BMI1 Roles in Cancer Stem Cells and Its Association with MicroRNAs Dysregulation in Cancer: Emphasis on Colorectal Cancer

Mohammad Hasan Soheilifar¹, Abdolvahab Moshtaghian², Hamid Maadi³, Fereshteh Izadi⁴ and Massoud Saidijam¹ *

¹Research Center for Molecular Medicine and Genetics, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran  
²Deputy of Research and Technology,Semnan University of Medical Sciences, Semnan, Iran  
³Department of Medical Genetics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada  
⁴Department of Plant Breeding and Biotechnology, Sari Agricultural Sciences and Natural Resources University (SANRU), Sari, Iran  
*Corresponding author: Massoud Saidijam, Research Center for Molecular Medicine and Genetics, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran. Tel: +98-9121324616, Email: sjam110@yahoo.com

Received 2018 April 02; Revised 2018 July 29; Accepted 2018 August 06.

Abstract

Context: Colorectal cancer (CRC) is among the most common cancers in the world. Despite the existence of different treatment strategies such as chemoradiation and surgery, CRC therapy still remains a significant challenge as a result of the existence of cancer stem cells (CSCs).

Evidence Acquisition: This review is comprised of research and review studies published in valid databases such as PubMed, ScienceDirect, Medline, Google Scholar, and Scopus, using the following keywords: BMI1, cancer stem cell, microRNA, and colorectal cancer.

Results: BMI1 (B cell-specific Moloney murine leukemia virus integration site 1) is a key component of polycomb repressor complex 1 (PRC1) and plays a significant role in CSCs self-renewal in various types of cancer including CRC. It has been proven that BMI1, in association with deregulated microRNAs (miRNAs), can promote cell cycle progression as well as epithelial to mesenchymal transition (EMT) in cancer.

Conclusions: BMI1 is a colon stem cell marker that is up-regulated in colon CSCs and can be taken as a promising target for CRC therapy. This review describes the role of BMI-1 in the self-renewal of CSCs and EMT in association with miRNA dysregulation (with emphasis on CRC).

Keywords: BMI1, Cancer Stem Cell, miRNA, Colorectal Cancer

1. Context

Cancer stem cells (CSCs) are among the most remarkable and attractive subjects in tumor biology and cancer research. CSCs are tumor-initiating cells having self-renewal and pluripotent properties and may contribute to tumor regrowth, metastasis, chemoradiotherapy resistance, and finally death (1). It has been reported that CSCs are involved in several malignancies such as leukemia and multiple solid cancer types such as colorectal cancer (CRC).

CRC is the third leading cause of cancer death worldwide, and its 5-year relative survival rate is only 8%, regardless of diagnostic and therapeutic advances (2). Colon CSCs are characterized by the expression of multiple markers such as the polycomb gene BMI1 (B cell-specific Moloney murine leukemia virus integration site 1) (3).

The BMI1 protein is a member of the polycomb group (PcG) proteins, which assembles into polycomb repressive complex 1 (PRC1) and acts as a transcriptional repressor of the Ink4a/Arf locus (4). The Ink4a/Arf locus has two distinct gene products, p16 (Ink4a) and p14 (Arf), which act as key tumor suppressors and control important physiological processes such as apoptosis and stem cell self-renewal (5).

BMI1 is a key regulator of CSC self-renewal and plasticity (6) and resides downstream of several signaling pathways such as wnt/β-catenin, notch, and hedgehog, which play important roles in maintaining the growth, proliferation, and functional integrity of CSC (7). Since BMI1 is overexpressed in many cancer types, including CRC (8) and plays an essential role in stem cell self-renewal and survival; it stands out as a promising target for controlling CSC function (9). The miRNAs are small endogenous non-
coding RNAs that play important roles in normal and cancer stem cells (10). The overexpression of BMI1, as a result of deregulated miRNAs, could result to cancer progression and metastasis. The present review summarized some functions of BMI1 in CSCs, especially colon CSCs, with an overview of miRNA regulation of BMI1 in different types of cancer.

2. Evidence Acquisition

The literature review of the present study utilized more than 80 articles published since 2002 in online databases, including PubMed, ScienceDirect, Medline, Google Scholar, and Scopus, using relevant keywords such as: BMI1, cancer stem cell, miRNA, and colorectal cancer. The present study investigated the relationship between BMI1 and miRNA dysregulation in various types of cancer. The role of BMI1 as a colon cancer stem cell marker is another topic, which has been explored in different related articles.

It was assumed that the association of BMI1 with miRNA could be useful as a therapeutic target and more identification of molecular mechanisms are involved in cancer.

