Abstract

Discovery of a kinome signature predicting sensitivity and resistance to RAF-MAPK pathway inhibitors in melanoma

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Introduction

RAF-MAPK pathway inhibition with BRAF inhibitors or the combination of BRAF and MEK inhibitors has become the mainstay of therapy of metastatic melanoma harboring BRAF V600E mutations with a response rate as high as 50-75%. A minority of patients present with primary resistance while all patients develop secondary resistance. We explored a reversed translational approach using a novel multiplex kinase assay to explore the mechanism of resistance.

Aim of the study

• Identify individuals not responding to therapy using baseline biopsy samples.
• Understand the mechanisms of resistance using patient-derived cell lines.

Melanoma patient samples: intrinsic resistance

Serine/threonine and tyrosine kinase activity of 7 melanoma biopsies harboring the BRAF V600E mutation was determined with and without dabrafenib on STK and PTK.

Melanoma cell lines: acquired resistance

Cells harboring the BRAF V600E mutation with acquired resistance to vemurafenib were obtained after chronic treatment with vemurafenib.

Conclusion

Resistance of tumors and cell lines to vemurafenib can affect kinase activity profiles as detected pre-dose using a multiplex kinase assay. This method allows separate investigation of the activity of STK and PTK in the presence and absence of inhibitors and showed that dabrafenib inhibition is stronger on tyrosine kinase than on serine/threonine kinase activity. In tissue lysates, concentration-dependent ex vivo inhibition with dabrafenib was stronger in the patients that were clinical responders to vemurafenib and in vemurafenib sensitive cell lines. Resistant BRAF mutant cell lines have an increased tyrosine kinase activity. Resistance to MAPK pathway inhibitors could be linked to an increase in tyrosine kinase activity of Src family kinases and increased AKT pathway activity. A role for Src family kinases has been reported in [4]. Combination of dabrafenib with the MEK inhibitor trametinib has a synergistic inhibitory effect on tyrosine kinase activity. Biomarkers are needed to identify patients in need of combined MAPK pathway inhibition.

References

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