Role of Fibroblast Growth Factor (FGF) in Suppressing Tumor in Patients with Colorectal Cancer

Charlie Javice*

University of East Anglia, Norwich Research Park, Norwich, United Kingdom

Abstract

In colorectal cancer, fibroblast growth factor 14 (FGF14) was selectively methylated (CRC). In this work, we sought to elucidate the biological action, molecular mechanism, and epigenetic control of FGF14 in CRC. By using PCR and Western blot, the expression of FGF14 in CRC cell lines, normal human colon epithelial cell lines, CRC tissues, and matched neighbouring normal tissues was found. FGF14 blocked the PI3K/AKT/mTOR pathway and caused mitochondrial death. In conclusion, FGF14 is a new tumour suppressor that activates the PI3K/AKT/mTOR pathway to mediate cell death and restrict cell growth.

Keywords: Fibroblast growth factor; Colorectal cancer; Tumour suppressor; DNA methylation; Apoptosis

Introduction

The second greatest cause of cancer-related mortality in both sexes in the US is colorectal cancer (CRC). Colon and rectal cancers were predicted to be the cause of 51,020 fatalities among digestive system locations in 2019 [1]. Unfortunately, the mechanism that prevents the development of cancer is incredibly complicated and diverse, thus using omics technology and early diagnosis are now the greatest ways to increase the likelihood that a therapy will be effective [2]. However, there is new evidence indicating a tumor-suppressing role for FGF14. Overexpression of fibroblast growth factor (FGF) in patients with colorectal cancer is often related with tumour development. This dual action provides new diagnostic possibilities for early FGF biomarker screening to personalise treatments. There is currently little information available on FGFs and if using them as a predictive tool for cancer treatment would be beneficial. According to reports, most known FGFs may be overexpressed in late-stage CRC patients, which might promote the differentiation and growth of cancer cells [3-5]. As a result, various strategies for using multikinase inhibitors and antibodies as targeted therapies to disrupt the FGF pathway have been published [6]. There are now 37 FDA-approved kinase inhibitors, but only one of these, Regorafenib, targets several tyrosine kinases, including the FGF receptor 1 and is specifically indicated for the treatment of metastatic colon cancer [7,8].

These kinase treatments have manifested unanticipated side effects that can be successfully avoided by using a tailored strategy with the use of cancer biomarkers [9]. Four monoclonal antibodies that bind to VEGF and EGFR are among the antibody treatments that are often utilised in CRC in conjunction with chemotherapy or radiation therapy [10]. These strategies are all geared on directly inhibiting signalling pathways in CRC cells. However, a newly released research by Su and colleagues [11] revealed that the signalling suppression in CRC needs activation of the FGF14 gene whose expression has been suppressed.

A member of the fibroblast growth factor family and an intracellular protein, FGF14 is found on chromosome 13q33. Su et al. [11] shown through a genome-wide screening strategy that promoter methylation silences FGF14, and that therapy with the authorised DNA methyltransferase inhibitor 5-Aza suppresses the methylation process in CRC, leading to gene suppression. These results imply that FGF activation by contemporary epigenetics functioning as methyltransferase inhibitors can successfully reduce cancer cell viability.

Surprisingly, FGF14 silence or down regulation was found in every CRC (10/10) cell, highlighting the possibility that promoter methylation may be a key factor in the growth of cancer. Su and colleagues also carried out a transfection investigation using the complementary DNA matching to the gene to ascertain if the restoration of the gene reduces cell growth. The outcomes demonstrated that malignant cells' expression of the FGF14 gene increases apoptosis. It was discovered that this was caused by mitochondrial activation of death pathways.

Using the appropriate apoptotic markers, the cleavage of PARP, cleaved-caspase-3, cleaved-caspase-7, and Bax was detected. Su et al. [11] hypothesised that overexpression of FGF14 can be exploited for cancer suppression since they were aware that this pathway's poor expression is linked to the development of colon tumours. The findings of the Western blot analysis confirmed what was predicted, with the overexpression of FGF14 inhibiting the activity of the well-known signalling proteins PI3K, Akt, and mTOR. This significant discovery showed that practically all human malignancies, including colon cancer, have dysregulated PI3K/AKT/mTOR signalling pathways. Activation of the FGF14 gene may be a triple inhibitor of these proteins. A very appealing focus of current research is the development of novel inhibitors of this system. Idelalisib is the only PI3K inhibitor that the FDA has approved, however several other medications are being tested in clinical studies [3,12]. Therefore, for the 60–70% of CRC patients who have PI3K/Akt mutations, activating FGF14 in conjunction with receptor tyrosine inhibitors may be a highly effective treatment [13]. Additionally, Su and colleagues in vivo tumorigenicity investigation on nude mice transfected with the gene validated the suppressive role of FGF14. The data obtained after 4 weeks of FGF14 injection showed a significant decrease in xenografted tumour volume (P<0.001). The significance of FGF14 as a promoter in CRC was therefore shown by