3. Results

3.1. Genetic and Protein Structure of BMI1

BMI1 has been recognized as a target of the Moloney virus insertion and identified as an oncogene that cooperates with c-Myc in the initiation of B-lymphoid tumors (11). The BMI1 gene is localized on the short arm of chromosome 10 (10p11.23), and consists of 10 exons and 9 introns. The BMI1 protein consists of 326 amino acids with molecular weight of 36.8 kDa and contains a conserved RING finger domain in its N-terminal end, which mediates stable interaction with RING1B (E3 ligase) to stimulate its activity (12). In addition, it contains a conserved helix-turn-helix-turn (H-T-H-T) motif (13), which is essential for prompting telomerase activity and immortalization of the human epithelial cell (14) and a PEST (proline (P), glutamic acid (E), serine (S), and threonine (T)) domain at the C-terminal (9) that acts as proteolytic signals leading to protein degradation (15). The deletion of PEST-like domain, which is rich in proline-serine (PS) residues, increased BMI1 stability and pro-oncogenic actions in human mammary epithelial cells (16).

3.2. BMI1 as an Epigenetic Repressor Plays an Important Role in the Self-Renewal Mechanism of CSCs and in Epithelial to Mesenchymal Transition (EMT)-Induced Cancer Stemness

Normal stem cells have self-renewal and pluripotency properties, which are similar to CSCs as a small portion of tumor cells in tumor mass (17). CSCs are involved in tumorigenesis, metastasis, chemoradiotherapy resistance, and tumor relapse (18, 19). Increasing evidences have shown that BMI1 plays a significant role in the proliferation, self-renewal, and differentiation of several types of human stem and progenitor cells (12). It has been indicated that BMI1 is crucial for the maintenance of self-renewal, symmetrical cell division, and proliferation induction in various types of stem cells, including adult hematopoietic stem cells (HSCs) and adult peripheral and central nervous system neural stem cells (NSCs) (20). Moreover, BMI1 is a marker of distinct intestinal stem cell (ISC) populations (21), which are dormant, radio resistant, and proliferate strongly after radiation damage (22). BMI1 is not only constantly necessitated for the self-renewal of diverse tissue-specific stem cells, but is needed for the proliferation of cancer cells in the same tissues (23). The central role of BMI1 in promoting the self-renewal of various types of stem cells as well as CSCs indicates that a common mechanism regulates the self-renewal and maintenance of these cells. Self-renewal mechanisms that allow stem cells to tolerate their proliferative capacity usually include proto-oncogenic pathways such as Wnt, Hh, Notch, and the polycomb group genes (24). It has been shown that the components of these signaling pathways are mutated or over-expressed in many malignancies and could contribute to cancer cell proliferation (25). BMI1 is downstream of Wnt, Hh, and Notch signaling pathways (26). In gastric cancer, BMI1 maintains the self-renewal ability of CSCs by activating the AKT/NF-κB signaling pathway (27). BMI1 up-regulates Nanog and promotes the self-renewal capability of breast CSCs through the NF-kB pathway (28). This signifies the involvement of BMI1 in another self-renewal pathway in CSCs. BMI1 as an epigenetic repressor, can suppress p16Ink4a and p19Arf (a homolog of human p14Arf) through the induction of histone 2A (H2A) ubiquitination and histone methylation by cooperating with different PRC1 components (29). The p16Ink4a protein inhibits the binding of Cyclin D to CDK4/6, leading to the suppression of retinoblastoma (Rb) activity and induction of cell cycle arrest (30). Moreover, p19Arf can prevent cell cycle progression by activating the p53 gene (31). Nonetheless, Xu et al. showed that BMI1 functions are independent of Ink4a/Arf repression in hepatic carcinogenesis, suggesting a link between BMI1 and other oncogenic signals (32). Altogether,
a crosstalk between these signaling pathways and epigenetic regulation has shown that BMI1 acts as a key factor in CSCs self-renewal, downstream of these signaling pathways (Figure 1) (2). Accumulating data show that BMI1 plays a crucial role in the EMT-induced stem cell-like property of tumor cells. The EMT mechanism is often activated during cancer development and it promotes the self-renewal ability (33). The increased expression of TWIST1 and BMI1 in association with the down-regulation of E-cadherin and p16Ink4a through chromatin remodeling is a mechanistic elucidation of the association between EMT and cancer stemness (34). Moreover, it has been revealed that the knockdown of either TWIST1 or BMI1 can reverse EMT and decrease stem-like properties (35). BMI1 contributes to the metastatic phenotypes of CSCs through expression alterations of E-cadherin and other molecules such as N-cadherin and vimentin, which result to unfavorable clinical consequences (36).

