Remodeling of Proteostasis Upon Transition to Adulthood is Linked to Reproduction Onset

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Abstract: Protein folding and clearance networks sense and respond to misfolded and aggregation-prone proteins by activating cytoprotective cell stress responses that safeguard the proteome against damage, maintain the health of the cell, and enhance lifespan. Surprisingly, cellular proteostasis undergoes a sudden and widespread failure early in Caenorhabditis elegans adulthood, with marked consequences on proteostasis functions later in life. These changes in the regulation of quality control systems, such as chaperones, the ubiquitin proteasome system and cellular stress responses, are controlled cell-nonautonomously by the proliferation of germline stem cells. Here, we review recent studies examining changes in proteostasis upon transition to adulthood and how proteostasis is modulated by reproduction onset, focusing on C. elegans. Based on these and our own findings, we propose that the regulation of quality control systems is actively remodeled at the point of transition between development and adulthood to influence the subsequent course of aging.

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PROTEOSTASIS NETWORKS MAINTAIN AND PROTECT THE CELLULAR PROTEOME

The folding and assembly of proteins and protein complexes is essential for all aspects of cellular function, with profound consequences on the long-term health of the cell, as well as organismal lifespan [1-5]. The challenge to proteome stability over the course of a lifespan is substantial and is impacted by mutations, expressed polymorphisms and intrinsic errors in gene expression on the one hand [5-7], and by the acute effects of environmental and metabolic stresses on the other [8-12]. The rate of error accumulation determines the flux of destabilized, meta-stable proteins that tend to misfold and aggregate, thereby putting the health of the cell at risk [7]. Proteostasis is achieved when the flux of metastable proteins associated with biosynthetic processes is balanced by the function of basal protein quality control networks, responsible for protecting the proteome [3, 7].

Because proteomic composition and stability are dynamic over the lifespan of an organism, the functional status of the proteome is also constantly monitored by stress signaling pathways so as to prevent protein misfolding and aggregation [5, 13-15]. Proteostasis is, therefore, closely associated with the regulation of stress response pathways, including the heat shock response [9], the unfolded protein responses [14, 15], the oxidative stress response [16], and the metabolic stress response [17, 18]. Over-expression of the corresponding stress response transcription factors, such as HSF-1, ATF-6 and IRE-1, SKN-1, and DAF-16, or enhancing the activity of chaperones, the ubiquitin proteasome system or autophagy, all have significant beneficial effects on lifespan extension and suppression of age-related misfolding diseases [12, 19-24].

PROTEOSTASIS COLLAPSE

While cells possess elegant and efficient mechanisms to autonomously activate stress response pathways and deploy resources proportional to their needs, there are provocative examples in which proteostatic networks fail to adjust to cellular demands or when stress responses are poorly activated. These include a limited heat shock response in early mammalian development and the absence of stress response activation in somatic cells of Caenorhabditis elegans mutants deficient in neuronal signaling. Other examples are, the reduced proteostasis capacity and stress response activation in different tissues of aged animals and in late-onset neurodegenerative diseases, including Huntington’s disease (HD), Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS) and Parkinson’s disease (PD) [5, 25-34].

Recent studies mainly conducted in C. elegans uncovered several cell-nonautonomous pathways that modulate cellular quality control systems [35]. This list includes cell-nonautonomous regulation of stress responses, such as the heat shock response [27] and the ER and mitochondrial Unfolded Protein Responses [36, 37], as well as intercellular signaling of proteostasis deficiencies in which the expression of misfolded protein in one tissue can induce a systemic response [38, 39]. Moreover, the same signal can inversely regulate proteostasis maintenance and the response of so-
motic cells to heat shock [33], suggesting that the capacity of quality control systems can be regulated cell-independently by various signals that can differentially modulate organellar responses to proteins damage. We, therefore, asked why does proteostasis become imbalanced with age? Specifically, is the accumulation of damaged proteins an inherent property of proteostatic networks? If not, are such networks malleable at different stages over the lifespan of an organism?

