Tension in fibrils suppresses their enzymatic degradation – A molecular mechanism for ‘use it or lose it’

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https://doi.org/10.1016/j.matbio.2019.06.001

Abstract

Tissue homeostasis depends on a balance of synthesis and degradation of constituent proteins, with turnover of a given protein potentially regulated by its use. Extracellular matrix (ECM) is predominantly composed of fibrillar collagens that exhibit tension-sensitive degradation, which we review here at different levels of hierarchy. Past experiments and recent proteomics measurements together suggest that mechanical strain stabilizes collagen against enzymatic degradation at the scale of tissues and fibrils whereas isolated collagen molecules exhibit a biphasic behavior that depends on load magnitude. Within a Michaelis-Menten framework, collagenases at constant concentration effectively exhibit a low activity on substrate fibrils when the fibrils are strained by tension. Mechanisms of such mechanosensitive regulation are surveyed together with relevant interactions of collagen fibrils with cells.

Introduction

Extracellular matrix (ECM) proteins are the most abundant proteins in animals and form a structural and functional framework for tissues and of course the cells within tissues. ECM proteins undergo varying extents of enzymatic degradation and synthesis under homeostatic conditions, but ECM also establishes the stiffness of solid tissues. This latter fact is easily demonstrated by the softening and fluidization of tissue that occurs rapidly upon addition of a collagenase enzyme. Physical properties of polymer systems such as elasticity and viscosity generally scale with polymer concentration [1], which is true for collagen-I (e.g. [2]), and polymer interactions, assembly, and crosslinking generally modulate such physical properties [3]. Tissue stiffness also scales with the levels of collagen type-I and several other fibrillar collagens as:

\[ \text{tissue stiffness } E \sim [\text{collagen}]^m, \text{ with } m \sim 0.6 \text{ to } 1.1 \]

Soft tissues such as brain and bone marrow (\( E \sim 0.1-1 \text{ kPa} \)) indeed possess much less collagen than stiffer tissues such as muscle (\( E \sim 10 \text{ kPa} \)) or bone [4]. The multi-tissue proteomic approach that revealed this scaling relationship has also been applied to developing heart in chick embryos, which exhibits similar scaling as collagen accumulates and stiffens the heart during its first days of beating [5]. Mechanical stresses sustained and/or generated by stiffer tissues tend to be higher than in softer tissues, consistent with an inter-relationship between: (i) tissue stiffness, (ii) the typical stress in the tissue (i.e. tissue stress \( \sim E \)), and (iii) the homeostatic balance of collagen synthesis and degradation. Mathematical modeling of this inter-relationship is rooted in the concept of ‘use it or lose it’ [4,5] which implies that amino acids not needed for the structure and integrity of a tissue (i.e. ECM) can be recycled after proteolysis for use in other proteins or pathways of greater importance.

The ECM of load-bearing connective tissues such as tendon exhibits a structural hierarchy (Fig. 1) that is built up primarily from multiple highly-conserved, triple-helical collagens (types I, II, III, V and XI) in the form of fibrils [6–10] plus other proteins that include small leucine rich proteoglycans (SLRPs) such as decorin, biglycan, fibromodulin, and their associated glycosaminoglycan (GAG) chains. Procollagens are secreted by cells, and end-terminal cleavage (via peptidase) yields collagen molecules that readily
self-assemble into the higher-order collagen fibrils, with assembly aided by lysyl oxidase LOX enzymes. Collagen fibrils are generally seen to be oriented in the direction of applied mechanical stress, even during growth. Collagen fibril assemblies present in tissues thus seem adapting to stresses and/or strains in physiological and pathological conditions [11], whether skeletal muscle [12–15], bone and cartilage [16], or lung [17].