3.3. Association Between miRNA Dysregulation and BMI1 in Different Types of Cancer

It has been recognized that BMI1 is involved in the proliferation, invasion, metastasis, and chemosensitivity of cancer cells (37). Increased expression of BMI1 in numerous types of cancer has revealed that BMI1 plays significant roles in cancer initiation and development. The overexpression of BMI1 as an oncogene has been shown in leukemia (38) and various solid tumors like CRC (39). The regulation of BMI1 expression by miRNAs has been shown in a number of malignancies (Table 1). miRNAs are endogenous small non-coding RNA, which play important roles in normal and CSCs (10). Accumulating evidences indicate the role of dysregulated miRNAs as oncopgenes and tumor suppressors in tumor development that suggesting their possible applications as tumor biomarkers (40-44). It has been shown that BMI1 expression repression by miRNAs leads to EMT suppression and sensitize tumor cells to chemotherapy in various types of cancer (supplementary file appendix I). miRNAs are involved in modulating chemo-resistance and the self-renewal characteristic of CSCs in cancers. The stemness properties of gastric cancer cells is regulated by miR-21 and miR-34a (Figure 2) (27). In glioma, the decrease in self-renewal of CSCs is due to BMI1 expression inhibition by miR-128 (45). Zhang et al. demonstrated a miRNA signature related to colon CSCs stemness markers like BMI1 (46). Therefore, miRNAs are identified as prominent regulators of BMI1 expression in association with the stemness characteristics of cancer cells (47).

3.4. BMI1 Role in CRC with Therapeutic Implications

CRC is the second most common cause of cancer in women and the third in men, responsible for considerable morbidity and mortality (66). Several studies have proven that BMI1 is up-regulated in CRC and associated with initiation, malignant development, and poor survival of CRC (67).

Although the prognostic importance of BMI1 expression in CRC is contradictory, several studies have introduced BMI1 as a prognosis marker for CRC (68). The level of BMI1 mRNA in circulation may serve as a non invasive prognostic biomarker for monitoring distant metastasis in CRC (69). In addition, Li et al. have indicated that the increased level of the BMI1 protein has a significant link with poor prognosis in colon cancer (70). Another study suggested that a combination of BMI1 and FSCN1 could be a novel prognostic indicator in CRC (71).

In 2007, colon CSCs isolated from bulk tumor cells were identified, using renal capsule transplantation in immunodeficient NOD/SCID mice, showing the ability to induce tumor regrowth upon serial transplantation, thereby providing strong evidence for the hierarchical model of human colon cancer (72). Network analysis showed that enrichment in zinc finger DNA binding protein and transcriptional regulator genes in BMI1 expressing tumor cells in CRC patients is consistent with stem cells self-renewal and pluripotency (71). Colorectal CSCs are plastic cells involved in intratumoral heterogeneity and are identified by chemoradiotherapy resistance, as well as metastatic and self-renewal activity (73). BMI1 mediates histone ubiquitination and is indispensable for colon cancer cells proliferation in vitro and in vivo (74). BMI1 is overexpressed in many CSCs including colon CSCs (75). Furthermore, BMI1 is up-regulated in circulating colon cancer cells, which show stem cell like properties (76). BMI1 expression is induced by IL-4Rβ in colon cancer and is involved in the IL-4Rβ/Zeb1 pathway, which is critical for the self-renewal ability of colon CSC (77). BMI1 up-regulation by HES1 mediates EMT through the PTEN/Akt/GSK3β pathway in colon cancer (78). NF-kB and β-catenin are involved in the generation of colon CSCs from tumor cells (79). It has recently been demonstrated that Fas signaling induces colon cancer stemness markers such as BMI1 (80). Therefore, BMI1 is a valuable therapeutic target for controlling the oncogenic potential of CSCs. For the first time, Kreso et al. reported that the self-renewal ability of colorectal CSCs can be targeted with PTC-209, a small-molecule inhibitor of BMI1, which leads to CRC growth and metastasis reduction without systemic toxicity (39). They revealed that by targeting BMI1, human colon CSCs in mouse xenografts can be successfully eradicated.

Int J Cancer Manag. 2018; 11(9):e82926.
Moreover, they showed that BMI1 knockdown by short hairpin RNA (shRNA) can diminish human CRC growth and reduce the self-renewal of colorectal CSCs. Furthermore, it has been demonstrated that targeting ZEB1, SALL4, and BMI1 via miR-508-3p can induce E-cadherin expression and inhibit cell migration, invasion, and EMT in the mesenchymal subtype of CRC (63). Using high-throughput miRNA profiling in the CRC cell line (HTC116) revealed that miR-215 directly targets CDX1 mRNA (81). CDX1 is an important mediator of differentiation in normal colon and CRC and regulates the expression of intestine and enterocyte-specific genes (82). MiR-215 acts as a target of CDX1 in colon cancer and by repression of BMI1, is involved in promoting tumor cell differentiation (Figure 3). Moreover, some drugs and negative regulators have been identified to decrease BMI1 expression (supplementary file appendix 2). By using PTC’s proprietary GEMSTM technology platform, Cao et al. demonstrated that the inhibition of BMI1 expression can selectively suppress the self-renewal of CSCs rather than normal stem cell, suggesting a safety therapeutic outcome in comparison to other BMI1 inhibitors such as histone deacetylase inhibitors (HDACi) and artemisinin (9).

