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RESEARCH ARTICLE

AN "OUT OF THE WORLD" APPROACH FOR CANCER TREATMENT

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Abstract

Cancer is still the major cause of mortality and morbidity around the world. Even with the advancements in medical science the number of patients recovering from the disease is low and furthermore chances of tumor relapse and metastasis complicate the disease further. Present tumor therapies either fail to specifically target cancer cells or are prohibitively costly. Significantly, even after decades of research we still do not clear understand the events which initiate tumor formation and thereafter their unchecked growth into a gigantic tumor mass. Like the formation of the universe following the big bang remains a mystery, the formation of the tumor mass following the generation of a single cancer cell is also elusive. Gravitational force plays a major role in shaping our universe, our lives and even cellular biological processes. Similarly, cancer cells could communicate and sense each other through mechanical forces, which have evolved to work in an environment where there's gravity. This thought has motivated various research works to observe the effect of gravity on cancer cells. This review highlights the effect of gravity on the cancer cells.

Introduction:-

Gravity is a universal force, which affects all the life forms on earth and the biological processes in them. Since the beginning of human space exploration, scientists started to investigate the effect of microgravity on human cells. In the past four decades, the development of the space industry has made people aware of the effects of microgravity on biological life and processes. Microgravity has been shown to alter important properties of cells, including cell morphology, proliferation, and migration [1]. It is confirmed that more than 1600 genes expression have been altered when cells are exposed to microgravity [2]. These genetic alterations result in corresponding alterations in the cell growth pattern, cell cycle, migration capabilities, cytoskeleton—(microtubule [MT], microfilament [MF] and intermediate filament [IF]), ECM, proliferation, and apoptosis [3]. Recently, researchers have shown that simulated microgravity can induce these alterations not only in normal cells, but also in tumor [4]. Malignant tumors are still the major cause of mortality in human. Even with development of molecular and cellular biology, treatment of tumor remains difficult and costly. Therefore, it is necessary to find new treatment modalities to overcome these difficulties. Compared to normal gravity, the morphological function of cancer cells is obviously altered as a result of the unique microgravity in space or microgravity condition stimulated on earth, which provides a new method to study these problems. Several biological processes, including apoptosis, cytoskeleton, adhesion/extra-cellular matrix (ECM), proliferation, cell cycle, DNA repair and DNA replication, stress response, proteolysis, enzyme binding, transcription factor binding, migration were differentially expressed in cancer cells following exposure to microgravity [5]. In this review, different effects of microgravity on the functioning of cancer cell are discussed.

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Effect Of Microgravity On The Functioning Of Cancer Cell:

Effect of microgravity on cancer cell viability:

Numerous studies have shown the inhibitory effects of microgravity on cancer cells viability and growth. Microgravity markedly decreased cell activity and the decrease in activity was directly proportional to the time they were cultured in microgravity condition [6]. Inhibition of an anti-apoptotic protein, BCL-2, BNIP3 and induction of the apoptosis-related proteins, p53, PARP and BAX in ML-1 thyroid cancer cells has been demonstrated, through the simulated microgravity condition [7]. Tumor antigen p53 responds to stimulated microgravity by induction of downstream proteins such as p21, MDM2 and BAX, which regulate the cell cycle and apoptosis [8]. Apoptosis of thyroid cancer cell lines ML-1 and ONCO-DG1 increased after 24 h exposure to microgravity [9], whereas apoptosis in MDA-MB-231 breast cancer and SGC-7901 gastric adenocarcinoma cells showed increase after 72 h of exposure [10,11]. Zhao et al. found that stimulated microgravity promotes apoptosis by upregulation of Caspase-3, 7 and 8. Moreover, downregulation of NF-κB pathway regulating molecules including UEV1A, TICAM, TRAF2, and TRAF6, leads to increased apoptosis [12]. Importantly, CAV1 protein which is a gravity-sensitive protein and regulates cellular proliferation, differentiation and apoptosis [13], decreases in cancer cells after 72h exposing to microgravity [14]

Effect of microgravity on cancer cell proliferation:

Cell cycle regulating proteins like CyclinD1 and B1 were down-regulated under simulated microgravity in breast and colorectal cancers [7, 10]. Flow-cytometery analysis further confirmed that the number of cancer cells arrested in the G2/M increased in microgravity conditions [12]. ATM/ATR and CDK1/2 proteins which are essential for cell cycle transition from S to G2 decreased under microgravity condition [12]. Interestingly, simulated microgravity inhibited the proliferation of lymphoma cancer cells, but normal cells were not affected (Figure 1) [15]. Also, the colony formation assay on cancer cells revealed that microgravity attenuates the cancer cell ability to form colonies [7, 12]. Furthermore, reduced gravity disturbs cell cycle controlling genes and proteins, so prevents cancer cells from proliferation and forming spherical colonies. The function of important protein complexes necessary for cell cycle like, PCNA-CDK-cyclin protein complexes decreased under stimulated microgravity conditions resulting in G1 arrest [16]. Stimulated microgravity induces the expression of p21 protein, which inhibits cell cycle and DNA replication. p21 forms complexes with PCNA which further forms super-complexes with CDK/cyclin, inhibiting CDK activity. This interaction prevents phosphorylation of RB proteins and the release of transcription factors that bind to it, resulting in cells failing to pass the G1 phase check point [16]. Stimulated microgravity also reduces the expression of EGF-R, thus hampering downstream PI3K/AKT signaling pathway leading to a decrease in cell proliferation. Microgravity decreased EGF-induced *c-Fos* and *c-Jun* expression around 50%, as compared to the normal gravity control samples [17] (Figure 1).

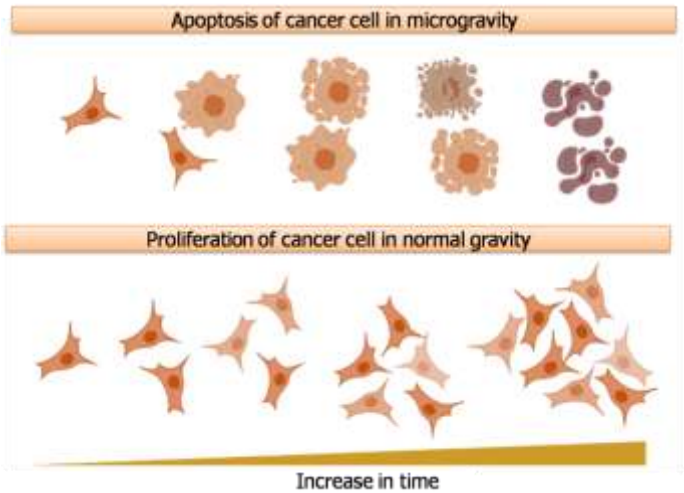

Figure 1:- Schematic diagram showing the proliferation of cancer cells under normal gravity and apoptosis under microgravity condition.

Effect of microgravity on cancer cell migration:
Transwell migration assay and wound healing assay showed a decrease in migration of MCF-7, MDA-MB-231 breast cancer cell lines and A549 lung cancer cell line following 24 h exposure in microgravity condition as compared to cells in normal gravity [13]. Expression of MMP2, MMP3 and MMP9 was reduced following exposure to microgravity [18]. Stimulated microgravity also increases the expression of TIMP genes which further results in downregulation of MMP genes and thus reduce cell migration [19]. Studies have also revealed that exposure to microgravity suppressed the expression of F-actin [20]. Block et al. found that under microgravity condition there is contraction of the cell and rearrangement of actin filaments in cell leading to contraction of the cell tail and thus affecting cell migration. Furthermore, it is also postulated that the destruction of the microtubule network under microgravity can affect the formation of pseudopodia and hinder the movement of cells [21]. CDC42 is an important switch controlling continuous activation and inactivation of GEF and GAP. Microgravity decrease CDC42 enzyme activity leading to corresponding changes in migration [21]. Migration of cancer cell leads to metastasis. Epithelial mesenchymal transition (EMT) is an important event in the process of cancer metastasis. Vimentin is an important regulatory factor responsible for EMT. Microgravity can rearrange vimentin forming nucleo-vimentin polymer, this alteration reduced the number of free vimentin molecules available to exert physiological effects, leading to altered migration ability of cancer cells. Microgravity disorganized focal adhesion (FA) of MCF-7 cells. FAs created in microgravity were less mature than those established in normal gravity. Fewer and smaller FAs can lead to the weaker cell spreading and migrating [6, 19].

