RESEARCH HIGHLIGHT

SUS(d6)pending MHC class I peptide presentation for cancer immunoevasion

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Reported recently in *Cell*, Chen et al. identify a novel membrane-based inhibitory complex composed of SUSD6 and TMEM127 that targets MHC class I complexes for lysosomal degradation in human and mouse acute myeloid leukemia cells. Ablation of these components enhances tumor immunogenicity, promotes T cell killing, and impairs tumorigenicity in a variety of mouse cancer models.

The presentation of peptides by MHC class I complexes provides circulating $CD8^+$ T cells a metaphorical window into the translatome of nearly all nucleated cells in the body. Immunosurveillance through this system is critical for defense against intracellular pathogens and tumors, as clearly shown by their manipulation of MHC-I antigen processing and presentation (APP) machinery to escape $CD8^+$ T cell pressure. Better understanding how peptide MHC-I complexes (pMHC) are generated and mechanisms that promote and impair MHC-I peptide presentation are important goals in the current era of rapidly advancing immunotherapies.[1]

Reported in *Cell*, Chen et al. use a battery of CRISPR screens to dissect mechanisms of antigen presentation in acute myeloid leukemia (AML).[2] While screens to identify regulators of MHC-I have been reported,[3–5] it is clear that regulators are often cancer- and cell type-specific.[3] Chen et al. incorporate two pMHC systems — the human truncated a-fetoprotein-HLA A2 and the mouse SIINFEKL-K^b systems — to identify regulators of specific pMHC complexes using TCR-like mAbs, in addition to screens for total MHC-I. Comparisons across screens generate a network of both positive and negative regulators of MHC-I in AML.

The authors focus predominantly on the transmembrane protein SUSD6, a negative regulator of MHC class I identified by multiple screens. Loss of this protein enhances cell surface expression of pan-HLA and individual pMHC complexes and promotes T cell recognition and killing of tumor cells. This extends to mouse AML, melanoma, and colon carcinoma in vivo and is critically dependent on tumor MHC-I expression and the presence of $CD8^+$ T cells.

Datasets from The Cancer Genome Atlas revealed that survival rates are statistically worse in AML patients with higher SUSD6 expression, and high SUSD6 also negatively correlates with activation signatures in bone marrow-derived $CD8^+$ T cells. Therefore, SUSD6 appears to play an important role in suppressing MHC-I presentation and may predict poor prognosis in human AML patients.

Chen et al. then examine the mechanism of MHC-I complex regulation by SUSD6. Using classic cell biology approaches such as cycloheximide chase and antibody-based internalization assays, the authors identify a role for SUSD6 in promoting lysosomal degradation of class I molecules. For example, using confocal microscopy imaging, depleting SUSD6 improves MHC-I surface expression while decreasing lysosomal localization.

The authors then provide evidence that SUSD6 functions with TMEM127 to recruit the E3 ubiquitin ligase WWP2 (both also identified by CRISPR screens), which targets MHC-I for lysosomal degradation via ubiquitylation. Depleting TMEM127 from tumor cells mimics the loss of SUSD6 by promoting tumor clearance in animals, indicating that the SUSD6/TMEM127/WWP2 complex is an important regulatory axis (Fig. 1). On the other hand, WWP2 appears to have some built-in redundancy, perhaps in the form of STUB1, another negative regulator with E3 ligase activity.

SUSD1, TMEM127, and STUB1 were recently identified and validated as negative regulators of MHC-I in genome-wide screens of diffuse large B cell lymphoma (DLBCL)[3] — perhaps not surprising given that SUSD1 expression is particularly strong in $CD19^+$ B cells. This suggests a possibly important immunoevasion role in hematological malignancies. As more genome-wide screens are conducted in different cellular/tumor models, comparing hits and exploring relevant convergent genes and pathways will be critical. For example, screens in AML and DLBCL both identified TRAF3, recently identified as a negative regulator of MHC-I in a murine melanoma model.[5] Other overlapping hits are surely worthwhile quarries.

By necessity, Chen et al. use genetic methods to study this inhibitory axis. Clinical application will likely require the identification of small-molecule inhibitors or antibodies that interfere with the SUSD6/TMEM127 complex. This could be facilitated by future studies that map protein interaction domains of the protagonists. Such inhibitors might greatly enhance checkpoint blockade or adoptive T-cell therapies and are worth the investment. In the meantime, examining the effect of clinically approved lysosomotropic agents (e.g., chloroquine) on SUSD6-mediated immunoevasion in vivo would be interesting. The success of proteasome inhibitors in cancer therapy shows the potential of such blunt hammers.

The authors' use of specific peptide/MHC tools represents an important step forward in identifying gene products that

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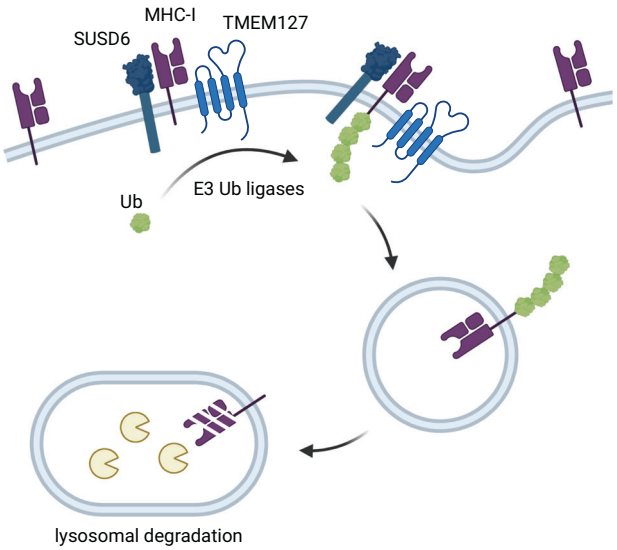

Fig. 1 Membrane proteins SUSD6 and TMEM127 coordinate a disposal route for MHC class I molecules by recruiting E3 ubiquitin ligases and initiating lysosomal targeting and degradation of MHC-I. Genetic loss of SUSD6 or TMEM127 increases surface MHC-I levels and promotes tumor clearance in a variety of cancer models, highlighting a potential therapeutic strategy to enhance tumor immunogenicity. Figure created with BioRender.com.

modulate antigen presentation. It will be of great interest in future studies to examine how the repertoire of APP regulators changes with the source of the peptide (e.g., a peptide derived from a secretory vs cytosolic protein) or with the MHC restriction element. It is long known that HLA allotypes vary enormously in efficiency of endoplasmic reticulum export, sensitivity to proteasome inhibitors, and the requirement of cofactors such as tapasin and molecular chaperones. How does the network of APP regulators affect these properties? These types of peptide-centric screens could be expanded to cross-presentation and other settings where our knowledge of the underlying cellular mechanisms is even more limited.

In summary, Chen et al. propose a clear model whereby the SUSD6/TMEM127 complex associates with surface MHC-I, recruits E3 ligases and induces the ubiquitin-dependent lysosomal targeting of MHC complexes. This axis is relevant in multiple human and murine tumors, indicating that it is likely a conserved pathway. Recent work has made it abundantly clear that manipulation of APP machinery extends beyond genetic and epigenetic levels — post-translational APP manipulation is clearly a tactic used by pathogens[6] and cancer cells.[7,8] While powerful and rapid sequencing technologies make it relatively easy to focus on genetic and transcriptomic changes, post-translational regulation allows tumor cells to adjust to immune pressure rapidly and likely contributes more to immunoevasion than we currently appreciate.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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