4. Conclusions

CSCs are a sub-population of tumor cells that share similarity such as self-renewal and pluripotency with normal stem cells and are responsible for initiation, maintenance, and relapse of various tumors. It has been shown that CSCs become resistant to chemotherapy and radiotherapy; therefore, undesirable clinical outcomes of CSCs highlight the significance of therapeutic strategies for targeting them in various types of tumor including CRC. Increasing evidences revealed that BMI1, as an epigenetic repressor, is important in maintaining the properties of CSCs and plays a critical role in self renewal, differentiation, and tumor initiation of CSCs by silencing major tumor suppressors such as p16, p14, and PTEN. The association of miRNA dysregulation and, subsequently, BMI1 hy-
Soheilifar MH et al.

| miRNAs          | Types of cancer                     | Results of BMI1 repression                                      | References |
|-----------------|-------------------------------------|----------------------------------------------------------------|------------|
| miR15 and miR16 | Ovarian                             | Significant decrease in ovarian cancer cell proliferation and clonal growth | (48)       |
| miR-30e*        | Gastrointestinal                    | miR-30e* regulation of BMI1 expression mediated by tumor-associated macrophages in gastric cancer progression | (49)       |
| miR-135a        | Pancreatic ductal adenocarcinoma    | Induced G1 arrest and apoptosis                                  | (50)       |
| miR-183         | Pancreatic ductal adenocarcinoma    | Decreased expression of CDK2 and CDK4                           | (51)       |
| miR-320a        | Nasopharyngeal carcinoma            | Inhibition of cell proliferation, migration, and invasion       | (52)       |
| miR-429         | Renal cell carcinoma                | Growth and metastasis suppression                                | (53, 54)  |
| miR-429         | Glioblastoma                        | Inhibition of cell proliferation and invasion                    | (55)       |
| miR-203 and miR-200c | Melanoma                   | Reduced cell invasion, tumor sphere formation, and increased expression of E-cadherin | (56, 57)  |
| miR-200c        | Bladder                             | Increase expression of E-cadherin and EMT inhibition            | (58)       |
| miR-200c        | Breast                              | Enhanced survival signaling                                     | (59)       |
| miR-139-5p      | Bladder                             | Inhibiting selfrenewal of bladder CSCs                         | (60)       |
| miR-200b and miR-15b | Tongue                   | Reversed the phenotype of EMT in chemotherapy-resistant tongue squamous cell carcinoma cell lines | (61)       |
| miR-218         | Colon                               | Inhibiting proliferation and inducing apoptosis                  | (62)       |
| miR-508-3p      | Colon                               | TGF-β induced EMT inhibition                                    | (63)       |
| miR-494-1p      | Oral squamous carcinoma cells       | Promotion of cellular senescence                                | (64)       |
| miR-487b        | Lung                                | Impaired WNT signaling                                          | (65)       |
| miR-21          | Gastric                             | Increased self-renewal, migration ability, and chemotherapy resistance | (27)       |

Figure 1. The miRNA regulation of BMI1 in colon CSCs. There is an inverse relationship between CDX1 and BMI1 expression. High expression level of CDX1 predicts good prognosis and is related to small population of CSCs in colon cancer.

peractivation revealed the substantial promotion of the self renewal capacity, as well as EMT and tumor growth in various types of tumors. Improvement of clinical outcomes can be achieved by conducting more investigations on the molecular mechanisms underlying the regulation
of BMI and other reliable biomarkers that are associated with pathways driving self-renewal in colon CSCs.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors’ Contribution: Not declared.

Conflict of Interests: The authors declare no conflict of interest.

Financial Disclosure: Not declared.