Mechanical stimulation influences the regulation of various ECM factors in addition to the fibrillar collagens [18,19], including proteoglycans [20], aggrecans [21], laminins and type IV collagens in basement membranes [22]. Mechanical forces on fibroblasts [23] among other cell types activate expression of collagens, fibronectin and proteoglycans, ultimately resulting in ECM that carries collagen fibrils aligned in the direction of load [24–27]. The actomyosin cytoskeleton within embryonic tendon cells facilitates deposition and alignment of collagen fibrils in the ECM [28], but roles for cell-generated forces remain unclear. Mechanical loads also affect expression of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) in mesenchymal stem cells (MSCs) [29], fibroblasts [25,30,31], osteoblasts [32,33] and chondrocytes [34,35]. For 3D collagen gels subjected to mechanical loading that is changed in its direction, embedded fibroblasts up-regulate expression of MMPs (MMP-1, 2, 3), which preferentially degrade unloaded collagen fibrils [25]. Such regulation seems to be one aspect of mechanically induced differentiation in vitro [36,37] and in vivo in tendon [38–43] and cartilage [44,45]. These MMPs act as primary mediators of tissue remodeling via collagen degradation; for example, tendons that are injured by load are remodeled by MMPs [46–48].

Direct mechano-sensitivity of collagen fibrils independent of cells was first reported decades ago [49], with subsequent studies of enzymatic cleavage under mechanical strain largely done with bacterial collagenase (BC) (i.e. *Clostridium histoliticum*

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Fig. 1. Tendon tissue at different length scales, with various factors affecting its enzymatic degradation. (A) Collagen-I fibrils establish the architecture of the tissue. (B) Enzymatic degradation of collagen fibrils depends on conformation of collagen molecules (regulated by intermolecular cross-links between collagen molecules) as well as solution physicochemical factors including temperature, pH, and concentrations of any type of collagenase and collagenase inhibitors present in the tissue.
collagenase, available as Col-G and Col-H forms [50,51]) rather than MMPs that are difficult to purify, activate, and keep stable [52,53]. Here, it is important to keep in mind that despite ~100 fold higher enzyme-substrate affinity of MMP-1 towards fibrillar than monomeric collagen (indicated by Michaelis constant) [52], MMP-1 catalyzes degradation of purified collagen type-I (from guinea pig) in monomer [54] as well as fibrillar [55] forms at similar rates (~25 collagen molecules per molecule of MMP-1 per hour). Interestingly, the packing of monomers into fibrils exposes only ~10% of total available collagen molecules (i.e. surface molecules depending upon fibril diameter) to MMP-1 and reduces “effective” degradation rate. Thus looking at architecture of ECM, mechanical load on it could in principle control collagen degradation (Fig. 2) by either: (i) changing collagen’s molecular conformation, (ii) changing collagenase mobility within ECM, and/or (iii) changing collagenase conformation.

Structural changes in collagen molecules or fibrils under load are certainly likely given the spectrum of collagen flexibility as revealed across different experimental approaches [56–62]. However, molecular scale simulations provide perhaps the clearest notions for how single collagen molecules respond, and conformational changes under forces [63–65] exhibit a dramatic transition at a tensile force of ~10 pN [66,67]. A similar level of force unfolds and exposes reactive residues (cysteines) within the helix-rich cytoskeletal protein spectrin in sheared cells [68], and so the collagen molecule simulations potentially provide realistic structural rearrangements at the molecular level. While intermolecular collagen crosslinks oppose enzymatic degradation of unloaded collagen, molecular scale simulations show forces still disrupt native conformation which might increase the susceptibility to degradation [69].

Collagen molecules are ~1.5 nm in diameter but further assembly into fibrils increases the diameter from 10s to 100s of nanometers, whereas collagenases have Stoke’s radii of a few nanometers [70]. The larger effective pore sizes of fibrillar collagen gels (few tens of nm’s) as compared to non-fibrillar collagen (4–6 nm) perhaps rules out mechanisms of hindered diffusion or collagenase deformation in mechanically strained ECM. Additionally, flexibility of collagen fibrils is determined by bendability of constituting collagen molecules [63], and therefore homotrimers and heterotrimer collagen molecules carrying distinct flexibilities result into two different type of fibrils carrying entirely different molecular packing densities as well as flexibilities [71] but ultimately result in ECMs carrying similar effective pore-sizes. Although under mechanical load, these ECMs may not facilitate significantly different diffusion from each other but at least underscore the importance of amino-acid sequence on overall physicochemical behavior of collagen fibrils.

