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Commentary Open Access

A Critical Role of FAK/Rhoa Signaling in Simulated Microgravity-Altered Cell Apoptosis, Proliferation and Metastasis

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Commentary

The spaceflight environment presents many stress factors such as microgravity and cosmic radiation that have adverse effects on cell biology and human physiology. For example, microgravity has profound effects on all human organs and systems, such as fluid redistribution, muscle changes and bone demineralization [1]. Microgravity has been demonstrated to inhibit tumor cell proliferation and metastasis [2], promote cell apoptosis [3,4] and suppress osteoblastic differentiation and mineralization leading to bone loss [5]. The cytoskeleton, as a cellular structural scaffold, plays a critical role in maintaining cellular shape, serving as an intracellular transport system, and modulating cell apoptosis [6] as well as tumor cell proliferation, migration, invasiveness and metastasis [7]. The eukaryotic cytoskeleton consists of three basic types of filaments (intermediate filaments, actin filaments and microtubules). Integrins are transmembrane proteins that are core constituents of cell-matrix adhesion complexes combined with cell surface integrins, intracellular cytoskeleton binds to the extracellular metrix at cellular membrane sites named focal adhesions [8]. The integrin-binding proteins (talin, vinculin and paxillin) recruit focal adhesion kinase (FAK) to focal adhesions. After binding of FAK to focal adhesions, focal adhesion complexes are formed composing another group of the ras homolog gene (Rho) family GTPases [9]. The Rho family members consist Rho family member-A (RhoA), cell division-control protein-42 (Cdc42) and ras-related C3 botulinum-toxin substrate-1 (Rac1), which control actin-binding protein's function to compose higher order structures such as stress fibers (actin/myosin bundles), lamellipodia (membrane ruffles at the leading edge) and filopodia (membrane protrusion) [10]. The Rho family members mediate some molecular pathway signals such as the mTORC1 (mammalian target of rapamycin complex-1) pathway [11-15]. FAK which regulates RhoA [16], mTORC1 and AMPK (AMP-activated protein kinase) pathways controls cell survival, proliferation, migration and differentiation [17]. In multicellular organisms, it is now fully clear that dynamic equilibrium of cell numbers is finely adjusted by cell division and rate of cell death. The later process is named as programmed cell death also termed as 'apoptosis' that was first raised in 1972 [18]. For the last four decades, dissection of the apoptotic cell death has unveiled that apoptosis is mediated by proteolytic enzymes called caspases [19]. Caspases have inactive precursors or procaspases in all cells, which are activated by the intracellular pathway regulated by Bcl-2 family members divided into anti- and pro-apoptotic members, and the extracellular pathway involved with activation of initiator pro-Caspase-8 being able to subsequently activate effector caspases [20]. It has been established that multiple pathways control formation of cell apoptosis, such as mTORC1, nuclear factor-kappa B (NF-κB), extracellular signal-regulated kinase-1/2 (ERK1/2) and P53/Puma [21].

Enhanced cellular apoptosis was observed in normal thyroid cells, human lymphocytes (Jurkat) and embryonic stem cells during microgravity in spaceflights or under simulated microgravity (SMG), a ground-based method using a random positioning machine (RPM) to mimic microgravity condition in space [4,6,22]. It has been demonstrated that SMG altered cytoskeleton and enhanced cell apoptosis in chondrocytes, thyroid cancer cells, endothelial cells and osteoblasts [23-27]. SMG was also found to induce thyroid carcinoma cell apoptosis *via* up-regulation of apoptosis-associated Fas, p53 and Bax molecules and down-regulation of an anti-apoptotic protein, Bcl [28]. It was demonstrated that microgravity inhibited the NF-kB pathway [29], which negatively regulates cell apoptosis [30]. We previously showed that B16 melanoma BL6-10 cells cultured under SMG (1 μg) altered cytoskeleton structure by losing most stress fibres and lamellipodia, and enhanced cell apoptosis through suppressing NF-κB pathway leading to up- and down-regulated pro-apoptosis (caspases 3,7,8) anti-apoptosis (Bcl-2 and Bnip3) molecules, compared to cells cultured under the control ground condition (1 g) [31]. However, the upstream signaling responsible for SMG-induced suppression of NF-κB leading to enhanced cell apoptosis is still unknown. It has been reported that signaling FAK and RhoA were associated with regulation of cell survival and protection of cells from apoptosis [32,33] and that mTORC1 regulated NF-κB controlling cell apoptosis *via* up-regulation of anti-apoptosis Bcl-2 molecule [34]. With a clinostat modeling SMG for the cultured BL6-10 melanoma cells, we demonstrated that SMG also reduced cell focal adhesions and inhibited activities of FAK and RhoA signaling [31], raising a possibility that FAK and RhoA might be the upstream signaling responsible for SMG-induced suppression of mTORC1-controlled NF-κB, leading to enhanced cell apoptosis. To assess the possibility, we performed SMG studies by using BL6-10 melanoma cells and demonstrated that SMG down-regulated mTORC1-downstream molecules S6K and ELF4E as well as mTORC1-regulated NF-κB and Bcl-2 [31,35] and switched cellular localization of phosphorylated NF-κB (pNF-κB, Ser337) from nuclear to cytoplasm [31,35]. To confirm the critical role of mTORC1 in SMG-induced enhancement of cell apoptosis, we used rapamycin, an inhibitor of mTORC1; in treatment of BL6-10 cells cultured less than 1 g. We showed that rapamycin administration increased cell apoptosis *via* down-regulation of the mTORC1/NF-κB/Bcl2 pathway in cells under 1 g [31,35]. To confirm the critical up-stream role of FAK/RhoA in SMG-induced enhancement of cell apoptosis *via* inhibition of the mTORC1/NF-κB pathway, we used an *E. coli* toxin CNF1 (a broad spectrum activator of Rho proteins) [36,37] in our

