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Epithelial-mesenchymal transition of brain tumor cells is differentially regulated in response to dexamethasone

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In the epithelial-mesenchymal transition of tumors, the loss of cohesivity and the migratory capability of cells determine the invasiveness and therefore the malignancy of the cancer. Understanding these biophysical mechanisms of cancer propagation will help control the disease thereby facilitating its treatment. In this study, cohesivity and invasiveness were characterized using three-dimensional aggregates constructed from human glioblastoma multiforme cells (HB cells). First, we showed that cohesivity was affected by the physical environment during incubation. Shear stress, simulated microgravity and normal 1g gravity conditions were produced respectively by incubation in a gyrotary shaker, in NASA's High Aspect Ratio Vessel (HARV) and in statically kept 24 well-plates. The surface morphology of the aggregates observed by field-emission scanning electron microscopy became rougher (indicative of a lower intercellular binding) as the forces acting upon it were reduced. Interestingly, the effects due to the environmental conditions were canceled by addition of an anti-cancer drug: dexamethasone (DEX), a corticosteroid often used as an anti-inflammatory agent. In a second experiment, the effect of DEX on the invasive pattern of HB-cells in three-dimensional collagen matrices was studied. We found that DEX slows down cell migration from the aggregate indicating that it modifies the interplay between cell-cell adhesion and cell-extracellular matrix interaction. One possible mechanism of DEX action is increase in intercellular binding due to higher N-cadherin expression, the predominant cell-adhesion molecule in brain cells. The quantity of N-cadherin proteins was assessed by immunolabelling and flow cytometry after HB cells were exposed for 24 hours to various doses of DEX (0 to 10-6M). Preliminary data indicate that cells treated with 10-9 to 10-6M DEX express 5 to 60% more N-cadherin than non treated cells. Further investigations are needed to determine the effect of DEX on other factors involved in cell motility such as cytoskeleton, integrins, metalloproteinases. Exploring the molecular bases that control the bulk physical properties of tumor tissues (modeled here by the multicellular aggregates) may create new means to control cancer metastasis.