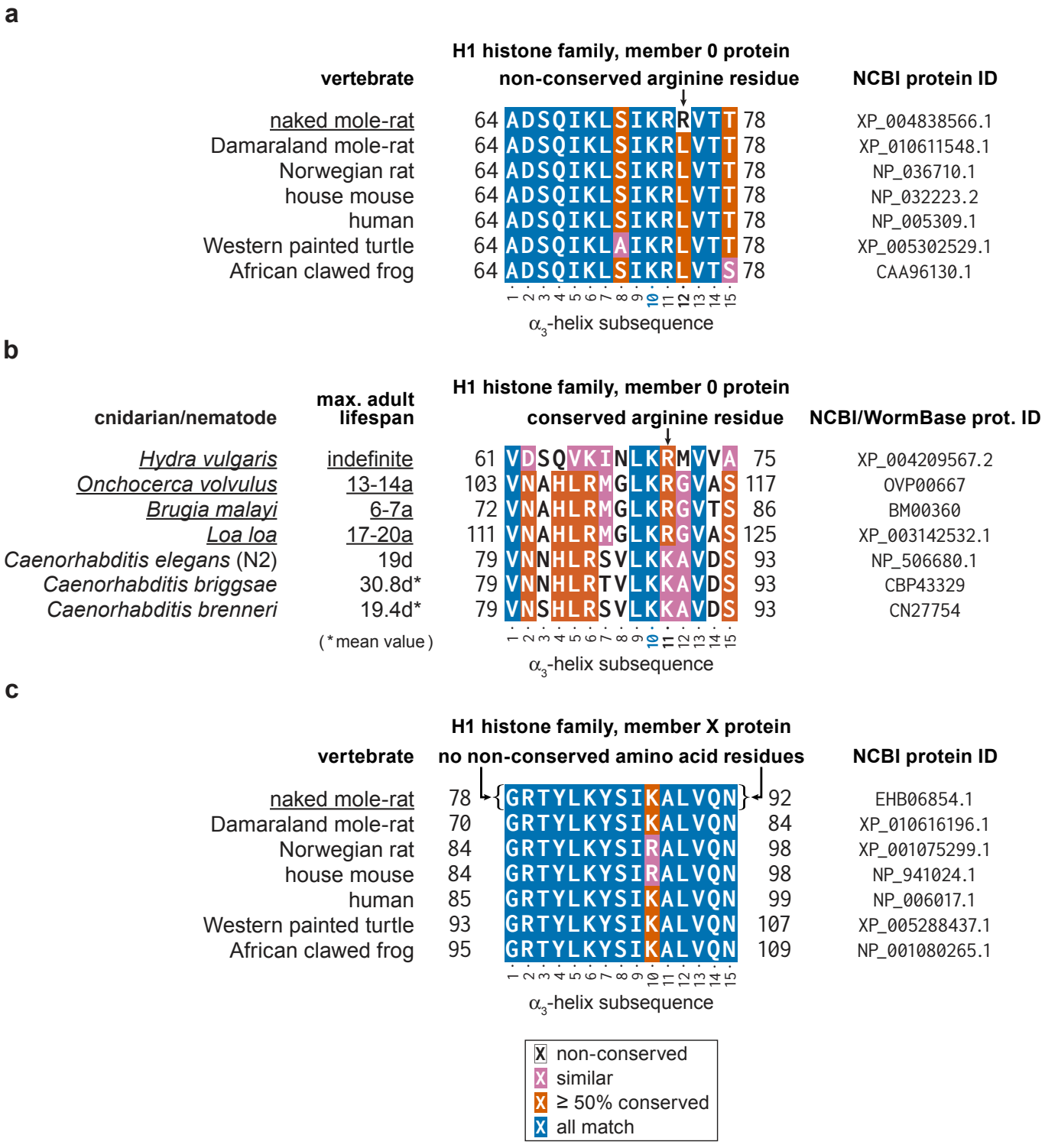


Fig. 2. α_3-helix motif subsequence within the multiple sequence alignment of the histone H1.0 and histone H1x proteins. (a) Naked mole-rat's histone H1.0 α_3-helix subsequence compared to those of other closely or distantly related vertebrate species. **(b)** Histone H1.0 α_3-helix subsequences of long-lived cnidarian/nematode species compared to those of short-lived nematode species. **(c)** Naked mole-rat's histone H1x α_3-helix subsequence compared to those of other closely or distantly related vertebrate species. Multiple sequence alignments were performed using the MAFFT (v7.419) program with its `--globalpair` method option [32]. Identification of the α_3-helix subsequences was done using the curated alignments available in the HistoneDB 2.0 database [12] as a guide.

