21P Uveal melanoma cell lines depend on multiple signaling pathways for survival

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Background: Uveal melanoma (UM) is a rare cancer that arises from melanocytes in the uveal tract of the eye. Despite effective treatment for primary UM, > 50% of patients develop metastatic disease. There is currently no effective treatment for metastatic UM and median life expectancy is < 8 months. About 90% of UM are characterised by mutations in the GNAQ or GNA11 GTPases and several signalling cascades downstream of G-protein activation have been identified as potentially targetable. These include the protein kinase C (PKC), mitogen activated protein kinase (MAPK), phosphatidylinositol-3-kinases (PI3K), mammalian target of rapamycin (mTOR), and YES-associated protein (YAP) pathways. Aim to understand the relative contribution of oncogenic signaling pathways in proliferation and survival of UM.

Methods: The response 11 UM cell lines to 6 selective inhibitors was investigated using cell viability assays and cell cycle analyses by flow cytometry. Inhibition of selected pathways was examined using Western analysis of downstream effector proteins. The inhibitors used in this study included PKC inhibitors (AEB071 and LXS196), MEK inhibitor (trametinib), PI3K/mTOR inhibitor (BEZ235), YAP inhibitor (verteporfin) and ARF6 inhibitor (NAV2729).

Results: PKC inhibitors were most effective with 8 GNAQ/11 mutant UM cell lines showing some degree of sensitivity to each of the inhibitors, although sensitivity was usually associated with proliferative arrest rather than cell death. (see Table) Expression levels of pMARCKS and pERK were strongly inhibited by PKC inhibitors, however inhibition of these effector proteins did not reflect the degree of UM cell sensitivity.

Table: 21P Summary of UM cell lines to each inhibitor. Combined result of cell viability assay and cell cycle analysis

Cell Line	Mutation	Trametinib	BEZ235	NAV2729	AEB071	Verteporfin	LXS196
Mel270	GNAQ	sensitive	sensitive	sensitive	sensitive	sensitive	sensitive
OMM1	GNA11	resistant	sensitive	intermediate sensitivity	sensitive	sensitive	sensitive
92.1	GNAQ	resistant	intermediate sensitivity	sensitive	intermediate sensitivity	sensitive	intermediate sensitivity
Mel202	GNAQ	resistant	intermediate sensitivity	sensitive	intermediate sensitivity	sensitive	intermediate sensitivity
OMM1.3	GNAQ	resistant	intermediate sensitivity	resistant	intermediate sensitivity	resistant	intermediate sensitivity
OMM1.5	GNAQ	resistant	resistant	resistant	intermediate sensitivity	resistant	intermediate sensitivity
MP41	GNA11	resistant	resistant	resistant	intermediate sensitivity	resistant	intermediate sensitivity
MP46	GNAQ	resistant	resistant	resistant	resistant	resistant	intermediate sensitivity
MP38	GNAQ	resistant	resistant	resistant	resistant	resistant	resistant
Mel290	Nil	resistant	intermediate sensitivity	resistant	resistant	resistant	resistant
Mel285	Nil	resistant	resistant	resistant	resistant	resistant	resistant

Conclusions: The sensitivity of GNAQ/11 mutation UM cell lines to 6 targeted drugs is heterogeneous and no single dominant signalling pathway was identified. This suggest that multiple, independent signal pathways contribute to the survival of UM. Thus, inhibition of any single pathway is unlikely to be effective in the treatment of majority of metastatic UM.

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