



HAL
open science

Perspectives for plant biology in Space and analogue environments

Veronica de Micco, Giovanna Aronne, Nicol Caplin, Eugénie Carnero-Diaz, Raúl Herranz, Nele Horemans, Valérie Legué, F Javier Medina, Veronica Pereda-Loth, Mona Schiefloe, et al.

► **To cite this version:**

Veronica de Micco, Giovanna Aronne, Nicol Caplin, Eugénie Carnero-Diaz, Raúl Herranz, et al.. Perspectives for plant biology in Space and analogue environments. NPJ Microgravity, In press, 9 (1), pp.67. 10.1038/s41526-023-00315-x . hal-04045474

HAL Id: hal-04045474

<https://hal.science/hal-04045474v1>

Submitted on 24 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

TITLE PAGE

TITLE

Perspectives for plant biology in Space and analogue environments

AUTHORS

Veronica De Micco^{1*}, Giovanna Aronne¹, Nicol Caplin², Eugénie Carnero-Diaz³, Raúl Herranz⁴, Nele Horemans⁵, Valérie Legué⁶, F. Javier Medina⁴, Veronica Pereda-Loth⁷, Mona Schiefloe⁸, Sara De Francesco¹, Luigi Gennaro Izzo¹, Isabel Le Disquet³, Ann- Iren Kittang Jost⁸

AFFILIATIONS

¹ Dept. Agricultural Sciences, University of Naples Federico II, via Università 100, 80055, Portici (NA), Italy

² SciSpacE Team, Directorate of Human and Robotic Exploration Programmes, European Space Agency (ESA), Noordwijk, Netherlands

³ Institute of Systematic, Evolution, Biodiversity, Sorbonne University, National Museum of Natural History, CNRS, EPHE, UA, 45, rue Buffon CP50, 75005, Paris, France

⁴ Centro de Investigaciones Biológicas Margarita Salas - CSIC, Ramiro de Maeztu 9, 28040 Madrid, Spain

⁵ Belgian Nuclear Research Centre (SCK CEN), Biosphere Impact Studies (BIS), Boeretang 200, 2400 Mol, Belgium

⁶ Université Clermont Auvergne, INRAE, PIAF, F-63000 Clermont-Ferrand, France.

⁷ GSBMS/ Evolsan UFR Santé, University of Toulouse III, France

⁸ NTNU Social Research, Centre for Interdisciplinary Research in Space (CIRiS) Dragvoll Allé 38 B, 7049 Trondheim, Norway

CORRESPONDING AUTHOR

Veronica De Micco

RUNNING TITLE

Plant Space Biology

Abstract

Advancements in plant Space biology are required for the realization of long-duration exploratory-class manned missions, where the re-supply of resources from Earth is not feasible for technical and economic constraints. Plants are key organisms in Bioregenerative Life Support Systems (BLSS) for the regeneration of resources (i.e. oxygen production through photosynthesis, water recovery by transpiration, and wastes recycling) and the production of fresh healthy food. Moreover, plants play a role in psychological support for astronauts. The definition of cultivation requirements for the design, realization and successful operation of BLSS must take into account the effects of Space factors on plant growth, development and reproduction. Altered gravitational fields and radiation exposure are the main Space factors inducing changes in gene expression, cell proliferation and differentiation, signaling and physiological processes, with consequences on tissue organization and organogenesis, thus on the whole organisms functioning. In this paper, the main findings of gravity- and radiation-related research of the last years are summarized, highlighting the knowledge gaps that is still necessary to fill. A focus on existing facilities as well as requirements for future facilities to achieve fundamental biology goals is reported. Possible future experiments in the short-medium-long term are proposed to achieve the targets of crewed Space exploration.

Introduction: why do we need plants in Space? What are the main constraints to plant cultivation in Space?

At the beginning of Space exploration, Space biology almost coincided with human Space biology with the main aim to gain fundamental understanding on the responses of human body to the stressful Space environment to ultimately prevent health risks and protect astronauts by managing Space-induced pathological issues.¹ In the last decades, increasing interest has been raised towards plant Space biology due to the awareness that plant cultivation in Space is a requirement in long-duration manned missions, where the regeneration of resources and plant-based food production onboard must be increased at the expense of re-supply from Earth.²

Plants play a crucial role in Bioregenerative Life Support Systems (BLSSs). Artificial ecosystems such as the BLSS are high-technology systems, based on the integration of physico-chemical and biological processes, to support long interplanetary missions.^{3,4} The BLSSs concept includes several interconnected compartments in which different organisms are used to sequentially recycle resources.⁵ Within BLSSs, the photoautotrophic compartment is the one enabling the production of edible biomass, oxygen, and water as resources for the astronaut starting from carbon dioxide, wastewater and other wastes.. An example of BLSS is the MELiSSA (Micro-Ecological Life Support System Alternative) loop by the European Space Agency (ESA) that aims to sustain astronaut life in Space missions to reduce the initial payload and dependency from Earth. Increasing effort is posed on plants to produce healthy food specifically designed to sustain crew in long term missions.^{6,7}

Additionally, research in space-plant biology and space-agriculture is required alongside the strong efforts to increase the knowledge on human biology in Space with the aim to predict risk factors, prevent disease(s), and implement effective countermeasures to manage health emergencies during missions. Among countermeasures for assuring astronauts wellbeing against degenerative diseases and psychological issues of humans in Space, there is the introduction in astronauts' diet of plant-derived fresh food produced directly on board. Further, there may also be benefits for crew mental health by having plants in the living and/or working environments in Space.^{8,9} Understanding the positive influence of plants on human psychology in the space environment will only be possible through allowing crews to participate in plant cultivation in space and may present a positive by-product from all other plant experimentation accessible by astronaut crews.

From an applied point-of-view, a better understanding of plant biology in Space is a needed requirement for the design and realization of BLSSs, because the altered growth and behavior of plants in Space can alter the input/output balance between the different compartments as well as the potential nutritional value. As any other living organism, plants survival and reproduction strongly depend on interactions with environmental factors (e.g. temperature, light, oxygen/carbon dioxide, water, and volume availability) including the new Space factors. Understanding plant acclimation and adaptation processes that determine the plant's capability to complete a full life cycle in Space (producing viable offspring) is of fundamental importance for plant biology in Space. The current knowledge platform allows us to pursue this goal for both model plants and crops. Among different environmental factors, altered gravity and ionizing radiation are recognized to be the main constraints for growth in Space conditions. In the following section we briefly synthesize the current knowledge about the effects of microgravity and radiation on plants.

What is already known about the effects of microgravity and radiation

To date, European scientists studying plant Space biology have focused on understanding the effects of altered gravity on several plant systems (e.g. different species/cultivars, target organs/tissues). Recently, more attention has been dedicated to the effect of ionizing radiation (IR) in so far as it represents a clear challenge for exploratory-class missions. Altered gravitational fields and IR exposure can induce changes in gene expression, cell proliferation and differentiation, signaling and physiological processes, with consequences on tissue organization and organogenesis, thus on the whole organisms functioning.

