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


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BACKGROUND & HYPOTHESIS

Inactivation of the tumor suppressor PTEN increases the level of PI3P, 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

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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