Review Article

Caenorhabditis elegans as a Model Organism for Special Environment

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ABSTRACT

Organisms living in special environments, namely deep-sea, high altitude, and space environment experience physiological, biochemical, and genetic changes. Human study in special environments may be time consuming and expensive, hence, the authors are proposing the use of *Caenorhabditis elegans* (*C. elegans*). This non-parasitic nematode has been widely used as model organism for various human diseases, such as cancer, neurodegenerative disorders, and aging-associated diseases. There are also physiological and biochemical parameters in humans established in *C. elegans*. Similarly, *C. elegans* carry ortholog genes that are associated with human genes. This paper reviews the physiological, biochemical, and genetic changes in humans under the different special environments and correlate these effects in the current understanding of the special environments in *C. elegans*. Both the deep-sea and high-altitude environment leads to hypoxia due to do the decrease in oxygen supply in humans. Hypoxia in *C. elegans* is regulated by p38 mitogen activated protein kinase (MAPK), which inhibits the oxygen sensor EGL-9 and activates hypoxia-inducible factor 1 (HIF-1). In space environment, humans and *C. elegans* experience are observed to have decreased muscle mass. The muscle morphogenesis in humans is associated with *MyoD*, which interestingly has a counterpart in *C. elegans*, *ceMyoD*. Even though there were studies using *C. elegans* in different special environments, there were some physiological and biochemical changes that are still not elucidated. It is interesting to study the effects of these different special environments by mimicking various environmental conditions on the lifespan and health span in *C. elegans*.

Key words: *Caenorhabditis elegans*, Deep-sea, High altitude, Humans, Space, Special environments.

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INTRODUCTION

Special environment is a surrounding condition with different abiotic factors challenging the survival of an organism.[1] There are three special environments depending on the altitude, namely deep-sea, high altitude, and space environment. Space environment is the enormous vacuum that fills the universe's vacant spaces beyond the atmosphere or surface of the earth.[2] The compartment inside a spacecraft can also be considered as part of the space environment. On the other hand, mountain ranges and the compartment inside an aircraft can be considered as high-altitude environment.[3] Lastly, deep-sea environment pertains to the underwater surrounding including frequent divers spot, ocean floor, and the compartment inside the submarine.[4]

There are different kinds of underwater diving namely, free diving, vessel diving, surface supplied diving, and self-contained underwater apparatus (SCUBA) diving. The physiological effects of these diving types differ to a leisure and a professional diver.[5] In free diving, a diver completes a dive by holding the air taken at the surface by closing the glottis and maintaining the intrathoracic pressure. In vessel diving, the divers are protected by a thick-walled vessel from ambient pressure,

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hence causing little physiological changes. Meanwhile, divers in surface supplied diving are vulnerable to air embolism when ascending too fast due to the difference in the air pressure supplied to them from the surface and the surrounding water pressure. Lastly, the most used diving method is the SCUBA diving since the pressure inside the lungs is maintained at any depth. However, the increased in gas density and partial pressures may contribute to physiological stress to the divers.[4] A single dive usually reduces the vital capacity and diffusing capacity airway conductance, which recovers shortly. The reduction in the diffusing capacity may also lead to the lower maximal oxygen consumption and increased vital capacity. Frequent young divers have observed significantly higher functional vital capacity compared to the non-divers. However, the functional vital capacity diminishes with age despite frequent diving. Cumulative diving exposures which often lead to hyperoxia affects the diffusing capacity of the lungs.

In high altitude environment, people experience vasodilation which causes a reduction in blood pressure and increased capillary permeability, these events lead to local hypoxia and escalated ventilatory pressure and blood pressure.[6] The partial oxygen pressure in the elevated locations begins to decrease with the increase in altitude. Associated symptoms of hypoxia become more noticeable, including lack of field of vision, a sensation of the skin, cyanosis, euphoria, which causes loss of consciousness.[7] Proteostasis was also disrupted by hypobaric hypoxia, which is associated with inflammation and apoptosis.[8] Immigrants of high-altitude communities mainly in Peru and Bolivia develop certain physiological changes such as higher volumes of the lung, smaller gradients of alveolar to arterial O_2, and less hypoxic pulmonary vasoconstrictor response.[9] Another special environment higher than the high altitude is the space environment, without the specially built bodysuit and spacecraft, the threats to survival will be enormous as the astronaut travels into space.[10] Astronauts may have decreased protein synthesis that leads to muscle tissue decreased load where muscles weaken and deteriorate and muscle atrophy that can be caused by direct effect on muscle fibers while in space travel.[11] Cosmic radiation-induced cellular and DNA damage leads to significant harm to space explorers, especially during long-term spaceflights.[12] Apoptosis is affected by space in different cell types and plays a significant role in tissue repair and organ development.[13]

Studying the impact of these special environment in humans appear to be laborious and expensive, especially during pre-liminary drug screening or introduction of interventions. One commo. Currently, *Caenorhabditis elegans* has been used to study aging, innate immune response, cancer, alcohol addiction, and neurodegenerative diseases.[14-17] This nematode carries interesting features, such as short lifespan, high brooding rate, short reproductive age, transparent body, and simple anatomical structure, which makes it ideal to observe several physiological parameters, like aging, fecundity, fertility pharyngeal pumping rate, and movement.[14-17] The presence of ortholog human genes in *C. elegans* makes it easier to observe the effects of silencing genes on the expression of protein and phenotypic attributes through genetic screening. Despite the abundance of information and association between the *C. elegans* and humans, there has been only few advances on the understanding of different special environments in the recent years.

This paper associates the physiological, biochemical, and genetic changes in *C. elegans* under different special environments, namely deep-sea, high altitude, and space environment in humans under these conditions.

Deep-Sea Environment

There are different stresses encountered in the deep-sea environment. The physical stress arises from the density of the water, which affects the pressure, buoyancy, and viscosity. The increased in depth below sea also increases the atmospheric pressure and the partial pressure of gasses, which leads to decreased in lung volume. This physical stress causes different physiological changes associated with ventilation, such as breath-holding and air supply. Similarly, the thermal properties of water can lead to breathing higher pressures of gasses, which leads to oxygen, carbon dioxide, and nitrogen toxicity. These stresses affect a professional diver and non-divers differently.

Apparently, habitual divers have more developed mammalian diving reflex than those non-divers. The mammalian diving reflex is a primitive reflex which elicits various physiologic response among mammals during water submersion.[18] Certain physiological changes are observed during this reflex, such as bradycardia, decreased in cardiac output, accumulation of lactate in under perfused muscles, and increased peripheral vasoconstriction due to apnea and hypoxia.

