Title: Neurotrophin TrkB receptor mediates the epithelial to mesenchymal transition in lung adenocarcinoma cells

Body: Lung cancer represents the leading cause of cancer-related mortality worldwide. Recent evidence indicates that tumors contain a small population of cancer stem cells that are responsible for tumor maintenance and spreading, the cancer stem cells (CSCs). Neurotrophins (NTs) are growth factor molecules that regulate the biology of embryonic stem cells and cancer cells, but still little is known about NTs and the onset of lung cancer. We investigate the role of the NTs and their receptors using as study system primary cell cultures, derived from malignant pleural effusions of patients with adenocarcinoma of the lung. We assessed the expression of NT and NT receptor expression in differentiated cells and spheroids enriched in cancer stem cell (CSC) markers. We also evaluated the inhibitory properties of K252a, a selective inhibitor of the tyrosine protein kinase activity of the Trk family. We observed that in spheroid cultures there are an higher expression of TrkB, both at the mRNA and protein level. This effect was confirmed by measuring the serial propagation of spheroids in quantitative spheroid forming assays. Interestingly, treatment with NTs ligands reverted the inhibitory effect of k252a in maintenance and formation of spheroids. Furthermore, loss of E-cadherin increase, after siRNA TrkB transfected spheroid cells indicates that the TrkB receptor may have a role in the epithelial to mesenchymal transition suggesting that TrkB may address cancer cell biology, phenotype and metastasis.