



OPEN ACCESS

EDITED BY

Changmin Peng,
George Washington University, United States

REVIEWED BY

Mukulika Bose,
University of Texas MD Anderson Cancer
Center, United States
Hongmie Wu,
Shaanxi Normal University, China

*CORRESPONDENCE

Subhash C. Chauhan
✉ subhash.chauhan@utrgv.edu

RECEIVED 20 October 2025

REVISED 20 December 2025

ACCEPTED 22 December 2025

PUBLISHED 15 January 2026

CITATION

Malik S, Sikander M, Yallapu MM and
Chauhan SC (2026) MUC13 is a crucial player
in YAP1- β -catenin survival complex mediated
cancer metastasis. *Front. Med.* 12:1727498.
doi: 10.3389/fmed.2025.1727498

COPYRIGHT

© 2026 Malik, Sikander, Yallapu and Chauhan.
This is an open-access article distributed
under the terms of the [Creative Commons
Attribution License \(CC BY\)](#). The use,
distribution or reproduction in other forums is
permitted, provided the original author(s) and
the copyright owner(s) are credited and that
the original publication in this journal is cited,
in accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

MUC13 is a crucial player in YAP1- β -catenin survival complex mediated cancer metastasis

Shabnam Malik^{1,2}, Mohammed Sikander^{1,2}, Murali M. Yallapu^{1,2}
and Subhash C. Chauhan^{1,2*}

¹Division of Cancer Immunology and Microbiology, Medicine and Oncology Integrated Service Unit, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX, United States, ²South Texas Center of Excellence in Cancer Research, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX, United States

KEYWORDS

chemoresistance, anoikis, metastasis, MUC13, Yap1, β -catenin

Colorectal cancer (CRC) is a one of most commonest cause of cancer related mortality worldwide, with 1.9 million new cases reported globally in 2022 and an estimated 150,000 new cases in the USA in 2024 (1). Despite significant advancements in diagnostic and therapeutic strategies, prognosis is still poor and long-term survival rate continues to be limited by advanced metastasis (2, 3). For instance, localized colorectal cancer demonstrates favorable prognoses with effective treatment modalities, achieving a 5-year survival up to 91%, whereas metastatic colorectal cancer (mCRC) is associated with a 5-year survival rate of approximately 13% (4). Metastasis is a multistage process involving the spread of tumor cells from the primary location following detachment from the extracellular matrix (ECM) or loss of cellular anchorage. In normal tissues, the loss of anchorage or detachment from the extracellular matrix triggers a form of programmed cell death known as anoikis, and the capacity of cells to evade this process is termed anoikis resistance (AR) (5). Only a small proportion (approximately 0.02%) of detached cells remain viable and are successful to establish a metastatic lesion (6). Metastasis is significantly slowed down by these anoikis after cells separate from the extracellular matrix (7–9). The detachment and dissemination of cancer cells from the extracellular matrix involve a number of critical steps that are essential for maintaining cancer cell viability (10). Additionally, it also encompasses the development of oncogenic phenotypes following their colonization of metastatic niches. Disruption at any level of cascade could hamper the formation of metastatic lesions, with AR being a critical step in the development of therapy (11, 12).

We, for the first time, have identified the pivotal significance of Mucin13 (MUC13), a transmembrane glycoprotein, in the process of cancer metastasis (13). MUC13 has demonstrated oncogenic potential in various cancer types, including colorectal carcinoma (14). MUC13 comprises three epidermal growth factor-like domains and a transmembrane domain and an active cytoplasmic tail. The cytoplasmic tail of MUC13 contains several potential phosphorylation sites (14–17). Our laboratory has demonstrated that MUC13 interacts functionally with and activates HER2 at the p1248 site, thereby triggering growth and survival signaling pathways such as FAK, ERK1/2, PAK1, and AKT. It also modulated metabolic reprogramming through the activation and nuclear translocation of NF- κ B p65, as well as the phosphorylation of I κ B, thereby contributing to tumorigenesis (18, 19). Moreover, the expression of MUC13 has been associated with the advancement of malignancies, clinical prognosis, and biophysical alterations within cancerous cells (20, 21). Despite the established involvement of this factor in tumorigenesis, encompassing various signaling pathways, its specific role in the process of cancer metastasis remains incompletely understood (17, 22–28).

