Understanding molecular mechanisms of cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is an aggressive form of cancer that forms in the biliary tract. CCA has high mortality and high rates of recurrence. While early diagnosis is critical, the molecular mechanisms by which CCA forms are poorly understood. A new study reports key interactions between three proteins during CCA development: TLR3, a mediator of both innate and adaptive immune responses and a promising target for anti-cancer therapy; IAP proteins that regulate apoptosis and orchestrate cancer cell death; and RIPK1, a multifunctional protein that regulates inflammation and cell death through apoptosis and necroptosis. TLR3 expression was found to be significantly higher in primary CCA tissue than in adjacent normal tissue. Meanwhile, Smac mimetic, an IAPs antagonist, sensitized CCA cell lines to TLR3 ligand, Poly(I:C)-induced apoptosis. This mode of cell death was switched to necroptosis in CCA cells expressing RIPK1, RIPK3, and MLKL. Analyses showed that one group of patients with high TLR3 and high RIPK1 expression tended to show longer disease-free survival. Further studies could help researchers better understand the interplay between TLR3, the Smac mimetic, and RIPK1, and how it might be harnessed to treat patients with cholangiocarcinoma.