The spectrum of TP53 mutations in Rwandan patients with gastric cancer

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論文題目

The spectrum of *TP53* mutations in Rwandan patients with gastric cancer
(ルワンダの胃癌患者における *TP53* 遺伝子変異スペクトラム)

論文の内容の要旨

[Introduction]

Gastric cancer is the sixth most frequently diagnosed cancer and third in causing cancer-related death globally. The most frequently mutated gene in human cancers is *TP53*, which plays a pivotal role in cancer initiation and progression. In Africa, particularly in Rwanda, data on *TP53* mutations are lacking. Therefore, this study intended to obtain *TP53* mutation status in Rwandan patients with gastric cancer.

[Materials and Methods]

Formalin-fixed paraffin-embedded tissue blocks of 95 Rwandan patients with histopathologically proven gastric carcinoma were obtained from the University Teaching Hospital of Kigali.

Microscopic examination of the biopsies was first performed at the University Teaching Hospital of Kigali, Rwanda. Tissue slides were reviewed by pathologists at Hamamatsu University School of Medicine, Japan. Next, DNA extraction was carried out.

After DNA extraction, all coding regions of the TP53 gene and the exon–intron boundary region of TP53 were sequenced using the Sanger sequencing. To detect the presence or the absence of H. pylori in the gastric cancer biopsies, conventional polymerase chain reaction (PCR) analysis for the ureC gene, which is present in H. pylori, but not in humans, was used after slightly modifying the previous quantitative PCR method by Suzuki et al. TP53 protein expression in gastric carcinoma with *TP53* missense mutations was evaluated via immunohistochemistry.

This study was approved by the institutional review board of the University of Rwanda College of Medicine and Health Sciences (Approval notice N° 295/CMHSIRB/2020 and N° 310/CMHSIRB/2021), the ethical committee of the University Teaching Hospital of Kigali (Ref.: EC/CHUK/2/064/2020) and the ethics committee of the Hamamatsu University School of Medicine (EC HUSM number: 20-011).

[Results]

Mutated TP53 were observed in 24 (25.3%) of the 95 cases, and a total of 29 mutations were identified. These TP53 mutations were distributed between exon 4 and 8 and most of them were missense mutations (19/29; 65.5%). Immunohistochemical analysis for TP53 revealed that most of the TP53 missense mutations were associated with TP53 protein accumulation. Among the 29 mutations, one was novel

(c.459_477delCGGCACCCGCGTCCGCGCC). This 19-bp deletion mutation in exon 5 caused the production of truncated TP53 protein (p.G154Wfs*10). Regarding the spectrum of TP53 mutations, G:C > A:T at CpG sites was the most prevalent (10/29; 34.5%) and G:C > T:A was the second most prevalent (7/29; 24.1%). Interestingly, when the mutation spectrum of TP53 was compared to three previous TP53 mutational studies on non-Rwandan patients with gastric cancer, G:C > T:A mutations were significantly more frequent in this study than in our previous study ($p = 0.013$), the TCGA database ($p = 0.017$), and a previous study on patients from Hong Kong ($p = 0.006$). Even after correcting for false discovery, statistical significance was observed. Immunohistochemical analysis for TP53 protein on 17 gastric cancer cases with *TP53* missense mutations showed an abnormal accumulation of TP53 protein in 16 (94.1%) out of 17 cases, suggesting the correctness of our TP53 gene sequencing. With regards to H. pylori status in gastric carcinoma lesions, it was detected in 7/95 (7.4%) cases through PCR analysis of the H. pylori ureC gene.

[Discussion]

In this study, the percentage of gastric cancer cases with *TP53* mutations was 25.3%, this result is comparable with the incidence of mutation (27.0%) in the previous study by Li-Chang et al., slightly lower when compared to the findings of Hwang et al., 37.4% and 43.3% of Tahara et al.

In this study, there were three frameshift mutations (deletions), one of them novel. The results from in silico tools show that this produces a truncated protein. Previous findings suggested that these types of mutations may interfere with protein translation and result in the production of an incomplete protein. Studies indicate that TP53 frameshift mutants lack C-terminal sequences and exhibit a mixture of residual antiproliferative (cellular senescence and aging) and neomorphic functions that may be differentially exploited for targeted therapy.

In our study, we found a significantly higher occurrence of the G:C > T:A transition in the TP53 mutation pattern in gastric cancer patients from Rwanda compared to those from non-African countries such as China, Hungary, Japan, Poland, Romania, the USA, and Hong Kong. It is possible that regional differences are associated with the variation in the frequency of G:C > T:A transition. The variation in environmental factors, infectious diseases, food contamination, and socio-economic status between Rwanda and other countries may result in a unique mutation spectrum specific to Rwanda.

[Conclusion]

Our results suggested that TP53 G:C > T:A transversion mutation in Rwandan patients with gastric cancer is more frequent than in non-Rwandan patients with gastric cancer, indicating at an alternative etiological and carcinogenic progression of gastric cancer in

Rwanda