REVIEW

**Editorial Process:** Submission:07/31/2024 Acceptance:03/17/2025

# Understanding the Role of Rho GTPase Activating Protein and Bone Marrow Kinase X: A Novel Target in Gastric Cancer Treatment

**Zakari Shaibu[1,2], Zhihong Chen[2], Fumeng Yang[1], Xiaofeng Xu[3], Yong Ji[3]*, Wei Zhu[1]***

## Abstract

**Objective:** To review the role of Rho GTPase Activating Protein (ARHGAP) and Bone Marrow Kinase X (BMX) in the progression and development of gastric cancer (GC), and to highlight their potential as therapeutic targets. **Method:** A comprehensive literature review was conducted to assess current evidence regarding the involvement of ARHGAP and BMX in GC, focusing on their expression levels, association with prognosis, and impact on tumor behavior. **Results:** Current research indicates that both ARHGAP and BMX are up-regulated in GC tissues, correlating with poor prognosis and aggressive tumor characteristics. These findings suggest that they play significant roles in the mechanisms underlying GC progression. **Conclusion:** The evidence supports the critical involvement of ARHGAP and BMX in GC, suggesting their potential as therapeutic targets. Further research is essential to clarify the mechanisms by which these proteins influence gastric cancer progression and to evaluate their viability as targets for new therapeutic strategies.

**Keywords:** Rho GTPase activating protein- ARHGAP family genes- BMX protein- Stomach neoplasm- Gene fusion

*Asian Pac J Cancer Prev,* **26 (3)**, 725-733

## Introduction

Gastric cancer (GC) is the fourth leading cause of cancer-related mortality worldwide and the fifth most common malignant tumor, with a persistently poor prognosis despite advances in diagnosis and treatment [1-3]. The majority of GC cases occur in countries with high human development indexes, with a high incidence in Asia, particularly China [2, 4-6]. Adenocarcinoma is the predominant histological type, accounting for 85-90% of all cases [7, 8]. GC affects males more frequently than females in developed nations, and the five-year survival rate is less than 20% [9, 4, 10-13]. Despite improvements in treatment, the prognosis for individuals with metastatic GC remains poor, with a median overall survival of less than a year [14-16]. Surgery is the primary treatment for GC, but its effectiveness is limited in advanced-stage cases. Chemotherapy is commonly used in advanced-stage GC, but it has a low response rate and short survival time and may result in severe side effects [17, 18]. Recently, immunotherapy has emerged as a promising treatment for advanced GC, with a better understanding of the tumor microenvironment facilitating the development of immunotherapies [19-24].

GC is a complex and multifaceted disorder, shaped by a dynamic interplay of environmental and genetic factors. Recent advances have implicated dysregulated gene expression and epigenetic modifications as key drivers of gastric carcinogenesis. These molecular aberrations can disrupt the delicate balance of cellular processes, paving the way for the malignant transformation of gastric epithelial cells [25].GC is one of several fusion genes implicated in cancer [26, 27]. Rho GTPase Activating Protein and Bone Marrow Kinase X (ARHGAP-BMX) is a novel gene fusion identified in GC [28]. Genetic changes leading to an imbalance of Rho/Rac/Cdc42-like GTPases may link the ARHGAP family to cancer [29, 30]. The ARHGAP family includes several cancer-related proteins, such as ARHGAP18, which inhibits GC growth and progression [31]. Inhibiting BMX-ARHGAP may suppress GC progression by blocking the JAK/STAT pathway [32]. BMX encodes a non-receptor tyrosine kinase, while ARHGAP12 encodes a protein activating Rho GTPase. Given BMX links to tumor development and spread, it is plausible that the chimeric transcript activated BMX-mediated tumorigenicity in GC patients [33, 34].

The persistently poor prognosis of GC despite advances in diagnosis and treatment highlights the need for

*[1]School of Medicine, Jiangsu University, Zhenjiang, Jiangsu,212013, China. [2]Department of Surgery, Jingjiang People's Hospital, Jingjiang, Jiangsu, 214500, China. [3]Department of Gastrointestinal Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu,212001, China. *For Correspondence: zhuwei@ujs.edu.cn, 42394176@qq.com*

novel therapeutic strategies. The identification of fusion genes, such as ARHGAP-BMX, offers a promising avenue for targeted therapies. As GC is a complex disease with heterogeneous molecular profiles, understanding the role of ARHGAP-BMX in GC growth and progression may provide insights into treatment approaches. This review aims to consolidate and analyze existing evidence on ARHGAP-BMX role in GC, exploring its influence on GC growth, progression, and potential therapeutic targets.

*The ARHGAP family*

The ARHGAP family is pivotal in regulating cancer development, primarily through its influence on Rho GTPase activity, a key factor in cancer progression [35]. Rho GTPases function as molecular switches that govern essential cellular processes and abnormal Rho GTPase signaling is frequently implicated in various cancers [35]. The human genome encodes 20 members of the Rho GTPase family, alongside various Rho guanine nucleotide exchange factors (RhoGEFs) and Rho GTPase-activating proteins (RhoGAPs), which collectively modulate Rho GTPase activity [36, 37].

While RhoGAPs are known for their promiscuity, allowing them to inactivate multiple GTPases in vitro, their substrate selectivity in vivo is more limited, suggesting that additional protein domains play a significant role in regulating specificity (Figure 1) [38, 39, 37, 40]. Although there is some redundancy in function among RhoGAP family members, recent studies indicate that this redundancy is less extensive than initially believed [41].

The dynamic interplay between RhoGEFs and RhoGAPs facilitates the cycling of Rho GTPases between their active and inactive forms, promoting the hydrolysis of guanosine triphosphate (GTP) and the release of guanosine diphosphate (GDP) [42]. Rho GTPases are essential for a variety of cellular processes, including cytoskeleton organization, gene regulation, vesicle trafficking, cell cycle progression, and cell migration [43]. Their involvement extends to pathological processes such as cancer, inflammation, and wound healing [44].

In summary, the ARHGAP family is crucial for cancer development, underscoring the significance of Rho GTPase signaling pathways. The intricate relationship between RhoGEFs and RhoGAPs highlights the complexity surrounding Rho GTPase activation and its implications for cancer progression. By further understanding the specific functions and interactions within the ARHGAP family, researchers can enhance their knowledge of cancer biology and identify potential therapeutic targets. Continued investigation into the ARHGAP family may lead to innovative strategies in precision medicine and cancer treatment.

