

P043 Targeting the PI3K pathway in melanoma
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Phosphoinositide 3-kinases (PI3Ks) play an important role in cell growth and cytoskeletal rearrangements in cell motility. Here we investigate the importance of the four PI3K class I isoforms in melanoma proliferation and survival. The catalytic PI3K subunits p110 α , β and δ are expressed in melanocytes, but expression of p110 δ was lost in some melanoma cell lines. Interestingly, p110 γ is the only class I PI3K isoform not expressed in melanocytes but detectable in around 15% of metastatic cells. Melanoma cells, already at early tumor stages, often show constitutive activation of MAPK and PKB, indicating that these pathways might be key targets in melanoma therapy. Treatment of cells with broadband PI3K inhibitors, such as wortmannin or LY294002, led to little reduction in cell proliferation and to minimal cell death, independent on the aggressiveness of the tumor cell lines. A new generation of potent PI3K inhibitors, NG1 and NG2, on the other hand, induced complete growth arrest and apoptosis of treated cells. Moreover, expression of cyclin D1 was reduced and a strong increase in the expression of the cell cycle inhibitor p27^{KIP1} was detectable. Targeted elimination of specific PI3K class I isoforms using GeneBloc technology or shRNA expression demonstrated cell line specific dependencies on PI3K isoforms regarding phosphorylation of PKB and cell death. These results provide a first step towards the identification of patient-specific requirements of the PI3K isoforms in tumor growth and migration and might provide a basis for anti-PI3K therapy with minimal side effects.