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Unraveling the non-senescence phenomenon in *Hydra*

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HIGHLIGHTS

- *Hydra* shows no signs of senescence under laboratory conditions.
- Within-cell repair is imperfect and cannot solely protect against damage accumulation.
- Cellular damage drift leads to accumulation of damaged cell lineages, hence senescence.
- High prevalence and continued division of *Hydra*'s stem cells act against damage drift.
- These features and efficient selection against damaged cells are crucial for non-senescence.

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ABSTRACT

Unlike other metazoans, *Hydra* does not experience the distinctive rise in mortality with age known as senescence, which results from an increasing imbalance between cell damage and cell repair. We propose that the *Hydra* controls damage accumulation mainly through damage-dependent cell selection and cell sloughing. We examine our hypothesis with a model that combines cellular damage with stem cell renewal, differentiation, and elimination. The *Hydra* individual can be seen as a large single pool of three types of stem cells with some features of differentiated cells. This large stem cell community prevents "cellular damage drift," which is inevitable in complex conglomerate (differentiated) metazoans with numerous and generally isolated pools of stem cells. The process of cellular damage drift is based on changes in the distribution of damage among cells due to random events, and is thus similar to Muller's ratchet in asexual populations. Events in the model that are sources of randomness include budding, cellular death, and cellular damage and repair. Our results suggest that non-senescence is possible only in simple *Hydra*-like organisms which have a high proportion and number of stem cells, continuous cell divisions, an effective cell selection mechanism, and stem cells with the ability to undertake some roles of differentiated cells.

1. Introduction

In most organisms senescence is defined by an increase in mortality and/or a decline in fertility with age as a result of organismal deterioration (but see Jones et al. (2014)). Three main evolutionary theories are invoked to explain this process: mutation accumulation, antagonistic pleiotropy and disposable soma. The first theory predicts that senescence evolved via the accumulation of deleterious mutations acting later in life (Medawar, 1952). Because only a few individuals survive to ages at which these mutations have a deleterious effect, there is a reduced force of selection against those mutations. The second theory proposes that senescence evolved via antagonistic pleiotropy (Williams, 1957). While pleiotropic genes have positive fitness effects at the early life stages, their effects can be disadvantageous later in life; i.e., a mutation acting positively early in life will be rapidly driven to fixation because its fitness value is then higher (Hamilton, 1966). The disposable soma theory assumes the organismal optimization of resource allocation (Kirkwood, 1977): i.e., that organisms have a choice about whether to utilize the available resources for reproduction or for the maintenance of the soma. The disposable soma theory is related to organisms witch distinction between germ and somatic cells: germ line does not accumulate damage during life while soma has to follow the senescence. As aging is a process that leads to the deterioration of the body via the accumulation of damage, an organism is usually unable to repair everything. However, this is not the case for freshwater polyp *Hydra*, a member of the Cnidaria (Hydrozoa) that shows under laboratory conditions no signs of any kind of senescence; i.e., *Hydra* experiences neither an increase in the probability of death nor a decline in budding reproduction with age (Martinez, 1998; Jones et al., 2014).

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Hydra has a body plan consisting of stem cells, a simple nervous system, and two differentiated tissue layers mainly present at the apical edges with a mouth at the top and a foot at the bottom of the animal (Bode, 1996; Steele, 2002). It consists of three active but separated stem cell communities: the ectodermal and endodermal epithelial stem cells, and the interstitial stem cell lineages (Schaible et al., 2014). *Hydra* individuals, called polyps, reproduce mainly clonally by budding, producing genetically identical buds (ramets); or less frequently, sexually by producing new clones (genets). *Hydra* has also no clear distinction between germ and soma cell lines (Bosch and David, 1987). Sexual reproduction of *Hydra* is based only on one cell lineage (interstitial cells), which can also contribute to the somatic cells (Bosch and David, 1987). Although in *Hydra* subpopulations of interstitial stem cells with germ cells-restricted capacities have been found, it seems that those specific cell lineages can be generated at any time from multipotent interstitial stem cells (Nishimiya-Fujisawa and Kobayashi, 2012). Furthermore, maintenance of a separate germ lineage would be difficult with the perspective of constant cell flow in Hydra to tentacles and buds. In the past there was general believe that the lack of senescence should be prescribed to the organisms without distinction to germ and soma lines. However, the lack of germ line sequestration in metazoans (like in *Hydra*) is not decisive to emerge the non-senescence phenotype (Martínez and Levinton, 1992). The stem cells in *Hydra* are always active, with a regular and continuous proliferation and without long periods of inactivity (Bosch and David, 1984). Epithelial stem cells are not completely unspecialized, but are instead tissue-specific, with special functions like forming an epithelial cell layer and providing a polyp its shape and morphogenesis (Technau and Steele, 2011). These stem cells are responsible for the polyp's extraordinary regeneration and survival ability (see Schaible et al. (2014)). Since an individual polyp cannot grow forever, there are three ways it can remove cells from the body: first, after a short migration along the body axis, the cells differentiate at the edges of the cell proliferation zone (at the foot and tentacle regions), and are then lost through death or sloughing (see Steele (2002)); second, the cells all over the body can be removed by apoptosis (Galliot and Ghila, 2010); and third, many cells of the central part of the gastric body can also migrate toward a growing bud (Campbell, 1967) that will later be separated from the mother.