Hypoxia in deep-sea environment

Hypoxic blackout is one of the most common medical problems associated with diving resulting to loss of consciousness due to inadequate oxygen transport to the brain.[19] During hypoxic condition, the production of ATP is minimized due to the disruption of ETC that

negatively affects the oxidative phosphorylation process.[20]

Cells detect hypoxia through intracellular oxygen sensors, which upregulates hypoxia-inducible factor 1 (HIF-1) that induces metabolism, metastasis, vascularization, cell proliferation and red blood cell production.[21] HIF-1also promotes anaerobic glycolysis by producing a variety of glucose transporters, such as pyruvate kinase M, aldolase A, and glycolytic enzymes that aids the cells in ATP production under hypoxic environment.[22]

Following hypoxia, the introduction of oxygen in a cell leads to the increased production of Reactive oxygen species (ROS), increasing the possibility of gene mutation. Although, some studies have reported that ROS also induces HIF-1activation. The missense substitution at p.Pro582Ser in *HIF-1* gene was associated with HIF-1 protein expression, however p.Val116Glu missense mutation does not affect its transcriptional activity.[23]

In *C. elegans*, certain behavioral patterns like avoidance to both hypoxic and hyperoxic environment are observed. Studies have shown that sublethal hypoxic environment (>0.5% oxygen) evokes stress response in *C. elegans* lengthening their lifespan. However, depriving the nematodes with oxygen (<0.3%) chronically leads to death or shorter lifespan.[24]

Similar with humans, HIF-1 is also responsible for the adaptive response of *C. elegans* under sublethal hypoxic environment. A moderate decrease in mitochondrial respiration leads to increase ROS production, which upregulates HIF-1 expression enhancing longevity.[25]

HIF genes in humans are also encoded in *C. elegans* as *hif-1* and *aha-1*, which is responsible for hypoxia-induced changes in the nematode. Studies have shown that *hif-1* deletion in *C. elegans* leads to the loss of resistance to various stresses, such as heat, hydrogen cyanide, and toxins produced by certain pathogens. Interestingly, *hif-1* mutant *C. elegans* strains age slower than the wildtype under normal condition, however, this slow-aging mechanism is independent of the dietary-restriction pathway.[26]

Hypothermia in deep-sea environment

Further descent underwater increases the depth leading to lower temperature.[27] The prolonged exposure of divers to extreme low temperatures leads to hypothermia. Under this environmental condition, the body experiences exothermic reaction, thus, loses more heat in the process. Also, cold temperature induces vasoconstrictor effect, which increases blood pressure, left ventricular wall stress, and myocardial consumption and augmenting venous return.[28] The increase in blood volume stimulates the stretch receptors in the thoracic vessels and left atrium leading to the release of natriuretic hormone, which increases osmolal clearance and urine flow. Consequently, heat and water loss induce bronchomotor response.

Chronic exposure to cold temperatures triggers the body to utilize the stored energy to maintain by balancing the lost heat.[29] Cold-induced thermogenesis in humans is associated with the brown adipose tissues (BAT). BAT induces non-shivering thermogenesis to generate heat by enhancing insulin sensitivity and increasing adiponectin levels, SIRT1 activity, irisin circulation, and UCP1 expression.[30]

The non-shivering thermogenesis does not involve contraction of skeletal muscle but relies on the thermogenic mechanism involving uncoupling protein 1 (UCP1).[31] This protein uncouples the fatty acid oxidation derived from ATP synthesis during BAT activation to generate heat.[32] Accordingly, UCP1 is primarily manifested in BAT and is situated in the inner portion of the mitochondrial membrane in which the catalyzed proton escapes through the membrane that leads to the oxidative phosphorylation dissociation from ATP production.[33] In addition, the inner part of the mitochondrial membrane protein acts as a proton transporter that enables heat production via the respiratory network, and thus uncouples the oxidative phosphorylation.[34]

Moreover, the *ucp-1* polymorphism which is 3826 bases away from the transcription site was observed to be frequently mutated and results to the variation in the *ucp-1* expression.[35] Additionally, intraperitoneal *ucp* expression was found to be lower in in obese individuals, while extraperitoneal UCP expression is unaffected.[36] However, the said study did not specify whether the UCP expression includes or particular to *ucp-1* gene.

The behavioral response in *C. elegans* upon detection of change in temperature elicits migration opposing the source of temperature change. Likewise, low temperature may not immediately place *C. elegans* in hypothermia, in contrast with humans, due to their thermotaxis behavior. Their thermotaxis behavior vary depending on the stimulation. For instance, nematodes demonstrate a thermophilic behavior when exposed in cold environment, whereas a cryophilic behavior when placed in a warm environment.[37] The thermophilic behavior of the nematode is regulated by the AIY interneuron through the excitation from the AFD neurons.[38]

The thermophilic behavior in *C. elegans* is associated with different proteins, namely Calcineurin A subunit, nPKC-epsilon/eta, LIM homeodomain protein, and POU (transcriptional factor).[39] Studies suggest that

calcineurin with the help of CAMKII phosphorylates DAF-16.[40] DAF-16, SIRT1, and ß-catenin regulates the expression of UCP4. The UCP4 is the *C. elegans'* counterpart of the human UCP genes.[41] However, there is still no sufficient evidence on the association of the other thermophilic behavior-associated proteins with the UCP expression.

Furthermore, the lack of complete deletion of ucp-4 may not affect stress resistance and lifespan in *C. elegans,* which allows them to with stand environment with low temperatures.[42]

High Altitude Environment

Altitude denotes elevation ranging from 2, 400 meters to 8,000 feet into the atmosphere. Low atmospheric pressure in high altitude regions is the primary reason on why they become much colder compared to an area that is closer to a sea level, gas molecules are oxygen, carbon dioxide and nitrogen.[43] Upon exposure to hypoxia, ventilation tends to increase, which means that the person is trying to breathe more and there is less oxygen that circulates and reach the muscles.[44] High altitude results to low oxygen saturation level and desaturation of human's blood. This phenomenon happens because of low air pressure that is present in high altitude area. Initially it begins as inability to do normal physical activities. In severe cases it can lead to hemorrhage in lungs, accumulation of fluid around the brain and pulmonary edema. Moreover, exposure to high altitude also leads to the disruption of proteostasis, it is said that proteostasis is a process that regulates protein, wherein it aids in maintaining the health of the cells and body.[45]

