Pathology & Oncology Research (2020) 26:2835–2837
https://doi.org/10.1007/s12253-020-00845-9

LETTER TO THE EDITOR

Landscape of RAS Variations in 17,993 Pan-cancer Patients Identified by Next-generation Sequencing

Shaoqiang Zhou[1] · Ding Zhang[2] · Junjie Li[3] · Jing Zhao[2] · Guoqiang Wang[2] · Yuzi Zhang[2] · Yuezong Bai[2] · Dedian Chen[1] · Hao Wu[4]

Received: 25 May 2020 / Revised: 25 May 2020 / Accepted: 10 June 2020 / Published online: 30 June 2020

Abstract

RAS family genes (HRAS, KRAS and NRAS) were frequently observed in several tumors. The expression of constitutively active RAS proteins mediated by RAS variations promote the development of tumors. KRAS is an important prognostic and drug resistance biomarker. It would also be a promising drug target. Several trials which evaluating the efficacy of RAS G12C inhibitor in solid tumors are initiated. Herein, we analyzed the alterations status of KRAS/NRAS/HRAS across diverse solid tumors. The sing nucleotide variants (SNV) and copy number variants (CNV) data of 17993 Chinese patients from 22 types of cancer were obtained in our database. Genomic profiling of DNA was performed through a next-generation sequencing on tissue. Only the pathogenic mutations and likely pathogenic mutations in clinical significance were rolled into our analysis. Among 17993 pan-cancer patients, the total RAS variants frequency was 22.58%. KRAS was the most frequently altered, followed by NRAS and HRAS. For the SNV, KRAS were most commonly found in pancreas cancer, intestine cancer and colorectal cancer. Further analysis among KRAS SNV patients showed that the mutation frequency of KRAS G12C, G12D, G12R, and G12V was 1.81%, 6.81%, 0.69% and 4.25%, respectively. A total of 21 in 22 types of solid tumors had KRAS G12C/D/R/V pathogenic or likely pathogenic mutation, which occurred most frequently in colorectal cancer, pancreas cancer and lung cancer. Our results suggested that a variety of solid tumors may harbor KRAS G12C/D/R/V mutation. These patients may benefit from KRAS inhibitors.

Keywords Carcinoma · Genetics · RAS gene · Next-generation sequencing

Background

RAS pathway plays an important role in the control of major cellular processes, such as cell proliferation, differentiation, cytoskeletal modulation, and survival [1]. Alterations of RAS family genes (HRAS, KRAS and NRAS) were frequently observed in a variety of tumors. KRAS and HRAS genes are identified as the transforming genes of the Harvey and Kirsten strains of oncogenic retroviruses, respectively. Whereas, NRAS is named for having been discovered in human neuroblastoma cells [3]. Their deregulations result in constitutively active RAS proteins expression, and then promote the malignant transformation and progression of tumors [4]. Mutations in KRAS are common and predominant in the lung, colon, and pancreatic cancer [5] and considered as biomarkers for patient prognosis and drug resistance [2]. Moreover, KRAS is also a promising drug target. AMG 510 which targeting KRAS G12C showed an ORR of 48% in patients with NSCLC [3]. Besides, several trials which evaluating the efficacy of RAS G12C/D/R/V inhibitor in solid tumors have been initiated [4, 5]. Herein, we analyzed the alterations status of KRAS/NRAS/HRAS across diverse solid tumors and evaluated the potential population who could benefit from RAS inhibitors.

✉ Dedian Chen
chendedian2006@126.com

✉ Hao Wu
whdactor@163.com

[1] Galactophore Department, The Third Affiliated Hospital of Kunming Medical University (Yunnan Tumor Hospital) , No.518 Kunzhou Road, Yunnan Province 650118 Kunming, China

[2] The Medical Department, 3D Medicines Inc, Shanghai, China

[3] Department of Anesthesiology, The Central Hospital of Zibo, Zibo, China

[4] Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, NO.300 Guangzhou Road, Nanjing, Jiangsu Province 210029, China

