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Original article

Double strand breaks may be a missing link between entropy and aging

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ABSTRACT

It has been previously suggested that an increase in entropy production leads to aging. However, the mechanisms linking increased entropy production in living mass to aging are currently unclear. Even though entropy cannot be easily associated with any specific molecular damage, the increase of entropy in structural mass may be connected with heat stress, which is known to generate double strand breaks. Double strand breaks, which are in turn known to play an important role in process of aging, are thus connected to both aging and an increase of entropy. In view of these associations, we propose a new model where the increase of entropy leads to the formation of double strand breaks, resulting in an aging phenotype. This not only offers a new perspective on aging research and facilitates experimental validation, but could also serve as a useful explanatory tool.

1. Introduction

Although our knowledge of the molecular mechanisms of aging has been increasing for decades, no universally accepted theory has yet been developed (Viña et al., 2007; Jin 2010; Trindade et al., 2013). Hundreds of competing theories were proposed by the 1990s (Medvedev 1990). Theories of aging can be divided into two main categories: programmed aging theories and damage or error theories. Programmed theories of aging argue that aging is caused and coordinated by an inner program of the organism while damage or error theories tend to emphasize the role of accumulation of specific damage at various levels (Davidovic et al., 2010; Jin 2010). However, this classical categorization has been disputed by proponents of more unified theories of aging (Rattan, 2006) and a new and more detailed classification has been developed (Trindade et al., 2013). Since it is unlikely for a complex process such as aging to be driven only by one specific kind of disturbance (Lenart and Krejci 2016), it may be expected that these approaches will be merged together in future.

Entropy is a physical concept which is directional with time (Kondepudi and Prigogine 2014); likewise, natural aging seems to always only go in one direction. This similarity has led some authors to suggest that an increase of entropy in cells and tissues is the main driver of the aging process (Bortz, 1986; Hayflick 2007), a basic proposition which may be termed the "entropic theory of aging". Other authors further suggest that the amount of entropy generated per unit of mass during the lifespan is fixed (Rahman 2007; Silva and Annamalai 2008; Silva et al., 2009). However, existing entropy theories have a common weak point: they do not identify any specific molecular mechanism connecting an increase of entropy in the tissue to the physical characteristics of aging.

The human body is considered to be an open thermodynamic system, with the final thermal state of the organism resulting from the specific interaction of the body with the environment. The specific internal order of the body, including the complex interactions between organ systems, is only made possible if the organism disposes of a greater amount of entropy to the surrounding environment via heat transfer, i.e. primarily by burning oxygen (Hayflick 2007). This internal order as well as specific system complexity both increase along with the entire body's entropy production, with growth and development which begins at conception and continues throughout childhood and into early adulthood. It must be mentioned that the Prigogine principle – which states that the biological organ displays a tendency toward achieving a state of minimum entropy production – is generally not valid for the human body (Prigogine and Nicolis 1985).

Although entropy production is potentially measurable by quantifying the flow of energy through the human organism and its directly associated to oxygen consumption and carbon dioxide production, the entropy content of the entire body is in principle

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immeasurable and increases through aging, until the accumulated entropy ultimately becomes incompatible with life and death occurs (Silva and Annamalai 2008).

It thus seems logical that the relationship between entropy and aging can be better understood if we consider a model of increased entropy production, e.g. heat stress. Heat stress is a well-studied event which results in a great variety of different kinds of molecular damage and which is clearly linked to events occurring on cellular and subcellular levels (Velichko et al., 2013). However, we believe that it is far better to focus on one well-described type of damage linking entropy and aging rather than attempt to analyze the entire array of damages and their complex relationships. This article thus focuses primarily on double strand breaks (DSBs), i.e. the most deleterious form of DNA damage (Polo and Jackson 2011). They are strongly connected to aging (White et al., 2015) and accumulate during heat stress (Takahashi et al., 2004) which – we believe – puts them in the position of a middleman between the increase of entropy and aging. In this article we examine the possibility that DSBs constitute one of the molecular damages linking the structural entropy of tissues with aging.

1.1. Heat stress represents a state of an increased entropy production

Heat stress is a state where heat overcomes the homoeothermic mechanisms of the organism, resulting in temporarily increased body temperature. Under such conditions, heat added to a system is thus necessarily much higher than heat eliminated, which thereby connects heat stress with an increase in entropy. Total entropy may be calculated as

$$\Delta s_{TOT} = \frac{Q_p - Q_e}{T_{body}}$$

where ΔS_{TOT} is change in total entropy, T_{body} is body temperature and Q_p and Q_e are produced and eliminated heat, respectively. Since Q_e is necessarily much lower than Q_p in an organism experiencing heat stress, this results in an increase in total entropy. Taking into account the above mentioned reasoning, we presume that heat stress is the biological state of a system characterized by an increase in entropy, which makes it possible to indirectly associate increased entropy with a variety of biological correlates of heat stress. We note that the above mentioned reasoning also implies that entropy increases, at least temporally, every time body temperature does. However, we are focusing primarily on heat stress – mainly because it can serve as a relatively simple model situation with well-defined outcomes in the form of molecular damage.