Hypoxia

Like deep-sea environment, human living in high-altitude experience drop in oxygen supply leading to hypoxia. Upon exposure to hypoxia several effects may be established such as levels of plasma, elevated amount of hematocrit, red blood cell mass, body weight, structures of muscle, exercise capacity, mental functioning of an individual and quality of sleep.[46] There can be minimal oxygen consumption because of inappropriate delivery of oxygen to tissues. The skeletal muscle and body weight is also affected because there is an increase in energy expenditure that leads to the basal metabolic rate and high levels of the physical activities, the inadequate intake of energy as well as dehydration and malabsorption.[47] High altitude results to increase in red cell number, hemoglobin concentration and amount of hemoglobin. Hemoglobin is a protein responsible for carrying oxygen and delivers it to the lungs, then it is supplied all throughout the tissues of the body.[48] When hemoglobin is increased in the blood it increases the amount of oxygen that the body needs making the blood sticky and viscous and makes the heart to have a hard time to pump blood around the body. Hence, Hypoxia happens where in the tissue fails to receive an adequate amount of oxygen.[49]

Oxygen deprivation impairs essential physiological process. It can result to apoptosis when cells cannot adopt to stress. Hypoxia happens when tissue perfusion becomes inadequate which results to anaerobic metabolic pathway. This results to change in function of cell such as mitochondrial activity. The activity is shortened because of insufficient supply of oxygen that is necessary for glycolysis and electron transport chain. Oxygen acts a final acceptor, and aids in moving electron down a chain resulting to the production of adenosine triphosphate (ATP) through a process called oxidative phosphorylation.[50] This happens because it needs to permit oxidative phosphorylation, primary metabolic pathway to produce ATP in the body. When hypoxia happens, it diminishes ATP production and lowers activity of electron transport chain through transcription of hypoxia- inducible factor 1 (HIF-1). HIF coordinates the transcriptional response to Hypoxia and induces metabolic shift from oxidative phosphorylation to an oxygen- independent glycolysis.[51] In response to a hypoxia, HIF orchestrates the reduction of cardiac output and interruptions in the cardiovascular changes. Perhaps, it is associated to increase peripheral resistance and heart rate. Alterations in heart rate, corresponds to an increase in intensity of body's metabolic activity.[52]

Hypoxia decreases capacity of repairing the pathway, contributing an increase in mutagenesis, genomic instability of the genome and mutation frequency by means of inhibiting DNA repair pathway.[53] The encoding of the hypoxia inducible factor factor-2α (HIF- 2α) was made possible by EPSA1 gene. This transcription factor is involved in the response of the body under hypoxia. It provides instruction in making HIF- 2α, which plays a significant role in the ability of the body to adapt in hypoxia. It regulates cell division, and formation of blood vessels. HIF oversees red blood cell production.[54] EPSA1 gene is also responsible for the body's ability to adapt to high altitude. The body compensates for a much lower oxygen levels by altering patient's breathing, production of more red blood cells and blood vessels. Hence, people who are living in high altitude are likely to produce more RBC, which helps them to avoid developing altitude sickness,

higher breathing rate, and blood vessels having better transport of oxygen.[55]

In *Caenorhabditis elegans*, under hypoxic condition, it exhibits random walk pattern of movement. However, this frequency is reduced when it encounters persistent low-oxygen environment. As consequence, it permits *C. elegans* to escape from insufficient amount of oxygen.

The reaction needs an oxygen sensor, EGL-9 oxygen, and it does not need HIF-α. *C. elegans* has a neuron that controls their locomotion, t is called the GLR-1. The purpose is to withstand, sustain random walk behavior and it must be maintained. Upon exposure to hypoxia the p38 Mitogen- activated protein kinase (MAPK) plays a significant part in the response of *C. elegans* in hypoxia. It inhibits oxygen sensor and triggers gene expression of HIF-α. Moreover, inhibiting p38 MAP initiates roaming behavior in *C. elegans* since it interferes with GLR-1 recycling and trafficking.[56] It could reduce oxygen sensors and trigger an expression of Hypoxia Inducible Factor (HIF).

Neurons are vulnerable to hypoxic environment; it utilizes a pathway to reduce and prevent its effect. The p38 MAK kinase (MAPK) regulates the hypoxia response pathway. As it reduces the response of the hypoxic pathway, it is also responsible for determination of neurons that are aging in a low oxygen environment. Lastly it stimulates the appearance and expression of a gene for *C. elegans* to adopt in a hypoxic condition, hif-1 gene encodes and produces bHLH-PAS protein for *C. elegans* to either adapt or escape from hypoxia. The protein plays a significant role in maintaining the cellular and systemic oxygen homeostasis, regulation of physiologic and developmental events.[57]

Disruption of proteostasis

Proteostasis regulates the balance of intracellular pool of functional proteins. Ensuring that there is a proper folding, handling, and degradation of proteins. Disrupted proteostasis was tightly coupled with degradative pathway, altered anabolic signaling, inflammation and apoptosis.

The disruption in proteostasis is associated with degradative pathway which results to alteration in anabolic signaling inflammation and apoptosis. Once a person is exposed to hypoxia severely it can affect the protein homeostasis and overwhelms muscular system towards the skeletal muscle atrophy.[8] The protein misfolding and alterations during a protein synthesis may overload the degradation mechanisms. The homeostasis of proteome prevents formation of impaired system.

The proteostasis machineries are said to be reduced, deteriorates with aging, and causes an accumulation of organelles that are damaged and proteins that are misfolded.[58] The rate of canonical protein synthesis pathway is impaired, affected and slowed because of limited amount of ATP that is available and produce.[59] The canonical pathway is important for activation of transcription factor and results to changes in the expression of target gene. It requires a large amount of ATP and hypoxia limits this translation pathway to synthesize proteins effectively and efficiently. Release of tryptophan and tyrosine suggest that there is a degradation of oxidized proteins by the proteasome pathway. Disruption of proteostasis contributes to a change in the distribution of nuclear- encoded mitochondrial proteins. It causes cumulative damage to the DNA, and cell cycle Mitochondrial.[60] The defect in the mitochondrial proteostasis have a substantial effect on the organisms' health, aging, cellular and physiological function.[61]

In *C. elegans,* it shows that hypoxia disrupts proteostasis in the nematode- coordination of protein synthesis, quality control and degradation of proteome.[62] Proteostasis includes the coordination of the protein synthesis, folding, degeneration and the quality control that is required to maintain a proteome that is functional.

The specific hypoxic conditions disrupt protein homeostasis, leading to aggregation and proteotoxicity. Furthermore, it can impact many, if not all, of the cellular processes that is involved in proteostasis.[62] Hydrogen sulfide (H_2S) stabilizes and activated hypoxia-inducible factor *(HIF)*. This result to the increase of chemical chaperone glycerol- this indicates that there is a low molecular weight that can help to enable mutant proteins to escape from quality control systems.