Table 1 Patient demographics and baseline characteristics

Characteristics	All patients (N = 17993)
Age, median (IQR range)	59 (1-100)
Sex, n (%)	
Male	10798 (60.01)
Female	7195 (39.91)
RAS Variant, n (%)	4063(22.58)
SNV, n (%)	3862(21.46)
KRAS	3527(91.33)
HRAS	104(2.69)
NRAS	255(6.60)
CNV, n (%)	266(1.48)
KRAS	227(85.34)
HRAS	18(6.77)
NRAS	23(8.65)
Germline, n (%)	1(< 0.01)
KRAS	1(100)
MSI status in RAS variants, n (%)	
MSI-H	176(4.33)
MSS	3431(84.44)
N/A	456(11.22)

Methods

From January 2017 to December 2019, a total of 17,993 patients who received next-generation sequencing (NGS) were screened. Patients who underwent tissue genetic tests including KRAS, HRAS and NRAS genes were included. Genomic profiling of DNA was performed through NGS on Illumina Nextseq 500 to > 500X coverage in 3DMed Clinical Laboratory Inc., a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. The single nucleotide variants (SNV) and copy number variants (CNV) data of these patients were analyzed. Tumor mutational burden (TMB) and microsatellite instability/stability (MSI/MSS) status were identified. Pathogenic and likely pathogenic mutations were interpreted by the bioinformatics specialist upon a joint consensus of the previous reports and the recommendation of American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMP-AMP).

Results

A total of 17,993 pan-cancer patients were included in this study. The baseline characteristics of the patients were shown in Table 1. The total RAS variants frequency was 22.58%, including 3862 patients (21.46%) with SNV, 266 patients (1.48%) with CNV and only 1 patient with germline mutation. Most patients with RAS variations (84.44%) displayed the MSS. Of the RAS mutations, KRAS was the most frequently altered gene (91.33% of RAS SNV, 85.34% of RAS CNV), followed by NRAS (6.60% of RAS SNV, 8.65% of RAS CNV) and HRAS (2.69% of RAS SNV, 6.77% of RAS

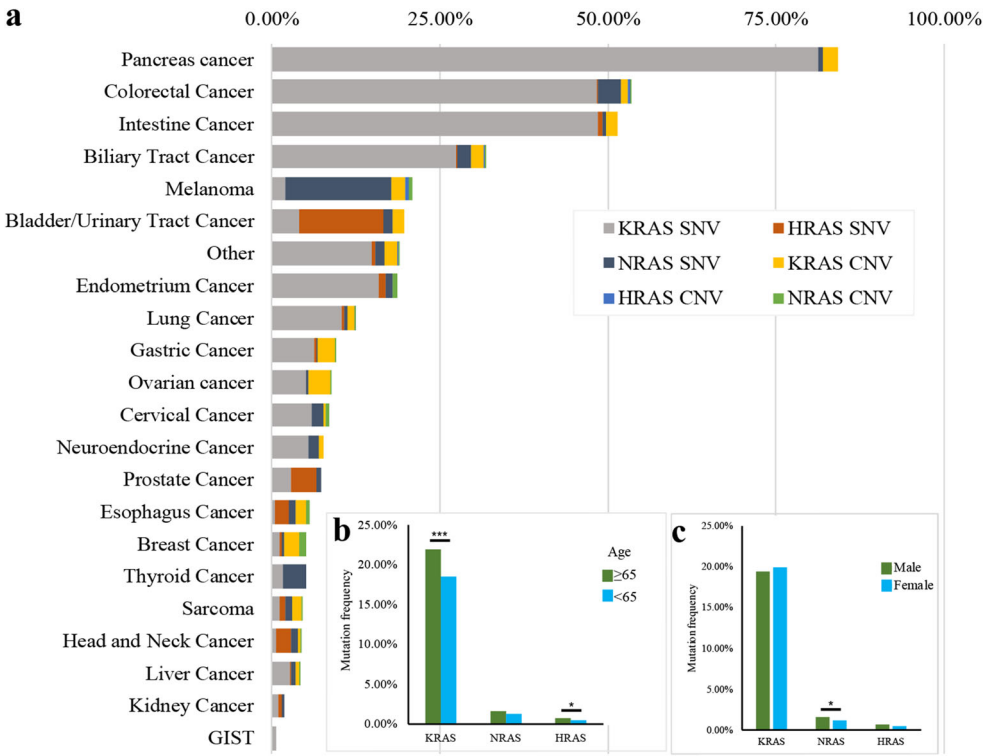

Fig. 1 **a** Prevalence of RAS variants (SNV and CNV) in 17,993 patients with different cancer types. **b** Correlation between RAS SNV and age. **c** Correlation between RAS SNV and sex

