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TUMOUR IMMUNOLOGY

PRC2-mediated MHC-I silencing drives immune evasion

Both MHC class I antigen presentation pathway (MHC-I APP) mutations and transcriptional repression of MHC-I have been associated with resistance to immune checkpoint inhibitors (ICIs). Now, Mark Dawson's laboratory reports an evolutionarily conserved mechanism whereby Polycomb repressive complex 2 (PRC2) mediates epigenetic silencing of MHC-I APP genes to promote immune evasion.

To identify key regulators of MHC-I repression, Burr et al. performed a genome-wide CRISPR–Cas9 screen in the MHC-I-low K-562 erythroleukaemia cell line. Remarkably, the top candidate genes encoded epigenetic regulatory proteins, with the top two hits (*EED* and *SUZ12*) encoding core components of PRC2, indicating a potential epigenetic regulatory mechanism.

Subsequent functional validation experiments in K-562 cells illustrated that *EED* knockout restored MHC-I cell surface expression, whereas concurrent *EED* overexpression reinstated MHC-1 silencing and restored histone H3 lysine 27 trimethylation (H3K27me3), suggesting that PRC2 mediates transcriptional repression of MHC-I APP genes. Indeed, pharmacological inhibition of the EZH2 methyltransferase subunit of PRC2 markedly depleted H3K27me3 levels and transcriptionally induced MHC-I APP genes in K-562 cells and restored MHC-I cell surface expression in both K-562 cells and MHC-I-low small-cell lung cancer (SCLC) and neuroblastoma cells. Moreover, mutation of a crucial catalytic residue in EZH2 impaired PRC2-mediated repression of MHC-I, whereas expression of a H3 variant with a K27M mutation strongly induced MHC-I expression. Further experiments demonstrated a pivotal role for EZH2-mediated H3K27me3 repressive marks in maintenance of MHC-I silencing in MHC-I-deficient cancers.

Interestingly, an MHC-I-low mouse SCLC (mSCLC) cell line, in which the previous K-562 findings were recapitulated, was found to be highly resistant to antigen-specific T cell-mediated killing and failed to induce cytokine production in T cells in vitro. This resistance was overcome by pretreatment with EZH2 inhibitors to induce MHC-I expression and, therefore, effective T cell activation, establishing the functional importance of MHC-I silencing.

Intriguingly, mSCLC cells were not eliminated by an allogeneic T cell response upon subcutaneous transplantation into non-histocompatible recipient mice, suggesting that MHC-I APP silencing facilitates immune evasion in transmissible cancers, as reported for Tasmanian devil facial tumours.

> “PRC2 has key immuno-modulatory functions that can be co-opted by cancer cells”

However, *Ezh2*-knockout mSCLC tumours were universally rejected upon allogeneic transplantation into immunocompetent, but not immunodeficient, mice, establishing a crucial role for PRC2-mediated MHC-I silencing in evasion of the antitumour $CD8^+$ T cell response in vivo. Furthermore, in three patients with *EGFR*-mutant lung adenocarcinoma that underwent SCLC transformation following EGFR inhibitor treatment and who subsequently failed to respond to ICIs, the transformed SCLC harboured marked downregulation of MHC-I APP components relative to the adenocarcinoma tissues, suggesting that neuroendocrine transformation can confer immune privilege to a tumour via MHC-I APP loss in the clinical setting.

Finally, chromatin immunoprecipitation followed by sequencing (ChIP–seq) experiments in MHC-I-deficient human and Tasmanian devil cells revealed that the presence of bivalent histone modifications, specifically activating H3K4me3 and repressive H3K27me3 marks, at MHC-I APP gene promoters was a conserved feature. Collectively, the authors hypothesized that this bivalency is maintained by an evolutionarily conserved function of PRC2 and is a physiological mechanism of MHC-I regulation.

Overall, the study reveals a conserved tumour-intrinsic role for PRC2 in MHC-I APP regulation, reinforcing the notion that PRC2 has key immunomodulatory functions that can be co-opted by cancer cells — through both genomic and non-genomic mechanisms — to evade immune surveillance.

“Our future research will explore potential therapeutic approaches incorporating PRC2 inhibition to overcome immunotherapy resistance in aggressive MHC-I-deficient malignancies, as well as predictive biomarkers for such combination strategies,” concludes Dawson.

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