Transcription Factors

Major finding: p63-dependent paracrine FGFR2 signaling is required for squamous cell carcinoma survival.

Mechanism: The ΔNp63 isoform directly induces FGFR2, which is activated by stromal cell–expressed ligands.

Impact: Pharmacologic FGFR2 inhibition triggers apoptosis and tumor regression via AKT suppression.

SQUAMOUS CELL CARCINOMAS ARE ADDICTED TO p63–FGFR2 SIGNALING

Activating mutations in clinically actionable oncogenes are rare in squamous cell carcinomas (SCC) of the skin, lung, esophagus, and head and neck (HNSCC), emphasizing the need to better understand the pathways driving SCC pathogenesis. SCC tumors frequently exhibit inactivation of the tumor suppressor p53 and overexpression or amplification of *TP63*, which encodes a p53-related transcription factor, p63, that is critical for normal epithelial development, but it is unknown how p63-regulated target genes and pathways contribute to SCC. To investigate this question, Ramsey and colleagues generated a mouse model of carcinogen-induced SCC that recapitulated many of the histologic and molecular features of human SCCs, including elevated expression of p63, in particular the ΔNp63 isoform. Tissue-specific deletion of *Tp63* triggered apoptosis and rapid regression of established oral and cutaneous SCCs without significant effects on normal epithelial tissues, indicating that endogenous SCCs are dependent on p63 for survival and growth. *Tp63* deficiency resulted in downregulation of genes involved in integrin signaling, RAS activation, and fibroblast growth factor (FGF) signaling, including FGF receptor 2 (*Fgfr2*), which was directly activated by ΔNp63 in murine SCCs and human HNSCC cell lines and correlated with Δ*Np63* expression in primary human HNSCCs. Consistent with a role for ΔNp63-driven FGFR2 signaling in SCC, overexpression of this p63 isoform or the FGFR2 IIIb isoform was sufficient to rescue the growth-inhibitory effects of p63 knockdown in HNSCC cells. FGFR2 activation was dependent on increased expression of FGFR2 ligands by tumor-associated stromal cells and deregulated paracrine signaling in SCC tumors. Moreover, pharmacologic inhibition of FGFR2 suppressed autochthonous SCC tumor growth via induction of apoptosis and diminished downstream AKT signaling. These findings identify a p63-regulated pathway critical for SCC tumor maintenance and suggest FGFR2 blockade as a strategy to target this oncogenic transcription factor. ■

Ramsey MR, Wilson C, Ory B, Rothenberg SM, Faquin W, Mills AA, et al. FGFR2 signaling underlies p63 oncogenic function in squamous cell carcinoma. J Clin Invest 2013;123:3525–38.

Leukemia

Major finding: BACH2-driven induction of p53 negatively selects pre-B cells and protects against leukemia.

Mechanism: BACH2 and BCL6 competitively regulate the pre–B-cell receptor checkpoint genes *CDKN2A* and *TP53*.

Impact: *BACH2* is mutated or deleted in pre-B ALL, and low *BACH2* levels predict poor clinical outcome.

BACH2 SUPPRESSES B-CELL TRANSFORMATION VIA ACTIVATION OF p53

During B-cell development, pre-B cells that fail to undergo functional V(D)J immunoglobulin heavy chain gene recombination are eliminated at the pre–B-cell receptor checkpoint. Recent studies have shown that B-cell lymphoma 6 (BCL6) represses p53 and ARF (encoded by cyclin-dependent kinase 2A, *CDKN2A*) and is required for the positive selection of productively rearranged cells; however, the mechanisms that mediate the negative selection of nonfunctional pre-B cells are unknown. Swaminathan and colleagues found that BTB and CNC homology 1, basic leucine zipper transcription factor 2 (BACH2), a B-cell–specific transcription factor, induced ARF and p53 expression at the pre–B-cell receptor checkpoint, suggesting that BACH2 promotes pre–B-cell negative selection. Consistent with this idea, BACH2 was necessary and sufficient for productive V(D)J recombination and clearance of nonfunctional, out-of-frame pre–B-cell clones. BACH2 and BCL6 bound to overlapping sites in the promoters of *CDKN2A* and *TP53* and reciprocally modulated the expression of these and other checkpoint regulator genes, indicating that the balance between BACH2 and BCL6 controls the pre–B-cell receptor checkpoint.

Intriguingly, *BACH2* was frequently inactivated in primary pre-B acute lymphoblastic leukemia (ALL) samples via promoter hypermethylation, missense mutations, and deletions, or via loss of its upstream regulator paired box 5 (PAX5), supporting a tumor-suppressive role for BACH2. Indeed, BACH2 stimulated p53-dependent cell death in human pre-B ALL cells, inhibited MYC-driven leukemic transformation, and suppressed MYC-dependent tumor growth *in vivo*. Furthermore, *BACH2* expression was decreased in relapsed leukemia samples, and low levels of *BACH2* were strongly correlated with poor clinical outcome independent of established predictors in patients with ALL. These results establish BACH2 as a critical modulator of negative selection in B-cell development and identify BACH2-mediated p53 activation as a safeguard against malignant transformation of pre-B cells. ■

Swaminathan S, Huang C, Geng H, Chen Z, Harvey R, Kang H, et al. BACH2 *mediates negative selection and p53-dependent tumor suppression at the pre-B cell receptor checkpoint. Nat Med 2013;19:1014–22.*