Several possible non-mutually exclusive mechanisms can explain the failure of proteostasis networks to maintain the proteome of aged animals. Protein damage and misfolding in aged individuals could result from a limited efficiency of cellular quality control networks in repairing or removing misfolded proteins throughout an organism’s life, leading to a gradual accumulation of damaged proteins over time (Fig. 1A). Alternatively, the function of cellular proteostatic networks may decrease with age. For example, declining translation fidelity may result in an increased load of damage proteins as the individual ages (Fig. 1B). Finally, the ability of cellular quality control networks to maintain the proteome and rebalance itself may be differentially regulated during the lifespan of the organism, leading to a rapid remodeling of cellular folding capacity and stress tolerance (Fig. 1C), thus placing the organism at risk for age-associated pathology. One prediction that ensues from these proposed mechanisms is that the rate of damage accumulation should determine whether proteostasis is remodeled during adulthood. If reprogramming of proteostasis that affects the efficiency of cellular quality control networks does occur, then the rate of damage accumulation should be modified over the course of an organism’s life, leading to differential deterioration of cellular proteome stability. Specifically, a rapid change in the regulation and activation of stress responses is expected.

**PROTEOSTASIS IS REMODELED UPON TRANSITION TO ADULTHOOD**

Studies in *C. elegans* have demonstrated that cellular quality control networks are modified as animals undergo transition to a reproductively mature stage. The temporal requirement for both *daf-16* and *hsf-1* was found to change upon transition to adulthood such that knockdown of *daf-16* during reproductive adulthood was sufficient to modulate lifespan, whereas knockdown of *hsf-1* during development was mostly associated with lifespan modulation [40, 41]. Altered temporal regulation was also apparent for *C. elegans* c-Jun N-terminal kinase (JNK) signaling. While the JNK homolog KGB-1 enhances DAF-16 nuclear localization and transcriptional regulation during *C. elegans* development, this function is reversed upon transition to adulthood [42]. Likewise, epidermal growth factor (EGF) signaling upregulated the expression of genes associated with the ubiquitin proteasome system yet down-regulated the expression of some chaperones at the time of transition to reproductive adulthood [43]. A change in the activation of JNK signaling and expression of proteasome subunits was also observed in adult *Drosophila melanogaster*, although expression modulation was not monitored early in adulthood [31, 44, 45]. Changes in expression of quality control machinery components are associated with changes in proteostasis function over time. For example, the rate of protein clearance is modulated early in adulthood in worms, flies and rats [43, 46-48]. Likewise, expression levels of autophagy-associated genes declined with age, concomitant with reduced autophagic activity in adult *Drosophila* and rats [31, 49]. These data demonstrate that major signaling pathways that modulate stress-resistance, proteostatic capacity and longevity demonstrate a switch-like change in behavior upon transition to adulthood (Fig. 2).

Such regulatory changes are associated with suppressed activation of several stress response pathways, including the heat shock response and the ER unfolded protein response (UPRER), at the point of transition to reproductive adulthood in worms and flies [37, 50, 51]. Stress responses enable the cell to adjust the expression of chaperones and other cytoprotective genes under proteotoxic conditions, thereby ensuring stress survival, recovery and adaptation [13]. Thermoresistance and induction of heat shock genes sharply declines 8-12 h following transition to adulthood [51]. Likewise, activation of stress resistance and the UPRER in response to a range of ER perturbations, such as exposure to tunicamycin or thapsigargin, declines early in adulthood [30, 37]. The induction of responses to other stress stimuli examined, such as the oxidative stress response and mitochondrial Unfolded Protein Responses (UPRmt), also declined sharply upon transition to adulthood (Itay Valenci, personal communication). These data suggest that stress-induced transcriptional activation is strongly dampened early in adulthood and exhibits switch-like behavior associated with reproduction onset. This supports the hypothesis that quality control networks are remodeled with age and highlights the transition to adulthood as being a critical window during which time regulation of proteostasis can be modified. However, proteostasis may also be remodeled at other stages during the lifespan of an organism, such as the modulation of the UPRmt [36] and heat shock response [52] seen during development.