The molecular chaperoning capacity of the cells, and protein degradation results to a damage in the DNA and impairment of the proteasome function shortens the *C. elegans* lifespan. A decline in the proteasome's function contributes to the accumulation of damaged proteins, and this might result to the process of aging.[63]

Space Environment

National Aeronautics and Space Administration (NASA) is considered the global leader in space exploration that is in charge of science and technology in aeronautics and space in United States that benefits the humanity.[64] NASA introduced a new model specimen known as *Caenorhabditis elegans* to speed the discovery of medicine and biology in space named as International *Caenorhabditis elegans* FIRST (ICE-FIRST), this experiment proved that *C. elegans* is an invaluable model for understanding biological changes and association with health concerns in human in spaceflight.[65]

Muscle Atrophy

Space travel causes physiological damages in human skeletal muscle, that includes muscle fatigue, weakness, soreness, and lack of coordination in movements due to loss of muscle mass that resulted in muscle atrophy.[66] Cellular shrinkage that leads to decrease in tissue size is known as atrophy, microgravity affects the muscle by reducing its tension that causes spaceflight-induced muscle atrophy.[67] In an 8-day Space Shuttle mission of 18 crew members, 4% in calf muscles, 6% in soleus, gastrocnemius and quadriceps, 8% in hamstrings, and 10% in intrinsic back muscles shows significant losses in muscle mass.[68]

Biochemically speaking, loss of muscle mass is associated in the muscle fiber since type II fiber is more susceptible to atrophy due to microgravity than type I fiber and it is supported in a post 17-day spaceflight that shows 26% decline in cross-sectional area of type IIa fiber in human soleus than the 15% decrease in type I fiber. Additionally, slow type I fiber also shows decrease of 2% to 19% in diameter and 39% in thinner myofibrils and length of Z-band, and 79% of these fibers expressed type I myosin heavy chain (MHC).[69] The activation of atrophy is characterized by its distinct pathways, specifically the ATP-dependent ubiquitin-proteasome system that required in muscle activity in removing sarcomeric proteins. Ubiquitin-proteasome systems is activated after the cleavage of ATP by E1 enzymes, ubiquitin is then move to E2 enzyme then catalyzed by E3 enzyme to form the final ubiquitylation reaction, and once it become polyubiquitylated it will be degraded in proteasome.[70]

More than 650 ubiquitin ligases are encoded by human genome that is needed in regulation of cellular processes, among the distinguished E3s are muscle specific and are up or downregulated during atrophy and called 'atrogenes' or atrophy-related genes that regulates the loss of muscle components.[71] The genes induced most strongly encoded two ubiquitin ligases specific for muscle are *Atrogin-1* or also called *MAFbx* that regulates MyoD degradation (key muscle transcription factor) and *eIF3f* (crucial in protein synthesis), and Muscle Ring Finger 1 or also called *MuRF1* that regulates the half-life of several muscle structural protein.[70] These two genes were greatly upgraded in the onset of muscle loss and encodes E3 ubiquitin ligases, protein that is responsible for substrate specificity, deletion of these genes can result in partial protection in muscle loss that shows their significance in muscle atrophy.[72]

Similarly, in *C. elegans* altered muscle development that leads to muscle atrophy was investigated in ICE-FIRST by using its muscle response to spaceflight. *C. elegans* exhibits decrease in muscle contractility and has small but significant movement defects which is the decrease in locomotion after a 10-day spaceflight that resulted in altered muscle development. This response of *C. elegans* in spaceflight is caused by the altered MHC expression in both body wall and pharyngeal muscle, that allows locomotion and function in feeding and pseudocoelomic circulation, respectively.[73]

Space flown *C. elegans* shows a 10% decrease in MHC and paramyosin bands that is due to the decreased muscle-specific MHC. In molecular level, decrease of 73.3% *myo-3* and 22.6% *unc-54* in body wall muscle-specific, decrease of 49% *myo-2* and 10.8% *myo-1* in pharyngeal muscle-specific, and decrease in myogenic transcription factor *hlh-1,* however*, skr-6* and *skr-18*, a ubiquitin ligase, shows an increased in expression levels in *C. elegans* due to the decrease of expression in muscle related genes.[73]

MyoD homologue in *C. elegans* or also known as *CeMyoD,* and *HLH-1,* a helix-loop-helix transcription factor which is detected in the *C. elegans'* body wall muscles and precursor cells that is essential in muscle function and morphogenesis.[74] *CeMyoD* in space flown *C. elegans* shows a modest decrease, therefore a decrease in *myo-3* and *unc-54* gene in body wall muscle that encodes for MHC A and paramyosin, respectively, while, *PEB-1, CEH-22* and *PHA-4,* a pharyngeal myogenic transcription factors also decreases. Additionally, levels of *myo-1, myo-2,* and *unc-54* genes also decreased that encodes the MHC D, C, and B and decrease in *unc-15* genes and gene encoding troponins and tropomyosins, *tnc-2, tnt-2, tnt-3, tnt-4,* and *lev-11* also decreases. These altered gene expression causes altered muscle development that lead in muscle atrophy in *C. elegans* in response to spaceflight.[73]

Apoptosis

Human lymphocytes cell line is used to study apoptosis in spaceflight, and one of the famous used lymphocytes is the Jurkat cells, a human T lymphoblastoid cell line that is similar to the known affected cells due to spaceflight.[75] Chromatin condensation, membrane blebbing, loss of nuclear envelope, and cellular fragmentation is observed in the follicular thyroid carcinoma cells nuclei after simulated microgravity that induces apoptosis due to the increase in cytoskeletal intermediate filament protein.[76] After the activation of microgravity for 4 hr of Jurkat cells, altered microtubule cytoskeleton in static and in-flight controls where the microtubule organizing centers (MTOC) were disrupted, and filaments are shortened, fused together and cell membrane lacks

normal branching that is stress induce due to the launch vibration, however, after 48 hr MTOC and microtubules are reorganized.[77]

Static space flown shows time-dependent increases or upregulated *Fas/APO-1* for approximately 15-fold at 4 hr and by 48 hr, concentration is greater than 65 times than that of 4 hr.[78] *Fas/APO-1* protein or also known as CD95 that is responsible for the programmed cell death in immune system that binds to *Fas* ligand (*FasL*) that results in the formation of death-inducing signaling complex (DISC) and initiates apoptosis by *Fas*-associated death domain protein (FADD) and *caspases 8,* and *caspases 10*.[77] Moreover, when *Fas*-DISC starts a positive feedback loop in type II cells, *caspases 8* activated BID, a BH4 domain-containing proapoptotic protein releases *cytochrome c* and *SMAC* that activates and binds to apoptosis protease activating factor 1 *(Apaf-1)*, known as the human homolog of *CED-4* gene in *C. elegans* that initiates apoptosis. This binds to *caspases 9* which results in apoptosome and activates *caspases 3* and caspases cascade that leads to cell death.[79]

