The Editor's Choice

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Transcriptional repression of the tyrosinase-related protein 2 gene by transforming growth factor-β and the Kruppel-like transcription factor GLI2

TRP2 is an enzyme involved in melanogenesis, that also exerts proliferative, anti-apoptotic and immunogenic functions in melanoma cells. TRP2 transcription is regulated by the melanocytic master transcription factor MITF. GLI2, a transcription factor that acts downstream of Hedgehog signaling, is also a direct transcriptional target of the TGF-β/SMAD pathway that contributes to melanoma progression and exerts transcriptional antagonistic activities against MITF. Pierrat MJ et al characterized the molecular events responsible for TGF-β and GLI2 repression of TRP2 expression. TGF-β and GLI2-specific TRP2 repression involves direct mechanisms that occur in addition to MITF downregulation by TGF-β and GLI2. Two functional GLI2 binding sites were identified within the TRP2 promoter that are critical for TGF-β and GLI2 responsiveness. GLI2 and CREB competing for the same cis-element is associated with opposite transcriptional outcome. Our results further refine the understanding of how TGF-β and GLI2 control the phenotypic plasticity of melanoma cells. Critical GLI2-bindingcis-elements within the TRP2 promoter region allow for its transcriptional repression independently from MITF concomitant downregulation.

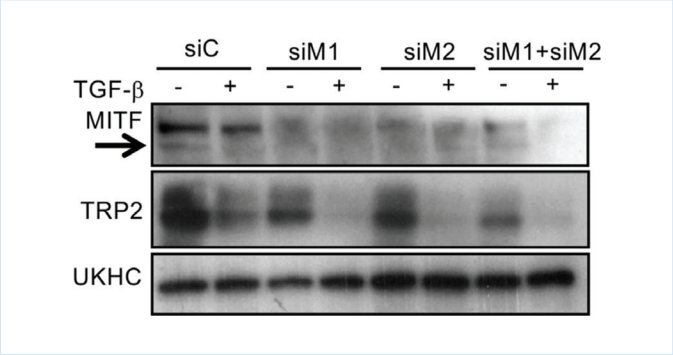

Fig. 2. TRP2 repression by TGF-β is partly independent from MITF downregulation. (B) 888mel human melanoma cells were transiently transfected with either control (siC) or MITF-specific siRNA oligonucleotides (siM1 and siM2), alone or in combination. 48 h later, medium was changed and cells were further incubated for 24 h without (-) or with (+) TGF-β (5 ng/ml), after which MITF and TRP2 protein levels were estimated by Western blotting. UKHC served as a control.

MicroRNA-664 functions as an oncogene in cutaneous squamous cell carcinomas (cSCC) via suppressing interferon regulatory factor 2

Aberrant expression of microRNA-664 was involved in tumor growth and metastasis of various cancers, whereas the specific role of miR-664 in cutaneous squamous cell carcinoma (cSCC) is yet to be elucidated. Le X et al aimed to investigate the molecular mechanisms underpinning of cSCC development and provide translational insights for future therapeutics. miR-664 was remarkably high in cSCC patient specimens and cSCC cell lines. Overexpression of miR-664 promotes tumorigenic behaviors such as increased cell proliferation, migration and invasion capacities in vitro and enhanced tumorigenicity in xenograft mouse model. IRF2 was identified as a direct downstream target of miR-664. Knockdown of IRF2 reverses protumorigenesis phenotype of miR-664; whereas IRF2 over-expression inhibits miR-664 tumorigenesis in cSCC. It revealed miR-664 functions as an oncogene in cSCC via suppression of IRF2. These data demonstrates that aberrant expression of miR-664 plays a critical role in carcinogenesis of cSCC. The discovery of novel targets such as miR-664 and IRF2 will facilitate future development of therapeutic interventions.

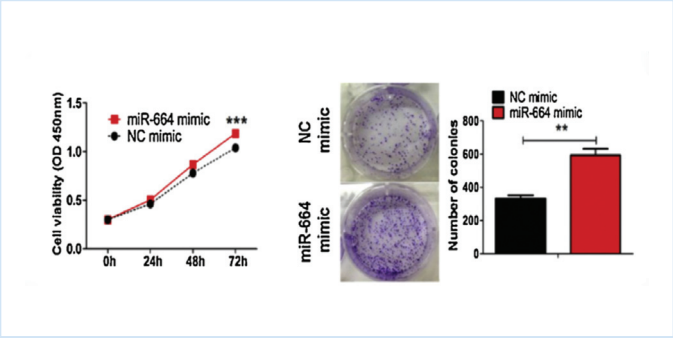

Fig. 2. miR-664 promotes tumorigenicity of cSCC. (A) Increased cell viability and proliferation were found in miR-664 over-expression (miR-664 mimic) *versus* NC transfected HSC-5 cells.

Long-term safety and efficacy of rupatadine in Japanese patients with itching due to chronic spontaneous urticaria, dermatitis, or pruritus: A 12-month, multicenter, open-label clinical trial

Rupatadine is a novel H1 antihistamine with platelet-activating factor antagonist activity. Its efficacy and safety on pruritic skin diseases have been demonstrated by 10 mg/day rupatadine in a two weeks clinical trial. Hide M et al investigated the long-term efficacy and safety of rupatadine in the management of pruritus, and the clinical effect of updosing to 20 mg in Japanese adult and adolescent patients. The therapeutic effect persisted up to Week 52. Adverse drug reactions (ADRs) were reported at an overall incidence of 18.0% (45 events in 37 patients). No serious or clinically significant ADRs were reported. Somnolence was the most common ADR (14.1%). This clinical trial demonstrated the short- and long-term benefits of rupatadine in the management of patients with chronic spontaneous urticaria, dermatitis, and pruritus. Rupatadine 10 and 20 mg doses are effective for the treatment of itch in adults and adolescents, and can be used safely on a long-term basis.

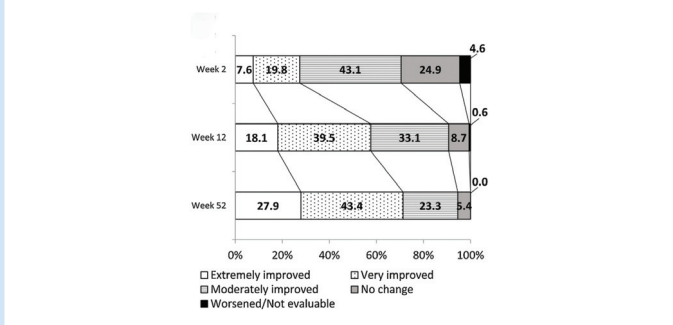

Fig. 2. Patient and physician overall impression: full analysis set. (a) Patient overall impression.