research using both in vitro and animal models. Therefore, rather than blocking all FGFs, doctors should concentrate on evaluating the genes that are expressed often before deciding whether to block or activate FGFs [14]. The discovery of the first FGF suppressor gene by Su et al. in CRC among known FGFs highlights the necessity to identify any further FGF suppressors that could be present within the same FGF11 subfamily. A new wave of personalised therapeutics for colon cancer and other diseases may become possible as a result of the enigma surrounding the distinct and varied signalling system of FGF genes, receptors, and their ligands. Treatment for CRC is evolving, and maybe reframing existing therapeutic modalities might involve screening for FGF genes in patients. Separately, research on FGF2 and FGF10 proteins in CRC by Matsuda et al. [4] and Qazvini et al. [3] proposed the use of anti-FGF receptor therapy to stop the overexpression of those receptors and restrain tumour growth. Therefore, the combination of FGF14 receptor activators with methyltransferase inhibitors that can activate the FGF14 gene opens up new therapeutic possibilities. Additionally, Jibiki et al's. research [15] revealed that FGF levels tend to fluctuate and advance in patients with advanced cancer; as a result, measuring the expression of FGF genes may potentially be able to determine the clinical stage of CRC for the individualization of the therapy.

Currently, the FDA has authorised a panel of tests with an epigenetic component to check blood and stool samples from CRC patients for the presence of mutant alterations in the epigenome. The most used test is FIT for detecting haemoglobin in faeces. Other procedures concentrate on analysing the methylation level of the genes BMP3, SEPT9, and CDC2 in stool or blood to determine the stage of the malignancy. A further test makes use of the biomarker miR-31-3p that was taken from the main tumours of colon cancer patients. Depending on its findings, a patient may require anti-VEGF or anti-EGFR medication. As a result, there are effective, commercially accessible diagnostics based on epigenetics that may determine the stage of CRC and the therapy [16]. Therefore, the development of new epigenetic biomarkers will advance precision medicine.

Since little is known about the roles of each FGF gene within the subfamilies, the remaining question is how soon we will be able to develop FGF biomarkers for CRC patients. Although there has been some improvement in identifying cardiometabolic disorders in patients using the FGF-21 biomarker and cancer, heart disease, and non-vascular illnesses in patients using the FGF-23 biomarker. Since the FGF marker does not fully depict the pathophysiology of a disease, this is often done in conjunction with other markers linked to that illness [17]. These indicators are often either proteins that are important to CRCs or tumour antigens and antibodies to them [18]. Notably, the screening was carried out using Olink PEA technology, which only allows for the detection of 92 proteins, among which FGF 2,5,19,21, and 23 are already present. Antibodies that are specific for a target protein that has been identified by microfluidic qPCR are used in this cutting-edge method. Although there aren't many FGFs currently on the market, the business is concentrating on expanding its protein library so that FGF14 might possibly be tested in colon cancer patients. So, diagnostic assays for FGF gene identification are now available; it is only a matter of time until doctors start using novel FGF biomarkers. Although most tests are expensive and difficult to use, there is hope that in the future they will be less complicated and less expensive. The discovery of the functions of each of the 23 FGFs and the molecules involved in its signalling pathway should be the primary focus of current research. It is necessary to design tests that can be used by doctors once biomarkers have been identified and verified. Although it may seem like there is a lot of research to be done,

there is significant potential for the advancement of precision medicine and the potential implementation of effective biomarkers in clinical practise. The fact that tailored medicine is replacing the one-size-fits-all approach in today's pharmaceuticals suggests that biomarkers will continue to play a significant role in the future. Some of them already provide individualised genomic analyses that make it possible to find a successful therapy.

