We have developed two groups of human prolactinoma cell lines referred to as responder (R) and non responder (NR). “Responder” cells were obtained from bromocriptine-sensitive tumors and are more differentiated, non tumorigenic and express an autocrine loop mediated by nerve growth factor (NGF). Non responder cells were obtained from tumors refractory to the bromocriptine therapy and are more transformed, have a high tumorigenic potential and lack NGF production. We have reported that NGF administration to NR cells promotes their differentiation, induces the expression of D2 receptors and inhibits their proliferation rate. In this study we investigated the mechanisms mediating the antiproliferative action of NGF in NR prolactinomas. Cell proliferation is controlled by specific repressors. In particular an important restriction point in the G1 phase has been identified, that is controlled by p53 and p21 tumor suppressor proteins. We first evaluated whether p53 expression in NR cells is modified by NGF treatment. The results showed that p53 is highly expressed in NR cells and its levels are not modified by NGF treatment. Since p53 activation implies its nuclear translocation, p53 cellular localization was evaluated in R and NR cells by immunocitochemistry. In NR p53 appears to be segregated in the cytoplasm, while in R cells it appears to be equally distributed in both the nucleus and the cytoplasm. Exposure of NR cells to NGF resulted in the redistribution of p53 to the nucleus and in the expression of p21 and Mdm2, two target genes of p53, suggesting that this treatment restores a functional p53-p21 pathway. In addition, the results show that NGF treatment significantly down-regulates cyclin A, Cyclin E and cdk2, suggesting that the antiproliferative effect of NGF in NR prolactinomas implies cell cycle arrest in G0/G1. The signal transduction pathway activated by NGF involves two different receptors: trkA and p75. With the aim of evaluating the role of these two different receptors in the antiproliferative effect of NGF we measured the action of NGF in the presence of specific inhibitors of the NGF receptors.

The results have shown that the antiproliferative effect of NGF is exclusively mediated by trkA-induced activation of PI-3 kinase.

List of most relevant papers related with the topic


Schlessinger J 2000 Cell signalling by receptor tyrosine kinases. Cell 103:221-225


Schematic representation of the two phenotypically different prolactinoma cell lines: “Responder” cells were obtained from bromocriptine-sensitive tumors and are more differentiated, non tumorigenic and express an autocrine loop mediated by nerve growth factor (NGF). Non responder cells were obtained from tumors refractory to the bromocriptine-therapy and are more transformed, have a high tumorigenic potential and lack of NGF production.

**Fig.1**  
Effects of NGF treatment on p53 subcellular localization in Non Responder cells. Cells were exposed for 5 days to 100 ng/ml NGF. The results obtained by western blot experiments (fig 1) on nuclear and cytoplasmic extracts show that NGF induces the p53 nuclear translocation. This data was confirmed by immunocitochemistry using an anti-p53 antibody. In untreated cells (fig 2A) p53 immunoreactivity is segregated into the cytoplasm; in NGF treated cells (fig. 2B) p53 immunoreactivity is localized into the nucleus.