Aug 9th, 10:15 AM - 12:00 PM

Defining the role of NRAS in melanoma maintenance

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Repository Citation
Challa, Sravya T. and Holmen, Sheri L., "Defining the role of NRAS in melanoma maintenance" (2011). Undergraduate Research Opportunities Program (UROP). 33.  
https://digitalscholarship.unlv.edu/cs_urop/2011/aug9/33

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Defining the Role of NRAS in Melanoma Maintenance

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Molecular Analysis of Human Melanoma

<table>
<thead>
<tr>
<th>Gene/Tissue</th>
<th>Familial/Sporadic</th>
<th>Alterations</th>
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<tbody>
<tr>
<td>RAS</td>
<td>S</td>
<td>Point mutation, deletion, promoter</td>
</tr>
<tr>
<td>BRF</td>
<td>S</td>
<td>Point mutation, deletion</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>S</td>
<td>De novo or gain of function</td>
</tr>
<tr>
<td>HGF</td>
<td>S</td>
<td>Gain of function</td>
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<tr>
<td>MYC</td>
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<td>PIK3CA</td>
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<td>PTEN</td>
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<tr>
<td>TP53</td>
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<td>De novo or gain of function</td>
</tr>
</tbody>
</table>

RAS/TVa Melanoma Mouse Model System

TVA reporter for early stage development. A) Schematic of the canonical RAS effector pathways RAF-MEK-ERK and PI3K-Akt and the mutations that most often activate NRAS.

Initial Validation of Melanoma Associated Genes

Expression of RAS in SK-MEL cells and growth in soft agar. Cell lines from untreated D-EEL tumor xenografts (+) or cells induced with doxycycline treatment containing either (A) NRAS or (B) TVA (were killed at the E85 level, amplified) treated (+) and untreated (+) are exposed to treated (B) or untreated (A) control cells and phase-contrast images (10X and 40X).

Results and Conclusions

- Knockdown of ARF in SK-MEL cells was achieved to below 50% by transfection with D-EEL vector alone or mock vector. The effect of ARF knockdown was evaluated by Western blot and immunostaining for ARF expression.
- Knockdown of RAS in SK-MEL cells was achieved to below 50% by transfection with D-EEL vector alone or mock vector. The effect of RAS knockdown was evaluated by Western blot and immunostaining for RAS expression.

Future Directions

- Evaluation of the role of NRAS in melanoma progression.
- Development of targeted therapies for melanoma.
- Investigation of the mechanisms of NRAS-mediated cell proliferation and survival.

ACKNOWLEDGEMENTS

- The project was supported by the National Institutes of Health (NIH) and the Nevada System of Higher Education (NSHE). The authors thank the Nevada Cancer Institute for their support.
- The graphical abstract was prepared by the Nevada Research Resources Center.

Figure 1: Schematic of the canonical RAS effector pathways RAF-MEK-ERK and PI3K-Akt, and the mutations that most often activate NRAS.