References

1. Wicha MS. Targeting self-renewal, an Achilles’ heel of cancer stem cells. Nat Med. 2014;20(1):14-5. doi: 10.1038/nm.3434. [PubMed: 24398956].
2. Garza-Trevino EN, Said-Fernandez SL, Martinez-Rodriguez HG. Understanding the colon cancer stem cell and perspectives on treatment. Cancer Cell Int. 2015;15(1):2. doi: 10.1186/s12935-015-0163-7. [PubMed: 25685060]. [PubMed Central: PMC4320853].
3. Espersen ML, Olsen J, Linnemann D, Hogdall E, Troelsen JT. Clinical implications of intestinal stem cell markers in colorectal cancer. Clin Colorectal Cancer. 2015;14(2):63-71. doi: 10.1016/j.clcc.2014.12.004. [PubMed: 25657049].
4. Bommi PV, Dimri M, Sahasrabuddhe AA, Khandekar J, Dimri GP. The polyclomb group protein BMI1 is a transcriptional target of HDAC inhibitors. Cell Cycle. 2010;9(13):2663-73. doi: 10.4161/cc.9.13.12477. [PubMed: 20543557]. [PubMed Central: PMC3083287].
5. GJ L Peters. Regulation of the INK4b-ARF-INK4a tumor suppressor locus: all for one or one for all. Nat Rev Mol Cell Biol. 2006;7(9):567-77. doi: 10.1038/nrm1987. [PubMed: 16921403].
6. Hamai A, Codojno P, Mehppour M. Cancer stem cells and autophagy: Facts and perspectives. J Cancer Stem Cell Res. 2014;2(5):3-11. doi: 10.15443/JSRC.2014-20065.
7. Roy S, Majumdar AP. Signaling in colon cancer stem cells. J Mol Signal. 2012;7(1):1-11. doi: 10.1186/1750-2187-7-11. [PubMed: 22866952]. [PubMed Central: PMC3485105].
8. Reinisch C, Kandutsch S, Uthman A, Pummer J. BMI1: a protein expressed in stem cells, specialized cells and tumors of the gastrointestinal tract. Histol Histopathol. 2006;21(11):3143-9. doi: 10.14470/hh.21L141. [PubMed: 16874656].
9. Cao L, Bombard J, Cintron K, Sheedy J, Weetall MI, Davis TW. BMI1 as a novel target for drug discovery in cancer. J Cell Biochem. 2011;112(10):2729-41. doi: 10.1002/jcb.23234. [PubMed: 21078481].
10. Sekar D, Krishnan R, Panagal M, Sivakumar P, Gopinath V, Basam V. Deciphering the role of microRNA in colon cancer stem cells (CSCs). Genes Diseases. 2016;3(4):277-81. doi: 10.1016/j.gendis.2016.05.002.
11. van Lohuizen M, Verbeek S, Scheijen B, Wientjes E, van der Gulden H, Berns A. Identification of cooperating oncogenes in E mu-myc transgenic mice by provirus tagging. Cell. 1991;65(5):737-52. [PubMed: 1904008].
12. Siddique HR, Saleem M. Role of BMI1, a stem cell factor, in cancer recurrence and chemoresistance: preclinical and clinical evidences. Stem Cells. 2012;30(3):372-8. doi: 10.1002/stem.1035. [PubMed: 22252887].
13. Dimri GP, Martinez JL, Jacobs J, Keblusek P, Itahana K, Van Lothuizen M, et al. The Bmi-1 oncogene induces telomerase activity and immortalizes human mammary epithelial cells. Cancer Res. 2002;62(16):4736-45. [PubMed: 1218443].
14. Huber GP, Albiniger-Hegyi A, Soltermann A, Roessle M, Graf N, Haerle SK, et al. Expression patterns of Bmi-1 and p16 significantly correlate with overall, disease-specific, and recurrence-free survival in oropharyngeal squamous cell carcinoma. Cancer. 2011;117(20):4659-70. doi: 10.1002/cncr.21448927.
15. Rechsteiner M, Rogers SW. PEST sequences and regulation by proteolysis. Trends Biochem Sci. 1996;21(7):267-71. doi: 10.1016/0968-0004(96)80016-4. [PubMed: 8755249].
16. Yadav AK, Sahasrabuddhe AA, Dimri M, Bommi PV, Sainger R, Dimri GP. Deletion analysis of BMI1 oncogene identifies its negative regulatory domain. Mol Cancer. 2010;9:358. doi: 10.1002/1465-4589.4518. [PubMed: 20569464]. [PubMed Central: PMC2900245].
17. Sohelifar MH, Jafari A, Amini H, Taha MF. Generation of dopamine-secreting cells from human adipose tissue-derived stem cells in vitro. Rejuvenation Res. 2018;21(4):360-8. doi: 10.1089/rej.2017.1994. [PubMed: 2920796].
18. Grotenhuis BA, Vijnhoven BP, van Lanschot JJ. Cancer stem cells and their potential implications for the treatment of solid tumors. J Surg Oncol. 2012;106(2):209-15. doi: 10.1002/jso.23069. [PubMed: 21771252].
19. Sohelifar MH, Taheri RA, Zolfaghari Emamre, Moshilaghan A, Kooshki H, Mortie MR. Molecular Landscape in Alveolar Soft Part Sarcoma: Implications for Molecular Targeted Therapy. Biomed Pharmacother. 2018;103:889-96. doi: 10.1016/j.biopha.2018.04.117. [PubMed: 29710505].
20. Yadiri G, Leinster V, Acquati S, Bhagat H, Shakhoova O, Marino S. Conditional activation of Bmi1 expression regulates self-renewal, apoptosis, and differentiation of neural stem/progenitor cells in vitro and in vivo. Stem Cells. 2011;29(4):700-12. doi: 10.1002/stem.604. [PubMed: 21305672].
21. Sangiorgi E, Capecci MR. BMI is expressed in vivo in intestinal stem cells. Nat Genet. 2008;40(7):955-90. doi: 10.1038/ng.165. [PubMed: 1835676]. [PubMed Central: PMC2900615].
22. Yan KS, Chia LA, Li X, Gotani A, Su J, Lee YJ, et al. The intestinal stem cell markers Bmi1 and Lgr5 identify two functionally distinct populations. Proc Natl Acad Sci U S A. 2012;109(2):466-71. doi: 10.1073/pnas.1118570909. [PubMed: 22199486]. [PubMed Central: PMC3255636].
23. Bruggeman SW, Hulsman D, Tanger E, Buckle T, Blom Z, Zevenhoven J, et al. Bmi1 controls tumor development in an Ink4a/Arf-independent manner in a mouse model for glioma. Cancer Cell. 2007;12(4):328-41. doi: 10.1016/j.ccr.2007.08.032. [PubMed: 17945558].
24. Beck B, Blanpain C. Unravelling cancer stem cell potential. Nat Rev Cancer. 2013;13(10):727-38. doi: 10.1038/nrc3597. [PubMed: 23060864].
25. Pardal R, Molofsky AV, He S, Morrison SJ. Stem cell self-renewal and cancer cell proliferation are regulated by common networks that balance the activation of proto-oncogenes and tumor suppressors. Cold Spring Harb Symp Quant Biol. 2005;70:177-85. doi: 10.1101/sqb.2005.70.057. [PubMed: 16869752].
26. Liu S, Dontu G, Wicha MS. Mammary stem cells, self-renewal pathways, and carcinogenesis. Breast Cancer Res. 2005;7(3):86-95. doi: 10.1186/bcr1021. [PubMed: 15987416]. [PubMed Central: PMC1435866].
27. Wang X, Wang C, Zhang X, Hua R, Lan L, Huang M, et al. Bmi1 regulates stem cell-like properties of gastric cancer cells via modulating miRNAs. J Hematol Oncol. 2016;9(1):90. doi: 10.1186/s12953-016-0323-9. [PubMed: 27644439]. [PubMed Central: PMC5029045].
28. Paranjape AN, Balaji SA, Mandal T, Krushik EV, Nagaraj P, Mukherjee G, et al. BMI regulates self-renewal and epithelial to mesenchymal transition in breast cancer cells through Nanog. BMC Cancer. 2014;14:785. doi: 10.1186/1471-2407-14-785. [PubMed: 25348805]. [PubMed Central: PMC4223733].