Effect of microgravity on cancer cell adhesion:
Organization of microtubules into specific pattern is gravity-dependent and these processes are hampered in microgravity conditions. Real and simulated microgravity activates various signal pathways, resulting in abnormal expression of various adhesion molecules, which leads to altered 3D structure. Real or stimulated microgravity resulted in decrease of actin stress fibers, which resulted in disappearance of complex cytoplasmic networks within the cells [22, 23]. Due to the reduction in quantity and aberrant distribution, stress fibers change from isometric shrinkage to isotensional contraction or show a mixture of the two and have a profound effect on cellular morphology [24, 25]. Microgravity also affects ATP, which hinders the formation polymer and changes in microfilament structure. [19]. Microtubules, which are important cellular components essential for maintaining the structure of the cell, were disrupted in MCF-7 cells within 4 h of exposure to stimulated microgravity [26]. Lewis et al. reported that microtubule organizing centers (MTOCs) were poorly defined in microgravity conditions. Stimulated microgravity significantly reduces the activation of focal adhesion kinase (FAK) and RHO family proteins (e.g., RHOA, RAC1 and CDC42), resulting in decreased cell migration and altered cellular morphology [27].

Using stimulated microgravity as a possible therapeutic approach:
Tumor cells change under altered gravity conditions. These changes include cell aggregation, cytoskeleton rearrangement, cell cycle arrest, migration and apoptosis, bringing the cells toward a less aggressive phenotype. This effect is greater in actual spaceflight; however, ground-based simulations have proved to be an essential tool in our understanding of the effects of gravity on a cellular and molecular level in cancer cells [6]. Stimulated microgravity is created by the one-axis clinostat and two-axis RPM modes. But these processes also create shear forces. These shear forces have a strong influence on function in cancer cells. Shear forces generated by two-axis RPM is greater as compared to shear forces generated by one-axis clinostat, thus the higher shear forces acting on the cancer cells during the RPM, might lead to the different results on the two-axis RPM and one-axis clinostat this problem can be averted by conducting experiments under actual microgravity conditions in space [19]. Spaceflight missions are very rare and costly. Therefore, subjecting the cancer cells to real microgravity remains a challenge thus most experiments are carried out using stimulated microgravity. Moreover, studies based on microgravity are conducted in vitro, and the evidence from human or animals experiments is rare. The most critical question which needs to be answered is regarding the safety of microgravity strategy on human. Another equally important problem is to figure out a strategy to create microgravity environment in body. The recent discoveries of nanomagnetic fluids, has opened up new avenues in cancer treatment. Various novel methods has been developed to use these magnetic fluid to expose the tumor cells to microgravity The concept of magnetic fluid-modelled microgravity to treat tumor is novel and economical. Magnetic fluids are delivered by outside magnetic field to tumor tissue either intravenously or through direct injection, and this is followed by application of a uniform external magnetic field that causes microgravity. This magnetic fluid-modelled microgravity might be suitable for clinical applications in future [6].

Conclusion:-

Several research conducted in a stimulated microgravity condition have shown promising results, but there are also evidences which suggest otherwise. There are some studies which suggested that microgravity favours growth of cancer cells. The migratory potential of human lung cancer cell lines increased following exposure to microgravity. Microgravity was also found to induce certain types of cancers like lungs, breast, ovarian, liver, head and neck cancers. Oncogenic KRAS pathway was also induced after exposure to microgravity condition also the expression of apoptotic gene like BAX was reduced [7]. Microgravity was observed to have dissimilar impacts on gene expression of various cancer cells. For example, a proto-oncogene, MYC, was up-regulated in the colorectal cancer and down-regulated in leukemia. Similarly, another proto-oncogene, CD117, was up-regulated in leukemia and down-regulated in the colorectal cancer [12]. Furthermore, most of the experiments are carried out in stimulated microgravity condition which exposes the cells to shear forces that might lead to aberrant results. Thus it will be more suitable to carry out experiments in actual microgravity conditions. Moreover the exact time duration for exposure must be determined for each cancer types. All in all, it seems too soon to decide about the microgravity therapeutic application in cancer. In the mean time through investigation on the effects of microgravity on both normal and cancer cells should be undertaken to understand the true potential of microgravity-based cancer treatment options.

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Conflict Of Interest:

There is no conflict of interest.

Ethics Approval:

Not applicable.

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