*The role of ARHGAP in GC*

The ARHGAP family encompasses a plethora of cancer-associated proteins, including ARHGAP18 and ARHGAP11A [30]. ARHGAP18 encodes solely the RhoGAP domain and has been implicated in both tumor-suppressive and oncogenic roles in cancer [45, 46]. In GC, ARHGAP18 exhibits downregulated expression levels in tumor tissues compared to normal tissues, suggesting a tumor-suppressive function [31]. Overexpression of ARHGAP18 in GC cells inhibits in vivo tumor formation, cell viability, migration, and invasion [31].

Conversely, ARHGAP11A has been identified as an oncogene with elevated expression in GC patients with lymph node metastasis [47]. Whole exon and genome sequencing revealed multiple metastases in a series of ongoing investigations, highlighting ARHGAP11A as a key gene contributing to the clonal evolution of metastatic GC [47]. However, the precise mechanisms by which ARHGAP11A promotes metastasis and its relationship with immune infiltrates, such as TILs, in GC remain obscure. In this study, we reviewed the expression of

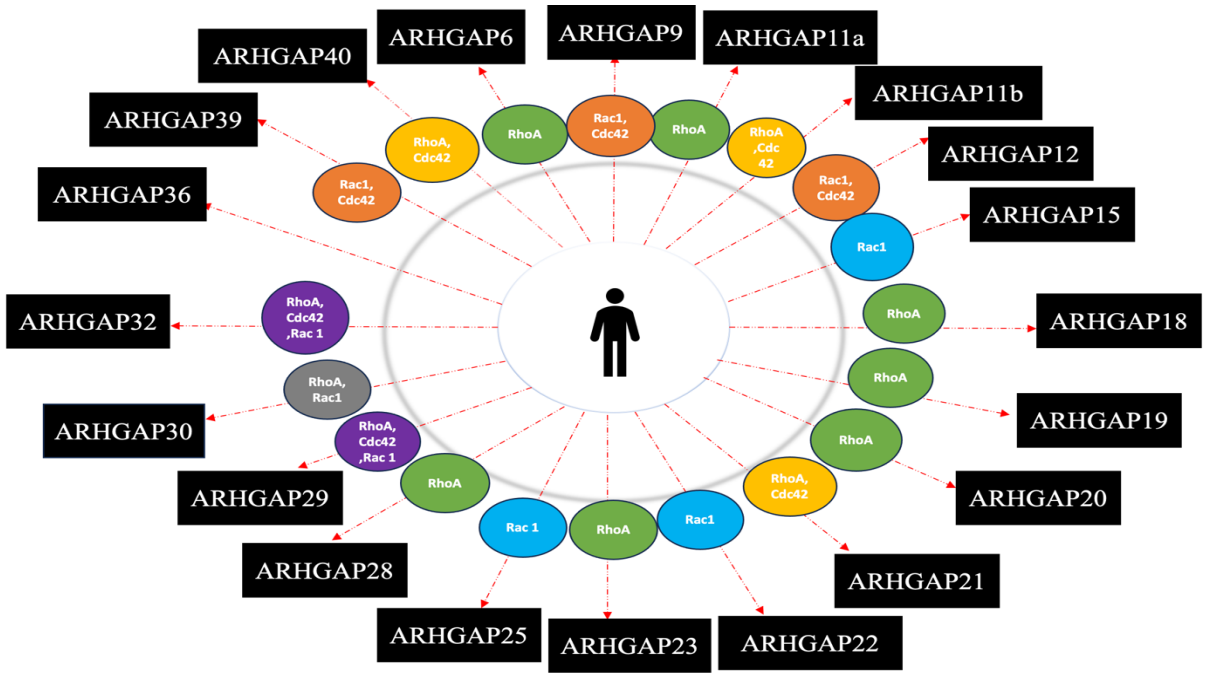


Figure 1. Schematic Representation of the ARHGAP Family. Adapted from by Rossman and colleagues [36]

ARHGAP11A in various tissue types and discovered significantly elevated expression in gastrointestinal malignancies, including adenocarcinomas of the stomach. These findings suggest that the ARHGAP family is implicated in the development of GC through multiple mechanisms. ARHGAP18 exhibits tumor-suppressive properties, while ARHGAP11A may promote metastasis. In summary, the ARHGAP family plays a complex role in GC development, and further research is necessary to clarify the specific processes behind their involvement. The potential of ARHGAP proteins as diagnostic and therapeutic targets in GC treatment warrants further investigation.

*BMX genes*

The kinase enzyme BMX, located on the X chromosome, has been linked to various forms of cancer, where it influences the viability and malignant potential of stem cells driving glioblastoma [34]. A fusion event combining BMX with ARHGAP12 may trigger a powerful oncogenic mechanism in gastric cancer patients, as BMX, a tyrosine kinase lacking a receptor, has been shown to enhance tumor progression and dissemination across multiple cancer types [48, 33, 34]. BMX is believed to play a role in promoting tumor growth by preventing the apoptosis that is typically induced by chemotherapy and radiotherapy in colorectal cancer [49]. This protein boasts two crucial domains: an SH2 domain that interacts with tyrosine-phosphorylated proteins and a PH-like domain that binds to membranes [50]. Notably, BMX is regulated by several oncogenes, including Src and phosphoinositide 3-kinase, and is also activated by inflammatory pathways[34]. Moreover, BMX has been linked to drug resistance, as overexpressing BMX can override the inhibitory effects of miR-495 on drug resistance[51]. Intriguingly, BMX has been shown to modulate the survival and tumorigenicity of cancer stem cells in glioblastoma and is expressed in a multitude of cancers [34].

In our view, the role of BMX in GC warrants further investigation, particularly in light of its potential to promote tumorigenicity and drug resistance. The interaction between BMX and ARHGAP12 may also have significant implications for our understanding of GC development and progression. Furthermore, the regulation of BMX by oncogenes and inflammatory pathways suggests that targeting BMX may be a promising strategy for cancer therapy.

*Rho GTPases Altered Expression and Mutations in Cancer*

Rho GTPases are crucial regulators of various cellular functions, including cell migration, survival, and proliferation. Consequently, it is unsurprising that aberrant expression of Rho GTPases or their upstream regulators is a common occurrence in cancer. Interestingly, Rho GTPases are often overexpressed in cancers, rather than being downregulated, suggesting that they play a significant role in promoting tumorigenesis [52-55].