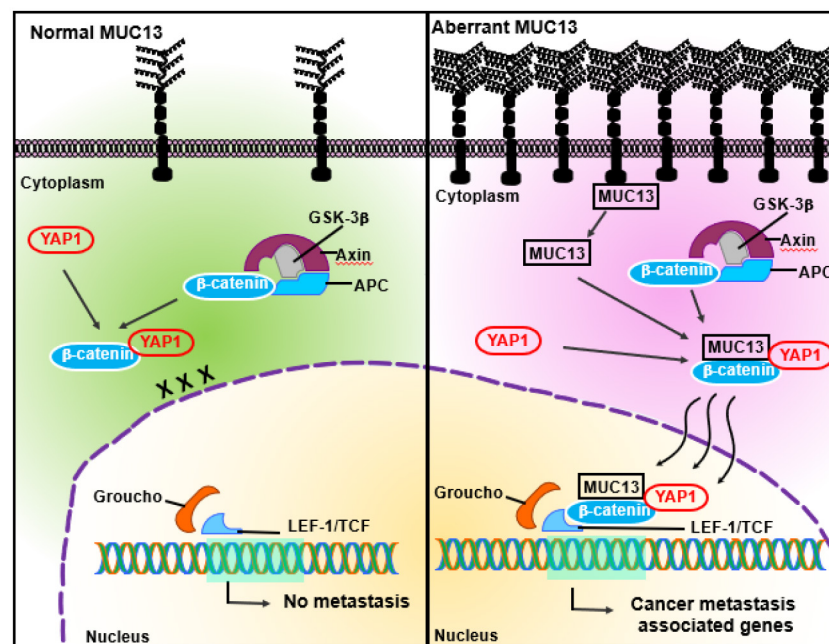


FIGURE 1

Simplified view of MUC13-mediated mechanism in metastatic colorectal cancer, highlighting the role of MUC13 in promoting the nuclear translocation of YAP1 and β -catenin.

Our research has demonstrated that MUC13 serves as a pivotal molecular determinant, promoting anchorage-independent survival and enhancing metastasis by modulating Yes-Associated Protein 1 (YAP1), a key transcriptional coactivator and regulator of the Hippo pathway (13) (Figure 1). Notably, we have demonstrated that MUC13 promotes metastasis primarily by modulating and inducing the nuclear translocation of YAP1, which leads to the activation and expression of genes involved in cell survival and metastatic progression (29–33). Abnormal expression of YAP1 has been observed in multiple malignancies including colorectal carcinoma especially *via* Hippo signaling pathway, governs numerous vital biological functions that underpin cellular viability, proliferation, differentiation, and organogenesis (29, 34, 35). Under normal condition, the Hippo–YAP1 signaling pathway is crucial for preserving cellular homeostasis in the colon, whereas YAP1 expression is elevated in colorectal cancers. The upregulation of YAP1 has been associated with increased cellular proliferation, improved cell survival, elevated drug resistance, induction of epithelial-to-mesenchymal transition, and anchorage-independent growth (29, 35). This novel molecular mechanism, mediated by MUC13–YAP1, provides a crucial survival benefit to anchorage-independent circulating tumor cells, thereby promoting successful extravasation, homing, and the aggressive metastasis of cancer to distant sites.