Effect of microgravity and altered gravity on plant growth and reproduction

Since they emerged from water some 475 million years ago, land plants have always evolved under the same 1g gravity level. Early pioneering Space experiments have demonstrated that plants are able to survive and grow in Space, although morpho-physiological alterations were soon reported.^{10,11} In early research, deficiencies in the experimental setup and in used facilities sometimes caused confusing and contradictory results. Now, however, we have evidence stating that the microgravity as present in Space environment does not prevent plant growth and reproduction but causes serious alterations in plant physiology and development.¹² Cells respond to changes in mechanical forces, thus gravity-related research offers a unique opportunity to elucidate the mechanisms of gravity perception which is necessary to better understand fundamental processes and the physiological changes in Space. Moreover, in exploratory-class long-term mission, an altered gravity rate is an important challenge that plants must overcome in order to adapt to the space environment in so far as plants will be confronted not only with a lack of gravity (or residual gravity) during spaceflight (and inside the International Space Station - ISS), but also to the lunar gravity (0.17g) and the Martian gravity (0.37g) which are substantially lower to what plants normally experience on Earth.

- Plant developmental patterns and gravity perception: from gene expression to cell cycle and organ development

Most studies to reveal the effect of altered gravity on plant developmental patterns have been focusing on the root meristem as this is the primary tissue involved in the graviresponse in plants (starch-statolith-theory).¹³ Experiments under microgravity simulation and onboard the ISS revealed the disruption of the meristematic competence in seedlings, i.e. the loss of the coordinated progress of cell proliferation and cell growth that characterizes meristematic cells underground gravity conditions.^{14–16}

An acceleration in the cell cycle was detected in *in-vitro* cultured cells grown in simulated microgravity resulting from a downregulation of genes involved in the G2/M transition checkpoint and upregulation of genes controlling the G1/S transition. Other phenomena were the downregulation of significant genes for ribosome biogenesis and the corresponding depletion of the levels of nucleolar proteins, the depletion of the nuclear transcription and an increase in chromatin condensation, related to the epigenetic regulation of gene expression.^{17,18} Experiments using

different levels of reduced gravity and hypergravity indicated a modulation of alterations for each level, with Mars gravity inducing milder alterations.^{19,20}

Auxin is suggested to be a key factor regulating the connection between perceived stimuli and cellular responses, controlling the balance between cell proliferation and cell differentiation, regulating the cell cycle progression and the coordination between cell growth and cell division.²¹⁻²⁴

Parallel transcriptomic experiments exploring how simulated and real microgravity change gene and protein expression have shown a complex response of plants, involving a reprogramming of the pattern of gene expression²⁵. Specific genes of response to gravity alteration have not been found, while the main and most frequent targets of this gene reprogramming are: genes coding for heat shock-related elements, cell wall remodeling factors, oxidative burst intermediates and components of the general mechanisms of plant defense against stressors, being non-equally affected at the different spaceflight, lunar and martian g levels.²⁶

- Interaction with other factors

Plants on Earth utilize gravity as the most reliable signal for their growth and morphogenesis, however, many plant responses concern its interaction with other physical, chemical, or biological factors. In the last decades, orbital platforms enabled comprehensive studies on the mechanisms underlying plant growth in microgravity.²⁷ Still, there is a need to further investigate the interactions between gravity and other environmental factors including temperature, light, oxygen/carbon dioxide, water availability, electric and magnetic fields, especially in the framework of plant morphogenesis and tropistic responses.²⁸ Except for a limited number of studies concerning microgravity interactions with magnetic, water or chemical stimuli,²⁹⁻³¹ previous research has mainly focused on the interactions between gravity and light. It has been shown that the sensitivity of plants to light is modified by microgravity and that phototropic curvature of shoot and root organs are largely affected by changes in gravity conditions.³² Experiments performed using the EMCS onboard the ISS or the ESA ground-based facilities resulted in discovering novel phototropic responses of plants, proving that the interaction between gravity and light changes according to the magnitude of g-force.³³⁻³⁵ In this framework, light quality has a prominent role in determining direction and strength of phototropic responses of shoots and roots, with major differences between blue and red wavelengths under a wide range of gravity levels.^{35,36} On the other hand, previous studies also showed that light can control the sensitivity of plants to gravity through phytochrome-regulated pathways, indicating that phytochromes play a key role in integrating multiple environmental stimuli.³⁷

Gene expression studies with different levels of altered gravity showed that the adaptive response appeared enhanced by red light photostimulation. Red light activates cell proliferation and ribosome biogenesis,³⁸ and in the "Seedling Growth" series of experiments in the ISS red light caused a concerted upregulation of marker genes for cell proliferation, cell growth and auxin polar transport.³⁹ Experiments with different levels of gravity (microgravity, Mars gravity and ground control gravity) with and without red light photoactivation have shown that red light restored the auxin distribution patterns which appeared altered under microgravity, while in roots grown at 0.3g, auxin polar transport was little altered, irrespective of photoactivation.⁴⁰ Red light was also shown to counteract the decoupling between cell proliferation and growth in root meristems reported in earlier experiments.⁴¹

Gene expression alterations, evaluated by RNAseq, showed different responses to different gravity levels and modulation of gene expression by red light photoactivation. As an example, Mars gravity level induced an adaptive response, consisting of the activation of environmental acclimation-related transcription factors (WRKY and NACs families),^{42,43} especially in photostimulated samples.⁴¹

It appears clear that plant cultivation in future space missions implies research-based strategies that involve gravity-substituting factors (e.g., light) to counteract the effects of microgravity or partial gravity conditions such as on Moon and Mars. Nowadays, the technological advancement in cultivation systems is providing effective and affordable tools to control environmental factors for plant growth in space with the possibility of using external cues for both application and research purpose.²⁷ Gravity might be replaced by specific stimulation in terms of light wavelengths and photon flux density for the regulation of plant growth and development. Prospectively, other factors are expected to play such a role including water, electric and magnetic fields, chemicals, or microorganism, but further investigation is needed.

- *Seed-to-seed cycle*

Nowadays, it is crucial to delve into the mechanisms by which altered gravity conditions can affect plant reproduction and seed viability, in order to develop cultivation strategies for the improvement of plant-based BLSSs in future human settlements on the Moon and Mars.⁴⁴ The completion of the seed-to-seed cycle, in fact, will be essential to produce viable seeds to be used for the cultivation of plants over time without relying on terrestrial supply.

Early studies with plants grown for extended periods in microgravity reported an overall reduction of plant growth and difficulties in the transition to reproductive stage.⁴⁵ Since the first seed production in Space by *Arabidopsis thaliana* plants in 1982,⁴⁶ few experiments on plant reproduction have been performed. Overall, previous studies showed that seed-to-seed cycle can be accomplished in most species tested in microgravity, although with reduced quality of embryos and seeds produced by plants due to delayed embryo development, modification in storage reserves, delayed starch use in cotyledons, and decreased cell number in cotyledons.^{45,47-49} Furthermore, ground experiments using simulated microgravity showed significant alterations during development of male gametes in several crop species.⁵⁰

Given that most studies have investigated the effect of microgravity on early stages of plant development with sporadic studies on plant reproduction, there is a large gap of information to be filled to fully address vegetative growth of plants in adult stage and plants reproduction in space.