Notably, the frequent overexpression of Rho GTPases in cancer highlights their potential as therapeutic targets. Moreover, understanding the specific mechanisms by which Rho GTPases contribute to cancer development and progression may provide valuable insights into novel treatment strategies. The altered expression of Rho GTPases in cancer also underscores the importance of investigating their regulatory pathways and upstream regulators, which may offer additional opportunities for therapeutic intervention.

*Fusion of ARHGAP-BMX gene in GC*

The fusion of the ARHGAP-BMX gene represents a critical area of exploration in the realm of GC research. This gene fusion was first identified through advanced bioinformatics tools such as Defuse [56] and TopHat [57] , marking a significant milestone in understanding the molecular intricacies of GC. Gene fusions, notably, lead to substantial alterations in gene structure, resulting in the production of proteins with modified molecular functions that can have profound implications for tumor development [58]. This mechanism of oncogenic activation is not unique to GC; it is also implicated in various malignancies, including leukemia, lymphoma, breast cancer, and prostate cancer [59].

The emergence of gene fusions like ARHGAP-BMX unveils a distinct pathway through which the dynamics of cancer stem cells are influenced. These fusions can significantly alter the tumorigenic capabilities of cancer stem cells, bestowing upon them the ability to proliferate and differentiate into diverse tumor cell populations. This phenomenon contributes to the heterogeneity of the tumor microenvironment and poses challenges in therapeutic efficacy due to the resultant resistance to interventions [58, 60].

The ARHGAP family, particularly ARHGAP12 and ARHGAP26, has been linked to cancer progression through genetic alterations that disturb the signaling balance of Rho, Rac, and Cdc42-like GTPases [30]. Notably, both BMX and ARHGAP independently facilitate tumor growth, further emphasizing their significance in oncogenesis. BMX plays a pivotal role in maintaining glioma stem cell-derived pericytes, and its inhibition has been associated with heightened sensitivity to chemotherapy [61]. Additionally, BMX has been identified as a promoter of castration-resistant prostate cancer, highlighting its ability to potentiate the activities of receptor tyrosine kinases via phosphotyrosine modifications in their activation loops [62].

The ARHGAP-BMX gene fusion has also been reported to alter endocytic pathways, specifically inhibiting clathrin-independent endocytosis—a process with implications for GC pathophysiology [29. 63]. Exploring this fusion's expression in GC tissues and cells has revealed promising insights, particularly regarding the SH2 domain-JAK/STAT3 axis, which plays a crucial role in maintaining GC stem cell characteristics. This axis, influenced by ARHGAP-BMX, suggests the presence of novel therapeutic targets for GC [64].

Moreover, research indicates that the suppression of ARHGAP-BMX leads to the inhibition of RhoA, thereby obstructing the JAK/STAT pathway from facilitating the progression of GC cells [32]. The compelling evidence surrounding the ARHGAP-BMX fusion gene underscores its potential as both a contributor to disease development

and a target for therapeutic intervention in gastric cancer.

In summary, the ARHGAP-BMX fusion gene emerges as a pivotal factor in understanding the molecular underpinnings of gastric cancer. As ongoing research delves deeper into the mechanisms at play, there is a critical need to elucidate the full spectrum of its implications for GC progression and treatment. This understanding could herald novel strategies for targeted therapies, establishing ARHGAP-BMX as a promising therapeutic target in the pursuit of more effective cancer treatments. Ultimately, the exploration of this gene fusion not only enhances our comprehension of gastric cancer biology but also opens new avenues for innovative therapeutic approaches.

*Fusion of ARHGAP with other proteins (Claudins 18) in GC*

The fusion of CLDN18 with ARHGAP in GC patients has emerged as a significant marker of poor prognosis. Recent systematic reviews and meta-analyses indicate that individuals with the CLDN18-ARHGAP fusion exhibit a notably higher risk of mortality compared to those without this genetic alteration [65]. This fusion protein may disrupt the structural integrity of the wild-type CLDN18, potentially compromising cancer cell adhesion and contributing to the aggressive behavior of tumors [66].

Moreover, the presence of the CLDN18-ARHGAP fusion is associated with an earlier onset of GC, suggesting that it may serve as a critical factor in the disease's progression and ultimately lead to poorer survival outcomes [67]. In particular, research by Dong et al. highlighted the oncogenic potential of the CLDN18-ARHGAP26/6 fusion, establishing its fusion status as an important predictor of metastatic spread in diffuse-type gastric cancer [68].

These findings collectively underscore the need for further investigation into the CLDN18-ARHGAP fusion, particularly regarding its role in GC development and its potential as a target for therapeutic strategies. Understanding the molecular mechanisms underlying this fusion could pave the way for novel interventions aimed at improving clinical outcomes for patients with gastric cancer.

*Expression of BMX-ARHGAP in GC tissues and cells*

Research reveals that GC tissues and cells demonstrate significantly higher levels of BMX-ARHGAP expression compared to normal gastric tissue. Several studies have documented elevated concentrations of the BMX-ARHGAP fusion gene in GC samples, with RT-PCR and gel analysis identifying this fusion in approximately 26.7% of GC patients' tumor tissues [29, 64]. Additionally, enrichment of ARHGAP-BMX has been observed in these malignant tissues [64].

Given that BMX encodes a nonreceptor tyrosine kinase and ARHGAP12 activates the Rho GTPase, the chimeric transcript BMX-ARHGAP is likely involved in BMX-mediated tumorigenesis in GC patients [33, 34]. However, the exact mechanistic role of BMX-ARHGAP in the progression and development of GC remains to be fully understood. This necessitates further research to explore its potential as both a therapeutic target and a diagnostic marker.

Notably, overexpression of ARHGAP-BMX has been shown to increase the expression of BMX-SH2 protein levels. A western blot analysis demonstrated that the presence of sh-ARHGAP-BMX resulted in a significant reduction of ARHGAP-BMX protein expression, while overexpression led to an increase [64]. Interestingly, no considerable changes were reported in the levels of BMX and ARHGAP proteins across different experimental groups. Furthermore, overexpressing ARHGAP12 negatively affected cellular invasion, scattering, and adhesion to fibronectin [69].

These findings collectively suggest that the ARHGAP-BMX fusion gene plays a pivotal role in tumor development, potentially serving as a target for innovative therapeutic strategies. The study underscores that high expression of ARHGAP-BMX is associated with poor prognosis in gastric cancer, highlighting the importance of this fusion in clinical outcomes.

