Transcription Factors

Major finding: Arginine methylation of E2F1 controls its opposing functions in proliferation and apoptosis.

Mechanism: Site-specific methylation by PRMT1 or PRMT5 is regulated by DNA damage, cyclin A, and p100-TSN.

Impact: The outcome of E2F1 activity is modulated by interplay between methylation readers and writers.

DIFFERENTIAL METHYLATION DETERMINES THE ROLE OF E2F1 IN GROWTH CONTROL

The transcription factor E2F1 promotes cell-cycle progression by activating the expression of proliferative genes but has also been shown to stimulate apoptosis in response to DNA damage. Although methylation of E2F1 by protein arginine methyltransferase 5 (PRMT5) has recently been suggested to regulate E2F1 activity, the mechanisms that control the outcome of E2F1 signaling with regard to its opposing biologic functions remain poorly understood. Zheng and colleagues found that, in addition to PRMT5, E2F1 also interacts with PRMT1, which mediates asymmetric arginine methylation of E2F1. PRMT1 and PRMT5 competitively interacted with E2F1, such that PRMT1 methylation at R109 and PRMT5 methylation at R111/R113 reciprocally interfered with each other and differentially affected E2F1 protein stability, suggesting that these modifications antagonistically modulate E2F1 function. Consistent with this idea, PRMT1-mediated asymmetric methylation promoted E2F1 transcriptional regulation of proapoptotic genes and E2F1-induced apoptosis, whereas PRMT5-driven symmetric methylation inhibited these genes and stimulated cell growth. DNA damage activated E2F1-induced apoptosis by enhancing the interaction of E2F1 with PRMT1, leading to increased R109 methylation and attenuated PRMT5 methylation of R111/R113. In contrast, cyclin A binding to E2F1 prevented PRMT1 binding and augmented the E2F1–PRMT5 interaction and PRMT5 methylation of R111/R113, resulting in inhibition of apoptosis and increased cell viability. This switch in E2F1 activity to promote proliferation and suppress apoptosis was dependent on the Tudor domain protein p100-TSN (also known as staphylococcal nuclease and Tudor domain containing 1), a methylation reader that specifically bound to symmetrically methylated E2F1 at R111/R113 and was present at the promoters of E2F1 target genes involved in cell-cycle progression. Together, these findings identify residue-specific arginine methylation and the interplay between readers and writers of these modifications as critical determinants of the outcome of E2F1 activity. ■

Zheng S, Moehlenbrink J, Lu YC, Zalmas LP, Sagum CA, Carr S, et al. Arginine methylation-dependent reader-writer interplay governs growth control by E2F-1. Mol Cell 2013;52:37–51.

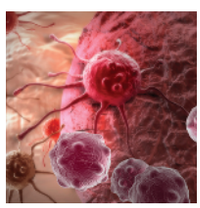
Inflammation

Major finding: c-FOS promotes preneoplastic epidermal lesions via recruitment of proinflammatory CD4$^+$ T cells.

Mechanism: c-FOS induces MMP10 and S100A7A15, which stimulate infiltration of IL-22–producing T cells.

Impact: Inhibition of these c-FOS targets may suppress T-cell recruitment and human SCC progression.

c-FOS ENHANCES SKIN TUMORIGENESIS VIA NON-CELL–AUTONOMOUS SIGNALING



Chronic inflammation has been implicated in the development of skin squamous cell carcinoma (SCC), but the signals that control this inflammatory response and the mechanisms by which inflammation regulates epidermal tumorigenesis remain unclear. In addition, upregulation of AP-1 transcription factors including c-FOS occurs in human SCC and has been suggested to contribute to SCC development in mice; however, the role of c-FOS in inflammation-associated epidermal proliferation is unknown. Briso and colleagues found that inducible, keratinocyte-specific expression of c-FOS in mice was sufficient to promote epidermal hyperplasia and the formation of preneoplastic skin lesions characterized by increased proliferation and inflammatory cell infiltration. Expression of c-FOS stimulated keratinocyte proliferation and survival via non–cell-autonomous signaling and the selective recruitment and chronic accumulation of interleukin-22–producing CD4$^+$ T cells in the skin. This T-cell infiltration was dependent on c-FOS–mediated transcriptional induction of matrix metallopeptidase 10 (*Mmp10*) and S100 calcium binding protein A7/A15 (*S100a7a15*), which encode for secreted proteins known to regulate immune cell recruitment, in keratinocytes; inhibition of MMP activity impaired T-cell recruitment, diminished keratinocyte proliferation, and suppressed the development of preneoplastic lesions. Furthermore, c-FOS cooperated with 7,12-dimethylbenz(a)anthracene (DMBA) to accelerate the formation of papillomas and invasive SCCs, whereas treatment with the anti-inflammatory drug sulindac suppressed SCC growth, further supporting a role for c-FOS–driven T-cell infiltration in SCC pathogenesis. Importantly, elevated c-FOS expression was correlated with increased levels of MMP10 and the human ortholog S100A15 and with CD4$^+$ T-cell infiltration in human SCC samples. These findings identify c-FOS as a critical factor linking proinflammatory responses and the formation of preneoplastic epidermal lesions and suggest that inhibition of the c-FOS targets MMP10 and S100A15 may be therapeutically beneficial in human SCC. ■

Briso EM, Guinea-Viniegra J, Bakiri L, Rogon Z, Petzelbauer P, Eils R, et al. Inflammation-mediated skin tumorigenesis induced by epidermal c-Fos. Genes Dev 2013;27:1959–73.