PHARMACOLOGICAL STUDIES FOR TREATMENT OF SPACE-RELATED DISORDERS

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Introduction: Exposure to microgravity during space missions can induce many changes in living organisms. Astronauts during and after long-term space missions present different health problems, involving all functional systems and organs, potentially affecting mission performance. Bone loss, muscle atrophy, immune system dysregulation, cardiovascular deconditioning and changes in gastrointestinal and metabolic activities are among the most common space-related disorders. These conditions can further have consequences on drug pharmacokinetics (PK) thus making commonly used pharmacological therapies ineffective in space. Considering deep space exploration and missions of long duration, it is mandatory to prevent and adequately treat typical space-related disorders as sleep disturbances, allergies, space motion sickness, pain and sinus congestion. The topic of our research is focused on how physio-pathological conditions related to long-term space missions influence drug bioavailability and therapeutic efficacy in astronauts. In particular, the main goal of this study is to set-up and consolidate in vitro cell and tissue models to accurately mimic low gravity conditions for the analysis of pharmacological parameters as PK and drug efficacy and safety. It is known that cells and tissues in the body are strongly influenced by microgravity in their architecture, intercellular communications, and overall functions. For in vitro cell culture models to accurately mimic low gravity conditions, the environment of the culture is a critical issue to be considered.

Materials and methods: The rotating wall vessel (RWV) bioreactor was designed by the National Aeronautics and Space Administration (NASA) to model microgravity. In the RWV bioreactor, cells are cultured with microcarrier beads or matrices that allow the cells to attach and spontaneously develop 3D ultrastructures representative of the parental tissue. As the cells grow and develop in a low fluid-shear environment, cellular aggregates form on beads and can be sampled at different time points to monitor the response to various stimuli, both physical ones pharmacological. The first step of the project was to set-up modeled microgravity studies on cultured endothelial cells and fibroblasts in order to evaluate the influence of microgravity on these cell types, fundamental for vessel tropism and angiogenesis, to assess the reciprocal molecular and functional interaction and to study the effect of conventional or novel drugs.

Results: The results obtained document that fibroblasts positively control endothelial cell migration (in the scratch assay) and network formation in Matrigel, while their exposure to modeled microgravity in the RWV impairs the angiogenic phenotype of endothelial cells. The functional responses correlated with the differential release of angiogenic mediators.

Conclusions: In conclusion the RWV is a valid method to model microgravity and to study cellular functions and molecular features, allowing interaction studies among different cell types. In perspective, fibroblast and endothelial pharmacological tuning appears a promising therapeutic approach to overcome problems related with tissue damage which can be worsened during life in space or in disease conditions very common on Earth.

Acknowledgements: The present project was funded by the European Space Agency (ESA) and Italian Space Agency (ASI).