SMG studies. We demonstrated that CNF1 significantly increased focal adhesions and reduced apoptosis in cells under SMG [38]. In addition, we further showed that CNF1 activated FAK signaling and enhanced RhoA activity and elucidated that CNF1 up-regulated the mTORC1/NF-κB/Bcl2 pathway in cells under SMG. Therefore, our data indicate that SMG reduces focal adhesions and FAK/RhoA activity, leading to promoting cell apoptosis *via* suppressing FAK/RhoA-regulated mTORC1/NF-κB/Bcl2 pathway (Figure 1).

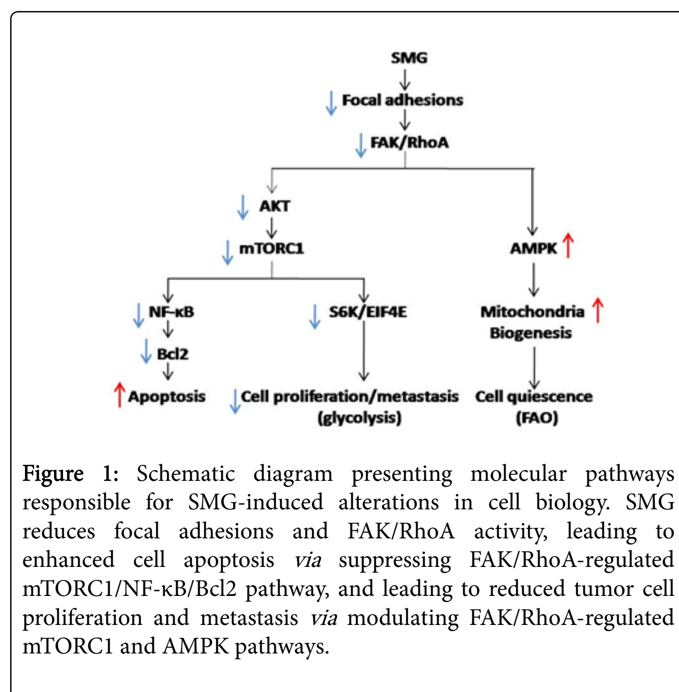

Figure 1: Schematic diagram presenting molecular pathways responsible for SMG-induced alterations in cell biology. SMG reduces focal adhesions and FAK/RhoA activity, leading to enhanced cell apoptosis *via* suppressing FAK/RhoA-regulated mTORC1/NF-κB/Bcl2 pathway, and leading to reduced tumor cell proliferation and metastasis *via* modulating FAK/RhoA-regulated mTORC1 and AMPK pathways.