To keep our brief review of the main topic systematic while also keeping in mind the limitations...
of past methods, we first discuss mechanical strain-dependent degradation of fibrillar collagen at various levels of structural hierarchy. We then describe molecular mechanisms of cleavage by different collagenases and briefly discuss the likely influence of cells on collagen molecule organization. Unfortunately, past studies on "enzyme mechano-kinetics" of tissues have used conventional stress (or load)–relaxation tests [49,72] that fit a three-parameter relaxation function [73], which is generally difficult to interpret directly in terms of tissue strain and degradation rate. These measurements are further complicated by dependencies on sample size, protein distribution, and estimations of strain [72], which might include “end effects” of local tissue drying and stress concentrations. We do not review such studies in quantitative detail, but try to point out a need for further innovative experiments.
Mechanical force suppresses enzymatic degradation of collagenous ECM of tissues

The rate of in vitro enzymatic degradation of mechanically stretched collagen fibers extracted from bovine Achilles tendon correlates with the extent of in vivo collagen degradation upon subcutaneous implantation in guinea pigs [74]. Yannas and co-workers provided the earliest, surprising evidence that mechanical load suppresses the turnover and degradation of ECM [49]. In these studies, tendon collagen was reconstituted as a tape (~3.2 μm thick, ~130 μm wide), stretched in a solution of BC, and the rate of force relaxation was used to approximate the rate of degradation. The degradation rate appeared to (i) decrease up to a fiber strain of ~4% and (ii) depend linearly on BC concentration, which is consistent with standard Michaelis-Menten enzyme kinetics. The degradation rate of the tendon collagen tape also was found: (iii) higher upon collagen denaturation which indicates the importance of molecular conformation, (iv) inhibited by collagen intermolecular cross-linking, (v) to follow an Arrhenius relationship for temperatures of 10–56°C, (vi) inhibited by EDTA, O-phenanthroline, 2,3-dimercaptopropanol, and D,L-cysteine, and (vii) to be maximal at neutral pH 7–8.

Michaelis-Menten kinetics is the standard model of enzyme kinetics, and it is useful to sketch out how it might apply in the present context. If a Protease (P) has a dissociation constant K (or Michaelis constant) that increases with strain (c) applied [75,76] to the collagen fibril substrate (S), then the initial enzyme-mediated degradation rate (V) of the substrate decreases according to:

\[ V(c) = \frac{c \cdot P \cdot S}{(K(c) + S)} \]

where V(c) and K(c) are functions of strain. If strains are small such as in the first experiments on strain-modulated degradation rate (c < 1), then it is reasonable to make a Taylor series expansion around ε = 0 (such as for an exponential function, K_c \exp(A \cdot c) , which gives K(c) = K_c + A \cdot c (Fig. 3A-i) where K_c reflects the activity at zero strain and A > 0 is a constant that reflects reduced activity with strain. Before much degradation of S occurs, the rate at zero strain is V_0 ≈ c \cdot P / (K_c + S). On the other hand, for sufficiently high strains (A \cdot c ≫ K_c + S), V(c) ≈ c \cdot P / (A \cdot c + c^2) term asymptotically approaches zero (Fig. 3A-ii). For pure collagen fibrillar gels treated with MMP-8 and locally strained (or not) by micro-needles [77], the initial degradation rate (when S ~ constant) is strain-suppressed locally from V_0 to V by a factor of ~2–3-fold (Fig. 3A-iii). Subsequent studies with micro-needles by the same group produced more measurements and estimated a ‘force per monomer’ of ~pN that gave a similar hyperbolic decay in ‘cleavage rate’ [78]. The Michaelis-Menten model thus seems appropriate.

Within a Michaelis-Menten equilibrium approximation, K(c) is a ratio of enzyme off-rate and on-rate in binding to substrate collagen, so that strain could increase the off-rate, or decrease the on-rate, or both. At lowest order as above, k_on(c) = k_on \cdot a \cdot c, and k_off(c) = k_off \cdot b \cdot c for which a, b ≥ 0. Given the linearity of K(c) = k_on(c) / k_off(c), the simplest model is a > 0 and b = 0, which stipulates that only the off-rate is strain sensitive. Such issues have yet to be fully resolved it seems, but the seminal studies to date ([78], for example) motivate many more investigations.