Effects of ionizing radiation on plant growth and development

Outside Low Earth Orbit the success of higher plant development and growth is constrained by the same factors that act on Earth, at different levels, and by additional space factors, especially IR which is variable in space and time.^{2,51}

IR can cause direct damage to the structures encountered, but also indirect due to the generation of reactive oxygen species (ROS).^{52,53} The oxidative stress due to ROS production may trigger important components of plant cells, including lipids and proteins, but especially DNA.^{54,55} The degree of direct DNA damage and proper functioning of DNA repair systems determine the consequences of IR exposure for plants also at morpho-structural and physiological level.⁵⁶

Nevertheless, plants responses to IR are not fully understood yet. Experiments in Space where plants were exposed to the cosmic radiation and on ground with exposure to low- and high- linear energy transfer (LET) radiation have shown that IR can have positive, null or negative effects on

plants, at genetic and morphophysiological levels depending on IR properties and plant intrinsic factors such as type of radiation, its LET, exposure time (acute or chronic), dose, plant species, developmental stage at the time of irradiation.⁵⁷ The effect of IR is also tissue-specific and depends on tissue architecture: complex tissues seem less sensitive to damage,^{58,59} and, on the contrary, the meristematic cells are the most sensitive to radiation.⁶⁰

High-LET radiation, like protons and heavy ions, are more harmful in inducing genetic mutations compared to low-LET radiation such as X- and γ -rays.^{61,62} Concerning the dose of exposure, high doses (>100 Gy for seeds; >50–70 Gy for vegetative stages) can lead to harmful outcomes, such as reduced levels of photosynthesis and germination, embryo lethality, loss of apical dominance, dwarf architecture, altered leaf anatomy, and accelerated senescence.^{55,57,63} Low doses of IR, on the other hand, appear to induce hormetic response in plants, stimulating germination, growth, photosynthetic and respiration rate, improving content in chlorophyll, carotenoids, non-enzymatic (ascorbic acid, glutathione, and anthocyanin) and enzymatic antioxidants (ascorbate peroxidase, catalase, and superoxide dismutase) and phenolic compounds, effective in counteracting the oxidant action of ROS, thus increasing plant nutritional value and radioresistance.^{63–68}

Most of the studies performed on plants have been conducted by irradiating dry seeds using acute doses (due to limitations in the volume and time of irradiation availability).^{63,69} A recent study has indicated that the effect of X-rays delivered to germinated seeds at different doses is strongly influenced by light quality during cultivation.⁷⁰ In experiments in which seedlings or mature plants are exposed to radiation often acute and high doses are used and most often only the vegetative state is exposed.⁵¹ Additionally, the number of studies on (crop) plants taking into account the effects on the yield, nutritional value as well as long term effects within and over generations are very limited and has mainly been focusing on using IR to introduce genetic variation and selecting interesting plant varieties.⁷¹

As a result, little information is available on the variation of radiosensitivity during the different phenological phases in the case of acute exposure and on the effects of chronic exposure. Indeed, it is important to emphasize that resistance to large doses of radiations delivered in an acute way (in shorter times than those necessary for the repair of cellular damage) often does not translate into resistance to chronic exposures for multiple generations and vice versa.⁷² Therefore, in sight of the future Space exploration, the time is ripe for increasing the efforts to investigate plant responses to chronic low dose-rate and high LET radiation to clarify all the processes and mechanisms behind the radioresistance phenomenon.⁵¹

Knowledge gaps in microgravity and radiation research in plant biology

According to the current scientific knowledge on plant interactions with Space factors, to successfully achieve the in-progress targets of crewed missions in Space, it is necessary to fill knowledge gaps in plant biology. They can be synthesized in the following five points (Fig. 1).

1 - Understanding the **fundamental ways** that plants sense and respond to **gravity** alone or in **combination with radiation other space and environmental/cultivation factors (also considering In Situ Resource Utilization - ISRU)**. This point is mainly related to acclimation strategies and includes studies on tropisms and morphogenesis.

2 - Studying the **long-term effects** of altered gravity, radiation and/or other space environment factors on plants and understanding how plants adapt to that environment.

3 - Studying **primary and secondary effects** of altered gravity, radiation and/or other space factors on plant **growth and reproduction**.

4 - Investigating the **interaction** between **microorganisms and plants** (beneficial and pathogenic) under space conditions in the light of the realization of cultivation modules in BLSSs.

5 - Investigating the effects of Space factors on yield and nutritional value and quality of edible organs targeting the use of plant-derived fresh food as countermeasure to improve astronauts' health.

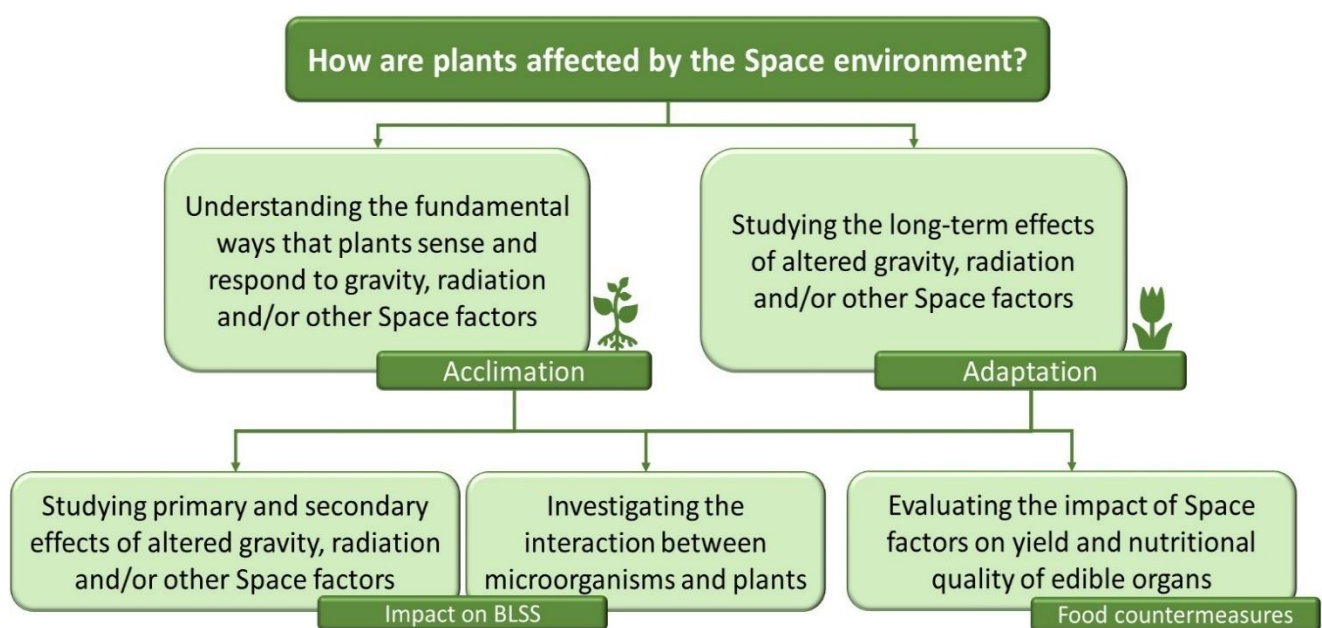


Fig. 1. Schematic view of the main knowledge gaps in plant biology which regard understanding processes of acclimation and adaptation to Space factors. Understanding such processes is fundamental to evaluate the impact on the functioning of BLSS and on the value of plant-derived food for the integration of astronauts' diet.

