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STAT3 – the switch of melanoma-associated NRAS mutations

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Mutations in *NRAS* represent almost 20% of driver mutations in malignant melanoma. Clinically, this entity of melanoma is characterized by worse survival rate, relapse rate and therapy response compared to wild type *NRAS* or *BRAF* mutations. Moreover, the treatment of *NRAS* mutated melanoma remains difficult where direct targeting has shown sobering attempts so far. Interestingly, the codon mutational status of *NRAS* mutations comprises almost exclusively codon 61 mutations (93%) rather than codon 12 or 13 mutations (5%) and depicts different biological behavior in previous studies. Therefore, we focused on revealing the differential activation of cellular signaling pathways of these codon mutations in primary melanocytes and in melanoma-like immortalized melanocytes.

We identified STAT3 as the switch of *NRASQ61*-mediated melanomagenesis to a more transformative phenotype in primary melanocytes and in immortalized melanocytes. In primary melanocytes, *NRASQ61*-mutated cells were able to circumvent oncogene-induced senescence (OIS), whereas *NRASG12/13*-mutated cells seemed to be more susceptible to OIS. Furthermore, immortalized melanocytes expressing *NRASQ61* presented higher proliferative, colony-forming and migratory capacities than *NRASG12/13* cells. Both, in primary and immortalized melanocytes, *NRASQ61* expression was associated with STAT3 activation.

The analysis of downstream targets of STAT3 revealed *MMP2*, *IL-1ß* and *IL1R* as mediators of NRASQ61-STAT3-axis and its oncogenic phenotype. Additionally, we identified a specific secretory phenotype and kinases activation for each *NRASQ61* and *NRASG12/13* mutated melanocytes.

Taken together, we show novel insights into molecular and cellular mechanisms that are activated upon different *NRAS* mutations and demonstrate the protumorigenic role of STAT3 in *NRAS* mutant melanoma which might help improving future therapeutic strategies.