If cellular quality control networks undergo remodeling upon transition to adulthood, one would expect proteostatic capacity to decline early in adulthood. As the activity of quality control networks reduces, interactions with a given protein could change the rate at which that protein misfolds. Indeed, in a model of Huntington’s disease in which animals express poly-glutamine (polyQ) containing 35 repeats, aggregation and toxicity followed the onset of reproduction when animals were cultured at 20°C (~4 days post-embryo) or 25°C (2.5 days post-embryo) [51, 53]. Thus, aggregation-prone proteins quickly became insoluble upon transition to adulthood.

Monitoring the functions and folding of meta-stable, temperature-sensitive (ts) mutant proteins demonstrated that these proteins also become unstable early in adulthood. For example, expression of a ts myosin resulted in age-dependent mislocalization of myosin and uncoordinated movement in *C. elegans*. Protein misfolding was already apparent at day 3 of adulthood in such animals [30]. The phenotype was not muscle-specific, as it was also apparent in neuronal cells and coelomocytes when animals expressing a ts mutant version of DYN-1 were examined [30]. Other temperature-sensitive mutant proteins assayed for changes in their folding capacity, such as ras, the acetylcholine receptor and perlcan (UNC-52), all showed a rapid loss of function early in adulthood (days 2-6 of adulthood) [30, 51].

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Fig. (1). Different mechanisms can explain proteostasis collapse in adulthood. (A) An integral deficiency of cellular quality control networks leads to a gradual accumulation of damaged proteins over time. (B) Age-dependent decline of translation fidelity can result in an increased load of damage proteins. (C) The ability of cellular quality control networks to maintain the proteome and rebalance homeostasis upon stress condition can be differentially regulated over the lifespan of the organism.

Fig. (2). Proteostasis is remodeled upon transition to adulthood. Changes in expression and function of chaperones, the ubiquitin proteasome system and autophagy modulate cellular proteostasis capacity, resulting in accumulation of misfolded and aggregated proteins during adulthood. This change coincides with the onset of oocyte biomass production.

Finally, wild type proteins also show age-dependent misfolding and associated decline in function, albeit later in adulthood [30, 51, 54]. For example, wild type myosin also showed age-dependent mislocalization and misfolding, although the onset occurred later in adulthood [30, 51]. The age-dependent misfolding of wild type proteins is supported by an unbiased examination of age-related aggregation of the C. elegans proteome using a systematic proteomic approach and mass-spectrometry, where an age-dependent increase in insolubility of several hundred proteins was seen. It is interesting to note that some proteins displayed an early onset of misfolding, i.e., as early as day 3 of adulthood [55]. The fact that many of the same proteins were identified in two independent studies [55, 56] emphasizes the vulnerability of some proteins to proteostasis capacity during adulthood. The wide-range remodeling of quality control networks upon transition to reproductive adulthood, therefore, results in age-dependent collapse of cellular proteostasis (Fig. 2), the severity of which depending on the genetic polymorphism of the organism [6, 57-59].

REPRODUCTION IS LINKED TO ADULT LIFESPAN

The transition between development and adulthood represents a critical window during which time individuals must partition resources between parent and progeny so as to maximize reproductive fitness. Because changes in proteostatic composition and capacity coincide with the onset of oocyte biomass production, it was suggested that disrupting the function of the reproductive system would affect the observed decline in proteostatic maintenance seen during adulthood [24, 30, 43, 51].
Reproduction is linked to aging by endocrine signaling from germline stem cells (GSCs) and the somatic gonad. Removal of GSCs by laser ablation or through mutations inhibiting proliferation increases the lifespan of *C. elegans* and modulates several signaling pathways (reviewed in [60]). In contrast, removal of the entire gonad did not lead to extended lifespan, suggesting that longevity triggered by germline elimination is not a simple consequence of sterility but that the somatic gonad likely emits signals that modulate lifespan [61, 62]. In fact, bile acid-like (dafachronic acids) steroid signals from the somatic gonad are modulated upon transition to adulthood and were found to extend *C. elegans* lifespan by activating the DAF-12 steroid hormone receptor [63-65]. Thus, there is a hormone-dependent switch upon transition to adulthood that regulates reproduction and lifespan [60].