When we look at constant cell proliferation, it is unclear how *Hydra* prevents the accumulation of damage, because it is generally the case that the more divisions a cell undergoes, the more the damage build ups in the cell's biochemical machinery. While it was long assumed that stem cells—and specifically human stem cells—were exempt from aging, in recent years molecular mechanisms have been identified that are associated with stem cell senescence (Beltrami et al., 2011). We should thus expect that *Hydra* would also accumulate damage and undergo senescence. Martinez (1998) and Jones et al. (2014) showed, however, that *Hydra* has a very low mortality level for more than four years, which indicates that the health status of these animals is not negatively affected by the accumulation of mutations or somatic damage with age. Two related questions then arise: how does *Hydra* rid itself of damage (including mutations), and what mechanisms are developed to protect the polyp against the accumulation of damage over time?

There are several processes preventing the accumulation of damage in the body. First, there are processes that prevent various forms of potential damage before they happen; for example, there are cellular defense mechanisms that absorb radical oxygen species. Second, damage can be directly repaired; for example, damaged DNA strands may be repaired, thus preserving the integrity of DNA. Third, damaged structures of the body can be replaced; for example, damaged cells may be removed by programmed cell death. For humans and other complex organisms, the efficient repair of various forms of damage seems to be the main mechanism that prevents damage from accumulating in cells (e.g., Freitas and de Magalhaes, 2011). But over the long term, the repair mechanism alone does not seem to protect an individual human from the aging process, as the efficiency of this mechanism appears to be limited (see Blanpain et al. (2011) and Seluanov et al. (2004)). Consequently, we assume that *Hydra* must have an alternative mechanism that prevents the accumulation of damage and enables it to achieve a long-term constant and low probability of death across all ages; and thus non-senescence.

To provide a qualitative conceptual answer to the question of why *Hydra* does not senesce, we propose a model based on a number of fairly specific assumptions about *Hydra* physiology. This model not only provides new insights into the proximate (cellular physiological) mechanisms that prevent aging, but also gives a rise to new predictions that could be tested empirically in the future. The core of the model is based on two processes that we believe are responsible for the long-term maintenance of a *Hydra*: the continuous and constant production of new cells of all three stem cell populations, and the continuous removal of cells by differentiation, programmed cell death, or budding. It is generally accepted that stem cell proliferation activity is related to the *Hydra's* ability to avoid aging (see review Schaible et al. (2014)). However, as a constant proliferation of stem cell populations could entail the constant accumulation of damage on the cellular level, it is reasonable to assume that cells with accumulated damage should be selectively removed from the body of a *Hydra*. If this process was effective, it would prevent the random accumulation of damaged cell lineages which could eventually undergo fixation in the organism, leading to a significant deterioration in fitness-relevant parameters like reproduction and lifespan. In light of these considerations, we hypothesize that *Hydra* is able to achieve "non-senescence" because of four specific characteristics of its body plan: (i) a large number of stem cells; (ii) the continuous division of stem cells; (iii) a high proportion of dividing cells relative to non-dividing cells within each polyp; and (iv) the constant removal of cells by differentiation, programmed cell death, or budding (see above). The last characteristic provides the basis for an efficient selection against damaged cells, and thus the prevention of the accumulation of damage by the selective elimination of most of the damaged cells within a polyp. Finding sufficient conditions for non-aging in *Hydra*-like animals is helpful for understanding why most animals, including humans, cannot easily avoid aging.

2. Materials and methods

2.1. General description of the algorithm in the biological context

In the model, we consider two kinds of cells: stem cells and differentiated cells. Differentiated cells do not divide, and stem cells divide with some probability in each time unit. Our model cell cycle of stem cells is simplified into two phases: a pre-division phase and a division phase. A cell can undergo one such stage in a unit of time. All of the cells preparing for division or resting are classified as non-dividing cells. The two kinds of cells are assumed to have different rates of damage accumulation and repairs, as we will describe later. In the model, we assume that stem cells are continuously proliferating with the probability of division q in each time unit (Fig. 1). The probability of cell division is explicitly affected by the average damage level of the cells in the organism, and is implicitly affected by resource acquisition dependent on the average damage (Fig. 3). A stem cell can divide into two differentiated cells with the probability p, or it can self-renew by producing two stem cells with the probability $1\text{-}p$ (Fig. 1).

In *Hydra*, the proportion of stem cells is stable and independent of the size of the individual animal (Bode et al., 1973, 1977). In the gastric region (middle part of the body) 80–90% of the epithelial stem cells