*The role of JAK/STAT3 in ARHGAP-BMX regulation*

The ARHGAP-BMX fusion gene plays a significant role in GC by acting as an activator of the JAK/STAT3 signaling pathway, which is critical for enhancing cell invasion, migration, and tumorigenicity [64, 70]. High levels of ARHGAP-BMX expression in GC tissues correlate with poor patient prognosis, making it an important target for therapeutic strategies aimed at treating this malignancy.

Mechanistically, the involvement of the JAK/STAT3 pathway is underscored by the increased phosphorylation of JAK2 and STAT3, indicating that the ARHGAP-BMX fusion is responsible for activating this signaling cascade. Interestingly, research has shown that targeting BMX can mitigate JAK2-mediated STAT3 activation, while BMX can also circumvent the inhibitory effects of SOCS3 on JAK2, providing a novel approach for the targeted elimination of glioma stem cells [71]. Moreover, knocking down BMX expression has been demonstrated to prevent STAT3 activation and inhibit the activity of transcription factors that drive tumorigenicity in glioblastoma stem cells [72].

The JAK/STAT3 pathway is intricately linked to invasion and metastasis in GC, with evidence indicating that blocking this pathway reduces migration and invasion of GC cells [73, 74]. Despite the need for further clarification on how this pathway regulates GC stem cells, it is recognized as a master regulator of cancer stem cell characteristics in other malignancies, such as hepatocellular carcinoma [75].

The oncogenic potential of the ARHGAP-BMX fusion gene in GC is manifested through the upregulation of BMX-SH2,[64], further affirming its role in activating the JAK/STAT3 signaling pathway. This activation is essential not just for tumor progression but also for the maintenance of cancer stem cell properties, highlighting the potential of ARHGAP-BMX as a valuable target for innovative treatment strategies in gastric cancer. The findings emphasize the need for continued research into the interplay between ARHGAP-BMX and JAK/STAT3,

which could lead to the development of effective therapies aimed at improving patient outcomes in GC as shown in Figure 2.

*Exploring the Clinical Potential of RhoGAP and BMX*

GC continues to be a major contributor to cancer-related deaths globally [1], underscoring the urgent need for new therapeutic targets and prognostic indicators. The identification of RhoGAP and BMX as critical regulators in the progression of GC has important ramifications for developing innovative treatment approaches. The inherent heterogeneity of GC presents a significant challenge for therapeutic interventions, making the exploration of drug therapies a critical area of research. Recent investigations have emphasized the involvement of RhoGAP and BMX in the development and progression of GC, highlighting their potential utility in clinical settings[28, 64].

Gene fusions are integral to the processes of tumor diagnosis and prognosis assessment [76-78]. Some fusion genes that are specific to certain cancer types can be effectively targeted with pharmacological agents [79-82]. The expression of BMX has been noted in a variety of cancers, influencing the survival and tumorigenic potential of cancer stem cells, particularly in glioblastoma [34]. BMX is believed to act as a tumor promoter by impeding apoptosis induced by chemotherapy and radiotherapy in colorectal cancer [83]. The ARHGAP family includes several proteins associated with cancer progression [30]. For instance, ARHGAP18 has been identified as a suppressor of tumor growth in GC [31]. Research conducted by Dong et al. indicates that the CLDN18-ARHGAP26/6 fusion plays an oncogenic role, and its presence is a distinct predictor for metastasis to distant organs in diffuse-type GC [66, 68]. The CLDN18-ARHGAP fusion exists in three variants, leading to dysfunctional behaviors of CLDN18 and ARHGAP, which causes the non-traditional epithelial-mesenchymal transition, impaired cell adhesion, and compromised epithelial integrity [67]. Patients harboring this fusion tend to be diagnosed at a younger age, exhibit a poorer prognosis, and show a higher frequency of diffuse GC [63, 84]. Additionally, recurrent fusions found in GC, such as CTNND1-ARHGAP26, ANXA2-MY09A, and BMX-ARHGAP, reveal that the RhoGAP domain frequently serves as the 3' fusion partner [32, 85] . Consequently, both BMX and ARHGAP are implicated in the oncogenic processes across various types of cancer.

The therapeutic potential of RhoGAP and BMX in GC offers valuable avenues for the development of targeted therapies. The BMX-ARHGAP fusion gene has emerged as a significant oncogenic factor in GC, enhancing self-renewal capabilities and promoting the proliferation and invasion of cancer stem cells through the activation of the SH2-domain-mediated JAK/STAT3 signaling pathway [58, 86]. Inhibiting this fusion gene has been shown to halt cancer progression by disrupting this critical pathway, which is closely linked to the characteristics of cancer stem cells and aggressive tumor behavior[73, 74, 87]. Furthermore, targeting the JAK/STAT signaling pathway has been associated with reduced angiogenesis and metastasis, as well as diminished migration and invasion of GC cells [58, 74]. Moreover, a combined approach of targeting the BMX-ARHGAP fusion gene and the JAK-STAT pathway could effectively reduce tumor growth and metastatic spread [62, 68]. The influence of BMX-ARHGAP on the markers associated with GC stem cells underscores the potential of therapies directed at this interaction to prevent cancer stem cell persistence

