Short comunication

Hypothetical role of hypoxia-inducible factor-1 in adaptations to microgravity

Papel hipotético del factor 1 inducible por hipoxia en las adaptaciones a la microgravedad

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ABSTRACT

Maintaining health in microgravity and overcoming environmental hazards such as cosmic radiation are essential for long-term space flight. Recent studies have focused on the involvement of hypoxia-inducible factor (HIF)-1 in altered gravity using cell-based or *in vivo* mouse model systems. HIF-1alpha and its target downstream gene expression are differentially expressed in hypergravity and microgravity. Nevertheless, underlying molecular mechanism of HIF-1alpha involvement is still unclear. Herein, we analyzed the 2019 Science paper by *Garrett-Bakelman* and coauthors in which NASA performed multidimensional analyses of long-term human spaceflight in identical twin astronauts. Correlations were found between the expression of HIF-1alpha related cytokines and prolonged space flight. We hypothesize that HIF-1alpha is a molecular target for the development of therapeutics to prevent the detrimental effects of microgravity and cosmic radiation on astronauts during long-term space flight.

Key words: microgravity; space flight; hypoxia-inducible factor.

RESUMEN

Mantener la salud en microgravedad y superar los peligros ambientales como la radiación cósmica son esenciales para los vuelos espaciales a largo plazo. Estudios recientes se han centrado en la participación del factor inducible por hipoxia (HIF) -1 en la gravedad alterada utilizando sistemas de modelos de ratones basados en células o in vivo. HIF-1alpha y su expresión génica secuencial objetivo se expresan diferencialmente en hipergravedad y microgravedad. Sin embargo, el mecanismo molecular subyacente de la participación de HIF-1alpha aún no está claro. Aquí, analizamos el artículo de Ciencia de 2019 de *Garrett-Bakelman* y coautores en el que la NASA realizó análisis multidimensionales de vuelos espaciales humanos a largo plazo en astronautas gemelos idénticos. Se encontraron correlaciones entre la expresión de citoquinas relacionadas con HIF-1alpha y el vuelo espacial prolongado. Presumimos que HIF-1alpha es un objetivo molecular para el desarrollo de terapias para prevenir los efectos perjudiciales de la microgravedad y la radiación cósmica en los astronautas durante los vuelos espaciales a largo plazo.

Palabras clave: microgravedad; vuelo espacial; factor inducible por hipoxia.

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INTRODUCTION

Prolonged space flight is necessary for future missions to Mars and beyond. Therefore, the physiological and adaptive changes occurring in the body during long-term space flight should be investigated. One important difference in the environment on Earth compared to that in space is the absence of gravity in space. Previous studies have investigated not only organism-wide changes, but also cellular-level changes, in gene expression associated with altered gravity. Although altered gravity is known to have detrimental effects on immune function, brain function, metabolism, and molecular and cellular processes, the detailed underlying molecular mechanisms remain unclear. Methods to understand how altered gravity, such as hypergravity and microgravity, affect molecular and cellular processes involve assessment of gene expression patterns. In

addition to the altered gravity environment, space travel involves chronic exposure to cosmic radiation, which is known to induce the production of reactive oxygen species (ROS), leading to both dysregulation of oxidation/reduction status and inflammatory responses.[1]

SPACE AND CYTOKINES

Many studies have provided insight into the relationships of specific conditions in space, such as altered gravity and cosmic radiation exposure, and hypoxia-inducible factor-1 (HIF-1)-mediated gene expression. Recent studies have focused on the function of HIF-1 in regulating gene expression under conditions of altered gravity[2] and radiation, to mimic cosmic radiation in space.[1] *Vogel J* and collaborators, investigated HIF-1-dependent signaling in the cancer cell lines by exposure to altered gravity and parabolic flight and suborbital ballistic rocket experiments, and found HIF-1alpha and HIF-1 dependent transcripts were differently regulated in altered gravity.[2] The hearts of mice showed elevated HIF-1alpha expression and p-ERK and p-Akt signaling from 3 hours after exposure to hypergravity by centrifugation.[3] On the other hand, significantly increased HIF-1alpha expression was observed in the rat hippocampus after long-term (28-days) exposure to simulated microgravity by tail-suspension.[4] Cosmic radiation in space induces ROS production, which is known to induce and stabilize HIF-1alpha at the protein level.[5] Therefore, cosmic radiation may affect HIF-1alpha expression.