Discussion

The development of FGF indicators would undoubtedly enhance knowledge of a patient's illness progression, particularly for cancer, which continues to be the second biggest cause of mortality worldwide. Early detection of cancer using FGF biomarkers would reveal how severe the disease is and which treatment is most likely to be effective for the patient. We currently use biomarkers to understand the nature of the disease, so why not keep developing new markers and diagnostic procedures to provide precision medicine.

Conclusion

According to the evidence presented here, FGF14 operates as a new tumour suppressor that triggers cell death by suppressing PI3K/AKT/mTOR signalling, and its decreased or silent expression is controlled by DNA methylation of this gene. To the best of our knowledge, this work is the first to analyse in detail the epigenetic control, biological role, and molecular mechanism of FGF14 in CRC. This analysis may help to clarify the role of FGF14 and the PI3K/AKT/mTOR signalling pathway in the development of colorectal cancer.

Acknowledgement

Conflict of Interest

None to declare

References

1. Sieg RL, Miller KD, Jemal A (2019) Cancer statistics. CA Cancer J Clin 69:7-34.

2. Aziz MA, Yousef Z, Saleh AM, Mohammad S, Al Knawy B (2017) Towards personalized medicine of colorectal cancer. Crit Rev Oncol Hematol 118:70-78.

3. Qazvini FF, Samadi N, Saffari M, Razavi ANE, Shirkoohi R (2019) Fibroblast growth factor-10 and epithelialmesenchymal transition in colorectal cancer. EXCLI J 18:530-539.

4. Matsuda Y, Ueda J, Ishiwata T (2012) Fibroblast growth factor receptor 2: expression, roles, and potential as a novel molecular target for colorectal cancer. Patholog Res Int 12:768.

5. Korc M, Friesel R (2009) The role of fibroblast growth factors in tumor growth. Curr Cancer Drug Targets 9:639-651.

6. Garcia AP, Barderas R, Torres S, Varas PH, Teixido J, et al. (2013) FGFR4 Role in epithelial-mesenchymal transition and its therapeutic value in colorectal cancer. PLoS One 8:63695.

7. García AM, Redondo M (2019) Targeting receptor kinases in colorectal cancer. Cancers 11: 433.

8. Goel G (2018) Evolution of regorafenib from bench to bedside in colorectal cancer: Is it an attractive option or merely a "me too" drug?. Cancer Manag Res 10:425-437.

9. Bhullar KS, Lagaron NO, McGowan EM, Parmar I, Jha A (2018) Kinase-targeted cancer therapies: Progress, challenges and future directions. Mol Cancer 17:48.

10. An L, Peng LY, Sun NY, Yang YL, Zhang XW, et al. (2019) Tanshinone IIA Activates Nuclear Factor-Erythroid 2-Related Factor 2 to Restrain Pulmonary Fibrosis via Regulation of Redox Homeostasis and Glutaminolysis. Antioxid Redox Signal 30:1831-1848.

11. Su T, Huang L, Zhang N, Peng S, Li X, et al. (2020) FGF14 functions as a tumor suppressor through inhibiting PI3K/AKT/mTOR pathway in colorectal cancer. J Cancer 11: 819-825.

12. Yang J, Nie J, Ma X, Wei Y, Peng Y, et al. (2019) Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer 18.

13. Pandurangan AK (2013) Potential targets for prevention of colorectal cancer: A focus on PI3K/Akt/mTOR and Wnt pathways. Asian Pac J Cancer Prev 14: 2201-2205.

14. Kliment CR, Oury TD (2010) Oxidative stress, extracellular matrix targets, and idiopathic pulmonary fibrosis. Free Radic Biol Med 49:707-717.

15. Jibiki N, Saito N, Kameoka S, Kobayashi M (2014) Clinical significance of fibroblast growth factor (FGF) expression in colorectal cancer. Int Surg 99:493-499.

16. Garcia JB, Verdegal RO, Molla SM, Giménez JLG (2019) Epigenetic IVD tests for personalized precision medicine in cancer. Front Genet 10:621.

17. Fu S, Liu X, Luo M, Xie K, Nice EC, et al. (2017) Proteogenomic studies on cancer drug resistance: towards biomarker discovery and target identification. Expert rev proteom 14:351-362.

18. Lech G, Slotwinski R, Slodkowski M, Krasnodebski IW (2016) Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances. World J Gastroenterol 22: 1745-1755.