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Linking Proteostasis to Epigenetic Reprogramming and the Metastatic Niche In SPOP-Mutated Prostate Cancer

Alexander Tang, Qianlin Gu and Di Zhao*

Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
***Corresponding Authors:** Di Zhao, PhD, Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, 6565 MD Anderson Boulevard, Houston, TX 77030, USA; email: dzhao2@mdanderson.org

ABSTRACT

Speckle-type POZ protein (SPOP) is a substrate-recognition adaptor of the CUL3-RING E3 ubiquitin ligase complex that is recurrently mutated in approximately 10% of prostate cancers (PCa). While loss-of-function SPOP mutations are known to stabilize key oncogenic substrates in early tumorigenesis, their contribution to organ-specific metastasis and tumor microenvironment remodeling remains less defined. This commentary highlights recent findings by Meng and colleagues identifying the SET-domain histone methyltransferase ASH1L as a novel proteolytic target of the CUL3–SPOP complex. Loss of SPOP function leads to the stabilization of ASH1L, which enriches permissive H3K4me3 and H3K36me3 histone marks at the MUC1 promoter to activate its transcription. Overexpression of MUC1 subsequently drives CD133-associated cancer stemness and promotes the recruitment of tumor-associated macrophages (TAMs) to the lung metastatic niche. Pharmacological or genetic inhibition of the resulting SPOP–ASH1L–MUC1–CD133 signaling axis significantly reduces metastatic burden, sphere-forming capacity, and TAM infiltration in preclinical PCa models. By integrating ubiquitin-mediated proteostasis, epigenetic regulation, and immune-niche remodeling, this study establishes a novel functional link between PCa driver mutations and organ-specific metastatic colonization, offering potential biomarker-guided therapeutic avenues targeting ASH1L or MUC1.

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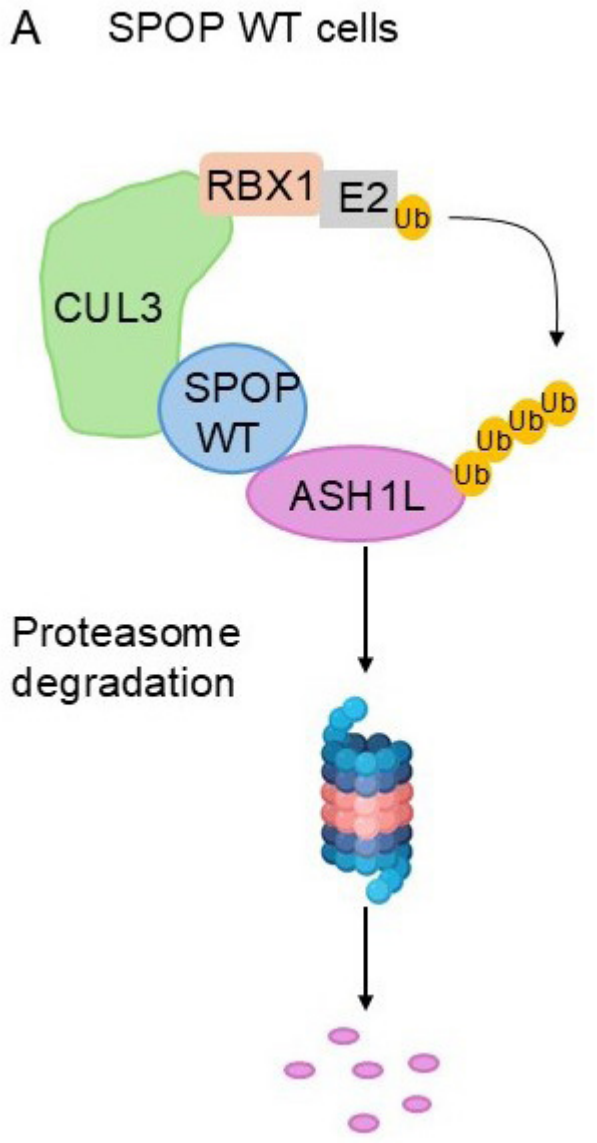
In advanced prostate cancer (PCa), metastatic progression represents the leading cause of patient mortality. Lethal progression requires more than sustained tumor proliferation. To metastasize, disseminated PCa cells must survive circulation, colonize distant tissues, adapt stem-like states, and recruit supportive stromal and immune cells. Thus, metastasis is an intricate process driven by interactions between tumor-intrinsic alterations and organ-specific niches [1, 2]. Understanding how genetic alterations coordinate these two processes to drive PCa metastasis is essential for identifying new therapeutic vulnerabilities.

