THE ATR-INHIBITOR CERALASERTIB MODULATES THE TUMOR MICROENVIRONMENT AND IMPROVES THE EFFECT OF ANTI-PDL1 BY ACTIVATING TYPE I IFN PATHWAY

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Background Ceralasertib is a specific ATR inhibitor (ATRi) that hinders the DNA damage response in tumor cells, making them more susceptible to death in situations of high replication stress. Ceralasertib in combination with the PD-L1 antibody durvalumab demonstrated encouraging clinical benefit in melanoma and lung cancer patients who progressed on immunotherapy. The mechanism of this effect remained unclear.

Methods In this study, we employed different mouse tumor models treated with ceralasertib to investigate the effect of the ATRi on tumor microenvironment.

Results Antitumor effect of ceralasertib was dependent on the presence of CD8 cells, since in vivo depletion of CD8 cells abrogated therapeutic effect of the ATRi. Analysis of the gene expression profile using RNAseq demonstrated significant up-regulation of type I interferon (IFNI) pathway in tumors of mice treated with ceralasertib. Neutralizing anti IFNI receptor (IFNAR1) antibody abrogated antitumor effect of ceralasertib. Antitumor effect of ceralasertib in combination with anti-PD-L1 was eliminated in mice reconstituted with bone marrow from IFNAR1-KO mice. Reconstitution with bone marrow from mice with constitutively active IFNAR1 markedly enhanced antitumor effect of ceralasertib. Treatment of tumor-bearing mice with ceralasertib caused accumulation of DCs with activated phenotype (up-regulation of CD40, CD86, MHC class II). DCs isolated from tumor of ceralasertib-treated mice demonstrated an enhanced ability to stimulate T cells in a mixed lymphocyte reaction assay. Notably, this effect was reversed when DCs were isolated from IFNAR1 KO mice. Moreover, in vitro-generated DCs treated with ceralasertib exhibited activation similar to that induced by lipopolysaccharide (LPS), but this effect was not observed in DCs generated from IFNAR1 KO mice. Treatment with ceralasertib led to the depletion in tumor of M-MDSC and TAMs, but not PMN-MDSC. However, PMN-MDSCs suppressive activity was abrogated after the treatment. This was associated with increased IFNI signature observed in tumor PMN-MDSC. Treatment with ceralasertib enhanced tumor antigen-specific response of T cells.

Conclusions Our findings demonstrate IFNI mediated modulation of TME by ceralasertib resulting in enhanced antitumor activity of T cells and potentiated effect of PD-L1 antibody.

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