Interactions between PP4 and PEA-15 in the regulation of cell proliferation and apoptosis of breast cancer cells

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Background

The serine/threonine protein phosphatase 4 (PP4) is recognised to regulate a variety of cellular functions. Our previous work has shown that the catalytic subunit of PP4 (PP4c) promotes cell death and inhibits proliferation in breast cancer cells, suggestive of a role of PP4c as tumour suppressor gene. Phosphoprotein enriched in astrocytes 15 (PEA-15), a member of the death effector domain protein family known to control cell survival, is reported to be regulated by PP4c. The aims of this study were to investigate the involvement of PEA-15 in mediating the effects of PP4c on breast cancer cells.

Method

PEA-15 phosphorylation was examined by western blot analysis on proteins extracted from MCF7 and MDA-MB-231 cells over-expressing PP4 and PP4 knock down cells. To investigate the role of PEA-15 in mediating the effects of PP4c, MCF7 and MDA-MB-231 were transfected with control (-) siRNA or with three different PEA-15 specific siRNAs. 48 h post-transfection, control cells (transfected with negative control siRNA) and cells transfected with PEA-15 siRNAs were transiently transfected with pcDNA3.1-PP4c expression construct or pcDNA3.1. Cell viability and apoptosis level were assessed post transfection.

Results

In MCF7 and MDA-MB-231 cells, the phosphorylation state of PEA-15 increased when PP4c expression was suppressed and decreased when PP4c was over-expressed. Over-expression of PP4c in cells transfected with (-) siRNA caused 50% reduction in viability compared to cells transfected with empty vector. Cells transfected with PEA-15 siRNAs showed a decrease in viable cell number and long term survival. However, over-expression of PP4c in these cells did not have any additional effect on the decrease in cell viability.

Conclusion

These observations suggest that the induction of apoptosis by over-expression of PP4c is mediated, at least in part, by the dephosphorylation of PEA-15. The interactions between PEA-15 and PP4c may therefore be critical in breast cancer tumorigenesis.