Overall, the main objective of research activities in plant space biology is to reveal potential acclimation and adaptation mechanisms and processes in the response of plants (crops and model plants) to microgravity, partial gravity and variable space radiation in combination with other environmental/cultivation conditions (e.g. air flow, light) through the development phases of a full life cycle.

To understand if exposure to adverse space conditions potentially leads to acclimation and adaptation, the long-term responses of plants have to be investigated through sequential studies of plants after different times of exposure to single or multiple Space factors, at different phases of the plant development. The acclimation has to be studied during the life cycle of the plant and adaptation has to be studied after several generations of plants exposed to a spatial environment.

The plant acclimation and adaptation processes, responsible for the capability of plants to achieve their entire life cycle in space, producing essentially viable adult individuals (including optimally nutritious crop plants in addition to model plants), are important for our fundamental understanding within plant biology and especially because plants are to be used as the producers in BLSSs and as sources of food for the crew. Therefore the nutritional value of crop plants must be investigated further to establish dietary impacts on astronauts.

Knowledge of plant-microorganism interactions is also important. Plants naturally attract microorganisms, some detrimental to plant health while others establish symbiotic relationships. Plants also have endophytes (bacteria and fungi) living between plant cells, some of which are transmitted to following generations. Understanding the activity of microorganisms to plants in the Space environment can help assess risks to future crew food supplies/astronaut health or discover opportunities for enhanced productivity through microorganisms that may increase crop yield.

Addressing the five points mentioned above becomes fundamental from an applied point of view to sustain long-term manned mission because they would allow to evaluate:

- How the growth processes and regeneration capacity of plants are affected by space factors and thus impact the cultivation requirements in producers modules of BLSSs
- If reproductive success is achieved and whether multiple generations of plants are possible to obtain, in order to guarantee the possibility to produce seeds for successive cultivation cycles
- If and how the yield and nutritional value and quality of edible organs are affected and thus impact on the astronauts' diet.

The two first points regard every plant species, not only crops but also model species as *Arabidopsis*, while the second and third mainly refer to crop species.

Facilities in Space and on Earth to study the effects of microgravity and radiation on plants

The ISS is an important research platform not only to study the effects of reduced gravity, but also the long-term consequences of low dose Space radiation on plants. The daily dose received in the ISS has been estimated at 0.5 mSv, assessed by physical dosimetry using phantoms.⁷³ By combining studies on ISS of plants exposed to various space factors (gravity/space radiation) and environmental cultivation conditions or exposures (e.g. different air flow or light conditions), additional required knowledge for future Space agriculture can be obtained. The main objective of the life science research on ISS is to obtain a fundamental understanding of plant growth and development under Space conditions and the research facilities have had a high priority on instrumentation and collection of scientific data. Long-term experiments and full cycle studies of plants require a minimum cultivation area. Although the growth area has become larger in the newer ISS facilities (compared to systems such as Kubik and Icecubes), they are still considered too small for crops and full life cycles. When a 1x gravity or simulated Moon/Mars gravity exposures is

required, the growth area is limited due to the diameter of the centrifuge rotor that has to fit into standard sized racks on the ISS. An extensive review was done on the Space plant growth systems where more than 20 systems are described.²⁷ The ESA BIOLAB facility on ISS has 4 Advanced Experiment Containers (AEC) on two rotors with a growth area of 0.077 m² per AEC. The BIOLAB allows unique experimental equipment to be built inside the AEC, and the available growth area for the plant will depend on the instrumentation required in the AEC to perform the experiment. The NASA systems such as Vegetable Production System (VEGGIE, 2014) and Advanced Plant Habitat (APH, 2017) have increased crop growth area, but they are still relatively small with 0.17 m² and 0.2-0.25 m² growth area, respectively. These two systems do not have centrifuges, so plant growth is performed in microgravity only. The APH is a closed, controlled growth system with full environmental monitoring and control. The VEGGIE system is a simpler system with less control and designed for more crew interaction. For plant experiments where smaller volumes are required, the NASA Advanced Biological Research System (ABRS) is available with two experimental research chambers (growth area 0.053 m²). The chamber has light and environment control, and one of the two chambers is outfitted with Green Fluorescent Protein Imaging System. The JAXA Plant Experiment Unit (PEU) is available on the Kibo laboratory on ISS equipped with a LED lighting system with red and blue LEDs, a growth chamber (growth area 0.027 m²), an automated watering system and a CCD camera.

What is further required?

Larger growth areas where both model plants and crop plants can be cultivated for a long-term (during the whole life cycle) are needed to fully understand the plant acclimation and adaptation to the Space conditions. Such a facility requires the control of environmental factors (including temperature, light, gasses, relative humidity, air flow, nutrient solution, watering), continuous imaging of the plant growth (e.g. visible light images, IR images using thermal cameras, fluorescence images). Environmental and imaging data should as a minimum be partially and periodically downloaded for feedback from the science teams collaborating from ground. To collect data for the molecular, cell and anatomical studies, plant samples need to be harvested after sequential exposures of reduced gravity, preserved on ISS either by freezing or chemical fixatives, and brought back to ground for analyses. In addition, the possibility to make microscopy analyses onboard has become a reality with the ESA/DLR Fluorescence Microscopy Analysis System (FLUMIAS), a high-resolution fluorescence microscope for live-cell imaging that is available on the ISS.

A specific point affecting the technical needs of Space facilities for plant culture is the possibility of performing comparative studies in spaceflight at different levels of gravity, including the Moon and Mars gravity, as well as the inflight 1g control. This is of the highest importance making the implementation of centrifuges in the facilities used for plant cultivation in the ISS mandatory. The advanced sophisticated facilities for plant cultivation now available on ISS, such as VEGGIE, APH and the Exposed Roots On-Orbit Test System (X-ROOTS), which have proven successful in the cultivation of a wide range of plant species, are not equipped with centrifuges. ESA in 2018 unfortunately decommissioned the European Modular Cultivation System (EMCS), a highly useful facility in which different successful experiments were carried out, some of them including pioneering comparative analyses at different levels of gravity in addition to the necessary in flight 1g controls. Later on, in 2020, ESA promoted a discussion group to adapt the ESA Biolab facility (Fig. 2), seriously underused up to now, but equipped with centrifuges, to plan experiments of different types. This group

produced a document of recommendations for Biolab to be capable of harboring experiments using crop species and encompassing the full plant life cycle. Whatever the final decision adopted, the need of an effective plant cultivation facility in Space with the capabilities mentioned above, as a key to support the human life in space exploration, is becoming more and more urgent within the next years.



Fig. 2. ESA astronaut Samantha Cristoforetti working with ESA's Biolab facility in the Columbus laboratory on the International Space Station. Credits: ©ESA/NASA.

Applications and benefits for Earth

Understanding how plants are able to grow and adapt to Space conditions will ensure reliable and predictable food supplies for human space exploration and has strong synergies with the United Nations Sustainable Development Goals, global food security and circular economy.