Microgravity, as an external stress, can affect not only apoptosis but also cell proliferation and metastasis [39]. Microgravity has been reported to inhibit proliferation of leukemia and lymphoma cells [40,41]. It has also been demonstrated that microgravity inhibited cell growth *via* down-regulation of cell cycle-regulating proteins such as Cyclin D1 and B1 in breast and colorectal cancer cells [42,43]. In addition, SMG also inhibited migration and metastatic potential of A549 lung adenocarcinoma cells *via* decreased expression of MKI67 (a nuclear protein necessary for cellular growth) and MMP2 (matrix metalloproteinase-2) related to cancer metastasis [2,44] and weakened metastatic potential of melanoma cells *via* reduced expression of guanylyl cyclases A and B (GC A/B) [45]. Kinase mTORC1 is a central regulator for cell growth *via* activation of EIF4E (eukaryotic initiation factor 4E) and S6K (S6 kinase) and a sensor of cellular energy status *via* triggering glycolysis metabolism [46]. Kinase AMPK also acts as a sensor of cellular energy status *via* activating mitochondrial biogenesis, leading to fatty acid oxidation (FAO) for energy production [47]. Both mTORC1 and AMPK have important effects on regulation of cellular metabolism for maintenance of energy homeostasis [48]. Recently, it has been demonstrated that SMG inhibited the mTORC1 pathway [49,50]. However, the molecular mechanism underlying the above SMG-induced changes in cell biology and cellular pathways [45] is still elusive. Since FAK and RhoA signaling were found to be up-regulated in cancer cells and related to cancer aggressiveness and metastasis [17,51,52], we assumed that FAK and RhoA might be the upstream signaling responsible for SMG-induced suppression of mTORC1, leading to inhibition of cell proliferation and metastasis. With clinostat-modelled SMG, we examined SMG's effects on BL6-10 melanoma cell proliferation, adhesion, invasiveness and metastasis compared to cells under 1 g. We found that SMG altered cytoskeleton structure and reduced formation of cell focal adhesions and down-regulated expression of pFAK (Tyr397) and RhoA as well as mTORC1-regulated pS6K (Ser235) and pELF4E (Ser209) and inhibited cell glycolysis metabolism in melanoma cells under SMG [38]. It has been reported that mTORC1 inhibited AMPK signaling *via* activation of S6K [53]. Interestingly, we found that SMG up-regulated AMPK pathway, leading to activation of mitochondrial biogenesis and FAO for energy production [38], which is suitable for cells in quiescence such as SMG-treated cells. Tumor aggressiveness is closely associated with tumor metastasis involving multiple steps, such as cell adhesion, migration and invasion [54,55]. MMP9 controlled by signaling through FAK and RhoA [56] has been found to modulate tumor cell invasion and metastasis [57]. BL6-10 melanoma cell surface glycoprotein Met72 was found to be associated with high metastasis of BL6-10 cells to lungs [58]. In this study, we demonstrated that SMG inhibits expression of MMP9 and Met72, leading to significant reduction in cell adhesion and invasiveness *in vitro* and tumor metastasis to lungs *in vivo*. To confirm the critical role of mTORC1 in SMG-induced inhibition of tumor cell proliferation and metastasis, we used rapamycin in treatment of BL6-10 cells cultured less than 1 g. We showed that rapamycin administration down-regulated mTORC1-regulated S6K and ELF4E and glycolysis, but up-regulated AMPK and activated mitochondrial biogenesis [31,35]. In addition, rapamycin administration also significantly inhibited BL6-10 melanoma cell proliferation and lung metastasis [31,35]. To confirm the critical up-stream role of FAK/RhoA in SMG-reduced cell proliferation and metastasis *via* inhibition of the mTORC1 pathway, we used an *E. coli* toxin CNF1 [36,37] in our SMG studies. We demonstrated that CNF1 was able to convert (i) SMG-induced inhibition of FAK/RohA activity and mTORC1 pathway, (ii) SMG-induced suppression of expression of these metastasis-related molecules, and (iii) SMG-induced reduction of cell focal adhesions, proliferation and metastasis in cells under SMG [38]. In this study, we for the first time, reveal that SMG dramatically reduces formation of focal adhesions and inhibits cell proliferation and metastasis through FAK/RhoA-mediated inhibition of the mTORC1 pathway and activation of the AMPK pathway (Figure 1). Microgravity has been demonstrated to suppress osteoblastic differentiation and mineralization leading to bone loss [5] often seen in rheumatoid arthritis [59]. However, the underlying mechanism for SMG-induced bone loss is not clearly understood. We, therefore, assume that the FAK/RhoA regulatory network may be important in other SMG-induced physiological alterations such as SMG-induced bone loss [5]. To assess this assumption, conducting similar SMG experiments using MC3T3 pre-osteoblast cell line [23] is underway in our laboratory.

Taken together, our data reveal a new molecular mechanism for SMG-induced alterations in cell biology, that SMG reduces focal adhesions and FAK/RhoA activity, leading to (i) enhanced cell apoptosis *via* suppressing FAK/RhoA-regulated mTORC1/NF-κB/Bcl2 pathway, and (ii) reduced tumor cell proliferation and metastasis *via* modulating FAK/RhoA-regulated mTORC1 and AMPK pathways (Figure 1). Thus, FAK/RhoA signaling may play a critical role in SMG-induced alterations in cell biology, and targeting FAK/RhoA regulatory network may become an important therapeutic strategy for astronauts in spaceflights and for other human diseases.

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