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Updated study on action mechanisms of cereblon as a novel prognostic biomarker for hepatocellular carcinoma

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Introduction : Cereblon (CRBN) is an important player in various cellular functions , but little is known in hepatocellular carcinoma (HCC). We presented the discovery process of CRBN as new prognostic biomarker of HCC and developed prognostic prediction models of HCC using CRBN.

Methods : Laboratory study was focused on assessment of CRBN expression status and regulatory mechanisms in in vitro and in vivo studies. Post-resection prognosis of 212 patients with HCC of 2–5 cm was assessed according to CRBN expression.

Results : CRBN was highly expressed in HCC cell lines and patient-derived HCC samples. CRBN depletion decreased HCC cell motility and induced down-regulation of MMP-9 and MMP-2, whereas overexpression of CRBN increased migratory ability of HCC cells and expression of MMPs. In vivo CRBN depletion in patient-derived xenograft mouse models resulted in inhibition of tumor growth and suppression of EGFR and AKT/SOX2 pathways. Clinical study revealed that high CRBN expression showed higher tumor recurrence rate ($p = 0.027$) and lower patient survival rate ($p = 0.015$) than low CRBN expression. Prognostic impact of CRBN on HCC recurrence was greater than that of microvascular invasion (hazard ratio 1.97 vs. 1.46). Prognostic prediction models combining CRBN and other risk factors enhanced the prognostic prediction power (Harrel's concordance index >0.63).

Conclusions : CRBN is associated with aggressive tumor biology and has a high prognostic impact in HCC. Tumor aggressiveness was artificially changed according to the expression status of CRBN in vivo mouse model, which is the world-first finding . We believe that CRBN is a new reliable prognostic biomarker of HCC.

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