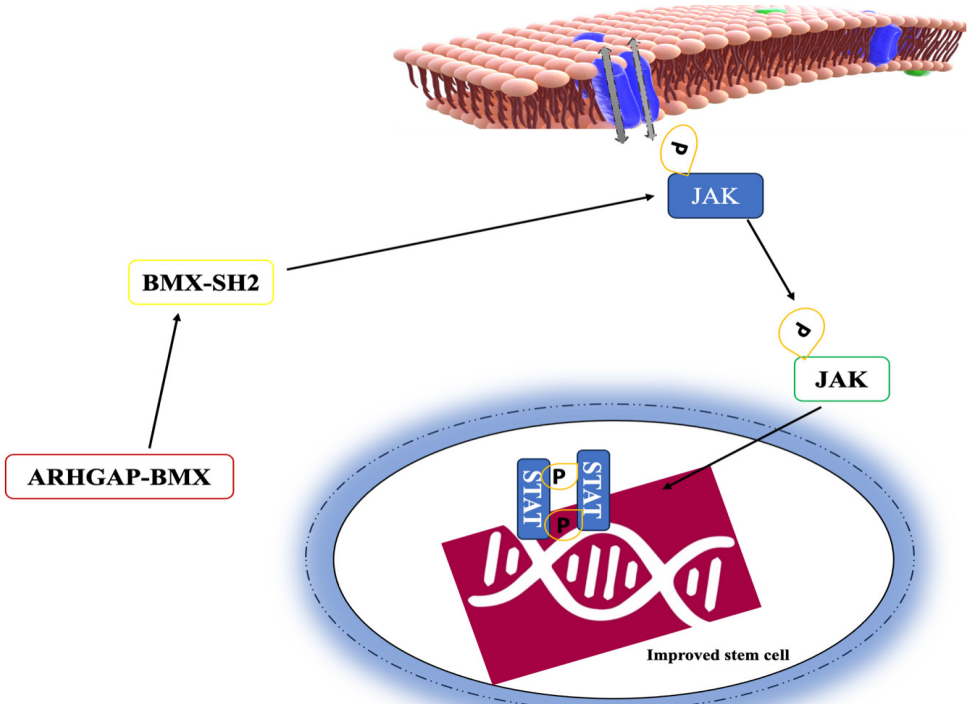


Figure 2. Schematic Representation of the Role of ARHGAP-BMX Regulation in GC Stem Cell Characteristics. By maintaining the stemness of GC stem cells and activating the JAK/STAT3 signaling pathway through the BMX-SH2 protein, the ARHGAP-BMX fusion gene increases the tumorigenicity of GC stem cells.

and tumorigenicity. Therefore, further investigation into the BMX-ARHGAP/SH2 domain/JAK/STAT3 signaling axis is crucial to advancing new and innovative treatments for GC.

Upcoming research should concentrate on carrying out clinical trials to evaluate the effectiveness of inhibitors aimed at these proteins in individuals diagnosed with gastric cancer. Additionally, exploring the possibility of using RhoGAP and BMX as predictive biomarkers for responses to current treatments, including chemotherapy and immunotherapy, may offer significant insights for tailoring personalized therapeutic approaches.

In conclusion, the analysis of the ARHGAP family, particularly in GC, highlights its multifaceted involvement in cancer biology. The dichotomy observed in the roles of different ARHGAP members, such as ARHGAP18 functioning as a tumor suppressor while ARHGAP11A appears to promote oncogenic processes, underscores the complexities of Rho GTPase signaling in tumorigenesis. The fusion events involving ARHGAP and other proteins like BMX and CLDN18 illustrate critical mechanisms through which these genes may drive disease progression, influence cancer cell behavior, and contribute to poor patient outcomes. Moreover, the interplay between ARHGAP-BMX and the JAK/STAT3 signaling pathway points to promising avenues for future therapeutic strategies that could target these pathways to mitigate tumor growth and metastasis. Elevated expression of the BMX-ARHGAP fusion in GC tissues indicates that it may serve as a viable diagnostic marker and therapeutic target. As the research continues to unfold, it is clear that a deepened understanding of these molecular interactions will be essential for the development of innovative and tailored approaches in precision medicine for GC. This area of study holds the potential for significant advancements in the diagnosis and treatment of gastric cancer, paving the way for improved prognoses and patient care. Continued investigation into the ARHGAP family and their associated pathways is not only warranted but crucial for unlocking new therapeutic opportunities in the battle against cancer.

## Author Contribution Statement

Zakari Shaibu, Zhihong Chen: Writing - Original draft preparation. Fumeng Yang, Xiaofeng Xu: conceived ideas and supervised the work. Yong Ji, Wei Zhu: Writing - Review & Editing.

## Acknowledgements

*Funding*

This work was supported by the Medical Research project of the Jiangsu Provincial Health Commission [grant number X373].

*Ethics Declaration*

This study reported only already published data. We had no direct access to the original data used in the included studies for the review. Therefore, no ethical approval was needed.

*Availability of data*

This work incorporates data previously published by other authors, with all data included in the findings section.

*Conflict of Interest*

The authors declare that there are no conflicts of interest concerning the content of the present study.

*Abbreviations*

ARHGAP: Rho GTPase Activating Protein
BMX: Bone Marrow Kinase X
GC: Gastric Cancer
JAK: Janus Kinase
STAT3: Signal Transducer and Activator of Transcription 3
SOCS3: Suppressor of Cytokine Signaling 3
RT-PCR: Real-Time Polymerase Chain Reaction
shRNA: Short Hairpin RNA
CLDN18: Claudin 18
RhoA: Ras Homolog Family Member A
GTPases: Guanosine Triphosphatases
RT-qPCR: Real-Time Quantitative Polymerase Chain Reaction
BMX-ARHGAP: Bone Marrow Kinase X-Rho GTPase Activating Protein

## References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33. https://doi.org/10.3322/caac.21654.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660.
3. Yoon J, Kim TY, Oh DY. Recent progress in immunotherapy for gastric cancer. J Gastric Cancer. 2023;23(1):207-23. https://doi.org/10.5230/jgc.2023.23.e10.
4. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021. https://doi.org/10.1002/ijc.33588.
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492.
6. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol. 2019;5(12):1749-68. https://doi.org/10.1001/jamaoncol.2019.2996.
7. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: Esmo-esso-estro clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi57-63. https://doi.org/10.1093/annonc/mdt344.
8. Chang JS, Kuo SH, Chu PY, Shan YS, Tsai CR, Tsai HJ, et al. The epidemiology of gastric cancers in the era of