To investigate the role of MUC13 in promoting anchorage-independent survival in cancer cells, we developed and validated an anoikis induction model (13). Stable cell lines SW480 cells overexpressing MUC13 and SW620 cells with MUC13 knockdown were generated. Our experimental findings indicate MUC13 contributes significantly to cancer cell survival

under anchorage-independent environment and facilitates AR. Proteomics and kinome array analyses were conducted to elucidate the specific molecular mechanisms by which MUC13 confers protection against cell mortality in anchorage-independent conditions. These assays indicated the differential expression of multiple genes associated with survival and metastasis. Proximity ligation assay (PLA) and Immunoprecipitation (IP) assays indicated a novel molecular interaction between MUC13 and YAP1. Studies have indicated a cooperative interaction between YAP1 and β -catenin in the survival of cancer cells through the upregulation of oncogenic effector proteins (36–40). β -catenin functions as a transcription factor that modulates the Wnt signaling pathway, reported to have a crucial role in the development of CRC (39, 41, 42). Consequently, an investigation into the impact of MUC13 on the YAP1/ β -catenin survival complex was performed. Ectopic expression of MUC13 promoted the nuclear translocation and localization of the YAP1/ β -catenin survival complex. Notably, the inhibition of MUC13 prevented the integration of this survival complex into the nucleus, as it was predominantly localized at the periphery of the nuclear envelope, and it regulated the expression of downstream genes linked to survival and metastasis.

The ability of cancer cells to survive in the circulatory system and subsequently invade distal sites is a critical characteristic of metastasis. To investigate the impact of MUC13-mediated nuclear translocation of the survival complex (YAP1– β -catenin) on metastatic potential, a tail vein metastasis model was used. It was demonstrated that ectopic MUC13 expression provided a metastatic advantage to SW480/MUC13 cells, as indicated by the presence of metastatic lesions in the kidneys, lungs, and liver. Conversely, no metastatic lesions were detected in

SW480+vector control cells. High expression of MUC13, YAP1, and β -catenin was observed in metastatic lesions of the lung and kidney. These findings indicate that MUC13 plays a vital role in promoting YAP1-driven oncogenic and metastatic signaling mechanisms within malignant cells. Numerous studies have demonstrated that mucins are crucial for anoikis resistance by aiding in detachment from the extracellular matrix and promoting the survival of tumor cells (43–46). This underscores the concept that MUC13 plays a pivotal role in promoting cancer progression and metastasis *via* the YAP1-dependent oncogenic pathway. While this study establishes a firm foundation for comprehending the function of MUC13 in the metastasis of colorectal cancer, several unresolved questions necessitate further investigation. For instance, it is essential to examine the precise mechanism by which MUC13 facilitates the nuclear translocation of YAP1.

Therefore, it is essential to examine whether MUC13, in addition to conferring resistance to anoikis in cancer cells, can also promote subsequent stages of the metastatic process. Are additional co-factors implicated in the MUC13-YAP1 interaction? The influence of the tumor microenvironment on modulating MUC13 expression, and the subsequent effects on YAP1 activity, introduces an additional level of intricacy that warrants further investigation. Last but not least, it would be valuable to investigate how the extracellular matrix components that encircle stromal and immune cells influence the function of MUC13. Specifically, small molecules and/or monoclonal antibodies designed to inhibit MUC13 could potentially interfere with its interaction with YAP1, thereby diminishing the activation of metastasis-related genes. Complementing therapies that directly target MUC13 with interventions aimed at these downstream effectors could facilitate the development of a multimodal strategy for disrupting the metastatic cascade.

Consequently, the biochemical modulation of this novel molecular interaction holds the potential to specifically address and treat cancer metastasis.

Author contributions

SM: Resources, Software, Writing – original draft. MS: Resources, Visualization, Writing – original draft, Writing – review & editing. MMY: Formal analysis, Writing – review & editing. SCC:

Conceptualization, Investigation, Supervision, Writing – review & editing.

