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Molecular mechanisms underlying resistance to MEK1/2 inhibitor in BRAF-mutated colorectal cancer

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Abstract

Colorectal carcinomas are characterized by multiple genetic alterations, including constitutive Wnt activity and gain-of-function mutations in K-RAS and B-RAF. BRAF encodes a Ser/Thr kinase acting in the Ras/MEK/ERK pathway and the V600E mutation found in 11% of colorectal cancers renders this kinase constitutively active. B-RAF mutated colorectal carcinomas represents a very aggressive entity with a poor prognosis. Understanding the molecular mechanisms activated downstream of mutated B-RAF is urgently needed to design new therapeutic avenues to treat B-ARF mutated colorectal carcinomas and to circumvent resistance to therapies targeting the Ras/Raf/MEK1/ERK1/2 pathway. In a search for candidates that critically contribute to both intrinsic and acquired resistance to MEK1 inhibition in B-RAF mutated colorectal cancer cells, we identified one scaffold protein whose expression is driven by both NF-kB and AP-1 families of transcription factors. This scaffold protein promotes the expression of HER2 and HER3 in colorectal cancer cells subjected to MEK1 or B-RAF inhibition (Selumetinib and Vemurafenib, respectively) and, as such, is critically involved in the intrinsic resistance to these targeted therapies. The same scaffold protein is also strongly induced in B-RAF but not K-RAS mutated colorectal cancer cells showing acquired resistance to MEK1 inhibition. Interfering with the expression of this scaffold protein circumvents both intrinsic and acquired resistance to Selumetinib in B-RAF mutated colorectal cancer cells. Our study defines a new molecular actor critically involved in oncogenic signaling pathways triggered by mutated B-RAF. Our study also defineS new combinatory therapies to better treat B-RAF-mutated colorectal carcinomas.

Keywords

Colorectal cancer, Resistance, MEK1/2 inhibitor, BRAF

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References