

Phaeochromocytomas Associated with PTEN Mutation Demonstrate Tissue Specificity in the Anti-tumour Effect of mTOR Inhibition.

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Transgenic mice harbouring a mutation of PTEN (Pten^{+/-}) develop a number of different tumour types the most frequent being Bcell lymphoma and phaeochromocytoma. Development of the tumours is further enhanced by the presence of a hypomorphic allele of the LKB1 gene (LKB1^{+/-}hypo). PTEN is a phosphatase regulating the activity of the PI3kinase dependent pathway which leads to activation of Akt and further downstream mTOR and S6 riboprotein activation. To test the effectiveness of mTOR inhibition as an anti-tumour agent groups of Pten ^{+/-} mice were treated with the mTOR inhibitor AZD8055 or control drug vehicle. While lymphomas responded to the drug treatment by dramatic reduction in bulk and histological presence of apoptosis the phaeochromocytomas were resistant to the anti-tumour effect of the treatment. We analysed the activity of the Akt pathway in phaeochromocytoma using antibodies to phospho-specific epitopes on Akt (Thr 308 PDK1 site, Ser 473 mTOR site), S6riboprotein (Ser235 mTOR site), p-PDK1, GSK3, Bcl2, Cyclin D1 and LKB1 and immunocytochemistry on fixed tissue samples with lymphomas from the same animals for comparison. In both treated and untreated phaeochromocytomas there was strong reactivity for Akt p-308 but not Akt p-473 whereas untreated lymphomas showed reactivity for both but treated lymphomas only for Akt p-308 suggesting that in the phaeochromocytoma mTOR was not activated. This was confirmed by a lack of S6p-235 staining. While cyclin D1 was seen in only a small minority of lymphomas it was uniformly positive in the phaeochromocytomas as was GSK3. These several data suggest that phaeochromocytomas harbouring PTEN mutations arise by a different cellular mechanism from the lymphomas in the same animals and that GSK3 activation of cyclin D1 is involved. These findings reveal tissue specificity in pathway involvement within tumours arising from the same mutation. (Path Soc Summer project.)