Funding

The author(s) declared that financial support was not received for this work and/or its publication. The authors gratefully acknowledge the support from the NH/NCI grants (NIH R01 CA206069, R01 CA210192, R01 CA204552, U54 MD019970, and SC1GM139727) and the CPRIT grants (RP210180, RP230419, and RP250567) to SC and MY.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author SCC declared that they were an editorial board member of *Frontiers*, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by *Frontiers* with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* (2024) 74:12–49. doi: 10.3322/caac.21820
2. Acha-Sagredo A, Andrei P, Clayton K, Taggart E, Antonioti C, Woodman CA, et al. A constitutive interferon-high immunophenotype defines response to immunotherapy in colorectal cancer. *Cancer Cell.* (2025) 43:292–307.e7. doi: 10.1016/j.ccell.2024.12.008
3. Jin Z, Li Y, Yi H, Wang M, Wang C, Du S, et al. Pathogenetic development, diagnosis and clinical therapeutic approaches for liver metastasis from colorectal cancer (review). *Int J Oncol.* (2025) 66:22. doi: 10.3892/ijo.2025.5728
4. American Cancer Society. Survival Rates for Colorectal Cancer. Available online at: <https://www.cancer.org/cancer/types/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html> (Accessed September 1, 2024).
5. Kim YN, Koo KH, Sung JY, Yun UJ, Kim H. Anoikis resistance: an essential prerequisite for tumor metastasis. *Int J Cell Biol.* (2012) 2012:306879. doi: 10.1155/2012/306879
6. Celià-Terrassa T, Kang Y. Distinctive properties of metastasis-initiating cells. *Genes Dev.* (2016) 30:892–908. doi: 10.1101/gad.277681.116
7. Frisch SM, Francis H. Disruption of epithelial cell-matrix interactions induces apoptosis. *J Cell Biol.* (1994) 124:619–26. doi: 10.1083/jcb.124.4.619