Genes associated in apoptosis are *Fas* gene that is found in chromosome 10 of human that encodes *Fas* receptor or also called *APO-1*, a type I transmembrane protein from tumor necrosis factor receptor (TNFR) family and responsible for the apoptosis through DISC and *caspases 8* activation.[77]

Programmed cell death or apoptosis in *C. elegans* related to spaceflight occurs in female germ line of adult *C. elegans* by the exposure to ionizing radiation that causes decrease in mitotic germ cells due to halt in cell cycle suspension.[80] After exposure of fourth larval (L4) of *C. elegans* in increasing levels of radiation, increase in apoptotic germ cell is observe and 45 dead cell is seen in the pachytene region of the germline and proves that DNA damage due to radiation resulted in apoptosis.[81]

Apoptotic signals upregulated *EGL-1,* that acts as inhibitor and belongs to the BH3-only protein that binds to *CED-9* bound to mitochondria that acts as activator and belongs to the BCL2-family protein which results in release of *CED-4* from the attachment to mitochondria by *CED-9* and binds to pro caspases *CED-3* that activates executioner caspase *CED-3* through proteolytic activation and leads to cell death.[82]

DNA microarray analysis of spaceflight control of *C. elegans* shows increase in the expression of 48 genes for more than 2 folds and decreased of 199 genes to less than half, these genes include the checkpoint and apoptosis-related genes namely, *ced-1, ced-2, ced-3, ced-4, ced-9, egl-1, nuc-1, cep-1, atl-1, mrt-2, rad-5,* and *read-52/rdb-1*.[82]

CONCLUSION

Special environments, such as high altitude, space, and deep-sea challenges the health of human and may result to pathological consequences. The high altitude and deep-sea environment leads to hypoxia due to the differences in the gas pressures in these environment, which affect the supply of oxygen. There are common hypoxia-induced response in humans and *C. elegans* associated with HIF-1. Consequently, hypoxic response in high altitude environment is associated with proteostasis in humans and in *C. elegans*. Similarly, the thermoregulatory response in humans under deep-sea environment reveal to be associated with *C. elegans'* UCP expression. Moreover, the current understanding on the response mechanism beyond the earth's atmosphere appears to be more focus on the muscle atrophy and apoptosis. Similar with the other special environments, the physiologic and molecular changes in humans in the space environment can also be associated with *C. elegans* under this condition. These evidences affirm that researches in *C. elegans* may not be limited to the common experiments currently done. Reconfiguring certain conditions to mimic high altitude, space, and deep-sea environments, may illuminate understanding in the stress response, healthspan, and lifespan of *C. elegans* under these special environments. Hence, the knowledge and association of *C. elegans* with humans will be significantly expanded.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MAPK: Mitogen activated protein kinase; **HIF:** Hypoxia Inducible Factor; **SCUBA:** Self-contained underwater apparatu; **ATP:** Adenosine triphosphate; **DNA:** Deoxyribonucleic acid; **ETC:** Electron transport chain; **ROS:** Reactive oxygen species; **BAT:** Brown adipose tissues; **NASA:** National Aeronautics and Space Administration; **ICE-FIRST:** International *Caenorhabditis elegans* FIRST.

SUMMARY

C. elegans has been long used as model organism for humans in various physiologic and molecular study. Currently, there are several studies using *C. elegans* in aging, cancer, immune response, and neurodegenerative research. This paper reviews the physiologic and molecular response of humans in different special environments, namely deep-sea, high altitude, and space environment and compared it with *C. elegans*.