helicobacter pylori eradication: A nationwide cancer registry-based study in taiwan. Cancer Epidemiol Biomarkers Prev. 2019;28(10):1694-703. https://doi.org/10.1158/1055-9965.Epi-19-0355.
9. Rawla P, Barsouk A. Epidemiology of gastric cancer: Global trends, risk factors and prevention. Prz Gastroenterol. 2019;14(1):26-38. https://doi.org/10.5114/pg.2018.80001.
10. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30. https://doi.org/10.3322/caac.21332.
11. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet. 2016;388(10060):2654-64. https://doi.org/10.1016/s0140-6736(16)30354-3.
12. Asplund J, Kauppila JH, Mattsson F, Lagergren J. Survival trends in gastric adenocarcinoma: A population-based study in sweden. Ann Surg Oncol. 2018;25(9):2693-702. https://doi.org/10.1245/s10434-018-6627-y.
13. Howlader N NA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA Seer cancer statistics review. National Cancer Institute. 2021;1975-2018.
14. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20. https://doi.org/10.1056/NEJMoa055531.
15. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of her2-positive advanced gastric or gastro-oesophageal junction cancer (toga): A phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97. https://doi.org/10.1016/s0140-6736(10)61121-x.
16. Jin X, Liu Z, Yang D, Yin K, Chang X. Recent progress and future perspectives of immunotherapy in advanced gastric cancer. Front Immunol. 2022;13:948647. https://doi.org/10.3389/fimmu.2022.948647.
17. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. https://doi.org/10.3322/caac.20107.
18. Xu W, Yang Z, Lu N. Molecular targeted therapy for the treatment of gastric cancer. J Exp Clin Cancer Res. 2016;35(1):1. https://doi.org/10.1186/s13046-015-0276-9.
19. Kono K. Advances in cancer immunotherapy for gastroenterological malignancy. Ann Gastroenterol Surg. 2018;2(4):244-5. https://doi.org/10.1002/ags3.12184.
20. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-9. https://doi.org/10.1038/nature10673.
21. Uppal A, Dehal A, Chang SC, Barrak D, Naeini Y, Jalas JR, et al. The immune microenvironment impacts survival in western patients with gastric adenocarcinoma. J Gastrointest Surg. 2020;24(1):28-38. https://doi.org/10.1007/s11605-019-04403-w.
22. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: Toward combination strategies with curative potential. Cell. 2015;161(2):205-14. https://doi.org/10.1016/j.cell.2015.03.030.
23. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61. https://doi.org/10.1126/science.aaa8172.
24. Xie J, Fu L, Jin L. Immunotherapy of gastric cancer: Past, future perspective and challenges. Pathol Res Pract. 2021;218:153322. https://doi.org/10.1016/j.prp.2020.153322.
25. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol. 2012;4(7):156-69. https://doi.org/10.4251/wjgo.v4.i7.156.
26. Kim HP, Cho GA, Han SW, Shin JY, Jeong EG, Song SH, et al. Novel fusion transcripts in human gastric cancer revealed by transcriptome analysis. Oncogene. 2014;33(47):5434-41. https://doi.org/10.1038/onc.2013.490.
27. Tao J, Deng NT, Ramnarayanan K, Huang B, Oh HK, Leong SH, et al. Cd44-slc1a2 gene fusions in gastric cancer. Sci Transl Med. 2011;3(77):77ra30. https://doi.org/10.1126/scitranslmed.3001423.
28. Xu X, Xu L, Gao F, Wang J, Ye J, Zhou M, et al. Identification of a novel gene fusion (bmx-arhgap) in gastric cardia adenocarcinoma. Diagn Pathol. 2014;9:218. https://doi.org/10.1186/s13000-014-0218-4.
29. Xu X, Xu L, Gao F, Wang J, Ye J, Zhou M, et al. Identification of a novel gene fusion (bmx-arhgap) in gastric cardia adenocarcinoma. Diagnostic Pathology. 2014;9(1):1-7.
30. Katoh Y, Katoh M. Identification and characterization of arhgap27 gene in silico. Int J Mol Med. 2004;14(5):943-7.
31. Li Y, Ji S, Fu L, Jiang T, Wu D, Meng F. Over-expression of arhgap18 suppressed cell proliferation, migration, invasion, and tumor growth in gastric cancer by restraining over-activation of mapk signaling pathways. Onco Targets Ther. 2018;11:279-90. https://doi.org/10.2147/ott.S130255.
32. Xu XF, Wang JJ, Ding L, Ye JS, Huang LJ, Tao L, et al. Suppression of bmx-arhgap fusion gene inhibits epithelial-mesenchymal transition in gastric cancer cells via rhoa-mediated blockade of jak/stat axis. J Cell Biochem. 2019;120(1):439-51. https://doi.org/10.1002/jcb.27400.
33. Guo S, Sun F, Guo Z, Li W, Alfano A, Chen H, et al. Tyrosine kinase etk/bmx is up-regulated in bladder cancer and predicts poor prognosis in patients with cystectomy. PLoS One. 2011;6(3):e17778. https://doi.org/10.1371/journal.pone.0017778.
34. Cenni B, Gutmann S, Gottar-Guillier M. Bmx and its role in inflammation, cardiovascular disease, and cancer. Int Rev Immunol. 2012;31(2):166-73. https://doi.org/10.3109/08830185.2012.663838.
35. Kreider-Letterman G, Carr NM, Garcia-Mata R. Fixing the gap: The role of rhogaps in cancer. Eur J Cell Biol. 2022;101(2):151209. https://doi.org/10.1016/j.ejcb.2022.151209.
36. Rossman KL, Der CJ, Sondek J. Gef means go: Turning on rho gtpases with guanine nucleotide-exchange factors. Nat Rev Mol Cell Biol. 2005;6(2):167-80. https://doi.org/10.1038/nrm1587
37. Tcherkezian J, Lamarche-Vane N. Current knowledge of the large rhogap family of proteins. Biology of the Cell. 2007;99(2):67-86. https://doi.org/10.1042/BC20060086
38. Fritz RD, Pertz O. The dynamics of spatio-temporal rho gtpase signaling: Formation of signaling patterns. F1000Res. 2016;5:F1000 Faculty Rev-749. https://doi.org/10.12688/f1000research.7370.1
39. Amin E, Jaiswal M, Derewenda U, Reis K, Nouri K, Koessmeier KT, et al. Deciphering the molecular and functional basis of rhogap family proteins: A systematic approach toward selective inactivation of rho family proteins. J Biol Chem. 2016;291(39):20353-71. https://doi.org/10.1074/jbc.M116.736967
40. Cherfils J, Zeghouf M. Regulation of small gtpases by gefs, gaps, and gdis. Physiological reviews. 2013;93(1):269-309. https://doi.org/10.1152/physrev.00003.2012
41. Dahmene M, Quirion L, Laurin M. High throughput strategies aimed at closing the gap in our knowledge of rho gtpase signaling. Cells. 2020;9(6):1430. https://doi.org/10.3390/cells9061430
42. Hodge RG, Ridley AJ. Regulating rho gtpases and their