Subsequent to the very first studies that showed strain inhibits collagen fiber proteolysis [74], the collagen degradation rates in strained tissues were measured by additional methods. One optics-based method for measuring strain [72] complemented conventional displacement measurements, and the degradation rate of collagen fibers present in rat tail tendon fascicles based on conventional stress-time response was observed to decrease linearly with strain; the results were interpreted as further indicating that strain-induced conformational changes in collagen molecules inhibit its enzymatic cleavage. Osmotic effects on the measured equilibrium stress in the conventional load-relaxation test with exposure of the fascicle to BC (or dextran) were also evident only for strains <4% but subsided quickly as compared to duration of experiments. Additionally, chemically cross-linked tendon fascicle samples carrying glycation cross-links (i.e. non-enzymatic cross-linking) were >5 times more resistant to degradation by BC than non-cross-linked ones in unloaded configuration but became highly susceptible to degradation under tensile deformation [79]. For various tissues, mechanical strains of various types (e.g. uniaxial tension, biaxial tension,
Mechanical strain suppresses collagen degradation at the fibril level

The micro-needle studies cited above focused on gels formed by reconstituted bovine collagen-I and revealed locally slowed fibril degradation by both BC [80] and MMP-8 [77]. The average force acting per collagen molecule in the fibril was estimated from the micro-needle forces as well as the diameter and elastic modulus of collagen fibrils [78]. As mentioned, the results seem consistent with Michaelis-Menten kinetics.

Proteolysis by MMP-1 is also suggested to be affected by mechanical loading of collagen fibrils obtained from rat tail tendon [81]. Because MMP cleavage sites of collagen molecules in fibrils are normally inaccessible due to molecular packing [82,83], fluorescent MMPs (MMP-1 and MMP-9) bind at positions with a highly regular spatial periodicity of ~1 μm [84]. This periodicity and fluctuations of the binding regions of fluorescently labelled MMP-1 on collagen fibrils has indicated that in unloaded collagen fibrils (Fig. 3B), the “buckled” conformation exposes the otherwise protected [83] but thermally labile MMP-1 cleavage site of collagen molecules [85–88], creating an entry point for initiation of proteolysis [84]. Binding to the buckled site often occurs without subsequent cleavage but is an obligatory and rate-limiting step in the proteolysis of fibrillar collagen [84]. Application of tensile load on fibril removes the buckled site in a switch-like manner and thereby inhibits degradation. The results seem consistent with the afore-mentioned Michaelis-Menten equilibrium approximation: $K(c) = k_{\text{off}}(c) / k_{\text{on}}$, in which strain increases only the off-rate.

Mechanical strain-dependent degradation of individual collagen molecules

Whether strain-dependent effects on fibril degradation also occur with isolated collagen molecules has remained ambiguous, even though fibrillar collagens fray to produce partially exposed collagen molecules during breakdown [89,90]. The uncertainty has implications for the many non-fibrillar collagens in diverse tissues, including collagen-IV trimers in basement membrane ECM [91]. This is relevant to various MMPs on plasma membranes, which co-localize with integrins that bind ECM [92]; such co-localization is required for degradation of both fibrillar collagen [93] and localized gelatin, i.e. partially denatured collagen [94]. Given that single integrin receptors can transmit >20 pN of force on the ECM [95], a combination of cell-generated traction forces and MMP activity might thus contribute to the degradation of isolated or exposed collagen molecules and possibly other ECM molecules.