Making sense out of the results

If these suggested experiments prove the hypothesis presented here to be correct, the following explanatory steps would apply:

- As previously reported, H1 histones facilitate chromatin condensation [14], low histone H1-to-NCP ratios significantly promote chromatin decondensation [42], and H1 histones also constrain the accessibility to the NCP [10]. In particular, H1 histones constrain hPTM changes in the NCP [42, 43]. Thus, with fully functional H1.0 histones in terminally differentiated cells, there is no chromatin decondensation problem, accessibility to the NCP is properly constrained as are hPTM changes in the NCP.

- Given that histone H1.0 proteins accumulate in terminally differentiated cells [17], the functional-adult scenario changes drastically in senescent multicellular organisms. With age, the highly conserved lysine (K) residue (relative position #10 in Fig. 2a) in the α_3-motif—and/or other lysine residues proximal to it—lower their positive electrostatic charge as a result of the accumulation of certain post-translational modifications, in particular acetylation [23, Table S1]. Consequently, as the histone H1.0 binding affinity to the negatively-charged DNA in the NCP decreases with age, all the aforementioned constraints progressively dissipate nearby all TSSs. This means all NCPs become more and more accessible, thereby building up hologenic constraints on hPTMs, at the expense of capacity for epigenetic constraints on them—in turn making the dysfunctional over-regulation of transcription (Fig. 1a) a chromatin-scale problem in all terminally differentiated cells.

- In the naked mole-rat, however, the extra arginine (R) residue in the histone H1.0 α_3 motif (relative position #12 in Fig. 2a) creates an additional "reservoir" of positive electrostatic charge in terminally differentiated cells. This arginine-based "reservoir" is possible because arginine is the most basic amino acid residue [33], displaying a virtually permanent positive charge (i.e., it is always protonated) under physiological conditions [34–36].

- This "reservoir" of positive electrostatic charge stabilizes histone H1.0-NCP binding affinities when the highly conserved lysine (K) residues (relative position #10 in Fig. 2a)—and/or other lysine residues proximal to it—accumulate post-translational acetylation with age (in general, lysine residues in H1 histones undergo post-translational modifications, including acetylation, as described in different multicellular phyla [23, 37–41]).

- In other words, histone H1.0-NCP binding affinities near TSSs in the naked mole-rat's terminally differentiated cells do not decrease with age as is the case for those of senescent multicellular organisms. Such a histone H1.0-NCP binding affinity stabilization is highly dynamic: in general, the mean residency time of H1 histones at any given NCP is less than five minutes [44, 45]—much shorter than that of core histones, but in general, longer than that of other chromatin-binding proteins, including transcription factors [46].

- The post-adulthood naked mole-rat chromatin thus remains under a highly dynamic yet stable constraint equilibrium. In this equilibrium, the respective capacities for hologenic and epigenetic information remain balanced—in particular by keeping hologenic information capacity growth at bay—which in turn maintains both transcriptional accuracy and transcriptional precision within functional ranges (as opposed to what happens in senescence processes; Fig. 1a). In summary, the otherwise increasing hologenic/epigenetic information imbalance that has been proposed to be the fundamental cause of senescence [6] is corrected by the particular constraints that stabilize the H1.0-NCP binding affinities in the naked mole-rat. Therefore, naked mole-rats display negligible senescence.

- These particular stabilizing constraints are also the reason why naked mole-rats display almost negligible cancer incidence: its histone H1.0-NCP binding affinities are highly stable and there is no significant senescence process that may force this rodent to "push back" against senescence at the chromatin level (see also Theoretical considerations and Fig. 1b). A related description of senescence in evolutionary terms has been presented previously [6].

Can the scope of the hypothesis be expanded?