REFERENCES

1. Suefeld P. Groups in special environments [internet]. p. c2001 [cited Jan 31 2021]. Available from: https://www.sciencedirect.com/topics/computer-science/special-environment.
2. Horneck G. Space environment. In:. Berlin, Heidelberg: Springer [internet]; 2015 Dec. Encyclopedia of astrobiology Gargaud M *et al*., editors [cited Feb 11 2021]. Available from: https://link.springer.com/referenceworkentry/10.1007%2F978-3-662-44185-5_1469#howtocite.
3. Aber J, Aber S. SFAP survey planning and implementation [internet]. c2019 [cited Feb 11 2021]. Available from: https://www.sciencedirect.com/topics/earth-and-planetary-sciences/high-altitude-environment.
4. Bove AA. Diving medicine. Am J Respir Crit Care Med. 2014 Jun;189(12):1479-86. doi: 10.1164/rccm.201309-1662CI, PMID 24869752.
5. Davis C. Altitude diving – scuba diving with an attitude [internet]. p. c2017 [cited Jan 31 2021]. Available from: https://www.deeperblue.com/altitude-diving-scuba-diving-attitude/.
6. Zoppi L. How does airplane travel affect the human body? [internet]. p. c2018. News-Medical [cited Jan 31 2021]. Available from: https://www.news-medical.net/health/How-Does-Airplane-Travel-Affect-the-Human-Body.aspx.
7. Pilmanis AA, Sears WJ. Physiological hazards of flight at high altitude [internet]. Lancet. 2003 Dec:~:text=As%20the%20partial%20pressure%20of,eventually%20unconsciousness%20at%20higher%20altitudes;362;Suppl:s16-7. doi: 10.1016/s0140-6736(03)15059-3, PMID 14698113.
8. Agrawal A, Rathor R, Kumar R, Suryakumar G, Ganju L. Role of altered proteostasis network in chronic hypobaric hypoxia induced skeletal muscle atrophy. PLOS ONE. 2018 Sep;13(9):e0204283. doi: 10.1371/journal.pone.0204283, PMID 30240405.
9. Julian CG, Moore LG. Human genetic adaptation to high altitude: evidence from the Andes. Genes (Basel). 2019 Feb;10(2):150. doi: 10.3390/genes10020150, PMID 30781443.
10. Cowan H. 10 Health hazards in outer space; n.d. Reader's Digest [internet] [cited Jan 31 2021]. Available from: https://www.readersdigest.co.uk/lifestyle/technology/10-health-hazards-in-outer-space.
11. Larina IM, Percy AJ, Yang J, Borchers CH, Nosovsky AM, Grigoriev AI, Nikolaev EN. Protein expression changes caused by spaceflight as measured for 18 Russian cosmonauts. Sci Rep. 2017 Aug;7(1):8142. doi: 10.1038/s41598-017-08432-w, PMID 28811532.
12. National Aeronautics and Space Administration. Studying DNA breaks to protect future space travelers [internet]. p. c2019 [cited Jan 31 2021]. Available from: https://www.nasa.gov/mission_pages/station/research/news/studying-dna-breaks-in-space.
13. Prasad B, Grimm D, Strauch SM, Erzinger GS, Corydon TJ, Lebert M, Magnusson NE, Infanger M, Richter P, Krüger M. Influence of microgravity on apoptosis in cells, tissues, and other systems *in vivo* and *in vitro*. Int J Mol Sci. 2020 Dec 9;21(24):9373. doi: 10.3390/ijms21249373, PMID 33317046.
14. Nas JS, Roxas CK, Acero RR, Gamit AL, Kim J, Renturar J, Ching A, Saludares A. *Solanum melongena* (Eggplant) Crude anthocyanin Extract and delphinidin-3-glucoside protects *Caenorhabditis elegans* against *Staphylococcus aureus* and *Klebsiella pneumoniae*. Philipp J Health Res Dev. 2019.
15. Nas JS. Exploring the binding affinity and non-covalent interactions of anthocyanins with aging-related enzymes through molecular docking. Vol. 24(3). p. 9-19 [internet]; 2020. Philippine Journal of Health Research and Development [cited Apr 29 2021]. Available from: https://pjhrd.upm.edu.ph/index.php/main/article/view/359.
16. Nas JB, Dangeros S, Chen PR, Dimapilis R, Gonzales DG, Hamja FA, Ramos CJ, Villanueva A. Evaluation of anticancer potential of Eleusine indica methanolic leaf extract through Ras- and Wnt-related pathways using transgenic *Caenorhabditis elegans* strains. J Pharm Negative Results. 2020 Jan;11(1). doi: 10.4103/jpnr.JPNR_7_20.
17. Nas JS, Catamin SQ, Cruz P, Estrada K, Mejia MA, Silvestre BR, Torres MJ, Turman FI. Influence of Basella alba methanolic extract on alcohol preference in *Caenorhabditis elegans* after acute and chronic alcohol withdrawal. Vol. 12(2) [internet]; 2020 Dec. Animal Biology and Animal Husbandry [cited Apr 29 2021]. Available from: https://search.proquest.com/openview/6017be13580d68724d58a6d4a76ad378/1?pq-origsite=gscholar&cbl=2046427.
18. Godek D, Freeman A. Physiology, diving reflex. StatPearls [internet]; 2020 Sep [cited Mar 06 2021]. Available from: https://bit.ly/3ugDkhR.
19. Wed MD [internet]. WebMD LLC; c2020 [cited Mar 03 2021]. Available from: https://www.webmd.com/asthma/guide/hypoxia-hypoxemia.
20. Wheaton W, Chandel N. Hypoxia. 2. Hypoxia regulates cellular metabolism. pan-Massachusetts challenge; 2010 Dec 1 [cited Mar 03 2021]; 300(3): C385–C393. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3063979/.
21. D'Alessandro S, Magnavacca A, Perego F, Fumagalli M, Sangiovanni E, Prato M, Dell'Agli M, Basilico N. Effect of hypoxia on gene expression in cell populations involved in wound healing. BRI. 2019 Aug 22;2019:Article ID 2626374. doi: 10.1155/2019/2626374, PMID 31534956.
22. Ziello JE, Jovin IS, Huang Y. Hypoxia-inducible factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia. Yale J Biol Med. 2007 Jun;80(2):51-60:~:text=HIF%2D1%20Regulates%20Shift%20to,metabolism%20for%20cellular%20energy%20production. PMID 18160990.
23. Morris MR, Hughes DJ, Tian YM, Ricketts CJ, Lau KW, Gentle D, *et al*. Mutation analysis of hypoxia-inducible factors HIF1A and HIF2A in renal cell carcinoma. Anticancer Res. 2009 Nov;29(11):4337-43. PMID 20032376.
24. Chandler-Brown D, Choi H, Park S, Ocampo BR, Chen S, Le A, *et al*. Sorbitol treatment extends lifespan and induces the osmotic stress response in *Caenorhabditis elegans*. Front Genet. 2015 Oct 27;6:316. doi: 10.3389/fgene.2015.00316, PMID 26579191.
25. Hwang AB, Lee SJ. Regulation of life span by mitochondrial respiration: the HIF-1 and ROS connection. Aging (Albany, NY). 2011 Mar 6;3(3):304-10. doi: 10.18632/aging.100292, PMID 21389351.
26. Zhang Y, Shao Z, Zhai Z, Shen C, Powell-Coffman JA. The HIF-1 hypoxia-inducible factor modulates lifespan in C. elegans. PLOS ONE. 2009 Jul 27;4(7):e6348. doi: 10.1371/journal.pone.0006348, PMID 19633713.
27. American Chemical Society [internet]. Chemistry for life; c2021 [cited Mar 04 2021]. Available from: https://www.middleschoolchemistry.com/lessonplans/chapter3/lesson6.
28. Korthuis RJ. Chapter 4, Exercise Hyperemia and Regulation of Tissue Oxygenation During Muscular Activity. Available from: https://www.ncbi.nlm.nih.gov/books/NBK57139/. Skeletal muscle circulation. San Rafael, (CA): Morgan and Claypool Life Sciences; 2011.
29. Haman F, Blondin DP. Shivering thermogenesis in humans: origin, contribution and metabolic requirement. Temperature (Austin). 2017 May 22;4(3):217-26. doi: 10.1080/23328940.2017.1328999, PMID 28944268.
30. Contreras C, Gonzalez F, Fernø J, Diéguez C, Rahmouni K, Nogueiras R, *et al*. The brain and brown fat. Ann Med. 2014 Jun;1047(2):150-68.
31. Nowack J, Giroud S, Arnold W, Ruf T. Muscle non-shivering thermogenesis and its role in the evolution of endothermy. Front Physiol. 2017 Nov 9;8:889. doi: 10.3389/fphys.2017.00889, PMID 29170642.
32. Fedorenko A, Lishko PV, Kirichok Y. Mechanism of fatty-acid-dependent UCP1 uncoupling in brown fat mitochondria. Cell. 2012 Oct 12;151(2):400-13. doi: 10.1016/j.cell.2012.09.010, PMID 23063128.
33. Tsuboyama-Kasaoka N, Tsunoda N, Maruyama K, Takahashi M, Kim H, Ikemoto S, *et al*. Up-regulation of uncoupling protein 3 (UCP3) mRNA by exercise training and down-regulation of UCP3 by denervation in skeletal muscles. Biochem Biophys Res Commun. 1998;247(2):498-503. doi: 10.1006/bbrc.1998.8818, PMID 9642158.

