DELOCALIZED ENTROPY AGING THEOREM

THERMODYNAMIC IMPLICATIONS OF THE CROSSLINKED EXTRACELLULAR MATRIX FOR THE EMERGENCE OF THE HALLMARKS OF AGING

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December 2024

1 Abstract

Age-related alteration of intracellular processes has been recognized as tipping of homeostatic balance towards increased entropy, reflected in, for instance, such hallmarks of aging as the loss of epigenetic information and disruption of proteostasis. Although the hallmarks of aging are useful for contextualizing geroscience research, the framework itself does not explain what fundamentally causes them to emerge in the first place. Herein, I propose a theorem that aims to explain the emergence of the hallmarks of aging as phenomena secondary to extracellular matrix chemical crosslinking, suggesting that the ensuant age-related extracellular matrix stiffening is a causative upstream agent in the aging process.

Keywords aging · entropy · extracellular matrix

"Truly, what is stiff and hard is a companion of death;
what is soft and weak is a companion of life."

– Tao Teh Ching

2 Introduction

Mechanisms of aging have been conceptually organized into the framework of hallmarks [1]. Although being an excellent introduction to biogerontology, the hallmarks concept does not conform to a full-fledged scientific paradigm, leaving out a few prominent characteristics of the aging process and not comprehensively explaining why the hallmarks emerge in the first place [2, 3]. At the same time, the mechanical properties of cells and their environment have been recognized as an important factor for a panoply of age-related derailments [4]. Despite the importance, the biogerontology field chronically neglects to include changes in extracellular matrix (ECM) biomechanics on the hallmarks list.

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Such short-sightedness can be explained by the current predominantly cell-centric sentiment on aging. I would argue that without taking into account the cellular environment the said view on tissue aging biology is incomplete. It's notable that some forms of chemical damage to the ECM components, i.e. sugar-derived crosslinks, accrue linearly with age and, when normalized by the component tissue residence time (turnover), proceed at the same rate regardless of the location in the body [5, 6].

Aging has been conceptualized as both time-dependent damage accumulation [7] and the increase in intracellular entropy [8]; although as of writing there is no field consensus on what aging is [9]. Below, I propose a theorem that aims to serve as a conceptual ground to incorporate the notion of ECM mechanics into the current biogerontology research framework by interpreting the hallmarks of aging as emergent and subordinate entropic events in relation to age-related ECM stiffening, resulting from the chemical crosslink accumulation.

3 Supposition

The theorem is based on a supposition that the cell, being an open system, and its environment, represented by the ECM, are thermodynamically connected to form a single unit. In other words, from a thermodynamics standpoint, the cell and processes therein cannot be regarded in separation from their environmental context.

The implications of this supposition have a profound significance for our understanding of the aging process, specifically – the emergence of the hallmarks of aging. The supposition, as I propose next, explains the emergent and subordinate nature of the hallmarks through the succession of lemmata:

Lemma 1 I propose that there exists a hypothetical point in time t_0, e.g. in a young organism, at which entropies inside and outside the cell, *C* and *E* respectively, are related such that the relationship ϕ between *C* and *E* is some constant value (**Figure 1**, left panel):

$$\exists t_0 : \quad \phi(C(t_0), E(t_0)) = \textit{constant} \tag{1}$$

Lemma 2 With age, at $t > t_0$, the accumulation of chemical damage to the ECM proteins in the form of intermolecular crosslinks leads to the reduction of overall relative mobility of fibrillar matrix components—e.g. through decreased lateral sliding of collagens—negatively affecting ECM viscoelasticity and altering its mechanical properties towards tissue stiffening [10]. The reduction in the said relative mobility is concurrent with the reduction of potential microscopic states in the ECM – diminished E. From (1), the decrease in *E* must result in the increased entropy inside the cell, *C*, such that:

$$\forall t > t_0 : \quad \frac{dC}{dt} \times \frac{dE}{dt} < 0 \tag{2}$$

Consequentially, I propose that the ensuing increase in *C* is what we observe as the hallmarks of aging (**Figure 1**, middle panel).