The sophisticated agro-technologies developed for Space applications (e.g. innovative lighting, watering and nutrient delivery systems, fine environmental monitoring with automated control, imaging systems to analyze plant health, etc.) bring innovations to agriculture on Earth to improve sustainable plant cultivation and food production. For example, developing volume-saving, highly efficient plant growth controlled environments is beneficial for food and drug production particularly in densely populated urban areas in line with vertical farming technologies, in underground facilities with no natural light source, and in general in extreme environments such as deserts and poles.

Developing smart and safe pest control methods is applicable in confined volumes where aerosols are undesirable and natural predation for the reduction/removal of pests is not possible.

Besides these more human operational and exploration-oriented goals it should also be stressed that the unique near weightlessness environment as well as the high levels of ionizing radiation also provides a research laboratory that cannot be obtained in on-ground laboratories and as such can answer specific and fundamental questions in life sciences. Improving the knowledge on how plants respond to ionizing radiation can provide information applicable in all the fields in which radiation is studied on Earth ranging from breeding programs, decontamination methods and radioecology.

Future perspectives and recommendations in the short and long term

Today there is a need for fundamental research that goes beyond the demonstration of a plant's ability to acclimate and adapt to the Space environment. A multi-parameter facility would help unravel effects of altered gravity in combination with other factors, either typical of Space (i.e. altered gravity and ionizing radiation) or of confined volumes of cultivation chambers. Moreover, by modulating the exposures to specific environmental conditions (e.g., air flow or light), it is possible to study the direct and indirect effect of the Space factors on plants; bridging the knowledge gaps of the acclimation/adaptation mechanisms.

Currently to study plant development in the Space environment through the whole life cycle of a plant, including crops/food plants, is currently possible only using the ISS research platform: no other active platforms possess capabilities for answering the plant biology research questions listed in this paper. The infrastructure present on ISS can be modernized to achieve the needed goals to point to sustainability of Space exploration with BLSSs.

Using the ISS platform for research will be the defining stepping stone into exploratory-class missions deeper into space. The Gateway platform is currently planned for lunar orbit in the mid-late 2020s. This should provide opportunities for experiments deeper into space, particularly outside of Earth's magnetic field and the unique radiation environment can be exploited to further develop our understanding on the effect that different types of radiation may have on plants in combination with other space factors.

It is not straightforward to indicate what are the more urgent goals of plant Space biology, since it has been recognized that Space farming is becoming more and more a necessity as long as the roadmap for human Space exploration goes beyond LEO. A summary of possible sub-goals within the main goals identified in the previous paragraphs is reported in figure 3.

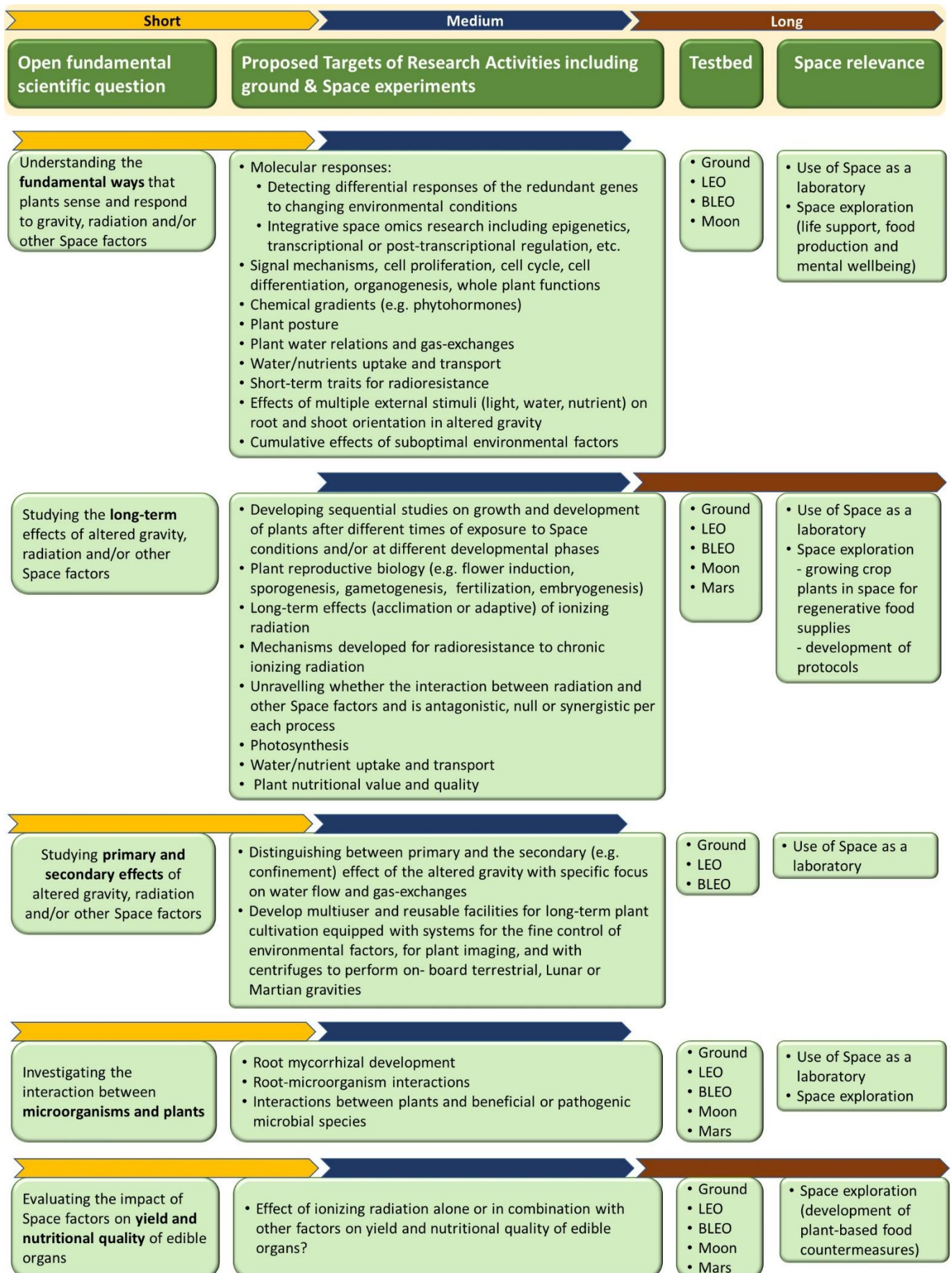


Fig. 3. Summary of possible sub-goals within the main goals of plant biology research priorities in Space in the timeframe of 2022-2030 and beyond (short-term, 2022-2024; medium-term, 2024-2030; long-term, beyond 2030) using primarily the ISS platform. Other research platforms such as ground, Moon, Mars and BLEO are also included. They represent both the basis for the research on ISS and future research activities post-ISS (e.g. the GATEWAY orbiting the Moon).