1.2. Heat stress results in damage to both proteins and DNA

Even a small change in temperature can lead to protein unfolding and unspecific aggregations (Richter et al., 2010). These changes can prevent proteins from performing their normal functions and may result in further damage to cellular components. Cells protect themselves against such deleterious effects by upregulating heat shock proteins (HSPs), which protect cells mainly by stabilizing proper protein folding and preventing random protein aggregation (Velichko et al., 2013). Accordingly, the predominant class of HSPs is now commonly addressed as a molecular chaperone, a term specifically labeling proteins helping other proteins acquire their active conformation. Chaperones comprise several major and broadly conserved families labeled by their molecular weight: HSP100s, HSP90s, HSP70s, HSP60s, HSP40 s and small HSPs (Richter et al., 2010; Hartl et al., 2011). HSPs promote resistance not only to heat but also to several other types of stresses and some of them have been reported as prolonging the life span of *Drosophila* and *C. elegans* (Tower 2011). Interestingly, the concentration of HSP70 in human populations decreases with age (Njemini et al., 2011), suggesting a possible role of HSPs in human aging. These findings seem to suggest a connection between an increase in entropy, HSPs, protein damage and aging. While the relationship between heat stress, protein unfolding and aging is truly intriguing, to consider it fully in all of its depth would require a separate article and is beyond the scope of this paper.

Heat stress has profound effects even on a cellular level; changes in morphology and function were reported in the case of several cellular structures including cellular membranes (Park et al., 2005; Balogh et al., 2005; Vigh et al., 2007), cytoskeleton (Pawlik et al., 2013), mitochondria, Golgi apparatus, endoplasmic reticulum (Welch and Suhan 1985; Cole and Armour 1988) and nucleus (Iliakis and Pantelias 1989). The above mentioned variety of outcomes may be used to argue that an increase of entropy could potentially lead even to such a complex phenotype as one connected to aging.

On a molecular level, heat stress may also promote oxidative damage (Mujahid et al., 2007; Cvjetko et al., 2013). This association can be of great interest for aging research, especially since the free radical theory of aging, postulated in the 1950s, suggests that reactive oxygen species (ROS) constitute the primary cause of aging; even though this theory is disputed, it is still widely recognized (Harman 2006; Maynard et al., 2015; Nóbrega-Pereira et al., 2016). Heat stress also negatively effects the activity of several DNA repair pathways including base excision repair (BER) (Dikomey et al., 1987), nucleotide excision repair (NER) (Muenyi et al., 2011), non-homologous-end joining (NHEJ) (Burgman et al., 1997) and homologous recombination (Krawczyk et al., 2011; Dynlacht et al., 2011). This strongly supports the idea that an increase in entropy leads to an accumulation of DNA damage – both directly, by supporting ROS production, and indirectly, by reducing the ability of cells to repair and react to it. Because genomic instability is one of the hallmarks of aging (López-Otín et al., 2013) and accumulation of DNA damage is the cause of several progeria syndromes (Burtner and Kennedy 2010) and its induction can accelerate aging in model organisms (White et al., 2015), it can be safely assumed that an increase in entropy during heat shock has the potential to cause aging. We further focus predominantly on the connection between entropy, DSBs and aging, especially because of the great severity of these lesion, their proposed causative role in aging (Han et al., 2008) and because we believe that their connection to increased entropy and aging is already supported by data. However, we do not think that DSBs are the only damage connecting increased entropy and aging – on the contrary, we in fact assume that they are only one of several other possible pathways linking these two phenomena.

1.3. DSBs constitute a direct link between entropy and aging

DSBs, a well-known type of DNA damage, are known to accumulate in both *in vivo* and *in vitro* aging experiments (Singh et al., 2001; Sedelnikova et al., 2004). Older cells have been found to require more time to respond to such DSB lesions (Sedelnikova et al., 2008) and to have decreased efficiency and fidelity of repair (Gorbunova and Seluanov 2005; Vaidya et al., 2014). In addition, dysfunctional telomeres are also recognized as DSBs which may trigger cellular senescence (Fagagna et al., 2003; Herbig et al., 2004). Recently it was shown that the induction of DSBs is sufficient to accelerate aging in the mouse liver. Within two months after the induction of DSBs in the liver, young mice showed multiple symptoms of aging similar to those of untreated normally aged mice, including changes in gene expression profiles (White et al., 2015). It is therefore more than likely that DSBs are one of the causes of aging. Furthermore, we propose that DSBs can be linked to an increase of total structural entropy in mammalian tissue. This proposition is supported