34. Palou A, Picó C, Bonet ML, Oliver P. The uncoupling protein, thermogenin. Int J Biochem Cell Biol. 1998 Jan;30(1):7-11. doi: 10.1016/s1357-2725(97)00065-4, PMID 9597749.
35. Esterbauer H, Oberkofler H, Liu YM, Breban D, Hell E, Krempler F, *et al*. Uncoupling protein-1 mRNA expression in obese human subjects: the role of sequence variations at the uncoupling protein-1 gene locus. PubMed. 1998 Apr;39(4):834-44.
36. Oberkofler H, Dallinger G, Liu YM, Hell E, Krempler F, Patsch W. Uncoupling protein gene: quantification of expression levels in adipose tissues of obese and non-obese humans. PubMed. 1997 Oct;38(10):2125-33.
37. Takeishi A, Takagaki N, Kuhara A. Temperature signaling underlying thermotaxis and cold tolerance in *Caenorhabditis elegans*. J Neurogenet. 2020 Apr 21;34(3-4):351-62. doi: 10.1080/01677063.2020.1734001, PMID 32316810.
38. Kuhara A, Ohnishi N, Shimowada T, Mori I. Neural coding in a single sensory neuron controlling opposite seeking behaviours in *Caenorhabditis elegans*. Nat Commun. 2011 Nov 23;2:355. doi: 10.1038/ncomms1352, PMID 21673676.
39. Okochi Y, Kimura KD, Ohta A, Mori I. Diverse regulation of sensory signaling by C. elegans nPKC-epsilon/eta TTX-4. EMBO. 2005 May 26;24(12):2127-37. doi: 10.1038/sj.emboj.7600697.
40. Tao L, Xie Q, Ding YH, Li ST, Peng S, Zhang YP, *et al*. CAMKII and calcineurin regulate the lifespan of *Caenorhabditis elegans* through the FOXO transcription factor DAF-16. eLife. 2013;2:e00518. doi: 10.7554/eLife.00518, PMID 23805378.
41. Pfeiffer M, Kayzer EB, Yang X, Abramson E, Kenaston MA, Lago CU, *et al*. *Caenorhabditis elegans* UCP4 protein controls complex II-mediated oxidative phosphorylation through succinate transport. J Biol Chem. 2011 Oct 28;286(43):37712-20. doi: 10.1074/jbc.M111.271452, PMID 21862587.
42. Slocinska M, Barylski J, Jarmuszkiewicz W. Uncoupling protein S of invertebrates: a review. IUBMB Life. 2016 Jul;68(9):691-9. doi: 10.1002/iub.1535. PMID 27385510.
43. Murdoch University. How does altitude affect the body?. c2018 [cited Apr 21 2021]. Available from: https://www.murdoch.edu.au/news/articles/opinion-how-does-altitude-affect-the-body.
44. Life E. Sciences [internet]. Proteostasis. [cited Apr 21 2021]. Available from: https://www.enzolifesciences.com/platforms/proteostasis/.
45. San T, Polat S, Cingi C, Eskiizmir G, Oghan F, Cakir B. Effects of high altitude on sleep and respiratory system and theirs adaptations. Scientific World Journal. 2013;2013:241569. doi: 10.1155/2013/241569, PMID 23690739.
46. Dünnwald T, Gatterer H, Faulhaber M, Arvandi M, Schobersberger W. Body composition and body weight changes at different altitude levels: A systematic review and meta-analysis. Front Physiol. 2019 Apr 16;10:430. doi: 10.3389/fphys.2019.00430, PMID 31057421.
47. Marengo-Rowe AJ. Structure-function relations of human hemoglobins. Proc (Bayl Univ Med Cent). 2006 Jul;19(3):239-45. doi: 10.1080/08998280.2006.11928171, PMID 17252042.
48. Cafaro RP. Hypoxia: its causes and symptoms. J Am Dent Soc Anesthesiol. 1960 Apr;7(4):4-8. PMID 19598857.
49. Alberts B, Johnson A, Lewis J, *et al*. New York: Garland Publishing Science; 2002. The Mitochondrion. c2002. Molecular biology of the cell. 4th ed [cited Mar 8 2021]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4244961/.
50. Wheaton WW, Chandel NS. Hypoxia. 2. Hypoxia regulates cellular metabolism. Am J Physiol Cell Physiol. 2011 Mar;300(3):C385-93. doi: 10.1152/ajpcell.00485.2010, PMID 21123733.
51. Cowburn AS, Macias D, Summers C, Chilvers ER, Johnson RS. Cardiovascular adaptation to hypoxia and the role of peripheral resistance. eLife. 2017 Oct 19;6:e28755. doi: 10.7554/eLife.28755, PMID 29049022.
52. Kaplan AR, Glazer PM. Impact of hypoxia on DNA repair and genome integrity. Mutagenesis. 2020;35(1, Jan):61-8. doi: 10.1093/mutage/gez019, PMID 31282537.
53. Medline plus. EPSA1 gene. c2020 [cited Apr 21 2021]. Available from: https://medlineplus.gov/genetics/gene/epas1/#resources.
54. Berkley Education [internet]. Evolving altitude aptitude. c2010 [cited Apr 21 2021]. Available from: https://evolution.berkeley.edu/evolibrary/news/101001_altitude.
55. Kumar G [internet]. Hypoxia: adapt or avoid. c2013 [cited Feb 12 2021]. Available from: https://elifesciences.org/articles/14345.
56. Kolonko M, Greb-Markiewicz B. bHLH-PAS proteinS: their structure and intrinsic disorder. Int J Mol Sci. 2019 Jul 26;20(15):3653. doi: 10.3390/ijms20153653, PMID 31357385.
57. Höhn A, Tramutola A, Cascella R. Proteostasis failure in neurodegenerative diseases: focus on oxidative stress. Oxid Med Cell Longev. 2020 Mar 27;2020:5497046. doi: 10.1155/2020/5497046.
58. Chee NT, Lohse I, Brothers SP. mRNA-to-protein translation in hypoxia. Mol Cancer. 2019 Mar 30;18(1):49. doi: 10.1186/s12943-019-0968-4, PMID 30925920.
59. Takenaka Y, Nakano T, Ikdea M, Kakinuma Y. Prolonged disturbance of proteostasis induces cellular senescence via temporal mitochondrial dysfunction and enhanced mitochondrial biogenesis in human fibroblasts. 2020 [cited Apr 5 2021]. Available from: https://www.biorxiv.org/content/10.1101/2020.01.22.916221v2.full.
60. Jensen MB, Jasper H. Mitochondrial proteostasis in the control of aging and longevity. Cell Metab. 2014;20(2):214-25. doi: 10.1016/j.cmet.2014.05.006, PMID 24930971.
61. Fawcett EM, Hoyt JM, Johnson JK, Miller DL. Hypoxia disrupts proteostasis in *Caenorhabditis elegans*. Aging Cell. 2015 Feb;14(1):92-101. doi: 10.1111/acel.12301, PMID 25510338.
62. Ghazi A, Henis-Korenblit S, Kenyon C. Regulation of *Caenorhabditis elegans* lifespan by a proteasomal E3 ligase complex. Proc Natl Acad Sci U S A. 2007;104(14):5947-52. doi: 10.1073/pnas.0700638104, PMID 17392428.
63. National Aeronautics and Space Administration [internet]. About NASA; c2021 [cited Apr 2 2021]. Available from: https://www.nasa.gov/about/index.html.
64. Adenle AA, Johnsen B, Szewczyk NJ. Review of the results from the International *C. elegans* first experiment (ICE-FIRST). Adv Space Res. 2009;44(2):210-6. doi: 10.1016/j.asr.2009.04.008. PMID 20161164.
65. Weight SP, muscle, bone loss during spaceflight: Another perspective. Eur J Appl Physiol. 2012 Nov;113(9).
66. Jackman RW, Kandarian SC. The molecular basis of skeletal muscle atrophy. Am J Cell Physiol. 2004 Oct;287(4):C834-43. doi: 10.1152/ajpcell.00579.2003, PMID 15355854&.
67. LeBlanc A, Schneider V, Shackelford L, West S, Oganov V, Bakulin A, Voronin L. Bone mineral and lean tissue loss after long duration space flight. J Musculoskelet Neuronal Interact. 2000;1(2):157-60. PMID 15758512.
68. Widrick J, Knuth S, Norenberg K, Romatowski J, Bain J, Riley D, *et al.* Effects of a 17-day space flight on contractile properties of human soleus muscle fibers. J Physiol. 2004 Sep;516(3):[about 915-930 p.].
69. 69. Bonaldo P, Sandri M. Cellular and molecular mechanisms of muscle atrophy. Dis Model Mech. 2013 Jan;6(1): [about 25–39 p.]. doi: 10.1242/dmm.010389, PMID 23268536.
70. McKinnell IW, Rudnicki MA. Molecular mechanisms of muscle atrophy. Cell. 2004 Dec;119(7):[about 907-910 p.]. doi: 10.1016/j.cell.2004.12.007, PMID 15620349.
71. Sacheck J, Ohtsuka A, McLary S, Goldberg A. AIGF-I stimulates muscle growth by suppressing protein breakdown and expression of atrophy-related ubiquitin ligases, atrogin-1 and MuRF1. Am J Physiol Endocrinol Metab. 2004 Apr;287: [about 591–601 p].
72. Higashibata A, Szewczyk NJ, Conley CA, Imamizo-Sato M, Higashitani A, Ishioka N. Decreased expression of myogenic transcription factors and myosin heavy chains in *Caenorhabditis elegans* muscles developed during spaceflight. J Exp Biol. 2006 Aug;209(16): [about 3209–3218 p.]. doi: 10.1242/jeb.02365, PMID 16888068.
73. Chen L, Krause M, Sepanski M, Fire A. The *Caenorhabditis elegans* MYOD homologue HLH-1 is essential for proper muscle function and complete morphogenesis. Development [internet]. 1994 Mar;120(6):1631-41. PMID 8050369.
74. National Aeronautics Space Administration [internet]. Gravitational physiology of human immune cells; A review of *in-vivo*, *ex-vivo* and *in-vitro* studies. c2013 [cited Apr 3 2021]. Available from: https://ntrs.nasa.gov/citations/20040089754.
75. Zou H, Henzel WJ, Liu X, Lutschg A, Wang X. Apaf-1, a Human Protein Homologous to C. elegans CED-4, Participates in cytochrome c-Dependent Activation of caspase-3. Cell. 1997 Aug;90(3): [about 204-413 p.]:405-13. doi: 10.1016/S0092-8674(00)80501-2.

