Osteosarcoma

Major finding: USP1 deubiquitinates and stabilizes ID1, ID2, and ID3.

Impact: A mechanism for ID protein stabilization in cancer and development is identified.

Clinical relevance: Differentiation therapies may be effective in osteosarcoma.

ID PROTEINS ARE STABILIZED BY USP1

Inhibitor of DNA-binding (ID) proteins are key developmental regulators that block cellular differentiation in multiple tissues. Because the members of the ID family (ID1–4) are highly expressed in pluripotent cells and aberrantly stabilized in tumors, they are believed to play critical roles in cancer stem cell biology. Williams and colleagues performed a screen of human deubiquitinases (DUB) to identify candidates whose overexpression could increase ID2 levels, and found that ubiquitin-specific peptidase 1 (USP1) specifically stabilized, bound, and deubiquitinated ID2 *in vitro*. Analysis of *USP1* gene expression patterns revealed that this DUB is more highly expressed in osteosarcoma samples compared to normal bone and correlates with high ID2 protein levels. It remains unclear how USP1 is upregulated, but amplification of the *USP1* locus has been identified in a subset of osteosarcomas. In osteosarcoma cell lines, USP1 knockdown led to decreased levels of ID1, ID2, and ID3 (ID4 is not proteasomally regulated), indicating that USP1 is required for ID protein stabilization. ID proteins antagonize basic-helix-loop-helix (bHLH) transcription factors that normally induce differentiation and block proliferation. USP1 knockdown increased bHLH transcriptional activity and induced p21-mediated cell cycle arrest in osteosarcoma cells. Combined suppression of IDs 1 to 3 phenocopied the effect of USP1 knockdown on osteosarcoma proliferation, suggesting that USP1-dependent stabilization of ID proteins may be a novel mechanism of cell cycle checkpoint bypass in oncogenic transformation. Indeed, forced overexpression of USP1 in NIH3T3 cells induced anchorage-independent growth that could be blocked by ID knockdown, and both USP1 and ID2 overexpression promoted aggressive tumor growth in mice. The authors also demonstrate that USP1 is required for bone development and that its overexpression inhibits osteogenic differentiation of mesenchymal stem cells. Collectively, these data suggest that stabilization of ID proteins by USP1 in osteosarcoma promotes tumor proliferation and maintenance of a stemlike phenotype that may be targetable by therapies that induce differentiation. ■

Williams SA, Maecker HL, French DM, Liu J, Gregg A, Silverstein LB, et al. USP1 deubiquinates ID proteins to preserve a mesenchymal stem cell program in osteosarcoma. Cell 2011;146:918–30.

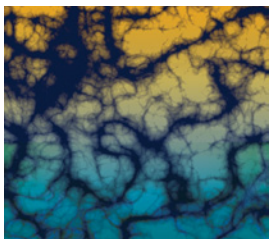
Medulloblastoma

Major finding: *FSTL5* is a prognostic biomarker that predicts poor outcome in MB.

Approach: Transcriptome and DNA copy number analyses were performed on primary MB.

Impact: *FSTL5* screening will improve stratification and prognostication of MB patients.

FSTL5 IS A BIOMARKER OF MEDULLOBLASTOMA THAT PREDICTS POOR PROGNOSIS



Medulloblastoma (MB) is the most common malignant pediatric brain tumor. Treatment regimens cure up to 75% of patients, yet leave many with cognitive and/or endocrine dysfunction. Based upon genomic and immunohistochemical analysis, four distinct molecular variants of MB have been identified: WNT (wingless), SHH (sonic hedgehog), group C, and group D. In contrast to WNT and SHH, the prognosis of non-WNT/non-SHH tumors is poor and the underlying genetic changes remain unknown. Hoping to identify new molecular biomarkers of non-WNT/non-SHH tumors that may aid in the stratification of high- versus low-risk patients, Remke and colleagues performed transcriptome and copy number analyses on primary MB. Their findings delineated genetic markers associated with the four MB subgroups and noted the association of group C and particularly group D tumors with advanced disease and poor prognosis. Interestingly, the gene for follistatin-like protein 5, *FSTL5*, was overexpressed in group C and some group D tumors and was significantly associated with reduced progression-free and overall survival across all disease variants. Little is known about the function of *FSTL5*, a member of the activin/follistatin system, and only a few reports link the gene family to cancer-related processes. Significantly, the current findings conclude that *FSTL5* is a reliable independent prognostic marker for MB. Addition of *FSTL5* to the four-class molecular staging system enhances prediction accuracy for non-WNT/non-SHH MB and will inform the development of more effective and less toxic treatment regimens for MB patients. ■

Remke M, Hielscher T, Korshunov A, Northcott PA, Bender S, Kool M, et al. FSTL5 is a marker of poor prognosis in non-WNT/non-SHH medulloblastoma. J Clin Oncol. 2011 Sept 12. [Epub ahead of print]

CANCER DISCOVERY

FSTL5 Is a Biomarker of Medulloblastoma That Predicts Poor Prognosis

Cancer Discovery 2011;1:375.