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ASPSCR1::TFE3 Drives Alveolar Soft Part Sarcoma by Inducing Targetable Transcriptional Programs

Ewa Sicinska [1], Vijaya Sudhakara Rao Kola [2], Joseph A Kerfoot [1], Madeleine L Taddei [1], Alyaa Al-Ibraheemi [3], Yi-Hsuan Hsieh [2], Alanna J Church [3], Esther Landesman-Bollag [4], Yosef Landesman [5], Matthew L Hemming [2]

Affiliations

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Abstract

Alveolar soft part sarcoma (ASPS) is a rare mesenchymal malignancy driven by the ASPSCR1::TFE3 fusion. A better understanding of the mechanisms by which this oncogenic transcriptional regulator drives cancer growth is needed to help identify potential therapeutic targets. Here, we characterized the transcriptional and chromatin landscapes of ASPS tumors and preclinical models, identifying the essential role of ASPSCR1::TFE3 in tumor cell viability by regulating core transcriptional programs involved in cell proliferation, angiogenesis, and mitochondrial biology. ASPSCR1::TFE3 directly interacted with key epigenetic regulators at enhancers and promoters to support ASPS-associated transcription. Among the effector programs driven by ASPSCR1::TFE3, cell proliferation was driven by high levels of cyclin D1 expression. Disruption of cyclin D1/CDK4 signaling led to loss of ASPS proliferative capacity, and combined inhibition of CDK4/6 and angiogenesis halted tumor growth in xenografts. These results define the ASPS oncogenic program, reveal mechanisms by which ASPSCR1::TFE3 controls tumor biology, and identify a strategy for therapeutically targeting tumor cell-intrinsic vulnerabilities.

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