ACETYLATION OF THE p53 CTD ABOLISHES SET BINDING TO ACTIVATE p53

The C-terminal domain (CTD) of p53 can be acetylated, but the exact function of this post-translational modification is not well understood. To identify p53 binding proteins dependent on CTD acetylation, Wang, Kon, and colleagues generated unacetylated and fully acetylated p53 CTD peptides and analyzed their binding partners by mass spectrometry, which identified SET as a specific binding partner of unacetylated p53. The acidic domain of SET bound directly to the CTD of p53, and expression of CREB-binding protein (CBP), which acetylates the p53 CTD, prevented SET binding to wild-type but not acetylation-deficient p53, further indicating that SET binds specifically to the unacetylated p53 CTD. Under unstressed conditions, SET acted as a transcriptional corepressor of p53; it bound DNA only when in complex with p53 and reduced p53 transcriptional activity and expression of p53 target genes. However, DNA damage induced CTD acetylation, disrupted the p53–SET interaction, and enhanced p53 transcriptional activity. In vivo, SET depletion reduced the growth of tumor xenografts in a p53-dependent manner, as SET depletion had no effect on tumor growth in p53-deficient tumors. Of note, SET also regulates other proteins with lysine-rich domains similar to the p53 CTD including KU70, FOXO1, and histone H3, and, similar to p53, acetylation blocked binding of the SET acidic domain to these proteins. These findings suggest a widespread function of the SET acidic domain as a “converse reader” that specifically recognizes unacetylated proteins. Moreover, mouse embryonic fibroblasts expressing an acetylation-mimicking p53 mutant exhibited a severe proliferation defect, increased senescence, and enhanced p53 activity. Collectively, these findings demonstrate the essential role of the p53–SET interaction in vivo and uncover a mechanism of acetylation-dependent p53 regulation that may extend to other proteins with lysine-rich domains.


Melanoma

Major finding: PGC1α inhibits melanoma metastasis independent of its role in mitochondrial energetic metabolism.

Mechanism: PGC1α promotes expression of ID2, which inhibits TCF4 to suppress integrin expression.

Impact: Targeting components of the PGC1α signaling cascade may suppress melanoma metastasis.

PGC1α REPRESSES MELANOMA CELL INVASION AND METASTASIS

PGC1α is a transcriptional coactivator involved in mitochondrial biogenesis and metabolic reprogramming in melanoma. Although it has been linked to poor prognosis, its expression has also been associated with less invasive growth, prompting Luo, Lim, and colleagues to explore the role of PGC1α in melanoma metastasis. PGC1α depletion increased expression of prometastatic genes, increased expression of integrins, and promoted activation of the downstream focal adhesion kinase, resulting in enhanced cell migration and invasion. In vivo, PGC1α suppression resulted in highly metastatic melanoma cells and widespread disease. In contrast, expression of PGC1α in PGC1α-negative cells reduced integrin expression and invasion. Melanoma cells exhibited heterogeneous PGC1α expression and mitochondria number. The mitochondrial/PGC1α population of cells displayed enhanced expression of prometastatic genes, whereas the mitochondria/PGC1α population exhibited enhanced proliferation. PGC1α bound at the promoter and increased expression of Inhibitor of DNA binding 2 (ID2), and, like PGC1α depletion, ID2 depletion promoted lung metastasis. Moreover, expression of ID2 in PGC1α-deficient cells suppressed the prometastatic gene programs and reduced metastasis, suggesting that ID2 acts downstream of PGC1α to suppress metastasis. Mechanistically, ID2 bound to and inactivated the transcription factor TCF4, thereby reducing integrin expression and suppressing metastasis. Of note, suppression of ID2 or TCF4 did not affect cellular metabolism, indicating that the role of PGC1α in suppressing metastasis is distinct from its role in metabolism. Treatment with a BRAFV600E inhibitor increased expression of PGC1α and ID2, and reduced TCF4 occupancy at integrin gene promoters, resulting in their downregulation. Further, vemurafenib suppressed melanoma metastasis in vivo, but its effects were reduced when PGC1α or ID2 were depleted. Together, these results indicate that targeting components of the PGC1α-ID2–TCF4–integrin signaling pathway may suppress melanoma metastasis, and suggest that early use of BRAFV600E inhibitors may have the potential to reduce metastasis.

# PGC1α Represses Melanoma Cell Invasion and Metastasis

*Published OnlineFirst September 16, 2016; DOI: 10.1158/2159-8290.CD-RW2016-171*

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