We have nothing to disclose.

The impact of activating *PIK3CA* mutations and PTEN haploinsufficiency on human adipocyte phenotype and biology

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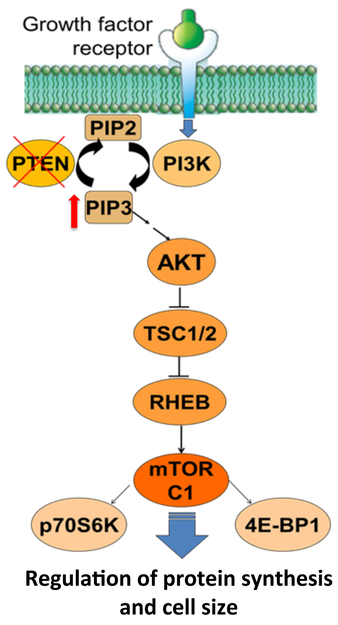
BACKGROUND & HYPOTHESIS



Regulation of protein synthesis and cell size

Inactivation of the tumor suppressor PTEN increases the level of PIP3, which activates AKT/mTOR signaling thus augmenting cellular proliferation and survival. Adipose tissue tumors are frequently seen in humans with germline *PTEN* or mosaic activating *PIK3CA* mutations. We assume that adipocytes from affected tissue show hyperproliferation and modified differentiation. We aimed to study preadipocytes *in vitro*, which were derived from affected regions of pediatric mutation carriers.

RESULTS

1 Adipocytes from *PTEN* or *PIK3CA* mutation carriers show increased cell size

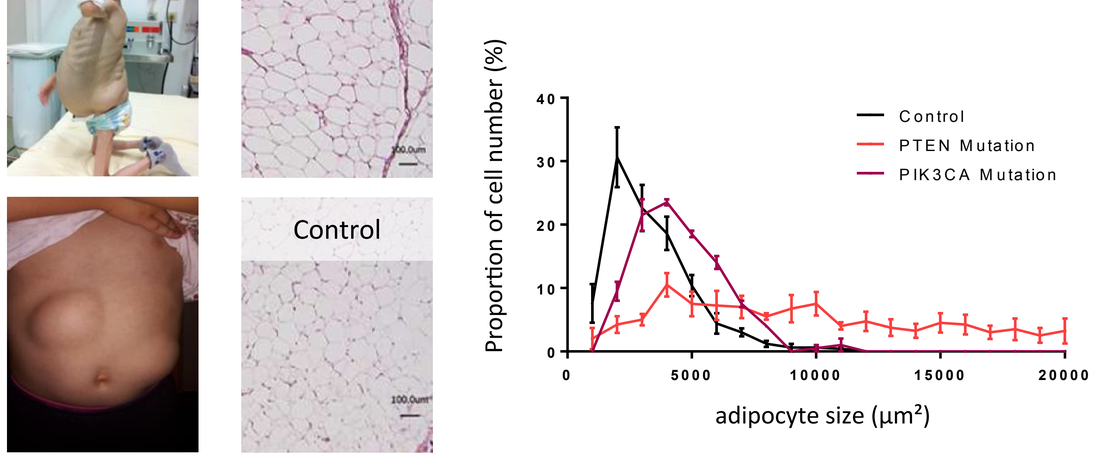


Fig. 1: Pediatric patients with PTEN haploinsufficiency and adipose tissue tumors (**A**), Histology of overgrowth and normal adipose tissue (**B**), Adipocytes from patients with germline *PTEN* (n=4) or mosaic activating *PIK3CA* (n=2) mutations were larger than sex- and age-matched control adipocytes (**C**).

2 PTEN deficiency leads to a higher phosphorylation of AKT

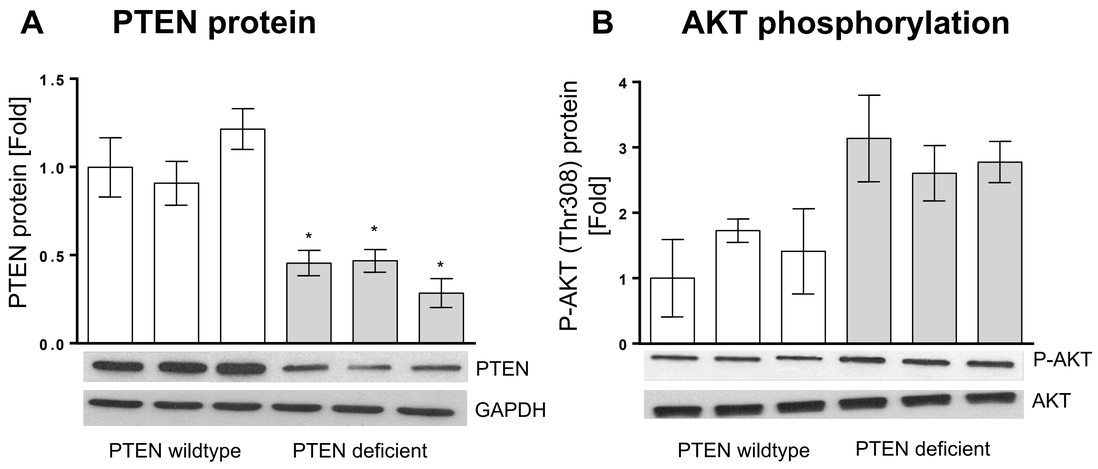
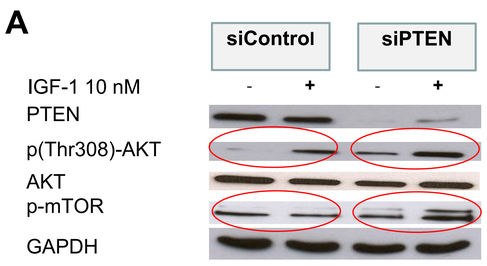