29. Bracken AP, Kleine-Kohlbrecher D, Dietrich N, Pasini D, Gargiulo G, Beekman C, et al. The Polycomb group proteins bind throughout the INK4A-ARF locus and are disassociated in senescent cells. Genes Dev. 2007;21(5):525–30. doi: 10.1101/gad.151205. [PubMed: 17744414]. [PubMed Central: PMC182094].

30. Park IK, Morrison SJ, Clarke MF. BMI, stem cells, and senescence regulation. J Clin Invest. 2004;113(12):1875–82. doi: 10.1172/JCI20800. [PubMed: 14722607]. [PubMed Central: PMC1144].

31. Molofsky AV, He S, Bydon M, Morrison SJ, Pardal R. Bmi-1 promotes neural stem cell self-renewal and neural development but not mouse growth and survival by repressing the pitx6 and pphpArf senescence pathways. Genes Dev. 2005;19(12):1432–7. doi: 10.1101/gad.299505. [PubMed: 15964994]. [PubMed Central: PMC15659].

32. Xu CR, Lee S, Ho C, Bommi P, Huang SA, Cheung ST, et al. BMI1 functions as an oncogene independent of INK4A/ARF repression in hepatic carcinogenesis. Mol Cancer Res. 2009;7(12):1937–45. doi: 10.1158/1541-7786.MCR-09-0133. [PubMed: 19994276]. [PubMed Central: PMC2966287].

33. Raimondi C, Gianni W, Cortesi E, Gazzaniga P. Cancer stem cells and epithelial-mesenchymal transition: revisiting minimal residual disease. Curr Cancer Drug Targets. 2010;10(5):496–508. [PubMed: 20184575].

34. Ren H, Du P, Ge Z, Jin Y, Ding D, Liu X, et al. TWIST1 and BMI1 and epithelial-mesenchymal transition: re-visited minimal residual disease. Curr Cancer Drug Targets. 2010;10(5):496–508. [PubMed: 20184575].

35. Wang MC, Li CL, Cui J, Jiao M, Wu T, Jing L, et al. BMI-1, a promising therapeutic target in human colorectal cancer. Mol Cancer Res. 2010;8(10):1283–91. doi: 10.1158/1541-7786.MCR-10-0223. [PubMed: 20729731]. [PubMed Central: PMC2986794].