Speckle-type POZ protein (SPOP) is recurrently mutated in approximately 10% of primary and metastatic PCa and defines a distinct molecular subtype of the disease [3, 4]. It is a substrate-recognition adaptor in the Cullin3-RING-based E3 ligase complex (CUL3-SPOP) and mediates the ubiquitination and proteasomal degradation of target proteins. Loss-of-function mutations impair substrate binding and stabilize oncogenic substrates [5-7]. While SPOP mutations are well established in early prostate tumorigenesis, their precise role in organ-specific metastasis and tumor immune microenvironment remodeling has remained less clear. Meng and colleagues identified the histone methyltransferase ASH1L (absent, small, or homeotic 1-like) as a previously unrecognized substrate of the CUL3–SPOP complex and report a critical mechanistic cascade—the SPOP–ASH1L–MUC1–CD133 axis—that links SPOP loss of function to epigenetic reprogramming and lung metastatic colonization [8].

ASH1L is a SET-domain histone methyltransferase that promotes H3K36 methylation and helps maintain transcriptionally permissive H3K4me3 chromatin states [9-12]. It has oncogenic functions in leukemia [9] and has increasingly been implicated in solid-tumor progression [13, 14]. Prior studies demonstrate that ASH1L plays an important role in promoting bone niche remodeling and bone metastasis [15]. Here, Meng and colleagues showed that wild-type SPOP promotes polyubiquitination and degradation of ASH1L protein (**Figure 1A**). PCa-as-

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Figure 1A. As a substrate recognition adaptor component of the CUL3 E3 ligase complex, wild-type SPOP recruits ASH1L to the CUL3 complex and promotes its ubiquitination and degradation.



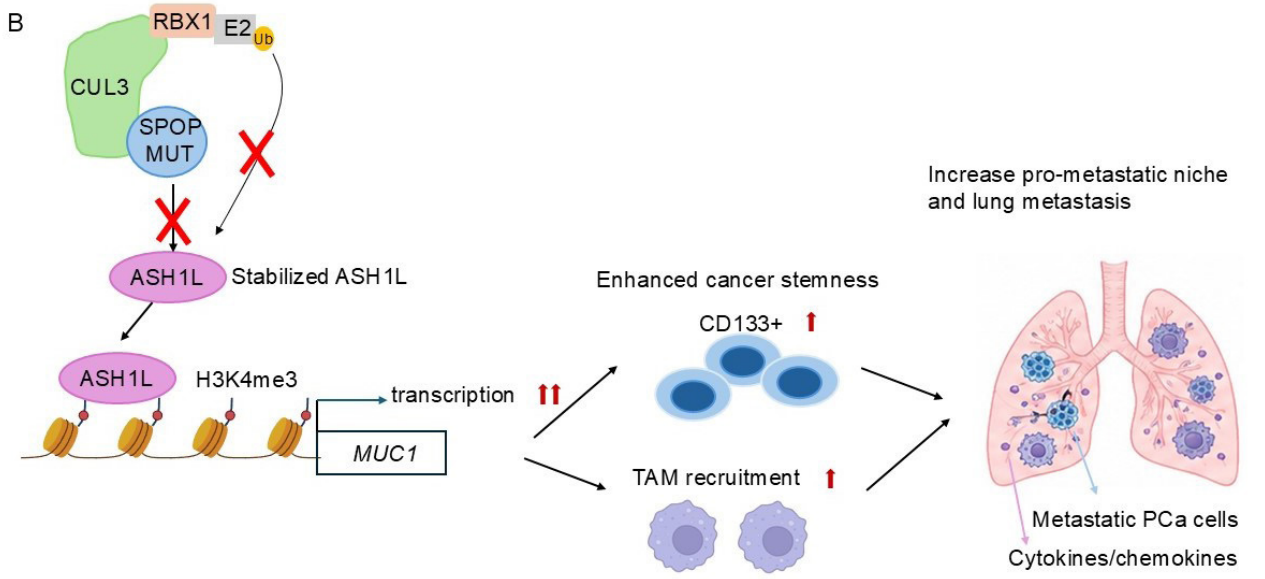
sociated SPOP MATH domain mutations impair this process, stabilizing ASH1L. Elevated ASH1L enriches permissive H3K4me3 and H3K36me3 marks at the MUC1 promoter, activating its transcription (**Figure 1B**) [8].