Conclusions

Whatever the goals, it is fundamental to apply an integrative approach merging together the information gained at different biological levels (e.g. molecular, cellular, tissue/organ up to the whole individual) as well as integrating knowledge among organisms (producers, consumers and degraders) also to understand the effect of Space factors on their capability of networking in the artificial ecosystem as in nature on Earth. Space biology has been historically divided into sub-disciplines dealing with animals/mammals, microbes and plants without much interaction. However, some processes of altered metabolism as those regarding DNA-repair mechanisms as well as ROS and peptide signaling as stress responses are well conserved among species (including animals and plants). This paves the way towards the need for making synergies among disciplines to achieve an integrated picture of common vs distinct responses to Space factors in different organisms. Possibly, the establishment of global standard operating procedures for space omics (including metagenomics) data sets generation and annotation, including but not limited to those generated within the framework of ESA and NASA projects, can allow the expansion of statistical power in Space flight experiments by means of the federation of data sets.

Indeed, it has been recognized that to achieve a better protection of human health and wellbeing in Space, especially for future long duration missions an integrated, multidisciplinary approach linking together different branches of life science (e.g. animal and human physiology, plant biology, microbiology, etc.) is needed, as well as the cooperation with physical sciences, technologies and engineering. To achieve BLSSs operating in Space, the above-listed disciplines are extremely interconnected fields. Therefore, there is the need to bridge and strengthen the interconnections between them also through the design, proposal, and realization of new studies and experiments.

References

1. Patel, Z. S., Brunstetter, T. J., Tarver, W. J., Whitmire, A. M., Zwart, S. R., Smith, S. M. & Huff, J. L. Red risks for a journey to the red planet: The highest priority human health risks for a mission to Mars. *NPJ Microgravity* **6**, 1-13 doi:10.1038/S41526-020-00124-6 (2020)
2. De Pascale, S., Arena, C., Aronne, G., De Micco, V., Pannico, A., Paradiso, R. & Rouphael, Y. Biology and crop production in Space environments: Challenges and opportunities. *Life Sci Space Res (Amst)* **29**, 30-37 doi:10.1016/j.lssr.2021.02.005 (2021)
3. De Micco, V., Aronne, G., Colla, G., Fortezza, R. & De Pascale, S. Agro-biology for bioregenerative life support systems in long-term space missions: General constraints and the Italian efforts. *J Plant Interact* **4**, 241-252 doi:10.1080/17429140903161348 (2009)

4. Tamponnet, C. & Savage, C. Closed Ecological Systems. *J Biol Educ* **28**, 167-174. (1994).
5. Gòdia, F., Albiol, J., Montesinos, J. L., Pérez, J., Creus, N., Cabello, F., Mengual, X., Montras, A. & Lasseur, C. MELISSA: A loop of interconnected bioreactors to develop life support in Space. *J Biotechnol* **99**, 319-330 (2002).
6. Tang, H., Rising, H. H., Majji, M. & Brown, R. D. Long-term space nutrition: A scoping review. *Nutrients* **14**, 194 doi:10.3390/nu14010194 (2022)
7. Perchonok, M. H., Cooper, M. R. & Catauro, P. M. Mission to mars: Food production and processing for the final frontier. *Annu Rev Food Sci Technol* **3**, 311-330 (2012).
8. Koga, K. & Iwasaki, Y. Psychological and physiological effect in humans of touching plant foliage - using the semantic differential method and cerebral activity as indicators. *J Physiol Anthropol* **32**, 1-9 (2013).
9. Odeh, R. & Guy, C. L. Gardening for therapeutic people-plant interactions during long-duration space missions. *Open Agric* **2**, 1-13 (2017).
10. Merkys, A. J., Laurinavičius, R. S. & Švegždienė, D. V. Plant growth, development and embryogenesis during Salyut-7 flight. *Advances in Space Research* **4**, 55-63 (1984).
11. Perbal, G., Driss-Ecole, D., Rutin, J. & Sallé, G. Graviperception of lentil seedling roots grown in space (Spacelab D1 Mission). *Physiol Plant* **70**, 119-126 (1987).
12. Vandenbrink, J. P. & Kiss, J. Z. Space, the final frontier: A critical review of recent experiments performed in microgravity. *Plant Science* **243**, 115-119 doi:10.1016/j.plantsci.2015.11.004 (2016)
13. Herranz, R. & Medina, F. J. Cell proliferation and plant development under novel altered gravity environments. *Plant Biol* **16**, 23-30 (2014).
14. Matía, I., González-Camacho, F., Herranz, R., Kiss, J. Z., Gasset, G., van Loon, J. J. W. A., Marco, R. & Javier Medina, F. Plant cell proliferation and growth are altered by microgravity conditions in spaceflight. *J Plant Physiol* **167**, 184-193 (2010).
15. Manzano, A. I., Larkin, O. J., Dijkstra, C. E., Anthony, P., Davey, M. R., Eaves, L., Hill, R. J. A., Herranz, R. & Medina, F. J. Meristematic cell proliferation and ribosome biogenesis are decoupled in diamagnetically levitated Arabidopsis seedlings. *BMC Plant Biol* **13**, 1-15 (2013).
16. Boucheron-Dubuisson, E., Manzano, A. I., Le Disquet, I., Matía, I., Sáez-Vasquez, J., van Loon, J. J. W. A., Herranz, R., Carnero-Diaz, E. & Medina, F. J. Functional alterations of root meristematic cells of Arabidopsis thaliana induced by a simulated microgravity environment. *J Plant Physiol* **207**, 30-41 (2016).
17. Kamal, K. Y., Herranz, R., van Loon, J. J. W. A. & Medina, F. J. Cell cycle acceleration and changes in essential nuclear functions induced by simulated microgravity in a synchronized Arabidopsis cell culture. *Plant Cell Environ* **42**, 480-494. (2019).
18. Kamal, K. Y., van Loon, J. J. W. A., Medina, F. J. & Herranz, R. Differential transcriptional profile through cell cycle progression in Arabidopsis cultures under simulated microgravity. *Genomics* **111**, 1956-1965. (2019).

