Study evaluates protein that regulates pigment cell development for role in skin cancer

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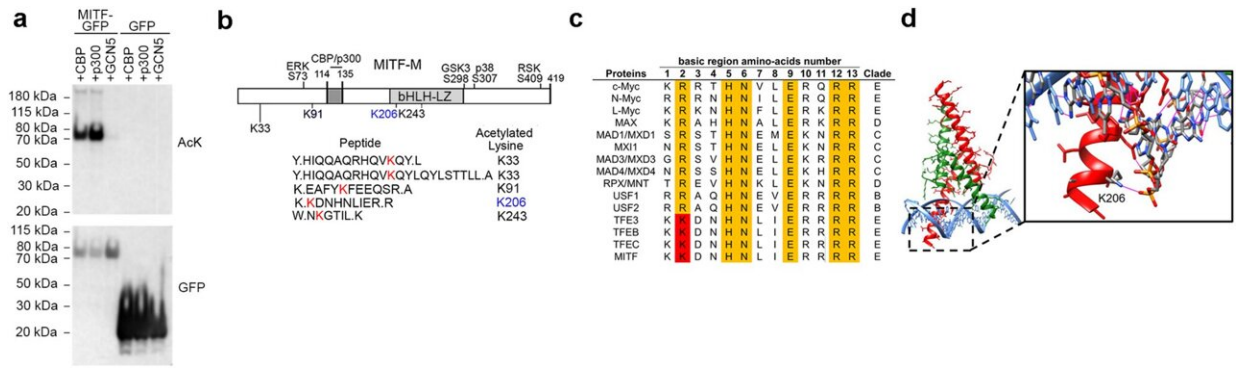

Acetylation of MITF at K206. a Western blot using anti-acetyl lysine or anti-GFP antibodies of immunoprecipitated GFP-tagged MITF co-expressed with CBP, p300 or GCN5 in Phoenix-AMPHO cells as indicated. AcK; Acetyl-Lysine. This experiment was repeated 3 times with similar results. b Schematic showing locations of MITF acetylation sites (red) detected in this study, and AcK206 in blue. Acetylated peptides derived from Mass Spec analysis are indicated below and phosphorylation sites and the p300 binding motif are indicated above. c Alignment of amino acids in the basic region of related bHLH-LZ family members. Yellow highlights highly conserved residues, and the red highlight (corresponding to K206 in MITF) indicates lysines conserved only in the MiT subfamily. d Depiction of the MITF-DBD-DNA co-crystal structure highlighting the K206-phosphate backbone interaction. MITF monomers are depicted in red or green, and DNA in blue. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-41793-7

The microphthalmia-associated transcription factor (MITF) is the master regulator of pigment cell development and, as a lineage survival oncogene, plays a crucial role in the skin cancer melanoma and its resistance to therapy. How MITF distinguishes between its seemingly incompatible differentiation and proliferation-associated targets in the genome has been a bit of a puzzle.

Ludwig Oxford's Pakavarin Louphrasitthiphol, Colin Goding and colleagues discovered that the ability of MITF to bind DNA is inhibited by CBP/p300-mediated acetylation of its lysine residue 206, which preferentially directs its binding away from DNA elements involved in differentiation. This suggests an explanation for why a mutation of that residue—K206Q—is associated with Waardenburg syndrome, which is often characterized by defects in pigmentation of hair, skin and eyes.

Reported in *Nature Communications*, the results also reveal that more than 40% of MITF molecules are tightly bound to DNA in the nucleus, with residence times of more than 100 seconds—compared to just a handful of seconds for most transcription factors. This makes MITF comparable to transcriptional repressor CTCF and polycomb repressive complex 1 (PRC1) and suggests that it might play similar roles in the establishment and maintenance of chromatin organization specific to the melanocyte lineage.

More information: Pakavarin Louphrasitthiphol et al, Acetylation reprograms MITF target selectivity and residence time, *Nature Communications* (2023). DOI: 10.1038/s41467-023-41793-7

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