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#### **ACCEPTED MANUSCRIPT**

# DA-Raf, a dominant-negative antagonist of the Ras-ERK pathway, is a putative tumor suppressor

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#### **Abstract**

Activating mutations of RAS genes, particularly KRAS, are detected with high frequency in human tumors. Mutated Ras proteins constitutively activate the ERK pathway (Raf-MEK-ERK phosphorylation cascade), leading to cellular transformation and tumorigenesis. DA-Raf1 (DA-Raf) is a splicing variant of A-Raf and contains the Ras-binding domain (RBD) but lacks the kinase domain. Accordingly, DA-Raf antagonizes the Ras-ERK pathway in a dominant-negative fashion and suppresses constitutively activated K-Ras-induced cellular transformation. Thus, we have addressed whether DA-Raf serves as a tumor suppressor of Ras-induced tumorigenesis. DA-Raf(R52Q), which is generated from a single nucleotide polymorphism (SNP) in the RBD, and DA-Raf(R52W), a mutant detected in a lung cancer, neither bound to active K-Ras nor interfered with the activation of the ERK pathway. They were incapable of suppressing activated K-Ras-induced cellular transformation and tumorigenesis in mice, in which K-Ras-transformed cells were transplanted. Furthermore, although DA-Raf was highly expressed in lung alveolar epithelial type 2 (AE2) cells, its expression was silenced in AE2-derived lung adenocarcinoma cell lines with oncogenic KRAS mutations. These results suggest that DA-Raf represents a tumor suppressor protein against Ras-induced tumorigenesis.

#### **Keywords**

Ras-ERK pathway; Raf; Alternative splicing; Transformation; Tumorigenesis; Tumor suppressor

#### 1. Introduction

The Ras small GTPases (H-Ras, K-Ras, and N-Ras) activated by extracellular signals exert a variety of cellular and physiological functions through activating diverse effector proteins including Raf, phosphatidylinositol 3-kinase (PI3K), and RalGDS [1–3]. The activation of

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