Molecular Profiling of BRAFi-Resistance in Melanoma Cancer Models using High-throughput Sequencing in Patient-Derived Xenografts

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I - The collection of Oncotest Melanoma PDXs

II - Mutational profiles in MEXFs and intrinsic BRAFi-resistance analysis

Introduction
- Patients with BRAF V600E mutant melanomas treated with BRAF inhibitors (BRAFi) such as Vemurafenib (PLX4032) paradoxically develop resistant aggressive tumors with high metastatic dissemination.
- Suitable models for studying mechanisms of resistance to BRAFi are therefore needed.
- In the present study, we applied next-generation sequencing techniques to characterize melanoma Patient-Derived Xenografts (PDXs) in order to identify the molecular mechanisms mediating either intrinsic or acquired BRAFi-resistance.

Materials and Methods

I - The collection of Oncotest Melanoma PDXs
- The MEXF series is a collection of PDXs created at Oncotest (www.oncotest.com) from patients treated at the melanoma center of the University of Freiburg (Germany).
- Patients with BRAF V600E mutant melanomas treated with BRAFi (PLX4032) paradoxically developed resistant aggressive tumors with high metastatic dissemination.
- Suitable models for studying mechanisms of resistance to BRAFi are therefore needed.
- In the present study, we applied next-generation sequencing techniques to characterize melanoma Patient-Derived Xenografts (PDXs) in order to identify the molecular mechanisms mediating either intrinsic or acquired BRAFi-resistance.

II - Mutational profiles in MEXFs and intrinsic BRAFi-resistance analysis
- The total number of mutations across all the melanomas PDXs (MEXFs) was heterogeneous and ranged from 462 to 535 genomes (Fig. 1A).
- The most frequently mutated genes in MEXFs were similar to those found in human melanoma cell lines from the Cancer Genome Atlas (Fig. 1B).
- Melanoma-specific mutations/signatures were detected in each MEXF cell line (Fig. 1C).
- MEXF HT144, which was not only BRAFch, showed the highest number of mutations between the MEXF and non-melanoma cell line (Fig. 1D).

Conclusions
- The analysis of whole-exome data revealed similarities in genetic alteration patterns between Melanoma PDXs and patient melanomas from the TCGA, confirming the Oncotest Melanoma PDX collection as a relevant and representative panel of models to study BRAFi-resistance and other mechanisms in melanoma.
- Up-regulation of RAS/RAF pathway genes combined with high mitotic levels may be associated with intrinsic BRAFi-resistance.
- A comprehensive RNAseq analysis of BRAFi-resistant MEF cell lines revealed different gene regulation mechanisms potentially leading to the reactivation of pathways or alternative pathways in the BRAFi-resistant acquiring.

References