HIF-1 regulates the expression of more than 500 genes directly and indirectly, and HIF target genes are involved in many molecular and cellular processes, such as cell proliferation, cell migration, angiogenesis, cell differentiation, pH regulation, vessel dilation, and mitochondrial respiratory inhibition, as shown in figure 1. HIF-1 is a master transcription factor that orchestrates processes involved in gene expression to adapt to various physiological conditions including hypoxic conditions. HIF-1 is a heterodimeric transcription factor composed of a HIF-1alpha subunit and a constitutively expressed HIF-1beta subunit (also known as ARNT).[6] HIF-1alpha is tightly regulated by oxygen at the protein level, while HIF-1beta is stable and aids in the binding of HIF-1alpha to its target DNA.[7] Therefore, HIF-1alpha is a key molecule promoting survival even in severely hypoxic microenvironments. HIF-1alpha protein expression is stabilized by elevated mitochondrial ROS levels[5] but it is also upregulated at the translational level by

sildenafil treatment through PI3K/Akt/mTOR signaling pathway[8] and induced by cytokines, as shown in figure 2.

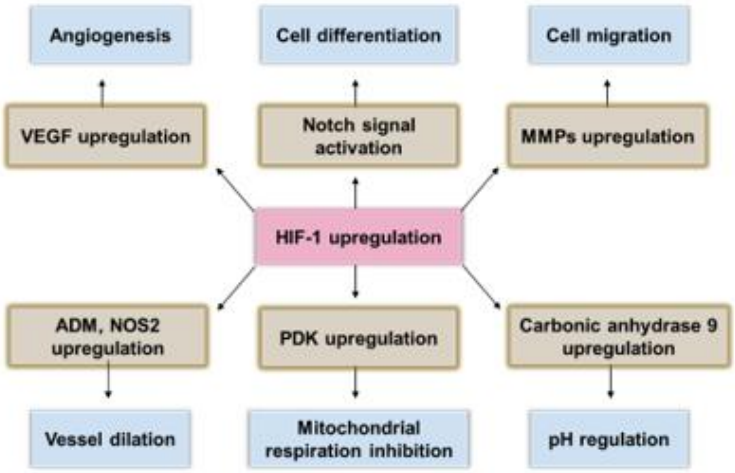

Fig. 1. HIF-1-mediated cellular responses by regulation of its target genes.

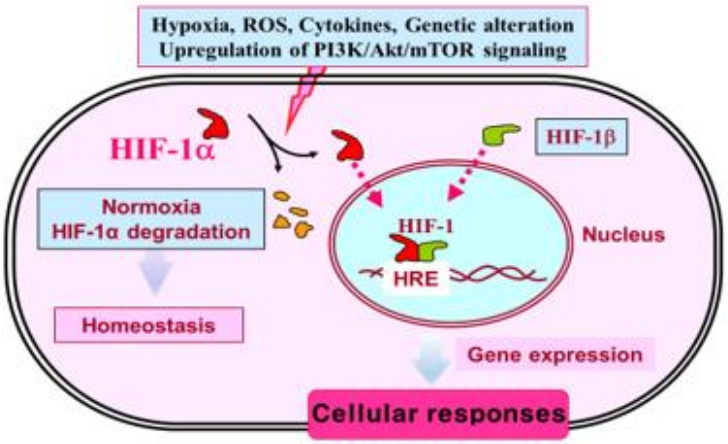

Fig. 2. Regulation of HIF-1 in responding to cellular stress.

Identical twins in space and cytokines

NASA performed a multidimensional analysis of long-term human spaceflight in identical twin astronauts,[9] where one member of a pair of male monozygotic twins spent 340 days aboard the International Space Station (ISS; flight subject: TW), while his identical twin remained on Earth (ground subject: HR).