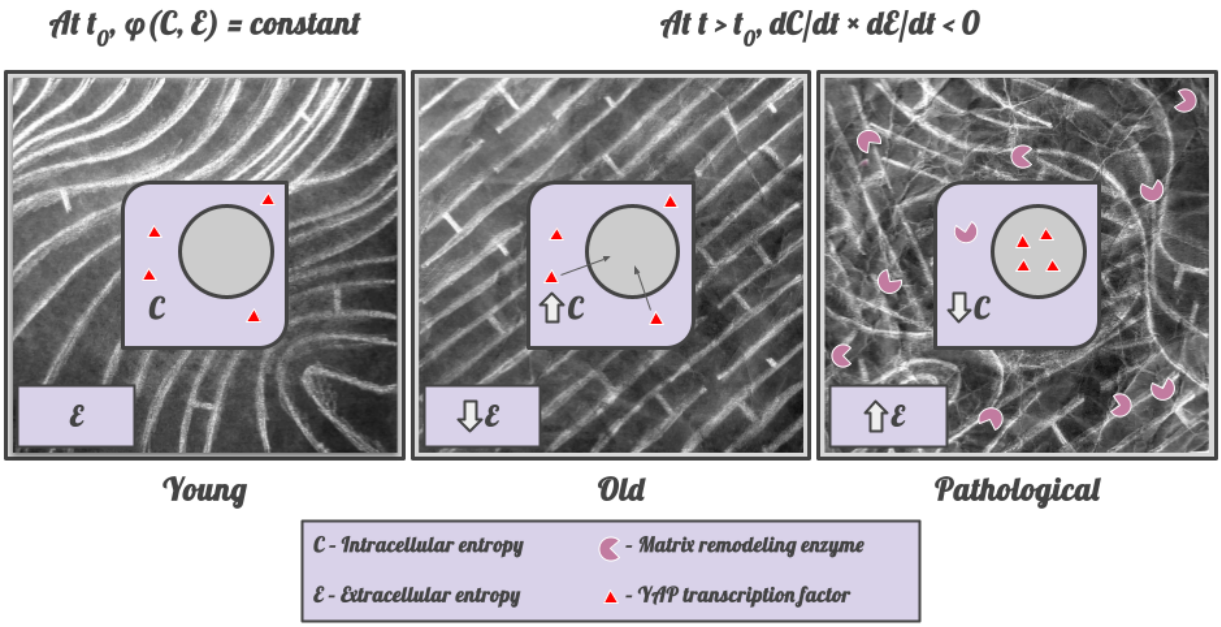

Figure 1: *Entropy delocalization during aging*

Lemma 3 The increased entropy in proximity to the genetic material presents a critical threat to the cell's survival, triggering a reaction – the entropy must be expelled away from crucial intracellular hotspots. This is done by mechanosensory pathways feeding into regulatory circuits governing the expression of ECM remodeling enzymes and ECM structural parts [11, 12]. The subsequent enzyme-mediated ECM fragmentation and aberrant *de novo* deposition of ECM constituents increases the entropy outside the cell, representing a survival strategy – within evolutionary constraints specific to a given species. From (2), as E increases, C must decrease, and vice versa:

$$\forall t > t_0 : \quad \frac{dC}{dt} = f(C, E) \quad \wedge \quad \frac{dE}{dt} = -g(C, E), \tag{3}$$

$$\text{where } f(C, E), g(C, E) > 0$$

This swing in the opposite direction is a temporary solution at the expense of physiological tissue homeostasis, eventually resulting in pathology (**Figure 1**, right panel).

Last, since we see, at least hypothetically, that entropy flows in and out of the cell, we can say that entropy is non-local, or delocalized; hence the theorem's name – **delocalized entropy aging theorem** (DEATh).

4 Conclusion

Theories proposing the accumulation of crosslinks as the root cause of aging have a remarkable ability to appear once in a generation: see **crosslinkage** [13] and **carbonyl toxification** [14] theories of aging. Like my predecessors, I'm inspired by the views and prominent ideas of my time, independently arriving at the same conclusions. Unlike them, I lay down a simple theoretical groundwork, framing the relationship between the cell and the cell context into a set of rules. One important caveat here is that I use the concept of entropy not in a thermodynamical, but rather biological sense. Even more so, I would say that the theorem, in its present incarnation, should be regarded as a device to communicate certain ideas – more logic than physics.

As with any theorem, DEATh must be proven. Since it's a biological theorem, it must be proven empirically.

Before I conclude, I must answer one seemingly simple question that no one has yet answered: why glycation? Glycation, because it's (a) stochastic, i.e. pervasive; (b) irreversible, i.e. unidirectional; and (c) vitally linked to metabolism, i.e. universal. All beings that convert sugars to harvest energy stored in chemical bonds will inevitably sustain some sort of glycation damage – in line with "we age because we live" reductionist reasoning. In multicellular organisms, low turnover rates of extracellular proteins and relatively high glucose concentrations in body fluids, leading to crosslink accumulation, make glycation, in my opinion, an ideal candidate for the observable and measurable manifestation of the **arrow of time**.

Given that tissue stiffening on account of crosslink accumulation can be viewed as a molecular manifestation of time itself, I see the associated change in ECM biomechanics as not solely a robust biomarker for aging rate and related disease risk, or as the additional hallmark, – I entertain the thought that aging, in its essence, is a biophysical phenomenon, a contextual separation between "hard" and "soft".

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