8. Simpson CD, Anyiwe K, Schimmer AD. Anoikis resistance and tumor metastasis. *Cancer Lett.* (2008) 272:177–85. doi: 10.1016/j.canlet.2008.05.029
9. Corkery DP, Clarke LE, Gebremeskel S, Salsman J, Pinder J, Le Page C, et al. Loss of PRP4K drives anoikis resistance in part by dysregulation of epidermal growth factor receptor endosomal trafficking. *Oncogene.* (2018) 37:174–84. doi: 10.1038/ncr.2017.318
10. Walker C, Mojares E, del Río Hernández A. Role of extracellular matrix in development and cancer progression. *Int J Mol Sci.* (2018) 19:3028. doi: 10.3390/ijms19103028
11. Fidler IJ. Critical factors in the biology of human cancer metastasis: twenty-eighth GHA clowes memorial award lecture. *Cancer Res.* (1990) 50:6130–8.
12. Gupta GP, Massagué J. Cancer metastasis: building a framework. *Cell.* (2006) 127:679–95. doi: 10.1016/j.cell.2006.11.001
13. Doxtater K, Tripathi MK, Sekhri R, Hafeez BB, Khan S, Zafar N, et al. MUC13 drives cancer aggressiveness and metastasis through the YAP1-dependent pathway. *Life Sci Alliance.* (2023) 6:e202301975. doi: 10.26508/lsa.202301975
14. Gupta BK, Maher DM, Ebeling MC, Stephenson PD, Puumala SE, Koch MR, et al. Functions and regulation of MUC13 mucin in colon cancer cells. *J Gastroenterol.* (2014) 49:1378–91. doi: 10.1007/s00535-013-0885-z
15. Chauhan SC, Vannatta K, Ebeling MC, Vinayek N, Watanabe A, Pandey KK, et al. Expression and functions of transmembrane mucin MUC13 in ovarian cancer. *Cancer Res.* (2009) 69:765–74. doi: 10.1158/0008-5472.CAN-08-0587
16. Chauhan SC, Ebeling MC, Maher DM, Koch MD, Watanabe A, Aburatani H, et al. MUC13 mucin augments pancreatic tumorigenesis. *Mol Cancer Ther.* (2012) 11:24–33. doi: 10.1158/1535-7163.MCT-11-0598
17. Sheng YH, He Y, Hasnain SZ, Wang R, Tong H, Clarke DT, et al. MUC13 protects colorectal cancer cells from death by activating the NF- κ B pathway and is a potential therapeutic target. *Oncogene.* (2017) 36:700–13. doi: 10.1038/ncr.2016.241
18. Khan S, Sikander M, Ebeling MC, Ganju A, Kumari S, Yallapu MM, et al. MUC13 interaction with receptor tyrosine kinase HER2 drives pancreatic ductal adenocarcinoma progression. *Oncogene.* (2017) 36:491–500. doi: 10.1038/ncr.2016.218
19. Kumari S, Khan S, Gupta SC, Kashyap VK, Yallapu MM, Chauhan SC, et al. MUC13 contributes to rewiring of glucose metabolism in pancreatic cancer. *Oncogenesis.* (2018) 7:19. doi: 10.1038/s41389-018-0031-0
20. Khan S, Zafar N, Khan SS, Setia S, Behrman SW, Stiles ZE, et al. Clinical significance of MUC13 in pancreatic ductal adenocarcinoma. *Hpb.* (2018) 20:563–72. doi: 10.1016/j.hpb.2017.12.003
21. Massey AE, Doxtater KA, Yallapu MM, Chauhan SC. Biophysical changes caused by altered MUC13 expression in pancreatic cancer cells. *Micron.* (2020) 130:102822. doi: 10.1016/j.micron.2019.102822
22. Shimamura T, Ito H, Shibahara J, Watanabe A, Hippo Y, Taniguchi H, et al. Overexpression of MUC13 is associated with intestinal-type gastric cancer. *Cancer Sci.* (2005) 96:265–73. doi: 10.1111/j.1349-7006.2005.00043.x
23. Walsh MD, Young JP, Leggett BA, Williams SH, Jass JR, McGuckin MA. The MUC13 cell surface mucin is highly expressed by human colorectal carcinomas. *Hum Pathol.* (2007) 38:883–92. doi: 10.1016/j.humpath.2006.11.020
24. Sheng YH, Lourie R, Lindén SK, Jeffery PL, Roche D, Tran TV, et al. The MUC13 cell-surface mucin protects against intestinal inflammation by inhibiting epithelial cell apoptosis. *Gut.* (2011) 60:1661–70. doi: 10.1136/gut.2011.239194
25. Sheng YH, Triyana S, Wang R, Das I, Gerloff K, Florin TH, et al. MUC1 and MUC13 differentially regulate epithelial inflammation in response to inflammatory and infectious stimuli. *Mucosal Immunol.* (2013) 6:557–68. doi: 10.1038/mi.2012.98
26. Sheng Y, Ng CP, Lourie R, Shah ET, He Y, Wong KY, et al. MUC13 overexpression in renal cell carcinoma plays a central role in tumor progression and drug resistance. *Int J Cancer.* (2017) 140:2351–63. doi: 10.1002/ijc.30651