The levels of cytokines that differed significantly between HR and TW, or among the pre-, in-, and post-flight periods, were examined (Fig. 3). The results pointed to the involvement of HIF-1 in adaptation to long-term space flight. The data for TW indicated

that some cytokines, i.e., HIF-1alpha-related cytokines such as TNFA, IL6, VEGF, IL1A, ICAM1, VCAM1 and IL18 (arrows in figure 3 reproduced from Garrett-Bakelman and collaborators.),[9] showed reduced expression in the in-flight sample and were markedly induced in the post-flight sample. Moreover, NOTCH3 which is known as a binding protein of HIF-1alpha shows global changes in DNA methylation during spaceflight.[9] Therefore, HIF-1 may be involved in the marked changes in cytokine expression occurring during different flight states. Based on its involvement in the hazards of space flight, HIF-1 may be a therapeutic target to prevent the detrimental effects of altered gravity and cosmic radiation on astronauts during long-term space flight.

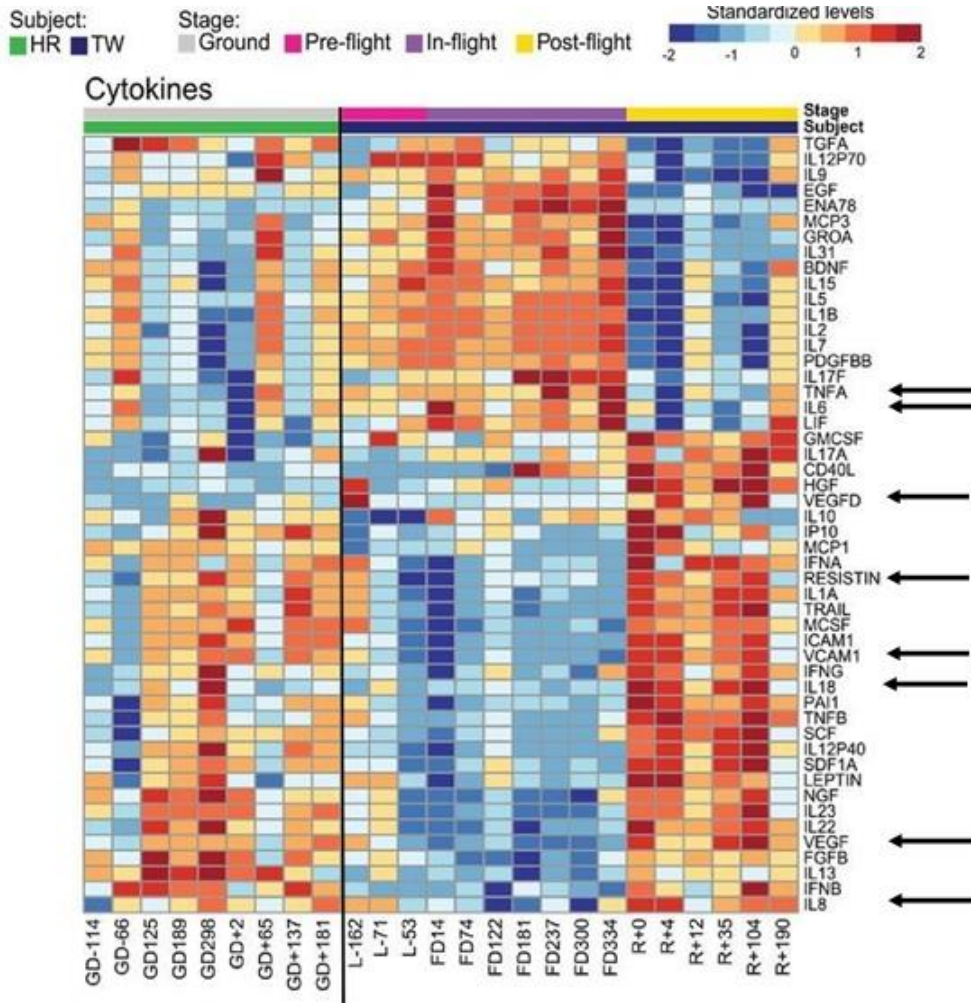

Fig. 3. Cytokines present at significantly different levels: difference in HR and TW or between pre-, in- and post-flight periods. Heatmap represents median-normalized log2 intensity for each analyte, scaled across all samples. Red color indicates relative enrichment, whereas blue indicates relative depletion. Arrows indicate HIF-1alpha-related cytokines. Reproduced from *Garrett-Bakelman.*[9]

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Conflict of interests

There is no conflict of interest in relation to the research presented.

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