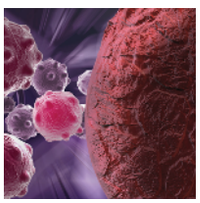
Immunology

Major finding: The stress sensor CHOP enhances the accumulation and inhibitory activity of MDSCs in tumors.

Mechanism: Tumor-derived reactive oxygen and nitrogen species induce CHOP expression in MDSCs through ATF4.

Impact: Targeting CHOP may overcome tumor-induced tolerance and enhance cancer immunotherapy.

THE IMMUNOSUPPRESSIVE ACTIVITY OF MDSCs REQUIRES EXPRESSION OF CHOP



Myeloid-derived suppressor cells (MDSC) accumulate within tumors and inhibit antitumor immune responses. However, the effects of tumor-induced stress responses on MDSC function remain unclear. Thevenot and colleagues found that expression of the cellular stress sensor C/EBP-homologous protein (CHOP) was increased in tumor-infiltrating MDSCs compared with other immune cell types. Stromal deletion of CHOP or generation of CHOP-deficient bone marrow chimeras reduced tumor growth in mice, suggesting a role for CHOP in the promotion of tumor growth. CHOP-deficient MDSCs exhibited enhanced accumulation in tumors, increased proliferation, and decreased apoptosis compared with wild-type MDSCs. In addition, CHOP deletion diminished the capacity of tumor-infiltrating MDSCs to inhibit activated T-cell proliferation and IFNγ production and resulted in reduced levels of molecules essential for MDSC activity. Moreover, CHOP-deficient MDSCs failed to induce T-cell tolerance *in vivo* and induced antitumor immune responses. This antitumor effect was dependent in part on increased infiltration and activation of $CD8^+$ T cells. Accordingly, CHOP deletion enhanced the efficacy of adoptive T-cell immunotherapy in tumor-bearing mice. Expression of CHOP in MDSCs was mediated by tumor-derived reactive oxygen and nitrogen species, which induced integrated stress responses and activating transcription factor 4 (ATF4)–driven induction of CHOP. Consistent with this finding, CHOP induction was reversed by antioxidant treatment, leading to a decrease in tumor growth. CHOP deletion decreased the activity of C/EBPβ, a critical regulator of MDSC function, resulting in reduced IL6 production and lower levels of phosphorylated STAT3, whereas IL6 expression was sufficient to rescue the immunosuppressive functions of CHOP-deficient MDSCs and restore tumor growth. Collectively, these observations demonstrate a primary role for CHOP in MDSC-induced immune suppression and suggest the potential for strategies targeting CHOP to overcome immune tolerance in cancer. ■

Thevenot PT, Sierra RA, Raber PL, Al-Khami AA, Trillo-Tinoco J, Zarreii P, et al. The stress-response sensor CHOP regulates the function and accumulation of myeloid-derived suppressor cells in tumors. Immunity 2014;41:389–401.

Retinoblastoma

Major finding: RB loss in human cone precursor cells promotes proliferation and retinoblastoma formation.

Mechanism: NMYC, MDM2, p107, and SKP2-driven p27 degradation are required for proliferation after RB loss.

Impact: Retinal cell-type–specific pathways render maturing cone precursors sensitive to RB depletion.

CONE PRECURSOR CELLS ARE THE CELL-OF-ORIGIN IN RETINOBLASTOMA

Germline mutations in the *RB1* gene are associated with a strong predisposition to the childhood retinal tumor retinoblastoma, suggesting that molecular pathways unique to a subpopulation of retinal cells may confer sensitivity to inactivation of this tumor suppressor. To test this hypothesis and characterize the potential cell-of-origin for retinoblastoma, Xu and colleagues depleted the RB protein in dissociated human fetal retinal cells, in purified retinal cell populations, and in intact retina. Loss of RB specifically enhanced the proliferation of postmitotic cone precursor cells but not retinal progenitor cells (RPC), rods, glia, or other retinal cell types. The sensitivity of cone precursors to RB depletion was associated with decreased apoptosis and increased expression of genes that regulate cell-cycle progression, whereas RB loss induced apoptosis in RPCs and glia. Similar to retinoblastoma cells, proliferation of RB-depleted cone precursors required expression of proteins highly expressed in this cell type, including NMYC, the E3 ubiquitin ligase MDM2, and markers of cone photoreceptor cells. Proliferation of both retinoblastoma cells and RB-deficient cone precursors was also dependent on the E3 ubiquitin ligase S-phase kinase-associated protein 2 (SKP2) and SKP2-mediated degradation of the cyclin-dependent kinase inhibitor p27. In addition, knockdown of the RB-related protein p130 (encoded by *RBL2*), which is often lost in human retinoblastoma, or overexpression of p107 (encoded by *RBL1*), an RB-related protein highly expressed in human retinoblastoma, enhanced the proliferation of RB-depleted cone precursors, suggesting that these proteins have opposing functions in human retinal tumorigenesis. Depletion of RB and p130 in cone precursors promoted the formation of differentiated, highly proliferative retinoblastoma-like tumors *in vivo*, which were characterized by the expression of cone-specific proteins and the absence of DNA copy number alterations, analogous to human retinoblastoma. These findings implicate maturing cone precursors as the cell-of-origin for retinoblastoma and support the notion that cell-type–specific signaling selectively initiates tumor formation in these cells following *RB1* inactivation. ■

Xu XL, Singh HP, Wang L, Qi DL, Poulos BK, Abramson DH, et al. Rb suppresses human cone–precursor–derived retinoblastoma tumours. Nature 2014 Sep 24 [Epub ahead of print].