The susceptibility of individual homotrimeric collagen type-I (α1(I)3) molecule to enzymatic cleavage is different from that of its heterotrimeric (α1(I)2 κ2) form, even upon application of tensile force. Collagen type-I molecules exist as heterotrimers in normal tissues, while the atypical homotrimeric form (α1(I)3) that is very resistant to MMP-1 cleavage is present in embryonic and cancer tissues [96]. Homotrimeric type-I (α1(I)3) molecules are also more resistant to cleavage by both MMP-1 and trypsin than other homotrimeric molecules including collagen type-II (α1(II)3) and collagen type-III (α1(III)3): this resistance is thought to be a function of the extent of hydrogen bonding in these homotrimeric forms [97]. Although type-I homotrimers are more flexible than type-I heterotrimers and thus form kinks [71], the cleavage region on the unloaded heterotrimer is thought to be locally unfolded in its equilibrium state, making it more susceptible to MMP-1 breakdown [96]. In particular, the locally unfolded region is found on the α2 chain near an MMP-1 cleavage site [98] as a result of disrupted hydrogen bonding in the native configuration [97]. This makes the α2 chain of heterotrimer more prone to MMP-1 cleavage than α1 chains [99], even in homotrimeric form (α2(I)3) [97]. Upon application of force, the naturally unfolded region of α2(I) chain in the heterotrimer refolds into a triple helical structure, potentially protecting the molecule against MMP-1 degradation. In contrast, a type-I collagen homotrimer retains a triple helical structure under no load which makes it more resistant to enzyme cleavage but applied force unfolds molecule and makes it prone to degradation [100]. These findings are consistent with the results...
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MMPs are far less efficient in degrading collagen fibrils than the highly studied BC [52]. In general, MMPs (MMP-1, MMP-8, and MMP-13) cleave collagen molecules at a single site (Fig. 3B) approximately ¾ of the length from its N-terminus [110], although binding may also occur at other sites [111]. More specifically, both MMP-1 and MMP-8 have been shown to cleave native type-1 collagen α1 chains between Gly775 and Ile776 and α2 chain between Gly775 and Leu776 [88]. BC on the other hand cleaves collagen molecules at multiple sites (Fig. 3C) but does show preferences for certain sites [112–114], for example Pro–X–Gly–Pro, where X is often a neutral amino acid targeted by BC [115]. Both BC and MMPs cleave all three chains within a collagen molecule, albeit through distinct predicted mechanisms. MMP-1 cannot dock all three chains simultaneously and instead unwinds the helical chains one by one near the target site prior to cleavage [101,102,106,116–118]. Unlike MMPs, the catalytic domain of BC is large enough to surround, unwind, and cleave the three chains of a single collagen molecule at once [102,107]. Brandstetter and colleagues [107] used structural and functional data to provide an integrated mechanistic model of collagen recognition and unraveling of collagen micro-fibrils into triple helices, as well as a model of triple helix cleavage by BC driven by opening and closing of its cleavage domain. More recently, AFM-based studies of BC movement along fibrils [119] revealed that intermolecular interactions between collagen molecules within a fibril prevent BC from engaging. BC molecules exhibit catalytic, zinc-dependent, and polarized movement along the fibril axis towards the collagen N-terminus, suggesting that their movement and function are tightly coupled. As BC degrades collagen, collagen molecules are occasionally rearranged and incorporated into neighboring fibrils. In contrast, measurements of MMPs (MMP-1, MMP-2, MT1-MMP) moving on fibrillar collagen through fluorescence correlation spectroscopy [120–122] and, more recently, direct single-molecule tracking of MMP-1 and MMP-9 [84], revealed that MMPs undergo one-dimensional diffusion on collagen fibril, frequently interrupted by transient binding. Degradation by MMP-1 initiates from a small subset of these binding events, with the initial cleavage event followed in rapid succession by ~15 or more cleavage reactions resulting in progressive bursts of MMP-1 motion along the collagen fibril [84] and rearrangement of collagen molecules surrounding cleavage site [83]. Cleavage followed by fibril relaxation and further cleavage (cleave-relax-cleave) is a burning bridge type mechanism [123] that would be limited by fibril length and some...
type of tethered diffusion (perhaps by collagen) to the next binding site before dissociation. Collectively, these findings suggest the collagenase-driven cleavage mechanisms of collagen molecules within fibrils are primarily dictated by collagen intermolecular interactions, which can be directly regulated by mechanical strain.

Collagen’s response to cellular forces

The idea expressed at the outset of this review that tissue stiffness scales with tissue stress and with collagen levels might apply locally to forces at cell membrane adhesions. Some MMPs are certainly membrane bound, and cells can exert -pN level tensions on ECM [95], which is relevant to affect degradation. Collagen molecules present in ECM have indeed been reported to directly interact with cells through various integrin receptors (i.e. α- and β-integrin isoforms e.g. α1β1, α2β1) [124-127], discoidin domain receptors (DDR1, DDR2) [128,129], plasma membrane glycoproteins (GPllb, GPIV, GPVI/p62) [130,131], immunoglobulin-like receptors (e.g. LAIR-1) [132-133], Annexin-A5 (also known as anchorin II) [134,135], glycosaminoglycan chains present in transmembrane proteins such as CD44 (and in proteoglycans) [136-139], and also indirectly via fibronectin involving α5β1 integrins [140]. Some of these receptors might mediate strong application of force to collagen fibrils, but more such measurements are needed, especially in relation to integrity of local fibrils.

