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TRB2-SKP2 signaling and SKP2 targeted therapy in human retinoblastoma and related tumors

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Retinoblastomas initiate in response to biallelic RB1 inactivation and loss of functional Rb protein in cone precursors, yet the cellular circuitry that sensitizes to Rb loss have been unclear. Previous studies showed that retinoblastomas exhibit cone precursor properties and depend on cone-specific thyroid hormone receptor β2 (TRβ2) and SKP2 signaling. Here, we show that TRβ2 promotes SKP2 expression by antagonizing TRβ1, which enables Emi1-dependent inhibition of APC/CCdh1-mediated SKP2 degradation. TRβ2 also antagonized TRβ1-mediated suppression of anterior pituitary tumors in Rb1+/- mice. Moreover, in certain RB1-wild type tumors, Rb appears to have a function similar to TRβ2, since phospho-Rb sustained Emi1 and SKP2 activity by suppressing TRβ1. While both TRβ1 and TRβ2 associated with phospho-Rb, Emi1, and SKP2, only TRβ1 suppressed SKP2 expression. These results suggest that loss of RB1, and the resulting loss of phospho-Rb, enables TRβ1-dependent suppression of Emi1 and SKP2, as a safeguard against RB1-deficient tumor formation. TRβ2 counteracts TRβ1, thus disrupting this safeguard and enabling the development of RB1-deficient tumors. SKP2-KD caused apoptosis of retinoblastoma, Rb deficient myxofibrosarcoma and small cell lung cancer cells (SCLC), indicating that SKP2 is a synthetic lethal gene in retinoblastoma and other Rb deficient cancers. Targeted therapy by SKP2 inhibitor C1 significantly suppressed retinoblastoma, SCLC, and myxofibrosarcoma tumor growth by suppressing SKP2 activity and promoting p27 accumulation in vitro and *in vivo*.

Biography

Xu is a principle investigator and group leader in Zhongshan Ophthalmic Center of Zhongshan University, Basic Research Co-leader and Senior Scientist at Memorial Sloan Kettering Cancer Center (MSKCC), and Assistant Professor at New York Eye and Ear Infirmary and New York Medical College. He got MD from Zhejiang University and PhD from Shanhai Jiaotong University. His research was the key to identifying the cell of origin of retinoblastoma and to identifying a central signaling pathway for the development of this cancer; this work resulted in first-author publications in Cell, Nature, and the American Journal of Pathology.

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