CNV). As shown in Fig. 1a, KRAS were most commonly found in pancreas cancer (685/842, 81.35%), intestine cancer (85/175, 48.57%) and colorectal cancer (1609/3329, 48.33%). NRAS occurred most frequently in melanoma (31/196, 15.82%), colorectal cancer (116/3329, 3.48%), and thyroid cancer (2/60, 3.33%). HRAS were most often found in bladder/urinary tract cancer (46/367, 12.53%), prostate cancer (5/137, 3.65%), and head and neck cancer (7/314, 2.23%). Among people who was 65 or older, the mutation frequency of KRAS and HRAS was significantly higher (shown in Fig. 1b, KRAS: $p < 0.001$; HRAS: $p < 0.05$). NRAS mutation was more common among males (shown in Fig. 1c, $p < 0.05$). CNV in KRAS, NRAS and HRAS were most commonly found in ovarian cancer (14/429, 3.26%), breast cancer (5/500, 1.00%), and melanoma (1/196, 0.51%), respectively. 362 patients (2.01%) harbored at least two RAS gene mutation, of which 89.36% of patients carried two different KRAS mutations and 86.69% were KRAS SNV and KRAS CNV coexistence. Moreover, a total of 21 in 22 types of solid tumors had KRAS G12C/D/R/V pathogenic, which occurred most frequently in colorectal cancer (5.29%), pancreas cancer (3.49%), and lung cancer (1.92%). Incidence rate of KRAS G12C, G12D, G12R, and G12V was 1.81%, 6.81%, 0.69% and 4.25%, respectively.

Discussion

RAS oncogenes comprised one of the most frequently mutated genes family in human cancers. KRAS is an important prognostic and drug resistance biomarker. In our cross-sectional study, the incidence of RAS mutation and KRAS mutation were 21.60% and 19.60%, which were similar with the data compiled from the Catalogue of Somatic Mutations (COSMIC). Over several decades, there remains a lack of FDA-approved anti-RAS therapeutics. However, recent findings provide renewed hope that RAS inhibitors will eventually be deployed in the clinic. AMG 510, which targeting KRAS G12C, showed an ORR of 48% in patients with NSCLC. Additionally, many drugs that target KRAS G12C/D/R/V were tested in ongoing clinical trials, including GI-4000 and LEE001. Our results suggested that a variety of solid tumors may harbor KRAS G12C/D/R/V mutation. These patients may benefit from KRAS inhibitors.

Funding Information The authors have not received addition funding to support the production of this article.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

Statement of Ethics Subjects have given their written informed consent. The authors have no ethical conflicts to disclose.

References

1. Vetter IR, Wittinghofer A (2001) The guanine nucleotide-binding switch in three dimensions. Science 294(5545):1299–1304
2. Wan XB, Wang AQ, Cao J et al (2019) Relationships among KRAS mutation status, expression of RAS pathway signaling molecules, and clinicopathological features and prognosis of patients with colorectal cancer. World J Gastroenterol 25(7):808–823
3. Lartigue JD (2019) New strategies generate optimism for targeting "Undruggable" KRAS. Oncol Live 20:19
4. Chaft JE, Litvak A, Arcila ME et al (2014) Phase II study of the GI-4000 KRAS vaccine after curative therapy in patients with stage I-III lung adenocarcinoma harboring a KRAS G12C, G12D, or G12V mutation. Clin Lung Cancer 15(6):405–410
5. Shepherd FA, Domerg C, Hainaut P et al (2013) Pooled analysis of the prognostic and predictive effects of KRAS mutation status and KRAS mutation subtype in early-stage resected non-small-cell lung cancer in four trials of adjuvant chemotherapy. J Clin Oncol 31(17): 2173–2181