The link between reproduction and lifespan is not specific to *C. elegans* but was also observed in other model animals. For instance, ablation of GSCs of the nematode *Pristionchus pacificus* [62, 66] or enhanced differentiation and loss of GSCs in *Drosophila melanogaster* [67] also extended lifespan. Moreover, transplantation of young ovaries into old mice increased the lifespan of the recipients by promoting longevity [68, 69], supporting a role for signals from the reproductive system, and specifically from GSCs, in modulating lifespan [70]. The association between the timing of proteostatic remodeling and longevity further supports a possible link between proteostasis and reproduction.

**SIGNALS FROM GSCs REMODEL PROTEOSTATIC NETWORKS**

To establish whether reproductive status is linked to the altered expression of and requirement for quality control machineries, as well as to restriction of protein folding capacity in adulthood, the effects of inhibiting reproduction, and specifically GSC proliferation, on proteostasis networks and their capabilities were examined in *C. elegans*. Removal of GSCs by laser ablation or mutations inhibiting GSC proliferation was shown to modulate the function of several transcription factors that mediate stress responses, such as DAF-16 and HSF-1 [61, 62, 71-73]. Moreover, germline-less mutant animals were found to induce the expression of autophagy-associated genes, such as lgg-1, bec-1 and unc-51 [74]. Likewise, inhibition of germline proliferation mildly reduced the expression of various proteasome subunits, while leading to a specific 3-fold induction in the expression of the *rpn-6.1* subunit. The augmented level of *rpn-6.1* was shown to affect expression of other proteasome subunits [24]. When the transcriptional response of *P. pacificus* was monitored following germline laser ablation, whole genome microarray analysis identified over 3000 differentially expressed genes. This population was highly enriched for ribosomal and translation-, proteasome-, protein folding- and refolding-associated genes [66]. Furthermore, the expression of TCER-1, a transcriptional elongation factor, and heat shock genes (following exposure to heat shock) was modulated in *C. elegans* [51, 72]. Thus, affecting GSC proliferation modulated the expression of different proteostatic components, including those belonging to the translational, chaperone, autophagic and proteasomal machineries [24, 51, 72, 74]. Given that the expression of specific sets of proteostatic components is determined by different signaling pathways [24, 51, 74], it would seem that GSC signaling activates several different regulatory programs that differentially modulate somatic functions. It is interesting to note that down-regulation of any of the GSC-dependent signaling pathways is required for increased lifespan [60], with these pathways differentially modulating proteostasis functions and stress response regulation [24, 51, 74]. This suggests that only the combined actions of all of these pathways are sufficient for lifespan enhancement, while proteostasis function can be modulated by partial activation of these pathways. This is in agreement with chemical and genetic manipulation of lifespan-extending pathways in which lifespan, proteostasis and stress resistance were mechanistically dissociated [75-78].

**SIGNALS FROM GSCs AFFECT SOMATIC PROTEOSTATIC FUNCTIONS**

Modulated expression of proteostasis components was shown to be tightly associated with widespread effects on proteostatic functions, specifically of quality control systems. Induced expression of autophagy genes in germline-less animals was associated with increased autophagosome numbers. GSC-dependent activation of autophagy is regulated by the FOXA transcription factor PHA-4, which was specifically required for the expression of autophagy genes and autophagosome formation [74]. Likewise, increasing the expression LPL-4, which is regulated by GSC signaling, can also activate autophagy [74, 79]. Thus, inhibition of GSC proliferation modulates autophagy in the soma of *C. elegans*.