27. Mito K, Saito M, Morita K, Maetani I, Sata N, Mieno M, et al. Clinicopathological and prognostic significance of MUC13 and AGR2 expression in intraductal papillary mucinous neoplasms of the pancreas. *Pancreatol.* (2018) 18:407–12. doi: 10.1016/j.pan.2018.04.003
28. Sheng YH, Wong KY, Seim I, Wang R, He Y, Wu A, et al. MUC13 promotes the development of colitis-associated colorectal tumors via β -catenin activity. *Oncogene.* (2019) 38:7294–310. doi: 10.1038/s41388-019-0951-y
29. Wierzbicki PM, Rybarczyk A. The Hippo pathway in colorectal cancer. *Folia Histochem Cytobiol.* (2015) 53:105–19. doi: 10.5603/FHC.a2015.0015
30. Zhao B, Li L, Wang L, Wang CY, Yu J, Guan KL. Cell detachment activates the Hippo pathway via cytoskeleton reorganization to induce anoikis. *Genes Dev.* (2012) 26:54–68. doi: 10.1101/gad.173435.111
31. Shao DD, Xue W, Krall EB, Bhutkar A, Piccioni F, Wang X, et al. KRAS and YAP1 converge to regulate EMT and tumor survival. *Cell.* (2014) 158:171–84. doi: 10.1016/j.cell.2014.06.004
32. Haemmerle M, Taylor ML, Gutschner T, Pradeep S, Cho MS, Sheng J, et al. Platelets reduce anoikis and promote metastasis by activating YAP1 signaling. *Nat Commun.* (2017) 8:310. doi: 10.1038/s41467-017-00411-z
33. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, et al. Oncogenic signaling pathways in the cancer genome atlas. *Cell.* (2018) 173:321–37.e10. doi: 10.1016/j.cell.2018.03.035
34. Mo JS, Park HW, Guan KL. The Hippo signaling pathway in stem cell biology and cancer. *EMBO Rep.* (2014) 15:642–56. doi: 10.15252/embr.201438638
35. Ma Y, Yang Y, Wang F, Wei Q, Qin H. Hippo-YAP signaling pathway: a new paradigm for cancer therapy. *Int J Cancer.* (2015) 137:2275–86. doi: 10.1002/ijc.29073
36. Konsavage WM Jr, Kyler SL, Rennoll SA, Jin G, Yochum GS. Wnt/ β -catenin signaling regulates Yes-associated protein (YAP) gene expression in colorectal carcinoma cells. *J Biol Chem.* (2012) 287:11730–9. doi: 10.1074/jbc.M111.327767
37. Rosenbluh J, Nijhawan D, Cox AG, Li X, Neal JT, Schafer EJ, et al. β -Catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. *Cell.* (2012) 151:1457–73. doi: 10.1016/j.cell.2012.11.026
38. Bernascone I, Martin-Belmonte F. Crossroads of Wnt and Hippo in epithelial tissues. *Trends Cell Biol.* (2013) 23:380–9. doi: 10.1016/j.tcb.2013.03.007
39. Krausova M, Korinek V. Wnt signaling in adult intestinal stem cells and cancer. *Cell Signal.* (2014) 26:570–9. doi: 10.1016/j.celsig.2013.11.032
40. Yang B, Sun H, Song F, Yu M, Wu Y, Wang J. YAP1 negatively regulates chondrocyte differentiation partly by activating the β -catenin signaling pathway. *Int J Biochem Cell Biol.* (2017) 87:104–13. doi: 10.1016/j.biocel.2017.04.007
41. Herbst A, Jurinovic V, Krebs S, Thieme SE, Blum H, Göke B, et al. Comprehensive analysis of β -catenin target genes in colorectal carcinoma cell lines with deregulated Wnt/ β -catenin signaling. *BMC Genomics.* (2014) 15:74. doi: 10.1186/1471-2164-15-74
42. Basu S, Haase G, Ben-Ze'ev A. Wnt signaling in cancer stem cells and colon cancer metastasis. *F1000Res.* (2016) 5:F1000 Faculty Rev-699. doi: 10.12688/f1000research.7579.1
43. Yu LG. Cancer cell resistance to anoikis: MUC1 glycosylation comes to play. *Cell Death Dis.* (2017) 8:e2962. doi: 10.1038/cddis.2017.363
44. Li YH, Sun X, Wang HB. Role of CD24 in anoikis resistance of ovarian cancer cells. *J Huazhong Univ Sci Technol Med Sci.* (2015) 35:390–6. doi: 10.1007/s11596-015-1443-0
45. Bose M, Sanders A, De C, Zhou R, Lala P, Shwartz S, et al. Targeting tumor-associated MUC1 overcomes anoikis-resistance in pancreatic cancer. *Transl Res.* (2023) 253:41–56. doi: 10.1016/j.trsl.2022.08.010
46. Sattari Fard F, Jalilzadeh N, Mehdizadeh A, Sajjadian F, Velaei K. Understanding and targeting anoikis in metastasis for cancer therapies. *Cell Biol Int.* (2023) 47:683–98. doi: 10.1002/cbin.11970