36. Rizos H, Moshagtian A, Amini R, Asefi M, Basiri P, Saidimaj D. BMI1 as a potential target of miR-130-3p in colorectal cancer. Middle East J Rehabil Health. 2018;3(2). doi: 10.7150/metherj.66075. [PubMed: 28879560].

37. Bhattacharya R, Nicoloso M, Arzio V, Wang E, Cortez A, Rossi S, et al. MiR-15a and MiR-16 control BMI1 expression in ovarian cancer. Cancer Res. 2009;69(23):9090–5. doi: 10.1158/0008-5472.CAN-09-2552. [PubMed: 19903441]. [PubMed Central: PMC2859686].

38. Sughihara I, Ishimoto T, Watanabe M, Sawayama H, Iwasaki M, Baba Y, et al. Identification of miR-30e regulation of BMI expression mediated by tumor-associated macrophages in gastrointestinal cancer. PLoS One. 2013;8(1):e58139. doi: 10.1371/journal.pone.0058139. [PubMed: 23432666]. [PubMed Central: PMC342972].

39. Dang Z, Xu WH, Lu P, Wu N, Liu J, Ruan B, et al. MicroRNA-15a induces cell proliferation by targeting BMI1 in pancreatic ductal adenocarcinoma. J Gastroenterol Hepatol. 2014;29(8):1707–13. doi: 10.1111/jgh.12602. [PubMed: 24808370]. [PubMed Central: PMC4359703].

40. Qiu X, Li J, Zhou C, Lv C, Tian M. MicroRNA-320a inhibits cell proliferation, migration and invasion by targeting BMI1 in nasopharyngeal carcinoma. FEBS Lett. 2014;588(20):3712–8. doi: 10.1016/j.febslet.2014.08.021. [PubMed: 2578660].

41. Peng G, Liao Y, Shen C. miRNA-429 Inhibits Astrocytoma Proliferation and Invasion by Targeting BMI1. Pathol Oncol Res. 2017;23(2):359–76. doi: 10.1007/s11604-016-0111-2. [PubMed: 27663885].

42. Chen W, Zhang B, Guo W, Gao L, Shi L, Li H, et al. miR-429 inhibits glioma invasion through BMKI suppression. J Neurooncol. 2015;125(3):435–45. doi: 10.1007/s11060-015-1887-x. [PubMed: 2627260].

43. Chan X, Sun Y, Han S, Zhu W, Zhang H, Lian S. MiR-200c inhibits melanoma invasive and proliferative abilities by targeting the polycomb group gene BMI1. Biochem Biophys Res Commun. 2015;456(3):360–6. doi: 10.1016/j.bbrc.2014.11.087. [PubMed: 25475727].

44. Liu S, TeztiJH, MT, Cui R, Xu X. MiR-200c inhibits melanoma progression and drug resistance through down-regulation of BMI-1. Am J Pathol. 2012;181(5):1823–35. doi: 10.1016/j.ajpath.2012.07.009. [PubMed: 22972826].
Liu L, Qiu M, Tan G, Liang Z, Qiu Y, Chen L, et al. miR-200c inhibits invasion, migration and proliferation of bladder cancer cells through down-regulation of BMI-1 and EZF3. J Transl Med. 2014;12(305). doi:10.1186/s12976-014-0305-2. [PubMed: 25367080]. [PubMed Central: PMC4226852].

Kopp F, Oak PS, Wagner E, Roidl A. miR-200c sensitizes breast cancer cells to doxorubicin treatment by decreasing TrkB and Bmi1 expression. PLoS One. 2012;7(11). e50469. doi:10.1371/journal.pone.0050469. [PubMed: 2329748]. [PubMed Central: PMC350380].

Luo H, Yang R, Li C, Tong Y, Fan L, Liu X, et al. MicroRNA-139-5p inhibits bladder cancer proliferation and self-renewal by targeting the Bmi1 oncogene. Tumour Biol. 2017;39(7):1.004283177814e+15. doi:10.17771/104283177814e+15. [PubMed: 28720065].

Sun L, Yao Y, Liu B, Lin Z, Lin Y, Yang M, et al. MiR-200b and miR-15b regulate chemotherapy-induced epithelial-mesenchymal transition in human tongue cancer cells by targeting Bmi1. Oncogene. 2012;31(4):432–45. doi:10.1038/onc.2011.263. [PubMed: 21725369].

He X, Dong Y, Wu CW, Zhao Z, Ng SS, Chan FK, et al. MicroRNA-218 inhibits cell cycle progression and promotes apoptosis in colon cancer by downregulating BMI1 polycomb ring finger oncogene. Mol Med. 2012;18(149):8. doi:10.1101/mmed.2012.00304. [PubMed: 3235074]. [PubMed Central: PMC3576472].