regulators. Nat Rev Mol Cell Biol. 2016;17(8):496-510. https://doi.org/10.1038/nrm.2016.67
43. Etienne-Manneville S, Hall A. Rho gtpases in cell biology. Nature. 2002;420(6916):629-35. https://doi.org/10.1038/nature01148.
44. Vega FM, Ridley AJ. Rho gtpases in cancer cell biology. FEBS Lett. 2008;582(14):2093-101. https://doi.org/10.1016/j.febslet.2008.04.039.
45. Chang GH, Lay AJ, Ting KK, Zhao Y, Coleman PR, Powter EE, et al. Arhgap18: An endogenous inhibitor of angiogenesis, limiting tip formation and stabilizing junctions. Small GTPases. 2014;5(3):1-15. https://doi.org/10.4161/21541248.2014.975002.
46. Maeda M, Hasegawa H, Hyodo T, Ito S, Asano E, Yuang H, et al. Arhgap18, a gtpase-activating protein for rhoa, controls cell shape, spreading, and motility. Mol Biol Cell. 2011;22(20):3840-52. https://doi.org/10.1091/mbc.E11-04-0364.
47. Fan B, Ji K, Bu Z, Zhang J, Yang H, Li J, et al. Arhgap11a is a prognostic biomarker and correlated with immune infiltrates in gastric cancer. Front Mol Biosci. 2021;8:720645. https://doi.org/10.3389/fmolb.2021.720645.
48. Chau CH, Clavijo CA, Deng HT, Zhang Q, Kim KJ, Qiu Y, et al. Etk/bmx mediates expression of stress-induced adaptive genes vegf, pai-1, and inos via multiple signaling cascades in different cell systems. Am J Physiol Cell Physiol. 2005;289(2):C444-C54. https://doi.org/10.1152/ajpcell.00410.2004
49. Potter DS, Kelly P, Denneny O, Juvin V, Stephens LR, Dive C, et al. Bmx acts downstream of pi3k to promote colorectal cancer cell survival and pathway inhibition sensitizes to the bh3 mimetic abt-737. Neoplasia. 2014;16(2):147-W16. https://doi.org/ 10.1593/neo.131376.
50. Zhang J, Ping P, Wang GW, Lu M, Pantaleon D, Tang XL, et al. Bmx, a member of the tec family of nonreceptor tyrosine kinases, is a novel participant in pharmacological cardioprotection. American Journal of Physiology-Heart and Circulatory Physiology. 2004;287(5):H2364-H6. https://doi.org/10.1152/ajpheart.00416.2004
51. Wei T, Zhu W, Fang S, Zeng X, Huang J, Yang J, et al. Mir-495 promotes the chemoresistance of sclc through the epithelial-mesenchymal transition via etk/bmx. Am J Cancer Res. 2017;7(3):628.
52. Haga RB, Ridley AJ. Rho gtpases: Regulation and roles in cancer cell biology. Small GTPases. 2016;7(4):207-21. https://doi.org/10.1080/21541248.2016.1232583
53. Fritz G, Brachetti C, Bahlmann F, Schmidt M, Kaina B. Rho gtpases in human breast tumours: Expression and mutation analyses and correlation with clinical parameters. Br J Cancer. 2002;87(6):635-44. https://doi.org/10.1038/sj.bjc.6600510
54. Del Pulgar TG, Benitah SA, Valerón PF, Espina C, Lacal JC. Rho gtpase expression in tumourigenesis: Evidence for a significant link. Bioessays. 2005;27(6):602-13. https://doi.org/10.1002/bies.20238
55. Kamai T, Yamanishi T, Shirataki H, Takagi K, Asami H, Ito Y, et al. Overexpression of rhoa, rac1, and cdc42 gtpases is associated with progression in testicular cancer. Clin Cancer Res. 2004;10(14):4799-805. https://doi.org/10.1158/1078-0432.CCR-0436-03
56. McPherson A, Hormozdiari F, Zayed A, Giuliany R, Ha G, Sun MG, et al. Defuse: An algorithm for gene fusion discovery in tumor rna-seq data. PLoS Comput Biol. 2011;7(5):e1001138. https://doi.org/10.1371/journal.pcbi.1001138.
57. Kim D, Salzberg SL. Tophat-fusion: An algorithm for discovery of novel fusion transcripts. Genome Biol. 2011;12(8):R72. https://doi.org/10.1186/gb-2011-12-8-r72.
58. Keysar SB, Eagles JR, Miller B, Jackson BC, Chowdhury FN, Reisinger J, et al. Salivary gland cancer patient-derived xenografts enable characterization of cancer stem cells and new gene events associated with tumor progressionsalivary cancer stem cells increase with disease progression. Clin Cancer Res. 2018;24(12):2935-43. https://doi.org/10.1158/1078-0432.CCR-17-3871
59. Heim S, Mitelman F. Molecular screening for new fusion genes in cancer. Nat Genet. 2008;40(6):685-6. https://doi.org/10.1038/ng0608-685.
60. Sundar SJ, Hsieh JK, Manjila S, Lathia JD, Sloan A. The role of cancer stem cells in glioblastoma. Neurosurg Focus. 2014;37(6):E6. https://doi.org/10.3171/2014.9.Focus14494.
61. Wang Z, Zhang J, Yang B, Li R, Jin L, Wang Z, et al. Long intergenic noncoding rna 00261 acts as a tumor suppressor in non-small cell lung cancer via regulating mir-105/fhl1 axis. J Cancer. 2019;10(25):6414-21. https://doi.org/10.7150/jca.32251.
62. Chen S, Cai C, Sowalsky AG, Ye H, Ma F, Yuan X, et al. Bmx-mediated regulation of multiple tyrosine kinases contributes to castration resistance in prostate cancer. Cancer Res. 2018;78(18):5203-15. https://doi.org/10.1158/0008-5472.Can-17-3615.
63. Yao F, Kausalya JP, Sia YY, Teo AS, Lee WH, Ong AG, et al. Recurrent fusion genes in gastric cancer: Cldn18-arhgap26 induces loss of epithelial integrity. Cell Rep. 2015;12(2):272-85.
64. Xu XF, Gao F, Wang JJ, Long C, Chen X, Tao L, et al. Bmx-arhgap fusion protein maintains the tumorigenicity of gastric cancer stem cells by activating the jak/stat3 signaling pathway. Cancer Cell Int. 2019;19:133. https://doi.org/10.1186/s12935-019-0847-5.
65. Tsukita S, Furuse M. The structure and function of claudins, cell adhesion molecules at tight junctions. Ann N Y Acad Sci. 2000;915:129-35. https://doi.org/10.1111/j.1749-6632.2000.tb05235.x.
66. Zhang WH, Zhang SY, Hou QQ, Qin Y, Chen XZ, Zhou ZG, et al. The significance of the cldn18-arhgap fusion gene in gastric cancer: A systematic review and meta-analysis. Front Oncol. 2020;10. https://doi.org/10.3389/fonc.2020.01214.
67. Nakayama I, Shinozaki E, Sakata S, Yamamoto N, Fujisaki J, Muramatsu Y, et al. Enrichment of cldn18-arhgap fusion gene in gastric cancers in young adults. Cancer Sci. 2019;110(4):1352-63. https://doi.org/10.1111/cas.13967.
68. Tanaka A, Ishikawa S, Ushiku T, Yamazawa S, Katoh H, Hayashi A, et al. Frequent cldn18-arhgap fusion in highly metastatic diffuse-type gastric cancer with relatively early onset. Oncotarget. 2018;9(50):29336-50. https://doi.org/10.18632/oncotarget.25464.
69. Gentile A, D'Alessandro L, Lazzari L, Martinoglio B, Bertotti A, Mira A, et al. Met-driven invasive growth involves transcriptional regulation of arhgap12. Oncogene. 2008;27(42):5590-8. https://doi.org/10.1038/onc.2008.173.
70. Ashrafizadeh M, Zarrabi A, Orouei S, Zarrin V, Rahmani Moghadam E, Zabolian A, et al. Stat3 pathway in gastric cancer: Signaling, therapeutic targeting and future prospects. Biology (Basel). 2020;9(6). https://doi.org/10.3390/biology9060126.
71. Shi Y, Guryanova OA, Zhou W, Liu C, Huang Z, Fang X, et al. Ibrutinib inactivates bmx-stat3 in glioma stem cells to impair malignant growth and radioresistance. Sci Transl Med. 2018;10(443):eaah6816. https://doi.org/10.1126/scitranslmed.aah6816
72. Guryanova OA, Wu Q, Cheng L, Lathia JD, Huang Z, Yang J, et al. Nonreceptor tyrosine kinase bmx maintains self-renewal and tumorigenic potential of glioblastoma stem