MUC1 (Mucin 1) is an oncogenic glycoprotein that drives tumor progression and metastasis. It is synthesized as a precursor that generates an extracellular MUC1-N subunit and a transmembrane MUC1-C subunit. MUC1-C can enter the nucleus and participate in transcriptional and epigenetic programs that promote lineage plasticity, epithelial–mesenchymal transition, stemness, and treatment resistance. In PCa, MUC1-C has been linked to neuroendocrine lineage plasticity and activation of the embryonic stem cell–associated BAF chromatin-remodeling program [16, 17]. Tumor-associated extracellular glycosylated MUC1-N was reported to interact with monocytes and macrophages and induce tumor-supportive myeloid phenotypes [18]. Consistent with these reported findings, Meng et al. also found that SPOP mutation-induced MUC1 overexpression enhances CD133-associated cancer stemness and promotes recruitment of tumor-associated macrophages (TAM) to the lung metastatic niche [8]. In xenograft and syngeneic models, this SPOP-ASH1L-MUC1 pathway is linked to greater lung metastatic burden, increased CD133 expression, enhanced sphere-forming capacity, and TAM accumulation. Although CD133 expression and spheroid formation support a stem-like phenotype, the mechanism linking MUC1 to CD133 transcription remains unresolved, and functional limiting-dilution or serial-transplantation studies would be needed to establish enhanced tumor-initiating capacity. The study therefore proposes a mechanistic cascade in which loss of SPOP-dependent protein degradation drives epigenetic reprogramming, tumor-cell plasticity, and immune-niche remodeling through an ASH1L–MUC1–CD133 axis (**Figure 1B**).

This work is significant because it integrates three processes often studied separately: ubiquitin-dependent protein turnover, epigenetic control of metastatic gene expression, and tumor–immune interactions within the metastatic niche. By identifying ASH1L as a pro-metastatic SPOP substrate, the study extends the biological consequences of SPOP mutations beyond stabilizing canonical oncogenic signaling proteins. It suggests that defective ubiquitin-mediated degradation can drive broad, sustained transcriptional changes by stabilizing a chromatin-modifying enzyme.

The authors further strengthened the significance of these findings by investigating the translational relevance. Depletion of ASH1L suppresses lung metastasis driven by SPOP mutations, while pharmacological or antibody-mediated inhibition of MUC1 reduces metastatic burden, CD133 expression, and TAM infiltration in preclinical models. These results indicate that both ASH1L and MUC1 are potential therapeutic targets in SPOP-mutant PCa. The authors further propose that patients bearing tumors with ASH1L amplification may also benefit from these target therapies in addition to those carrying SPOP

Figure 1B. PCa-associated SPOP mutations abolish SPOP-ASH1L interaction and stabilize ASH1L protein by preventing its ubiquitination and degradation, leading to epigenetic activation of MUC1 via H3K4me3 and H3K36me3. The ASH1L-MUC1 axis enhances CD133-associated cancer stemness and recruits TAMs, reprogramming the metastatic niche to promote lung metastasis.



mutations. Because several therapeutic strategies targeting MUC1 or epigenetic regulators are already in development, the pathway identified in this study may offer a more direct route to biomarker-guided clinical translation.

Collectively, this study provides a compelling mechanistic link between defective proteostasis, epigenetic reprogramming, tumor-cell plasticity, and remodeling of the metastatic myeloid niche. Its conceptual advance lies not merely in identifying ASH1L as another SPOP substrate, but in showing how stabilization of a chromatin regulator can coordinately alter both the metastatic "seed" and its immune "soil." Nevertheless, the reliance on experimental lung-colonization models, ectopic SPOP-mutant expression, and limited validation of the therapeutic response in immunocompetent settings constrains the interpretation of organ specificity and clinical applicability. Future studies using endogenous SPOP-mutant, orthotopic, and spontaneous-metastasis models should define the respective contributions of MUC1-C and shed MUC1-N, identify the signals responsible for macrophage recruitment, and determine whether the pathway extends to bone metastasis. Spatial validation of the complete SPOP–ASH1L–MUC1–CD133–TAM axis in human metastatic specimens will be critical for establishing its value as a biomarker-guided therapeutic vulnerability.

Authors' Contributions Statement

A. T. wrote the manuscript, and Q. G. revised the manuscript. D. Z. provided funding support.

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