Poster session 5. Translational research

P05.01 ESTABLISHMENT OF NOVEL PRECLINICAL MELANOMA MODELS RESISTANT TO VEMURAFENIB

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Background: Metastatic melanoma is one of the most treatment-refractory types of cancer and accounts for more than 80% of skin cancer deaths. Approximately 50% of melanomas harbor BRAF mutations, most of them being a valine to glutamic acid substitution at codon 600 (V600E). The recently approved RAF-selective inhibitor vemurafenib demonstrates remarkable anti-tumor response rate in patients with oncogenic BRAFV600E mutant melanoma. However, despite initial response, most patients acquire resistance within a year of treatment. Alternative therapeutic strategies to overcome primary or acquired resistance are required and therefore appropriate modelling of resistance is necessary to identify these novel therapies.

Materials and Methods: We undertook in parallel two complementary approaches in order to develop relevant preclinical models of resistance to vemurafenib. First we generated a model of acquired resistance by chronic exposure of the V600EBRAF-mutant melanoma cell line A375 to the drug. We also set up a collaborative workteam with clinicians to explore primary resistance using tumor samples derived from refractory patient metastatic melanomas.

Results: Melanoma cell line with acquired resistance to vemurafenib (A375-R) was generated by propagating parental A375 cells with continuous exposure to the drug during two months. A375-R cell line was more than 30 times less sensitive to the vemurafenib antiproliferative activity than its parental counterpart. A375-R cells were then grafted in vivo and vemurafenib activity was assessed. Vemurafenib led to inhibition of ERK phosphorylation in tumors of A375 xenograft mouse model and displayed potent anti-tumor activity (2/5 complete regressions and 3/5 partial regressions) whereas A375-R model was highly resistant to the drug (0/5 regression). Thanks to our collaboration with clinicians, surgically resected tumors samples were obtained from patients with metastatic melanoma before and after vemurafenib treatment. Human melanoma samples were grafted into NSG mice. Preliminary results showed that tumor xenografts derived from a primary refractory patient’s metastatic melanoma retained complete resistance to vemurafenib in animals.

Conclusions: We developed alternative approaches to select in vivo melanoma models of primary and acquired resistance to vemurafenib. Our results suggest that they will be useful to explore underlying mechanisms and to propose novel therapeutic strategies.