Oncogenic CARMA1 couples NF-κB and β-catenin signaling in diffuse large B-cell lymphomas.

Abstract:
Constitutive activation of the antiapoptotic nuclear factor-κB (NF-κB) signaling pathway is a hallmark of the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphomas (DLBCL). Recurrent oncogenic mutations are found in the scaffold protein CARMA1 (CARD11) that connects B-cell receptor (BCR) signaling to the canonical NF-κB pathway. We asked how far additional downstream processes are activated and contribute to the oncogenic potential of DLBCL-derived CARMA1 mutants. To this end, we expressed oncogenic CARMA1 in the NF-κB negative DLBCL lymphoma cell line BJAB. By a proteomic approach we identified recruitment of β-catenin and its destruction complex consisting of APC, AXIN1, CK1ε and GSK3β to oncogenic CARMA1. Recruitment of the β-catenin destruction complex was independent of CARMA1-BCL10-MALT1 complex formation or constitutive NF-κB activation and promoted the stabilization of β-catenin. The β-catenin destruction complex was also recruited to CARMA1 in ABC DLBCL cell lines, which coincided with elevated β-catenin expression. In line, β-catenin was frequently detected in non-GCB DLBCL biopsies that rely on chronic BCR signaling. Increased β-catenin amounts alone were not sufficient to induce classical WNT target gene signatures, but could
augment TCF/LEF-dependent transcriptional activation in response to WNT signaling. In conjunction with NF-?B, ?-catenin enhanced expression of immunosuppressive interleukin-10 and suppressed antitumoral CCL3, indicating that ?-catenin can induce a favorable tumor microenvironment. Thus, parallel activation of NF-?B and ?-catenin signaling by gain-of-function mutations in CARMA1 augments WNT stimulation and is required for regulating the expression of distinct NF-?B target genes to trigger cell-intrinsic and extrinsic processes that promote DLBCL lymphomagenesis.