In general, collagen receptor(s) bind to the collagen triple helix at particular site(s) carrying either a highly specific motif (present in a particular collagen type) or a common sequence (in various collagen types), although some receptors also show affinity towards cryptic binding sites and/or non-collagenous domains present in collagen molecules [141]. Cells exert contractile forces on collagen molecules [23,24,142-144] via focal-adhesions containing clustered integrins. Moreover, force magnitudes somehow orchestrate focal-adhesion size in a reversible manner, and this occurs on a time scale of seconds to minutes (not hours) while maintaining overall constant traction force per unit area of focal adhesion [145]. This force-dependent focal adhesion size dynamics is notably similar to force-dependent assembly and disassembly of fibronectin molecules into fibrils [146,147] which are well known to mediate cell-collagen interactions using α5β1 integrins [6,140]. Although the role of various collagen-receptors in dictating collagen molecular packing and organization is not clear but certainly relevant to the ‘force per fibril’, fibronectin [148,149] and particular integrin subtypes (e.g. α5β1, α6β4) [150,151] are implicated in collagen fibrillogenesis [6].

Concluding prospectus

As homeostasis and adaptation of tissues is partially governed by the mechanosensitive nature of ECM with collagen protein as its primary component, it is of fundamental importance to understand collagen’s force-dependent degradation by enzymes. In addition to large tensile stress bearing tissue such as tendon, other tissues also show tension-dependent enzymatic degradation – although precise measurements have been limited by complexities associated with load-relaxation tests and unknown strain relationships among various levels of the structural hierarchy. Tissue level studies show tension-inhibited degradation by BC, but because of the differences of their catalytic domain sizes and target sites on collagen molecules as well as physiological importance, the use of MMPs in tissue level studies would likely be more interesting. Similar to tissues, individual collagen fibrils show strain-inhibited degradation against both BC and some MMPs – but at the molecular level, collagen seems to show biphasic behavior with smaller loads conferring resistance against cleavage and larger loads conversely making them more susceptible to degradation. Thus, improved and standardized characterization of how mechanical force, at various magnitudes, regulates collagen ECM remodeling at each structural hierarchy level appears necessary. Furthermore, mechanical strain dependent exposure of collagen cryptic sites as well as sequestration of recognition sites for collagen receptors could dramatically change cell-ECM interactions and downstream pathways including cell fate and function. Understanding the very local processes of cell adhesion and collagen stability could indeed shed light on mechanisms of mechanosensing matrix elasticity and phenotype. Molecular and systems-level mechanistic insight gained from such studies will likely further benefit the treatment of a broad range of ECM-associated pathological conditions, which range from cardiovascular injury/disease to numerous solid cancers.

Acknowledgements

The authors in this study were supported by the National Institutes of Health National Cancer Institute under Physical Sciences Oncology Center Award U54 CA193417, Human Frontier Science Program grant RGP0024, National Heart, Lung, and Blood Institute award R01 HL124106, SERB Indo-US Postdoctoral Fellowship 2016-157, the United States-Israel Binational Science Foundation, National Science Foundation Materials Science and Engineering Center grant to the University of...
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Pennsylvania and also grant agreement CMMI 15-48571. This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other granting agencies.

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions

K.S. and D.E.D. interpreted results of experiments, prepared figures and drafted manuscript; K.S., S.C., L.J.D., and D.E.D. edited, revised and approved final version of manuscript.

Received 31 January 2019; Received in revised form 31 May 2019; Accepted 7 June 2019

Available online xxxx

Keywords: Tissue; Extracellular matrix; Collagen; Collagenase; Matrix metalloproteinases (MMPs); Degradation; Strain

used:

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A molecular mechanism for use it or lose it


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