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Role of PDGFR and Akt in Tumorgenesis of Tuberous Sclerosis Complex

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The PI3K-Akt-mTOR pathway plays a pivotal role in regulating various cellular processes such as proliferation, growth, apoptosis or angiogenesis. The tumor suppressor TSC1/TSC2 complex has emerged as the sensor and integrator of growth conditions in this pathway, relaying signals from multiple signaling pathways to modulate mTORC1 activity. TSC1 and TSC2 are mutated in the tumor syndrome TSC (tuberous sclerosis complex) leading to aberrant mTORC1 activation. Recent investigations demonstrated that phosphorylation of the oncogene Akt in TSC1 and TSC2 deficient cells is reduced compared to wildtype cells. Furthermore, we observed that levels of PDGFRα and PDGFRβ, both receptor tyrosine kinases which regulate intracellular signal transduction, were reduced in cells lacking TSC1 or TSC2.
This study demonstrates that reduction of Akt activity is partly due to lower levels of PDGFRα and PDGFRβ in TSC1 and TSC2 deficient MEFs. Rapamycin treatment restores PDGFR levels, indicating that loss of TSC1/TSC2 complex blocks Akt signaling through a mTORC1-dependent negative feedback mechanism.
Interestingly, we observed that Akt activation in response to EGF and insulin was also reduced in *Tsc1*$^{-/-}$ and *Tsc2*$^{-/-}$ MEFs while expression of EGFR or insulin receptor in the *Tsc2*$^{-/-}$ cells were equal compared with wildtype cell lines. Although the mechanism must be further clarified, this study provides evidence that transactivation of RTKs like PGDFR, EGFR, IR can happen through a mechanism of RTK cross-talk. Alternatively to receptor heterodimerization, PDGFR might serve as a scaffold or adaptor protein which facilitates PI3K signaling.
TSC is an autosomal dominant multisystemic disorder characterized by the development of numerous benign tumors (mostly hamartomas) most commonly affecting brain, kidney, skin, lungs and heart. While mTOR activation is frequently observed in solid and hematological malignancies, development of malignant tumors in TSC patients is rare. The mouse model in this study indicates that blocked Akt signaling upon loss of the TSC1/TSC2 complex can, in fact, attenuate tumor progression *in vivo*. This data demonstrates that diminished PDGFR signaling is one mechanism for less aggressive tumor growth *in vivo*.
Taken together, these data emphasize that cells find various ways to fine tune signaling pathways. While interreceptor cross-talk appears to adapt RTK activation, these data give evidence that mTORC1-dependent negative feedback mechanisms can modulate upstream oncogenic pathways driving the malignancy potential of tumors.