19. Kamal, K. Y., Herranz, R., van Loon, J. J. W. A. & Medina, F. J. Simulated microgravity, Mars gravity, and 2g hypergravity affect cell cycle regulation, ribosome biogenesis, and epigenetics in Arabidopsis cell cultures. *Sci Rep* **8**, 1-16 (2018).
20. Manzano, A., Herranz, R., den Toom, L. A., Te Slaa, S., Borst, G., Visser, M., Medina, F. J. & van Loon, J. J. W. A. Novel, Moon and Mars, partial gravity simulation paradigms and their effects on the balance between cell growth and cell proliferation during early plant development. *NPJ Microgravity* **4**, 1-11 (2018).
21. Muday, G. K. & Murphy, A. S. An emerging model of auxin transport regulation. *Plant Cell* **14**, 293-299 doi:10.1105/tpc.140230 (2002)
22. David, K. M., Couch, D., Braun, N., Brown, S., Grosclaude, J. & Perrot-Rechenmann, C. The auxin-binding protein 1 is essential for the control of cell cycle. *Plant Journal* **50**, 197-206 (2007).
23. Perrot-Rechenmann, C. Cellular responses to auxin: division versus expansion. *Cold Spring Harb Perspect Biol* **2**, a001446 doi:10.1101/cshperspect.a001446 (2010)
24. Medina, F. J. & Herranz, R. Microgravity environment uncouples cell growth and cell proliferation in root meristematic cells: The mediator role of auxin. *Plant Signal Behav* **5**, 176-179 (2010).
25. Manzano, A., Carnero-Diaz, E., Herranz, R. & Medina, F. J. Recent transcriptomic studies to elucidate the plant adaptive response to spaceflight and to simulated space environments. *iScience* **25**, 104687 (2022).
26. Herranz, R., Vandenbrink, J. P., Villacampa, A., Manzano, A., Poehlman, W. L., Feltus, F. A., Kiss, J. Z. & Medina, F. J. RNAseq Analysis of the Response of Arabidopsis thaliana to Fractional Gravity Under Blue-Light Stimulation During Spaceflight. *Front Plant Sci* **10**, 1529 (2019).
27. Zabel, P., Bamsey, M., Schubert, D. & Tajmar, M. Review and analysis of over 40 years of space plant growth systems. *Life Sci Space Res (Amst)* **10**, 1–16 (2016).
28. Muthert, L. W. F., Izzo, L. G., van Zanten, M. & Aronne, G. Root Tropisms: Investigations on Earth and in Space to Unravel Plant Growth Direction. *Front Plant Sci* **10**, 1807 (2020).
29. Hasenstein, K. H., Scherp, P. & Ma, Z. Gravisensing in flax roots - Results from STS-107. *Advances in Space Research* **36**, 1189-1195 (2005).
30. Morohashi, K., Okamoto, M., Yamazaki, C., Fujii, N., Miyazawa, Y., Kamada, M., Kasahara, H., Osada, I., Shimazu, T., Fusejima, Y., Higashibata, A., Yamazaki, T., Ishioka, N., Kobayashi, A. & Takahashi, H. Gravitropism interferes with hydrotropism via counteracting auxin dynamics in cucumber roots: clinorotation and spaceflight experiments. *New Phytologist* **215**, 1476-1489 (2017).
31. Izzo, L. G., Romano, L. E., De Pascale, S., Mele, G., Gargiulo, L. & Aronne, G. Chemotropic vs Hydrotropic Stimuli for Root Growth Orientation in Microgravity. *Front Plant Sci* **10**, 1547 (2019).

32. Kiss, J. Z., Wolverton, C., Wyatt, S. E., Hasenstein, K. H. & van Loon, J. J. W. A. Comparison of Microgravity Analogs to Spaceflight in Studies of Plant Growth and Development. *Front Plant Sci* **10**, 1577 doi:10.3389/fpls.2019.01577 (2019)
33. Millar, K. D. L., Kumar, P., Correll, M. J., Mullen, J. L., Hangarter, R. P., Edelmann, R. E. & Kiss, J. Z. A novel phototropic response to red light is revealed in microgravity. *New Phytologist* **186**, 648-656. (2010).
34. Vandenbrink, J. P., Herranz, R., Medina, F. J., Edelmann, R. E. & Kiss, J. Z. A novel blue-light phototropic response is revealed in roots of *Arabidopsis thaliana* in microgravity. *Planta* **244**, 1201-1215 (2016).
35. Izzo, L. G., Romano, L. E., Muthert, L. W. F., Iovane, M., Capozzi, F., Manzano, A., Ciska, M., Herranz, R., Medina, F. J., Kiss, J. Z., van Loon, J. J. W. A. & Aronne, G. Interaction of gravitropism and phototropism in roots of *Brassica oleracea*. *Environ Exp Bot* **193**, 104700 (2022).
36. Kiss, J. Z., Millar, K. D. L. & Edelmann, R. E. Phototropism of *Arabidopsis thaliana* in microgravity and fractional gravity on the International Space Station. *Planta* **236**, 635-645 (2012).
37. Boccalandro, H. E., De Simone, S. N., Bergmann-Honsberger, A., Schepens, I., Fankhauser, C. & Casal, J. J. PKS1 regulates root phototropism and gravitropism. *Plant Physiol* **146**, 108-115 (2007).
38. Reichler, S. A., Balk, J., Brown, M. E., Woodruff, K., Clark, G. B. & Roux, S. J. Light differentially regulates cell division and the mRNA abundance of pea nucleolin during de-etiolation. *Plant Physiol* **125**, 339-350 (2001).
39. Valbuena, M. A., Manzano, A., Vandenbrink, J. P., Pereda-Loth, V., Carnero-Diaz, E., Edelmann, R. E., Kiss, J. Z., Herranz, R. & Medina, F. J. The combined effects of real or simulated microgravity and red-light photoactivation on plant root meristematic cells. *Planta* **248**, 691-704 (2018).
40. Medina, F. J., Manzano, A., Villacampa, A., Ciska, M. & Herranz, R. Understanding Reduced Gravity Effects on Early Plant Development Before Attempting Life-Support Farming in the Moon and Mars. *Frontiers in Astronomy and Space Sciences* **8**, 148 (2021).
41. Villacampa, A., Ciska, M., Manzano, A., Vandenbrink, J. P., Kiss, J. Z., Herranz, R. & Medina, F. J. From spaceflight to MARS G-levels: Adaptive response of *A. thaliana* seedlings in a reduced gravity environment is enhanced by red-light photostimulation. *Int J Mol Sci* **22**, 899 (2021).
42. Van Aken, O., Zhang, B., Law, S., Narsai, R. & Whelan, J. AtWRKY40 and AtWRKY63 modulate the expression of stress-responsive nuclear genes encoding mitochondrial and chloroplast proteins. *Plant Physiol* **162**, 254-271 (2013).
43. Phukan, U. J., Jeena, G. S. & Shukla, R. K. WRKY transcription factors: Molecular regulation and stress responses in plants. *Front Plant Sci* **7**, 760 doi:10.3389/fpls.2016.00760 (2016)

