TARGET WATCH

STK19: a new target for NRAS-driven cancer

Oncogenic mutations in RAS GTPases occur in ~20–30% of human tumours. However, RAS proteins are highly challenging drug targets, and no selective direct inhibitors of NRAS have been reported. Serine/threonine-protein kinase 19 (STK19) has recently been identified as a regulator of NRAS activity (*Cell* **176**, 1113–1127; 2019), and the development of STK19 inhibitors could be a novel intervention opportunity.

Biological functions

STK19 was first described more than two decades ago as a novel serine/threonine protein kinase that could phosphorylate α-casein and histones (*J. Biol. Chem.* **273**, 30954–30960; 1998), but its characterization has been very limited until recently. In 2019, Yin and colleagues reported a kinome-wide siRNA screen that showed that knockdown of STK19 inhibited NRAS activity (*Cell* **176**, 1113–1127; 2019). They found that mutant STK19 had an important role in driving melanomagenesis through activating downstream signalling by the most prevalent mutant form NRAS-Q61R, which is trapped in a constitutively active conformation (*Front. Oncol.* **24**, 965; 2019). Furthermore, STK19 depletion decreased the amount of active NRAS, reducing downstream signalling and the proliferation and tumour-forming ability of melanocytes. The interaction between STK19 and NRAS was also investigated, and it was found that phosphorylation of an evolutionarily conserved Ser89 residue in NRAS by STK19 enhances the interaction between NRAS-Q61R and the effector proteins BRAF, CRAF and PI3Kα (FIG. 1a).

STK19 is altered in around 25% of skin cutaneous melanoma cases. Analysis of the TCGA database revealed that an STK19-D89N mutation represents ~42% of the STK19 alterations, and it was found to be a gain-of-function mutation (*Cell* **176**, 1113–1127; 2019). Interestingly, if the oncogenic NRAS-Q61R was also present, STK19-D89N further promoted human melanocyte proliferation and tumour formation. In mice, a sevenfold increase in melanoma incidence after 1 year was observed if both proteins are mutated compared with NRAS-Q61R alone.

Together, these findings indicate the potential of STK19 inhibition as a therapeutic strategy for NRAS-driven melanomas. Furthermore, the Ser89 residue in NRAS, which is phosphorylated by STK19, is conserved in other RAS family members, potentially increasing the range of cancers for which STK19 could be a promising target.

Chemical tools

Literature tool compounds for STK19 are sparse, mainly owing to its lack of inclusion in wider kinome screening panels. However, the recent paper by Yin and colleagues showed that the quinazoline-based kinase inhibitor ZT-12-037-01 (FIG. 1b) is a potent and highly selective inhibitor of STK19 (IC_{50} = 35 nM). ZT-12-037-01 shows dose-dependent inhibition of STK19 phosphorylation and inhibition of the growth of NRAS-Q61R mutant melanoma in mouse xenograft models (*Cell* **176**, 1113–1127; 2019).

The natural product chelidonine (FIG. 1b) was also recently identified as an STK19 inhibitor (IC_{50} = 113 nM), with less selectivity than ZT-12-037-01 (*Clin. Cancer Res.* **26**, 3408–3419; 2020). Chelidonine inhibited NRAS-driven tumour growth in a mouse model.

These two inhibitors provide excellent starting points for further investigating STK19 biology and identifying potential drug candidates for RAS-driven cancers.

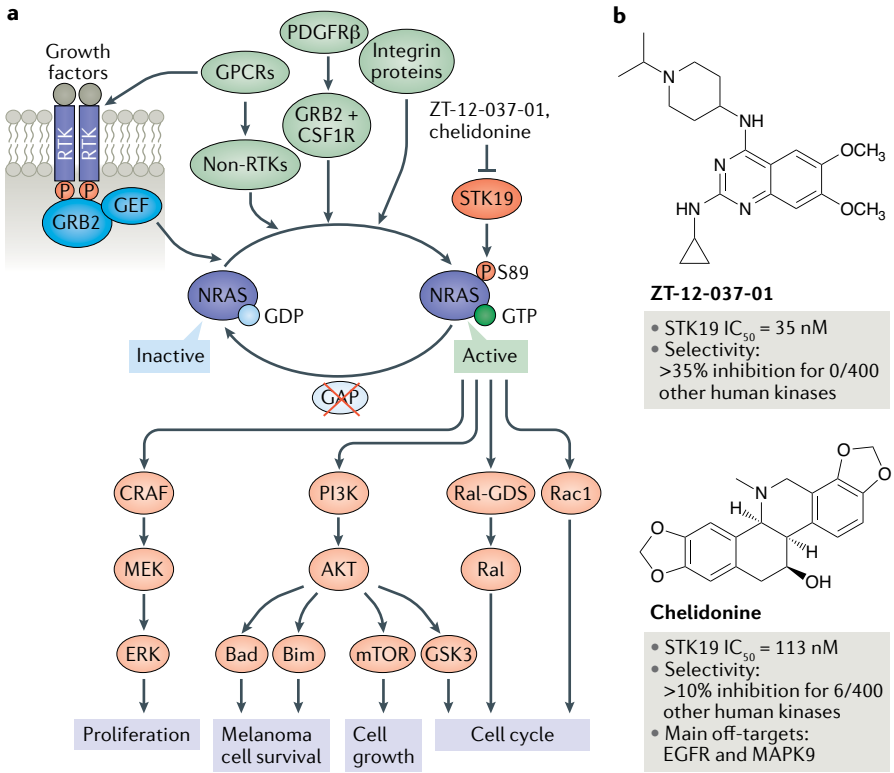

Fig. 1 | **STK19 as an anticancer drug target. a** | A simplified overview of the NRAS signalling pathway in melanoma. For details, see *Front. Oncol.* **24**, 965; 2019 and *Oncogene* **32**, 3009–3018; 2013. **b** | Structures and characteristics of two reported STK19 inhibitors.

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Competing interests

The authors declare no competing interests.

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