76. Wajant H. Mapping cellular signaling. Wajant, author. The Fas Signaling Pathway: more than a paradigm. Sci Cell Bio. 2002 May;296(5573): [about 1635-1636 p.].
77. Lewis ML, Reynolds JL, Cubano LA, Hatton JP, Lawless BD, Piepmeier EH. Spaceflight alters microtubules and increases apoptosis in human lymphocytes (Jurkat). FASEB J. 1998 Aug;12(11): [about 1007-1018 p.]. doi: 10.1096/fasebj.12.11.1007, PMID 9707173.
78. Berry D. Molecular Animation of Cell Death Mediated by the Fas Pathway. Science's STKE. 2007 Apr;2007(380):tr1-. doi: 10.1126/stke.3802007tr1.
79. Stergiou L, Hengartner MO. Death and more: DNA damage response pathways in the nematode C. elegans. Cell Death Differ. 2004 Dec;11(1): [about 21-28 p.]. doi: 10.1038/sj.cdd.4401340, PMID 14685168.
80. Gartner A, Stuart M, Ahmed S, Hodgkin J, Hengartner M. A Conserved Checkpoint Pathway Mediates DNA Damage-Induced Apoptosis and Cell Cycle Arrest in *C. elegans*. Molecular Cell [Internet} [cited Apr 3 2021]. Available from: http://www.lifesci.dundee.ac.uk/groups/anton_gartner/pdfs/Gartner.Milstein....pdf. Vol. 5(1): [about 435-443 p.]; 2000 Mar.
81. Nakajima YI, Kuranaga E. Caspase-dependent non-apoptotic processes in development. Cell Death Differ. 2017 Aug;24(8):1422-30. doi: 10.1038/cdd.2017.36, PMID 28524858.
82. Higashitani A, Higashibata A, Sasagawa Y, Sugimoto T, Miyazawa Y, Szewcyk NJ, Viso M, Gasset G, Eche B, Fukui K, Shimazu T, Fujimoto N, Kuriyama K, Ishioka N. Checkpoint and physiological apoptosis in germ cells proceeds normally in spaceflown *Caenorhabditis elegans*. Apoptosis. 2005;10(5): [about 949-954 p.]. doi: 10.1007/s10495-005-1323-3.

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