

Role of Enolase/MBP-1 in non-tumorigenic and cancer cells

The glycolytic enzyme α -enolase is a highly conserved protein involved in multiple functions (Díaz-Ramos A et al 2012). Besides the mainly cytoplasmic localization, the protein has been detected on the surface of prokaryotic and eukaryotic cells where it functions as a plasminogen receptor, while a shorter variant, called Myc promoter-binding protein-1 (MBP-1), is mainly located in the nucleus.

Several lines of evidence indicate that MBP-1 acts as a tumor suppressor, negatively regulating cell proliferation or promoting apoptosis of cancer cells. Although a few reports indicate that stressful conditions, such as glucose deprivation or hypoxia, may modulate MBP-1 expression in mammalian cells the putative signaling pathway(s) underlying MBP-1 expression still remains largely elusive.

On the other hand, elevated expression of α -enolase has been observed in many tumor types and its surface expression has been reported in lung, pancreatic and breast cancer cells. The involvement of surface α -enolase in invasion and metastasis has recently been demonstrated in lung cancer (Hsia K-C et al 2013), nevertheless the molecular mechanisms of its transport from cytoplasm to cell membrane are still object of hypothesis and speculative models (Didiasova M et al 2014).

Since either the nuclear or the surface function of α -enolase may be potential target of novel therapeutic approaches in cancer, the present study was aimed at the identification of the signaling pathways involved in these alternative functions.

To dissect the pathways leading to MBP-1 expression, we used a breast cancer cell line, SKBr3, and 293T cells that ectopically overexpress α -enolase/MBP-1. We demonstrate that the glycolysis inhibitor 2-Deoxyglucose and the ER stress inducing drug Thapsigargin promote MBP-1 expression through the AKT, PERK, eIF2 signalling axis.

In order to investigate how α -enolase moves to cell surface and to identify the signaling pathways involved in this process, we stimulated non tumorigenic mammary epithelial cells and breast cancer cells with receptor ligands and analyzed the variation in the level of surface α -enolase using biochemical assays and immunolabeling techniques. We show that Epidermal growth factor (EGF) and pro-inflammatory endotoxin Lipopolysaccharide (LPS) treatments up regulate the cell-surface expression of α -enolase through interaction with their receptors, EGFR and TLR 4, respectively.

Moreover, we partially dissected the putative signaling pathways underlying α -enolase translocation to cell membrane in mammary epithelial and breast cancer cells, suggesting the involvement of MAPK/ERK and Src pathways.

Our results contribute to shed light on the molecular mechanisms regulating MBP-1 and surface α -enolase expression in normal and cancer cells.