44. Kordyum, E. & Hasenstein, K. H. Plant biology for space exploration – Building on the past, preparing for the future. *Life Sci Space Res (Amst)* **29**, 1-7 doi:10.1016/j.lssr.2021.01.003 (2021)
45. Musgrave, M. E. & Kuang, A. Plant Reproductive Development during Spaceflight. *Adv Space Biol Med* **9**, 1-23 doi:10.1016/S1569-2574(03)09001-4 (2003)
46. Merkys, A. L. & Laurinavicius, R. S. Complete cycle of individual development of *Arabidopsis thaliana* (L.) Heynh. plants on board the Salyut-7 orbital station. *Doklady Akademii Nauk SSSR* **271**, 509–512 (1983).
47. Link, B. M., Busse, J. S. & Stankovic, B. Seed-to-seed-to-seed growth and development of *Arabidopsis* in microgravity. *Astrobiology* **14**, 866-875 (2014).
48. Kuang, A., Popova, A., Xiao, Y. & Musgrave, M. E. Pollination and embryo development in *Brassica rapa* L. in microgravity. *Int J Plant Sci* **161**, 203-211 (2000).
49. Kuang, A., Xiao, Y., McClure, G. & Musgrave, M. E. Influence of microgravity on ultrastructure and storage reserves in seeds of *Brassica rapa* L. *Ann Bot* **85**, 851-859 (2000).
50. De Micco, V., De Pascale, S., Paradiso, R. & Aronne, G. Microgravity effects on different stages of higher plant life cycle and completion of the seed-to-seed cycle. *Plant Biol* **16**, 31-38 doi:10.1111/plb.12098 (2014)
51. De Micco, V., Arena, C., Di Fino, L. & Narici, L. Radiation environment in exploration-class space missions and plants' responses relevant for cultivation in Bioregenerative Life Support Systems. *Front Plant Sci* **13**, 1001158 (2022).
52. Caër, S. le. Water radiolysis: Influence of oxide surfaces on H₂ production under ionizing radiation. *Water (Switzerland)* **3**, 235-253 doi:10.3390/w3010235 (2011)
53. Caplin, N. & Willey, N. Ionizing radiation, higher plants, and radioprotection: From acute high doses to chronic low doses. *Front Plant Sci* **9**, 847 doi:10.3389/fpls.2018.00847 (2018)
54. Hasanuzzaman, M., Hossain, M. A., da Silva, J. A. T. & Fujita, M. Plant response and tolerance to abiotic oxidative stress: antioxidant defense is a key factor. *Crop Stress and its Management: Perspectives and Strategies*, 261-315 (2012).
55. Gudkov, S. v., Grinberg, M. A., Sukhov, V. & Vodeneev, V. Effect of ionizing radiation on physiological and molecular processes in plants. *J Environ Radioact* **202**, 8-24 doi:10.1016/j.jenvrad.2019.02.001 (2019)
56. Agathokleous, E., Feng, Z. Z. & Peñuelas, J. Chlorophyll hormesis: Are chlorophylls major components of stress biology in higher plants? *Science of the Total Environment* **726**, 138637 doi:10.1016/j.scitotenv.2020.138637 (2020)
57. De Micco, V., Arena, C., Pignalosa, D. & Durante, M. Effects of sparsely and densely ionizing radiation on plants. *Radiat Environ Biophys* **50**, 1-19 (2011).
58. De Micco, V., Arena, C. & Aronne, G. Anatomical alterations of *Phaseolus vulgaris* L. mature leaves irradiated with X-rays. *Plant Biol* **16**, 187-193 (2014).

59. De Micco, V., Paradiso, R., Aronne, G., De Pascale, S., Quarto, M. & Arena, C. Leaf anatomy and photochemical behaviour of *Solanum lycopersicum* L. Plants from seeds irradiated with low-LET ionising radiation. *Scientific World Journal* **2014**, 187-193 (2014).
60. Fulcher, N. & Sablowski, R. Hypersensitivity to DNA damage in plant stem cell niches. *Proc Natl Acad Sci U S A* **106**, 20984-20988 (2009).
61. Arena, C., Turano, M., Hay Mele, B., Cataletto, P. R., Furia, M., Pugliese, M. & de Micco, V. Anatomy, photochemical activity, and DNA polymorphism in leaves of dwarf tomato irradiated with X-rays. *Biol Plant* **61**, 305-314 (2017).
62. Shikazono, N., Tanaka, A., Kitayama, S., Watanabe, H. & Tano, S. LET dependence of lethality in *Arabidopsis thaliana* irradiated by heavy ions. *Radiat Environ Biophys* **41**, 159-162 (2002).
63. Arena, C., De Micco, V., Macaeva, E. & Quintens, R. Space radiation effects on plant and mammalian cells. *Acta Astronaut* **104**, 419-431 (2014).
64. Luckey, T. D. *Hormesis with Ionizing Radiation*. CRC Press, Boca Raton, FL. 1980.65.
Van Hoeck, A., Horemans, N., Nauts, R., Van Hees, M., Vandenhove, H. & Blust, R. Lemna minor plants chronically exposed to ionising radiation: RNA-seq analysis indicates a dose rate dependent shift from acclimation to survival strategies. *Plant Science* **257**, 84-95 (2017).
66. Mulinacci, N., Valletta, A., Pasqualetti, V., Innocenti, M., Giuliani, C., Bellumori, M., De Angelis, G., Carnevale, A., Locato, V., Di Venanzio, C., De Gara, L. & Pasqua, G. Effects of ionizing radiation on bio-active plant extracts useful for preventing oxidative damages. *Nat Prod Res* **33**, 1106-1114. (2019).
67. Rezk, A. A., Al-Khayri, J. M., Al-Bahrany, A. M., El-Beltagi, H. S. & Mohamed, H. I. X-ray irradiation changes germination and biochemical analysis of two genotypes of okra (*Hibiscus esculentus* L.). *J Radiat Res Appl Sci* **12**, 393-402 (2019).
68. Volkova, P. Y., Bondarenko, E. V. & Kazakova, E. A. Radiation hormesis in plants. *Curr Opin Toxicol* **30**, 100334 doi:10.1016/j.cotox.2022.02.007 (2022)
69. Shi, J. M., Guo, J. G., Li, W. J., Zhang, M., Huang, L. & Sun, Y. Q. Cytogenetic effects of low doses of energetic carbon ions on rice after exposures of dry seeds, wet seeds and seedlings. *J Radiat Res* **51**, 235-242 (2010).
70. De Micco, V., Amitrano, C., Vitaglione, P., Ferracane, R., Pugliese, M. & Arena, C. Effect of light quality and ionising radiation on morphological and nutraceutical traits of sprouts for astronauts' diet. *Acta Astronaut* **185**, 188-197 (2021).
71. Riviello-Flores, M., Cadena-Iñiguez, J., Ruiz-Posadas, L., Arévalo-Galarza, M., Castillo-Juárez, I., Soto Hernández, M. & Castillo-Martínez, C. R. Use of Gamma Radiation for the Genetic Improvement of Underutilized Plant Varieties. *Plants* **11**, 1161 (2022).
72. Shuryak, I. Review of resistance to chronic ionizing radiation exposure under environmental conditions in multicellular organisms. *J Environ Radioact* **212**, 106128 (2020)
73. Cucinotta, F. A., Kim, M. H. Y., Willingham, V. & George, K. A. Physical and biological organ dosimetry analysis for international space station astronauts. *Radiat Res* **170**, 127-138 (2008).

Acknowledgements

This work was supported by the European Space Agency (ESA). This perspective paper is based upon work from the Contributors to the Topic C “Plant Biology” of the ESA SciSpacE white paper “Biology in Space and Analogue Environments”, listed in alphabetic order: Giovanna Aronne, Nicol Caplin, Eugénie Carnero-Diaz, Raúl Herranz, Nele Horemans, Ann-Iren Kittang Jost (Coordinator), Valerie Legue, F. Javier Medina, Veronica De Micco, (Coordinator), Veronica Pereda-Campos, Mona Schiefloe

Contributions

VD, GA, NC, EC, RH, NH, VL, JM, VP, MS and AK developed the concept of this perspective paper. VD, GA, SD and LI developed a first structure of the manuscript. VD took lead in coordination and writing; GA, NC, EC, SD RH, NH, LI, IL VL, JM, VP, MS and AK wrote specific parts of the manuscript. All authors provided critical feedback and helped shape the concept and perspectives. All authors revised and approved the submitted version of the manuscript.

Competing interests

The authors declare no competing interests.