The induced expression of *rpn-6.1* in germline-less mutant animals resulted in increased levels of chymotrypsin-like proteasome activity and decreased levels of highly polyubiquitinated proteins in *C. elegans*. This activity is mediated mainly by *daf-16* and *kri-1* but not by *hsf-1*. Over-expression of *rpn-6.1* was sufficient to increase proteasome activity in wild type animals. Moreover, *rpn-6.1* is essential not only for animals lacking GSCs but also for other long-lived mutants, such as those with reduced IIS (*daf-2*), mitochondrial electron transport chain (*isp-1*) or food intake (*eat-2*) levels [24]. Inhibition of GSC proliferation thus modulates *C. elegans* proteasomal function.

Thermo-resistance is also modulated by GSCs [51, 80]. In this case, diverse mutations in the *C. elegans* reproductive system were examined to determine whether disrupting reproduction modulates stress resistance in adulthood. When decline in the ability to induce a heat shock response was monitored, it was noted that only mutants exhibiting defects in GSC proliferation but not other sterile mutants gained the ability to mount an effective stress response in different somatic tissues during adulthood [51]. In agreement, inducing DNA damage in germ cells or inhibiting checkpoint genes also gave rise to thermo-resistance in adulthood [81, 82]. Other repair and defense responses, such as the oxidative stress response [61, 81] or the innate immune response to pathogenic bacteria [83, 84], are also modulated in germline-less animals. Together, these observations demonstrate that signals from GSCs can regulate different stress responses and improve *C. elegans* survival under stress conditions.
Inhibition of GSCs proliferation also modulated the ability of somatic cells to prevent protein aggregation. When a model for Huntington’s disease in C. elegans in which animals expressing polyQ with 35 repeats in the body wall muscle was considered, germline-less animals displayed reduced aggregation, as well as reduced toxicity [51]. Likewise, mimicking GSC-dependent activation of proteasomal function by over-expression of RPN-6.1 was sufficient to reduce aggregation and toxicity in animals expressing polyQ with 67 repeats in C. elegans neurons [24], suggesting that proteostatic capacity is increased when germline proliferation is inhibited.

Proteostatic capacity was also monitored by employing metastable proteins, such as temperature-sensitive UNC-52, as probes over the lifespan of C. elegans. While the functions of disparate metastable proteins in wild type animals were compromised with age [30], UNC-52(ts) function was rescued in germline-less animals [51]. In a similar manner, age-dependent myofilament disruption was associated with myosin misfolding and declined motility [30]. While the myofilaments of wild type animals were mostly disrupted, myofilament integrity in germline-less animals was well maintained and was associated with improved motility. Furthermore, age-dependent mislocalization of the neuronal protein DYN-1 was modified by inhibition of GSC proliferation [51]. Thus, inhibition of GSC proliferation abrogated the decline in protein quality control seen early in adulthood in different somatic tissues.

GSC-dependent modulation of proteostasis involves several different signaling pathways. For example, while daf-16/kri-1/tcer-1 and hsf-1 are required for the activation of the heat shock response in adulthood [51], other modifiers, such as daf-12, daf-9, daf-36, nhr-80, andpha-4, differentially modulate other aspects of somatic quality control function [24, 51, 74, 80]. Taken together, several different signaling pathways are modulated upon transition to adulthood by GSC inhibition, with these signaling pathways drastically remodeling somatic proteostasis. Thus, a switch-like mechanism links GSC status with the maintenance of somatic proteostasis via regulation of the expression and function of different quality control machineries and cellular stress responses that progressively leads to a decline in the maintenance of proteostasis in adulthood. This link ties reproduction to maintenance of the soma.

IS THERE A TRADEOFF BETWEEN REPRODUCTION AND SOMATIC MAINTENANCE?

