VEGF autocrine secretion is enhanced by EGFR activation trough ERK1/2 phosphorylation in human Adrenocortical Carcinoma cell lines

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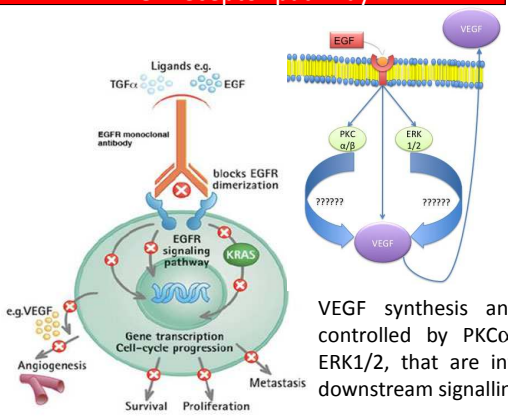
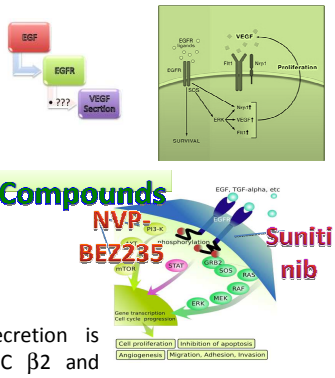
Background

Adrenocortical cancer (ACC) is still orphan of medical treatment. ACC medical treatment is mainly represented by Mitotane alone or in association with chemotherapy, with variable results.

Our preliminary data show that EGF induces ACC cell lines proliferation (+20% and +10% vs. control in SW13 and NCI-H295 cell lines, respectively). EGF receptor (EGFR) expression is higher and ubiquitous in SW13 cells, while it is weaker in NCI-H295 cells, where it is present only on the membrane.

EGF receptor pathway





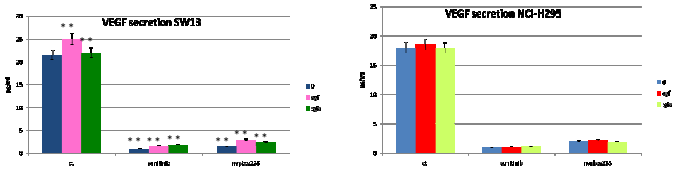
VEGF synthesis and secretion is controlled by PKCα, PKC β2 and ERK1/2, that are involved in EGFR downstream signalling.

Aim of our study is to analyze EGFR downstream signalling in ACC cell lines

RESULTS

Evaluation of VEGF secretion

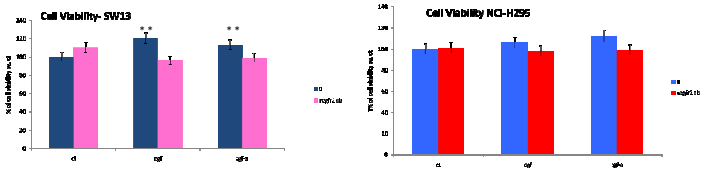
* * p< 0,001



EGF and TGF-a enhanced VEGF secretion only in SW13 cells while had no effects on NCI-H295.

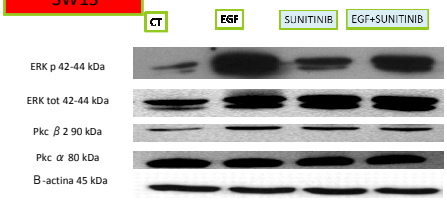
Effects of VEGR2 blocking antibody on EGF induced cell

* * p< 0,001



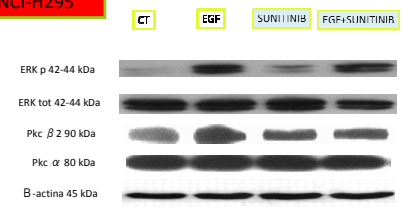
VEGF receptor (VEGFR) blocking antibody significantly reduced EGF effects on SW13 cells proliferation, while it had negligible effects on NCI-H295 cells

WESTERN BLOT SW13



PKCα and PKC β2 were not modulated by treatment with EGF or with Sunitinib (an EGFR inhibitor), nor by the combination of EGF and Sunitinib. ERK1/2 phosphorylation was strongly enhanced by EGF, an effect slightly counteracted by Sunitinib . These effects were more evident in SW13 as compared to NCI-H295 cells.

WESTERN BLOT NCI-H295



Conclusion

These data demonstrate a crosstalk between EGF and VEGF signalling pathways that is, at least in part, mediated by ERK 1/2 , and could indicate novel molecular targets possibly useful in the future design of ACC medical therapy. Further studies are needed to deeply understand these pathways in ACC