

Reporting Summary

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Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study. For final submission, please carefully check your responses for accuracy; you will not be able to make changes later.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

- | n/a | Confirmed |
|--------------------------|---|
| <input type="checkbox"/> | <input checked="" type="checkbox"/> The <u>exact sample size</u> (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> A description of all covariates tested |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> A full description of the statistics including <u>central tendency</u> (e.g. means) or other basic estimates (e.g. regression coefficient) AND <u>variation</u> (e.g. standard deviation) or associated <u>estimates of uncertainty</u> (e.g. confidence intervals) |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> Clearly defined error bars
<i>State explicitly what error bars represent (e.g. SD, SE, CI)</i> |

Our web collection on [statistics for biologists](#) may be useful.

Software and code

Policy information about [availability of computer code](#)

Data collection The structural analysis is based on the data acquired from PDB:BRAF-BRAF (PDB: 4E26) and CRAF-CRAF (PDB: 3OMV)

Data analysis The densitometry analysis was done by Image J, all the graphs are generated by Graphpad Prism 6.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

We have included a statement "Source data and all other data supporting this work are provided in Supplementary information." in the Availability of Data.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was chosen based on previous studies. The sample sizes have been shown to be sufficient for the statistical analysis.
Data exclusions	No data were excluded from the analysis.
Replication	All experimental findings were reliably reproduced. We have indicated the replicates of the experiments in the Figure Legends.
Randomization	The mice are randomized in each test groups in the animal studies.
Blinding	All experiments were conducted in unblinded conditions. The experiments are designed based on preliminary data and pilot experiments, and a detail protocol is required for the animal core to run the studies.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems		Methods	
n/a	Involved in the study	n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Unique biological materials	<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies	<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines	<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants		

Antibodies

Antibodies used	Western blot and immunoprecipitation (IP) were performed as described ^{1,20} . Antibodies used include: anti-p217/p221-MEK1/2 (p-MEK1/2) (#9154, lot#14), anti-p202/p204-ERK1/2 (p-ERK1/2) (#4370, lot# 17), anti-MEK1/2 (#4694, lot# 6), and anti-ERK1/2 (#4696, lot# 16) from Cell Signaling; anti-V5 (46-1157, lot# 1902786) from Invitrogen; anti-BRAF (cat# sc-5284, lot# C0116), anti-Cyclin D1 (cat# sc-718, lot# G1411) and anti-ARAF (cat# sc-166771, lot# A2617) from Santa Cruz Biotechnology; anti-FLAG (cat# F1804, lot# SLBT7654) from Sigma; anti-CRAF (cat# 610152, lot#7208706) from BD Transduction Laboratories; and anti-RAS (cat# 1862335, Lot # S1259698) from the active RAS pull-down and detection kit (Thermo Fisher Scientific, cat# 16117). For immunoprecipitations of tagged proteins, we used: anti-V5 agarose affinity gel (Sigma, cat# A7345, lot# SLBR7667V) and anti-FLAG M2 affinity gel (Sigma, cat# F1804, lot# SLBT7654), protein G agarose gel (Thermo Fisher Scientific cat# 15920010). The secondary antibodies used for Western blot are: goat anti-rabbit, HRP (Sigma, cat# A4914, lot# SLBM7730U) and donkey anti-mouse, HRP (Amersham, cat# NXA931, lot# 9708064). The primary antibodies used in Western Blot are diluted in 1:1,000, secondary antibodies are diluted in 1:5,000. The antibodies used in IP assay, are diluted in 1:200. All these antibodies have been validated in the previous studies.
Validation	All the antibodies have been validated in our previous work.

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	Cell lines A375: CRL-1619, 22Rv1: CRL-2505, H1666: CRL-5885, H508: CCL-253, H661: HTB-183, SKBR3: HTB-30, A549: CCL-185, BEAS-2B: CRL-9609, primary epidermal melanocytes: PCS-200-012 and primary epidermal keratinocytes: PCS-200-011 was obtained from American Type Culture Collection. SK-MEL-239, SK-MEL-239 C4, SK-MEL-2, SK-MEL-30, SK-MEL-246 and SK-MEL-285 were from MSKCC cell collection. CAL-12T: ACC433 and JVM-3: ACC18 were from DSMZ. 293H cells
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(#11631017) were purchased from ThermoFisher Scientific. MDST8 cells were from Millipore Sigma (#99011801). The conditional RAF knockout MEF cell line was from M. Barbacid lab.

Authentication	All the cell lines used in this study have been validated in previous work. Genetic alterations in cell lines from the MSKCC cell collection were confirmed by IMPACT sequencing.
Mycoplasma contamination	All cell lines tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No Commonly misidentified cell lines are used in this study.

Animals and other organisms

Policy information about [studies involving animals: ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals	4-6 weeks old, female NSG mice were used in this study.
Wild animals	The study did not involve wild animals.
Field-collected samples	No field-collected samples are used in this study

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	<p>Tumor samples were collected from MSK patients (Patient with BRAF G466V tumor: 55yo, Female, (Right) colon cancer, PDX collected after treatment with standard chemotherapy; Patient with BRAF K601E tumor: 41yo, Female, (Left) colon cancer, PDX collected after treatment with standard chemotherapy; no patient has received RAF inhibitor treatment when the samples are collected).</p> <p>The patient tumor samples were transplanted orthotopically into NSG mice to make the PDX (IRB protocols 06-107, 14-091 (13)). Studies were performed in compliance with institutional guidelines under an IACUC approved protocol and all analysis of human tissues was conducted under institutional Review Board/Privacy Board approved protocol.</p>
Recruitment	The patients are not recruited for specific study. The Patient samples are defined by IMPACT sequencing and selected by certain genetic alterations. The Patient ID information have been removed when samples are collected.

