ZINC REGULATORS DRIVE A DYSFUNCTION-SPECIFIC GENE MODULE

Chronic inflammation causes CD8+ T cells to become dysfunctional, or exhausted, and thus lose their effector function, express high levels of inhibitory receptors, and undergo transcriptional changes. To identify the molecular programs that drive the activation and dysfunction of CD8+ tumor-infiltrating lymphocytes (TIL), Singer, Wang, and colleagues generated bulk RNA profiles of activated, partially dysfunctional, and fully dysfunctional CD8+ TILs identified by their differential expression of inhibitory receptors. Cross-TIL subpopulation evaluation of the gene signature associated with fully dysfunctional CD8+ TILs revealed that metallothionein 1 (MT1), a zinc chaperone that regulates zinc metabolism, was the most differentially expressed gene across the TIL subpopulations. Depletion of metallothioneins in vivo restored CD8+ T-cell effector function and delayed tumor growth in a CD8+ T-cell–dependent manner. Further, CD8+ T cells depleted of metallothioneins exhibited no change or a slight increase in expression of inhibitory receptors, suggesting uncoupling of dysfunctional phenotype and inhibitory receptor expression. Analysis of expression profiles generated from bulk activated, partially dysfunctional, and fully dysfunctional CD8+ TILs from tumor-bearing wild-type versus CD8+ TILs that do not exhibit dysfunction from MT1 knockout mice identified distinct transcriptional programs for CD8+ T-cell activation and dysfunction. Consistent with these findings, single-cell RNA sequencing of CD8+ TILs showed that the transcriptional programs of dysfunctional and activated CD8+ T-cell populations were uncoupled at the single-cell level. GATA binding protein 3 (GATA3) was the most overexpressed transcription factor in the dysfunctional CD8+ T-cell gene signature; CRISPR/Cas9-mediated targeting of GATA3 in naïve CD8+ T cells increased T-cell effector function, caused no change in the expression of inhibitory receptors on CD8+ T cells, and delayed tumor growth in vivo. This comprehensive molecular characterization of activated and dysfunctional T cells may provide insights into the development of therapies targeting dysfunctional T cells. ■


RICOLINOSTAT MAY ENHANCE LENALIDOMIDE AND DEXAMETHASONE EFFICACY

Histone deacetylase (HDAC) inhibitors have demonstrated activity against multiple myeloma. The pan-HDAC inhibitor panobinostat has been approved as part of a combination drug regimen for the treatment of multiple myeloma, but it is associated with serious toxicities. Thus, more tolerable HDAC inhibitors are desired. Selective HDAC6 inhibitors are attractive candidates, as multiple myeloma cells are sensitive to HDAC6 inhibition, and such agents target the aggresome protein degradation pathway without substantially affecting gene expression or cell-cycle progression and thus may have an improved safety profile compared with pan-HDAC inhibitors. In a multicenter phase I/II dose-escalation trial, Yee and colleagues evaluated the safety and preliminary activity of the selective HDAC6 inhibitor ricolinostat in combination with lenalidomide and dexamethasone in 38 patients with relapsed or refractory multiple myeloma. The primary outcomes were dose-limiting toxicities, maximum tolerated ricolinostat dose, and the recommended dose and schedule of ricolinostat for future phase II trials. Secondary outcomes included ricolinostat pharmacokinetics and pharmacodynamics in combination with lenalidomide and dexamethasone, and preliminary antitumor activity. Ricolinostat was well tolerated, with adverse events similar to what has been observed with lenalidomide and dexamethasone alone. Two patients experienced dose-limiting toxicities, but the maximum tolerated dose was not reached. Ricolinostat selectively inhibited HDAC6 with minimal inhibition of class I HDACs at the dose recommended for further trials, and coadministration of ricolinostat and lenalidomide did not significantly alter the pharmacokinetics of either drug. An overall response was observed in 55% of patients, and the median progression-free survival was 20.7 months. Altogether, these findings indicate that selective HDAC6 inhibition may be a strategy to avoid toxicity associated with pan-HDAC inhibitors and suggest that ricolinostat may safely enhance the antitumor activity of lenalidomide and dexamethasone in patients with multiple myeloma, supporting further clinical investigation of ricolinostat in larger clinical trials. ■


MAJOR FINDING: Zinc regulation drives a dysfunction-specific gene module.

CONCEPT: Selective HDAC6 inhibition may limit side effects linked to pan-HDAC inhibition and improve efficacy.

IMPACT: Ricolinostat plus lenalidomide and dexamethasone warrants further study in patients with multiple myeloma.

Ricolinostat plus lenalidomide and dexamethasone in combination therapy for multiple myeloma.