Impact of Microgravity on Human Cancer Cells

Our research program aims to find differentially expressed genes and changes in protein content or secretion behavior of cancer cells cultured under altered gravity conditions. We aim to extend our knowledge in understanding the biology of thyroid and other cancer types by using microgravity as a new method, which may be useful to detect interesting future target proteins. To do this, we have to know the effects of microgravity on cancer cells and the underlying mechanisms. Then the next step is to develop drugs or antibodies against cancer proteins.

Research Platforms
Long-term microgravity has an impact on astronaut’s health. They present muscle- and bone loss, as well as a hampered immune system and cardiac problems. These symptoms are, however, only indirect results of microgravity, but we are interested in the direct and immediate reactions of human cells to microgravity. To obtain a better view on this question, we use different microgravity platforms (fig. 1 and 2). Our experiments are conducted in various real microgravity conditions, ranging from extreme short-term microgravity during parabolic flights (22 s) and microgravity-exposure of medium duration in sounding rocket experiments (6 min), up to periods of days and weeks in unmanned spacecrafts or experiments on the ISS (fig. 1). Unfortunately, experiments under real microgravity conditions are rather rare, which is why we also use simulation devices. These devices make use of the principle of microgravity, which is a continuous free-fall (fig. 2). Small human cells are cultivated in a chamber, which rotates around the horizontal axis, thus counteracting the sedimentation process and keeping the cells in a constant state of free-fall.

Cytoskeletal Changes
Findings after parabolic flights indicated that cells react immediately to the absence of gravity. The investigated cells showed a differential expression of a variety of genes, including extracellular matrix proteins, after the first parabola (22 s of microgravity). In addition, cells, which were fixed after the first parabola exhibited a reorganized cytoskeletal structure [1]. For quite some time, the cytoskeleton is believed to be a mediator between physical forces (microgravity) and mechanisms of gene regulation [2].
The immediate impact of microgravity on the cytoskeleton of human cells was just recently proven on a TEXUS campaign (sounding rocket). In April 2015, a fluorescence microscope was installed on a sounding rocket, holding transfected human thyroid cancer cells (fluorescent cytoskeleton- Lifeact-GFP), which enabled us to observe a live picture. The rocket reached a height of 250 km, underwent a microgravity period of 6 minutes, and returned back to Earth. Directly after the onset of microgravity a reorganization of the cytoskeleton was visible [3].

Multicellular Spheroid Formation
Short-term effects of microgravity are alterations of the cytoskeleton, a change in cell adhesion, altered cytokine release or an increase in programmed cell death (apoptosis) [4]. It also influences the morphologic appearance of the thyroid cancer cells on a longer time scale. We discovered, using the mentioned simulation devices, that culturing cells for longer time periods forces adherent cells to detach from the surface and to assemble in 3-dimensional structures (multicellular spheroids). These spheroids exhibit a tissue-specific morphology depending on their origin. Thyroid cancer cells started to form metastases-like structures [5], endothelial cells arranged themselves to a primary intima of blood vessels [6], while primary chondrocytes produced small cartilage pieces [7]. Comparable results were obtained during the Sino-German space mission SIMBOX/SHENZHOU-8, where thyroid cancer cells were used as well [4, 8].

Inhibition of Neoangiogenesis
Furthermore, we are interested in the molecular mechanisms behind the phenomenon of spheroid formation. This is why we try to characterize the spheroids with the help of OMICS methods (Genomics, Proteomics, Metabolomics). Analyzing samples of various time periods in real and simulated microgravity revealed that factors are changed preferentially, which have an impact on differentiation, proliferation and neoangiogenesis (building of new blood vessels). In particular neoangiogenesis is of high importance for self-supplying tumors. One factor, which
is involved in neoangiogenesis, is Vascular Endothelial Growth Factor (VEGF), which is produced by a variety of malignant cell types. We found both gene expression and the secretion of VEGF to be significantly decreased during microgravity. In addition, proteins of the down-stream signaling cascade were affected (proliferation and apoptosis) [5]. These observations are in concert with previous findings of increased apoptosis rates in samples exposed to microgravity [9]. This allows the assumption that under these conditions low-differentiated thyroid cancer cells have the ability to redifferentiate.

Summary
Since the first astronauts entered Space it has been known that microgravity has an impact on their health. Our discoveries of reduced viability of cancer cells and the identification of proteins involved in inhibition of spheroid formation under microgravity conditions have attracted much attention. Hence, new inventions and increased knowledge within this area have impact on the global scale. By connecting expertise in altered gravity conditions, space medicine and biomedical research we will be able to establish a competitive space medicine program. The hunt for novel cancer treatment strategies stands out as one of the primary tasks in life sciences. Based on our previous work, we now have unique opportunities to address this task by using altered gravity conditions in a new creative way. We will employ this platform as propellant for development of pioneering cancer medicines and the possible clinical translation of cancer treatment based on novel target proteins identified by microgravity.

Authors
Sascha Kopp1, Markus Wehland1, Jessica Pietsch1, Manfred Infanger1, Daniela Grimm1,2
1 Gravitational Biology and translational regenerative Medicine Group, Otto-von-Guericke-University, Magdeburg, Germany
2 Biomedicine und Pharmacology, Aarhus University, Aarhus, Denmark

Contact
Prof. Daniela Gabriele Grimm
Biomedicine and Pharmacology
Aarhus University
Aarhus, Denmark
dgg@biomed.au.dk

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[1] Ganna Aleshcheva, Markus Wehland, Jayashree Sahana, Johann Bauer, Thomas J. Corydon, Ruth Hemmersbach, Timo Frett, Marcel Egil, Manfred Infanger, Jirka


[9] Daniela Grimm, Johann Bauer, Peter Kossmehl, Mehdi Shakibaee, Johann Schönberger, Holger Pickenhahn, Gundula Schulze-Tanzil, Roland Vetter, Christoph