If prediction #2 holds, it would not be surprising that the constraints on chromatin dynamics embodied by a mutant H1.0 histone (or its protein ortholog) in other model organisms confer to the respective model organism significant resistance to senescence. Examples include

- NP_506680.1 (NCBI protein ID, encoded by the *hil-1* gene) with the site-directed amino acid substitution(s) K89R or {K89R, A90R} in the roundworm *Caenorhabditis elegans* (N2),

- NP_724341.1 (NCBI protein ID, encoded by the *His1* gene) with the site-directed amino acid substitution(s) S96R or {S96R, A97R} in the fruit fly *Drosophila melanogaster*, and

- NP_955846.1 (NCBI protein ID, encoded by the *h1f0* gene) with the site-directed amino acid substitution L74R in zebrafish (*Danio rerio*).

IMPLICATIONS OF THE HYPOTHESIS

The following discussion is made under the assumption that the hypothesis presented here will be verified by experiments.

Basic science implications

The work presented in this paper was conducted under two specific assumptions: the constraint-based theoretical descriptions of (i) the evolution of individuated multicellular organisms and their developmental self-regulatory dynamics [5] and (ii) the senescence and age-related cancer processes [6] are both correct.

The sole verification of the hypothesis presented here does not logically imply that any of its theoretical basis is correct. Nevertheless, given the highly specific nature of the hypothesis, its verification should make the fundamental approach underpinning the work presented here worth some consideration. Indeed, the generic form of this approach has been around for more than a decade and its great explanatory power is still largely underused. To a large extent, this subsection aims to address this issue.

To date, a number of theorists, myself included, have argued at lengths that phenomena such as abiogenesis [47, 48], individuated multicellularity [5], senescence and cancer [6], mental processes [49], biological complexity [50, 51], and the life phenomenon itself [49, 52] should be fundamentally understood in terms of an emergent, higher-order constraint (i.e., a constraint on constraints or *teleodynamic* constraint) on the release of energy—thereby performing teleodynamic work [49]. Notably, this approach has also been independently framed and discussed in terms of a "closure of constraints" [53, 54].

Higher-order or teleodynamic constraints emerge from and supervene on synergistically coupled lower-order constraints [49]. The supervenience concept—applied here in its simplest form [55]—means there can be no change in a higher-order constraint without a change in some of the lower-order constraints it emerges from. In this sense, the naked mole-rat's resistance to both senescence and cancer is supervenient on lower-order constraints. These lower-order constraints can in turn be drastically altered with the build-up of constraints embodied by something as small and subtle as a very specific amino acid residue in a very specific motif within a very specific protein encoded by a very specific gene.

Thus, under this view of living systems—grounded on teleodynamics—we should avoid understanding any gene, protein, motif, or amino acid residue as *the* senescence gene, protein, motif, or amino acid residue. Instead, we should understand living systems, and in particular development-related processes, in terms of higher-order constraints. Such constraints are local and level-of-scale specific thermodynamic boundary conditions that are multiply realizable on lower-order molecular dynamics. Although higher-order constraints harness the release of energy into work to preserve themselves, they can be completely dissipated (i.e., death), disrupted (e.g., an insult to a tissue or organ), or subject to a constraint imbalance such as that described for senescence.

Biotechnological and biomedical implications

A direct implication of the hypothesis (*sensu stricto*, if its prediction #2 holds) is the prospect of modifying the natural constraints on chromatin dynamics—by engineering replication-independent H1 histones and/or nucleic acid sequences encoding them—that may confer negligible senescence to species other than the house mouse, including our own. Importantly, stopping senescence and eliminating the incidence of age-related cancer have been proposed to be one and the same technical challenge [6]. Thus, the verification of prediction #2 may open the door to the development of efficient therapeutic, and even prophylactic, applications for the group of diseases we call cancer.

ABBREVIATIONS

H1.0/H1°/H1(0)/H5/H1δ/RI H1: H1 histone family, member 0; hPTMs: histone post-translational modifications; NCP: nucleosome core particle; TSS: transcription start site; CT: cell type; PDF: probability density function; wHTH: "winged" helix-turn-helix structural motif; α_3: third (from N- to C-terminus) alpha-helix motif within the major wHTH motif; H1x/H.10: H1 histone family, member X

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COMPETING INTERESTS

The author discloses that two patent applications related to this paper have been filed with the United States Patent and Trademark Office. Patent application numbers: US62803987, US62833244. Inventor: Felipe A. Veloso, Santiago (CL). Applicant: Qualus Research SpA, Santiago (CL).

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