Why would inhibition of germline proliferation lead to improved quality control in the soma? A restricted capacity of somatic maintenance has been suggested to result from the allocation of resources to reproduction at the cost of somatic tissue maintenance and lifespan [85]. The link between GSC proliferation and somatic functions may, therefore, stem from GSCs communicating their commitment to reproduction to the somatic gonad [65]. Proliferation of GSCs then activates signaling cascades that modulate metabolism and somatic functions that, in turn, would affect the rate of aging. If so, then not just inhibition of GSC proliferation but any damage to the germline would be expected to be reported to the soma and affect somatic maintenance, in general, and protein quality control networks, specifically. In agreement, different mutations in DNA damage checkpoint genes or mutations that block programmed cell death affect somatic stress resistance and lifespan [82, 86]. These mutations likely only affect proliferating GSCs, since C. elegans somatic cells are post-mitotic and resistant to DNA damage-induced program cell death [87]. In fact, somatic cells of intact and germline-less animals do not express DNA damage response-signaling proteins or activate programmed cell death [88]. Although it should be noted that use of the thymidine synthase inhibitor 5-fluoro-2'-deoxyuridine (FUDR), suggested to inhibit DNA replication in GSCs, was found to modulate proteostasis and stress resistance in germ-line- and gonadogenesis-defective mutants [52]. Given that radiation, inactivation of checkpoint proteins and impairment of nucleotide excision repair in GSCs all lead to improved stress survival and activation of proteasome expression and function [81], it would seem that DNA damage in the germ-line, like inhibition of GSC proliferation, results in improved activation of stress responses and changes in the expression of proteostatic components [81, 82, 86]. Signals to the soma can be transmitted via induction of an innate immune response [81], while cell-nonautonomous signals from the soma, requiring kri-1, mediate germline cell death in response to DNA damage [89]. It is of note that kri-1 was also shown to affect protective signals from the GSC to the soma [71], suggesting the existence of crosstalk between the germ-line and the soma.

A tradeoff between reproduction and somatic maintenance would also be expected to respond to environmental conditions that impact reproductive success. Given that reproduction is affected by environmental conditions, such as food availability and temperature [90, 91], crosstalk between GSCs and the soma should result in the transmission of environmental cues to the GSCs. Indeed, starvation conditions in adulthood often lead to death due to internal hatching of progeny and to reduced germline number and size [91, 92]. Animals starved from the early fourth larval stage (i.e. before the onset of oocyte biogenesis) were more likely to escape this fate by delaying the onset of oogenesis and embryo production and hence producing fewer viable progeny, suggesting that environmental cues uncouple GSC proliferation from stem cell maintenance [92, 93]. Not only food deprivation but also changes in food sources can be buffered by somatic functions to maintain the germline and thus enhance reproductive robustness [94]. The transition to adulthood may, therefore, correspond to a regulatory window during which time environmental conditions and GSC competence are weighed to determine reproductive potential and the mode of proteostasis required. However, current data have not uncovered the nature of the signals originating from the reproductive system, how and by whom they are received, or the mechanism of proteostatic remodeling.