Fig. 2: Preadipocytes from affected tissue show decreased PTEN protein (**A**) and increased activation of AKT (**B**).

3 PTEN knockdown does not influence cell proliferation, nor differentiation despite higher AKT phosphorylation



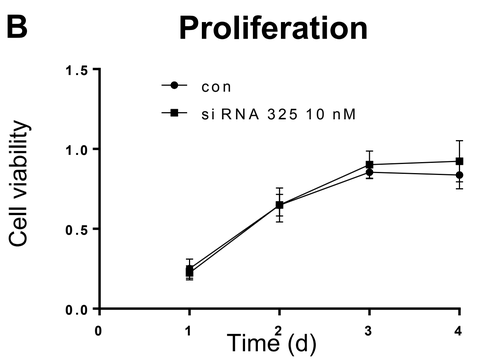


Fig. 3: AKT and mTOR phosphorylation was higher in PTEN knockdown SGBS preadipocytes compared to control SGBS cells (**A**). PTEN knockdown does not influence cell viability (**B**), nor adipocyte differentiation (**C**).

4 Activating *PIK3CA* mutation leads to a higher phosphorylation of AKT and increased lipid accumulation

Control: PI3K-wild type; Patient #1 and #2: activating PI3K mutation; Control cells and lipoma cells #1 were derived from the same patient.

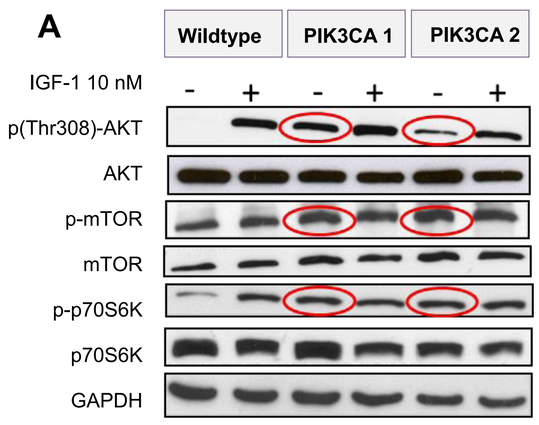
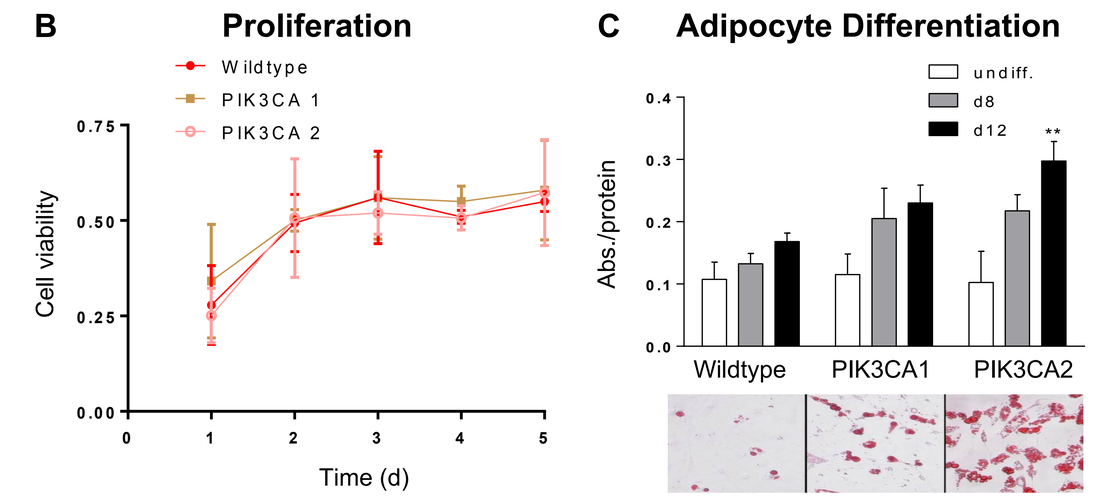


Fig. 4: Basal AKT, mTOR and p70S6K phosphorylation was higher in lipoma preadipocytes with a *PIK3CA* mutation compared to PI3K-wildtype preadipocytes (**A**).
PIK3CA mutations do not influence cell viability (**B**), but adipocyte differentiation was enhanced (measured by Oil Red O staining (**C**)).



CONCLUSION

PTEN deficiency or mutations in *PIK3CA* lead to hypertrophic adipose tissue with constitutive phosphorylation of AKT in cells, but not to increased proliferation *in vitro*.

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