cells by activating stat3. Cancer cell. 2011;19(4):498-511. https://doi.org/10.1016/j.ccr.2011.03.004
73. Xu W, Fu J, Wu H, Sun W. Human epidermal growth factor receptor 2 expressions and janus-activated kinase/signal transducer and activator of transcription 3-suppressor of cytokine signaling 3 pathway may be associated with clinicopathological features and prognosis of gastric cancer. J Cancer Res Ther. 2018;14(Suppl 2):S311-S8. https://doi.org/10.4103/0973-1482.235348
74. Wang X, Che X, Liu C, Fan Y, Bai M, Hou K, et al. Cancer-associated fibroblasts-stimulated interleukin-11 promotes metastasis of gastric cancer cells mediated by upregulation of muc1. Exp Cell Res. 2018;368(2):184-93. https://doi.org/10.1016/j.yexcr.2018.04.028
75. 78. Jiang C, Long J, Liu B, Xu M, Wang W, Xie X, et al. Mir-500a-3p promotes cancer stem cells properties via stat3 pathway in human hepatocellular carcinoma. J Exp Clin Cancer Res. 2017;36(1):1-13. https://doi.org/10.1186/s13046-017-0568-3
76. Gao Q, Liang WW, Foltz SM, Mutharasu G, Jayasinghe RG, Cao S, et al. Driver fusions and their implications in the development and treatment of human cancers. Cell Rep. 2018;23(1):227-38.e3. https://doi.org/10.1016/j.celrep.2018.03.050.
77. Kalina JL, Neilson DS, Lin YY, Hamilton PT, Comber AP, Loy EMH, et al. Mutational analysis of gene fusions predicts novel mhc class i-restricted t-cell epitopes and immune signatures in a subset of prostate cancer. Clin Cancer Res. 2017;23(24):7596-607. https://doi.org/10.1158/1078-0432.Ccr-17-0618.
78. Tomlins SA, Aubin SM, Siddiqui J, Lonigro RJ, Sefton-Miller L, Miick S, et al. Urine tmprss2:Erg fusion transcript stratifies prostate cancer risk in men with elevated serum psa. Sci Transl Med. 2011;3(94):94ra72. https://doi.org/10.1126/scitranslmed.3001970.
79. Druker BJ. Translation of the philadelphia chromosome into therapy for cml. Blood. 2008;112(13):4808-17. https://doi.org/10.1182/blood-2008-07-077958.
80. Mertens F, Johansson B, Fioretos T, Mitelman F. The emerging complexity of gene fusions in cancer. Nat Rev Cancer. 2015;15(6):371-81. https://doi.org/10.1038/nrc3947.
81. Rutkowski P, Van Glabbeke M, Rankin CJ, Ruka W, Rubin BP, Debiec-Rychter M, et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: Pooled analysis of two phase ii clinical trials. J Clin Oncol. 2010;28(10):1772-9. https://doi.org/10.1200/jco.2009.25.7899.
82. Dai X, Theobard R, Cheng H, Xing M, Zhang J. Fusion genes: A promising tool combating against cancer. Biochim Biophys Acta Rev Cancer. 2018;1869(2):149-60. https://doi.org/10.1016/j.bbcan.2017.12.003.
83. Potter DS, Kelly P, Denneny O, Juvin V, Stephens LR, Dive C, et al. Bmx acts downstream of pi3k to promote colorectal cancer cell survival and pathway inhibition sensitizes to the bh3 mimetic abt-737. Neoplasia. 2014;16(2):147-57. https://doi.org/10.1593/neo.131376.
84. Shu Y, Zhang W, Hou Q, Zhao L, Zhang S, Zhou J, et al. Prognostic significance of frequent cldn18-arhgap26/6 fusion in gastric signet-ring cell cancer. Nat Commun. 2018;9(1):2447. https://doi.org/10.1038/s41467-018-04907-0.
85. Yang H, Hong D, Cho SY, Park YS, Ko WR, Kim JH, et al. Rhogap domain-containing fusions and ppapdc1a fusions are recurrent and prognostic in diffuse gastric cancer. Nat Commun. 2018;9(1):4439. https://doi.org/10.1038/s41467-018-06747-4.
86. Xiao H, Huang X, Xu H, Chen X, Xiong W, Yang Z, et al. A novel splice-site mutation in the atp2c1 gene of a chinese family with hailey-hailey disease. J Cell Biochem. 2019;120(3):3630-6. https://doi.org/10.1002/jcb.27640.
87. Yan Q, Jiang L, Liu M, Yu D, Zhang Y, Li Y, et al. Angptl1 interacts with integrin α1β1 to suppress hcc angiogenesis and metastasis by inhibiting jak2/stat3 signaling. Cancer Res. 2017;77(21):5831-45. https://doi.org/10.1158/0008-5472.CAN-17-0579.