Answering these questions will further our understanding of how protein folding is regulated in multi-cellular organisms. This is particularly important given the large number of diseases associated with age and misfolding. Understanding the nature of the signal and how it is received may, therefore, offer novel directions for treatment of protein misfolding diseases; diseases with different etiologies but similar underlying biology.
CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Drummond, D.A.; Wilke, C.O. Mistranslation-induced protein misfolding as a dominant constraint on coding-sequence evolution. Cell, 2008, 134(2), 341-52.
[2] Rutherford, S.L.; Lindquist, S. Hsp90 as a capacitor for morphological evolution. Nature, 1998, 396(6709), 336-42.
[3] Balch, W.E.; Morimoto, R.I.; Dillin, A.; Kelly, J.W. Adapting proteostasis for disease intervention. Science, 2008, 319(5856), 916-9.
[4] Taylor, R.C.; Dillin, A. Aging as an event of proteostasis collapse. Cold Spring Harb. Perspect. Biol., 2011, 3(5), a004440.
[5] Gidalevitz, T.; Przybysz, A.J.; Choe, K.P.; Roberts, L.J.; Strange, K. Increased age is associated with alterations in proteostasis and metabolic syndrome? J. Cell Biol., 2012, 198(10-11), 14914-9.
[6] Haynes, C.M.; Petrova, K.; Dillin, A.; Yu, R.; Ron, D. ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans. Dev. Cell., 2007, 13(4), 467-80.
[7] Han, J.H.; Blackwell, T.K.; Curran, S.P. Mitochondrial SKN-1/Nrf Mediates a Conserved Neurodegenerative Disease System in C. elegans. PLoS Genet., 2008, 4(2), e24.
[8] VanHoesen, A.P.; Manning, G.; Dillin, A. PEP-6 determines C. elegans longevity under proteotoxic stress conditions. Nature, 2012, 489(7415), 263-8.
[9] Bienz, M. Developmental control of the heat shock response in Xenopus. Proc. Natl. Acad. Sci. U S A., 1984, 81(10), 3138-42.
[10] Heydari, A.R.; Wu, B.; Takahashi, R.; Strong, R.; Richardson, A. Expression of heat shock protein 70 is altered by age and diet at the level of transcription. Mol. Cell. Biol., 1993, 13(5), 2909-18.
[11] Prahlad, V.; Cornellius, T.; Morimoto, R.I. Regulation of the cellular heat shock response in Caenorhabditis elegans by heat shock factor and molecular chaperones. BMC Biol., 2008, 3, 100.
[12] Simonsen, A.; Cumming, R.C.; Brech, A.; Isakson, P.; Schubert, D.R.; Finley, K.D. Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult Drosophila. Autophagy, 2008, 4(2), 176-84.
[13] Labbadia, J.; Cunliffe, H.; Weiss, A.; Katsyuba, E.; Sathasivam, K.; Seredenina, T.; Woodman, B.; Moussaoui, S.; Frenzel, S.; Luthi-Carter, R.; Pagani, P.; Bates, G.P. Altered chromatin architecture underlies progressive impairment of the heat shock response in mouse models of Huntington disease. J. Clin. Invest., 2011, 121(8), 3306-13.
[14] Haynes, C.M.; Fiorese, C.J.; Lin, Y.F. Evaluating and responding to mitochondrial dysfunction: the mitochondrial unfolded-protein response and beyond. Trends Cell Biol., 2013, 13(3), 491-9.
gagna, F. Differential regulation of DNA damage response activation between somatic and germline cells in Caenorhabditis elegans. *Cell death Differ.*, **2012**, *19*(11), 1847-55.

[89] Ito, S.; Greiss, S.; Gartner, A.; Derry, W.B. Cell-nonautonomous regulation of C. elegans germ cell death by kri-1. *Curr. Biol.*, **2010**, *20*(4), 333-8.

[90] McMullen, P.D.; Aprison, E.Z.; Winter, P.B.; Amaral, L.A.; Ruvinsky, I. Macro-level modeling of the response of C. elegans reproduction to chronic heat stress. *PLoS Comp. Biol.*, **2012**, *8*(1), e1002338.

[91] Schafer, W.R. Egg-laying. *WormBook* **2005**, *14*, 1-7.

[92] Seidel, H.S.; Kimble, J. The oogenic germline starvation response in C. elegans. *PLoS One* **2011**, *6*(12), e28074.

[93] Angelo, G.; Van Gilst, M.R. Starvation protects germline stem cells and extends reproductive longevity in C. elegans. *Science*, **2009**, *326*(5955), 954-8.

[94] Gracida, X.; Eckmann, C.R. Fertility and germline stem cell maintenance under different diets requires nhr-114/HNF4 in C. elegans. *Curr. Biol.*, **2013**, *23*(7), 607-13.