

Significance of Dok2 Protein in Cancer Prognosis and Progression

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Abstract

Cancer is the most leading cause of deaths worldwide. Despite present understanding and experimental advancements, the morbidity and mortality still remain high. Dok2 have been visualized as a key player in multiple biological processes as inflammation, differentiation, cellular migration and even as an important marker for tumor progression. Recent reports have vividly discussed the regulatory aspects and prognostic aspects of Dok2. Here, we sought to summarize the recent shreds of evidence of Dok2 involvement in carcinogenesis. Dok2 represents an attractive marker for cancer progression and represents a valuable therapeutic target.

Keywords: Dok2; Cancer; Progression; Klf2; EGFR

Introduction

Search strategy

We executed systematic search using search engines as PubMed, Scholar Google for research articles of Dok2 in association with cancer. The search was limited to study revealing basic functions in light of its molecular mechanisms of action. References of published articles were seen for eligible details.

Study selection

The study selection included articles elaborating detailed mechanism of action and articles which are in relevance to cancer progression. We found very few articles elaborating detailed downstream targets. Papers were read carefully to know the experimental validation for downstream signaling proteins as well as its prognostic efficacy.

Data extraction

The search included papers with basic and experimental details in reverence to carcinogenesis. The cross references was screened for more clarity and basic details. The details included cancer type, prognosis details and experimental evidences for downstream targets.

Biology of Dok2

Downstream of tyrosine kinase (Dok2) belongs to a family of adapter protein reported to be responsive for the protein tyrosine kinase signaling. Dok family of proteins is known to localize on chromosome no 8. Members of Dok family of protein have three domains: A N terminal homology domain, a phospho tyrosine bonding domain and a C terminal proline rich domain with few tyrosine residues. This C- terminal with SH2 and SH3 domain recruits the signaling intermediates on growth factor stimulation [1-4]. Epidermal growth factor receptor signaling is essentially been viewed as an Important player in shaping cancer microenvironment [4] and an important target for cancer therapy [5]. Dok1-3 are reported to modulate epidermal growth factor receptor [6,7] as well as platelet derived growth factor receptor and associated signaling pathways [1,8,9]. Knock out mutants with Dok-1/Dok-2 have been reported to be associated with leukemia genesis [10,11]. Dok1 and Dok2 are related with an array of signaling pathways including TLR4 [12], CD200R pathway [13] and by signaling lymphocyte activation molecule (SLAM) [14]. Dok1 and Dok2 have been preferentially known to be expressed on immune cells but predicted to have non-immunological functions as well on account of its expression on cells of non-hematopoietic lineage [13,14]. Studies have shown that Dok1 and Dok2 plays an important role in TLR2

based signaling in astrocytes and microglia. This study also shows that activation of Dok1 and Dok2 results in cytokine production mediated by RasGAP dependent ERK and NF- κ B activation. Dok1 and Dok2 are shown as novel targets for neuroinflammatory conditions [15]. In addition, Dok2 proteins has been connected with multiple biological processes including differentiation [16], cellular motility [17,18]. It has been reported that constitutive expression of Dok2 negatively regulates T cell development through interaction with RasGAP and Nck [19].

Dok2 and cancer

Dok2 expression has been reported to be associated with EGFR expression in lung adenocarcinoma. Here, it has been shown that EGFR mutations are coupled with genomic loss of Dok2. This loss of Dok2 in genetically engineered mouse cooperates with EGFR to promote tumorigenesis [20]. In gastric cancer studies, Dok2 has been reported to express in normal gastric mucosa while difference in expression pattern was observed in gastric cancer cell lines. Further, these studies notes that Dok2 could be a useful marker to predict prognosis after curative resection [21]. Another study points that Dok2 was lost in 42% of gastric cancer cases. However, the concomitant molecular mechanisms in gastric cancer are still remains at large [22]. In colorectal cancer studies, Dok2 has been reported to express in 66.7% of gastric cancer samples. It is further predicted as marker for poor prognosis [23]. Another independent study shows that Dok2 was lost on 36% of colorectal cancer [22]. However, the mechanisms behind these alterations are not known yet. Chronic myelomonocytic leukemia (CMML) studies show that a mutation (L238P) in Dok2 is unable to inhibit ERK activation [24]. Studies in mouse erythroleukemia cells shows that Dok2 regulates the expression of Klf1 by binding to its promoter region and have a role in erythropoiesis. This study also shows that Dok2 is localized in cytoplasm and nucleus [25]. Epigenetic analysis of 45 ovarian cancer samples reveals that Dok2 underwent extensive methylation and its

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Gene	Cancer	Target genes	References
Dok2	Lung adenocarcinoma	Ras	[20]
	Gastric cancer	--	[21,24]
	Colorectal cancer	--	[23,22]
	chronic myelomonocytic leukemia (CMML)	ERK	[24]
	Erythroleukemia	Klf1	[25]
	Ovarian cancer	--	[26]
	Astrocytoma	--	[27]

Table 1: Association of Dok2 expression in cancer.

repression was found to increase carboplatin resistance by hampering apoptosis and anoikis [26,27].

Discussion

We have reported that Dok2 protein and RNA are overexpressed in low and high grade astrocytoma tissue samples and its overexpression was correlated to poor prognosis. Real time PCR and western blotting results were supported by immunohistochemistry analysis. We further show that Dok2 expression was region specific with dominance of frontal and temporal lobes [23]. We also report that Dok2 is expressed in U87 malignant glioma cell lines and nitidine chloride can be the candidate drug targeting its expression [28]. The details of Dok2 reports with reported target genes have been presented in Table 1.

Concluding Remarks

Dok2 may be viewed as an attractive marker for cancer progression. Its reported therapeutic value warrants further investigations.

Conflict of Interest

None

Ethical Approval and Informed Consent

Not applicable.

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