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Abstract

Sag/Rbx2 E3 Ubiquitin Ligase: From Target Validation to Drug Discovery †

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Abstract: SCF (SKP1, Cullins, and F-box proteins) E3 ligase, also known as CRL1 (Cullin-RING ligase-1), the founding member of CRLs, is the largest family of E3 ubiquitin ligases, consisting of four components: (1) An adaptor protein SKP1, (2) a scaffold protein cullin-1 (CUL1), (3) a substrate-recognizing F-box protein, and (4) a RING protein with two family members, RBX1 or RBX2 (also known as SAG). By promoting ubiquitylation and degradation of many key regulatory proteins, SCF E3s play critical roles in many biological processes, including signal transduction, cell cycle progression, DNA replication, development, and tumorigenesis. SAG/RBX2 is the RING component of CRLs, required for its activity. SAG is overexpressed in a number of human cancers, which is associated with poor survival of patients. We recently found that SAG deletion remarkably suppressed tumorigenesis in the lung, triggered by KrasG12D, and in the prostate, triggered by Pten loss, indicating that SAG is an oncogenic cooperating gene. We have launched a drug discovery project to find small molecule inhibitors that target SAG E3 for anticancer application. More details will be presented.

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