Ren L, Chen HY, Hong J, Fang Y. A master microRNA miR-508-3p modulates the mesenchymal subtype of colorectal cancer by targeting ZEB1/BMI1/SALL4 network. Clin Gastroenterol H. 2015;13(7). e81. doi:10.1016/j.cgh.2015.04.058.

Weng JH, Yu CC, Lee YC, Lin CW, Chang WW, Kuo YL. miR-494-3p induces cellular senescence and enhances radiosensitivity in human oral squamous carcinoma cells. Int J Mol Sci. 2016;17(7). doi:10.3390/ijms170707092. [PubMed: 27399693]. [PubMed Central: PMC4964468].

Xi S, Xu H, Shan J, Tao Y, Hong JA, Inchauste S, et al. Cigarette smoke mediates epigenetic repression of miR-487b during pulmonary carcinoma. J Clin Invest. 2013;123(12):1241–64. doi:10.1172/JCI61271. [PubMed: 23426183]. [PubMed Central: PMC3582015].

Colussi D, Brandi G, Bazzoli F, Ricciardiello L. Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. Int J Mol Sci. 2013;14(3):2635–85. doi:10.3390/ijms140302635. [PubMed: 23965595]. [PubMed Central: PMC3759916].

Li X, Zheng X, Xu B, Zhang D, Xu Y, Xie Q, et al. Lower Bmi-1 Expression May Predict Longer Survival of Colon Cancer Patients. Cell Physiol Biochem. 2016;39(6):2422–6. doi:10.1007/s00255-016-4520-9. [PubMed: 2765398].

Espersen ML, Linnemann D, Christensen IJ, Alamili M, Troelsen JT, Hogdall E. The prognostic value of polycomb group protein B-cell-specific moloney murine leukemia virus insertion site 1 in stage II colon cancer patients. APMS. 2016;124(7):541–6. doi:10.1111/apm.12539. [PubMed: 27026322].

Zhang X, Yang X, Zhang Y, Liu X, Zheng G, Yang Y, et al. Direct serum assay for cell-free bmi-1 mRNA and its potential diagnostic and prognostic value for colorectal cancer. Clin Cancer Res. 2015;21(5):1225–33. doi:10.1158/1078-0432.CCR-14-1761. [PubMed: 2554767].

Li DW, Tang HM, Fan JW, Yan DW, Zhou CZ, Li SX, et al. Expression level of Bmi-1 oncoprotein is associated with progression and prognosis in colon cancer. Cancer Res Clin Oncol. 2000;136(6):997–1006. doi:10.1007/s00432-009-0745-7. [PubMed: 20024662].

Alajez NM. Significance of BMI and FSCN1 expression in colorectal cancer. Saudi J Gastroenterol. 2016;22(4):288–93. doi:10.4103/1319-3767.187602. [PubMed: 2748823]. [PubMed Central: PMC4991199].

O’Brien CA, Pollerr A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature. 2007;445(7123):306–10. doi:10.1038/nature05372. [PubMed: 1722772].

Zeuner A, Todaro M, Stassi G, De Maria R. Colorectal cancer stem cells: from the crypt to the clinic. Cell Stem Cell. 2014;15(6):692–705. doi:10.1016/j.stem.2014.11.012. [PubMed: 25479747].

Yu T, Chen X, Zhang W, Colon D, Shi J, Napier D, et al. Regulation of the potential marker for intestinal cells, Bmi1, by beta-catenin and the zinc finger protein KLF4: implications for colon cancer. J Biol Chem. 2012;287(6):5760–80. doi:10.1074/jbc.M111.316349. [PubMed: 2270059]. [PubMed Central: PMC328178].

Chen D, Wu M, Li Y, Zhang X, Li M, Qi M, Kikuyama-Salvo M, et al. Targeting Bmi1(+)/Cancer Stem Cells Overcomes Chemoresistance and Inhibits Metastases in Squamous Cell Carcinoma. Cell Stem Cell. 2012;20(3):621–34 e6. doi:10.1016/j.stem.2012.07.003. [PubMed: 2282590]. [PubMed Central: PMC458906].

Scholch S, Garcia SA, Iwata N, Niemietz T, Betzler AM, Nanduri I, et al. Circulating tumor cells exhibit stem cell characteristics in an orthotopic mouse model of colorectal cancer. Oncotarget. 2016;7(19):27322–42. doi:10.18612/oncotarget.8373. [PubMed: 2702905]. [PubMed Central: PMC5053645].

Li Y, Wang I, Pappan I, Galliher-Beckley A, Shi J. Hb-beta promotes stemness and invasiveness of colon cancer cells through Zeb2 activation. Mol Cancer. 2012;12:187. doi:10.18632/oncotarget.4598-H1-87. [PubMed: 2374041]. [PubMed Central: PMC3552017].

Gao F, Huang W, Zhang Y, Yang T, Zheng L, Ma F, et al. Hes promotes cell proliferation and migration by activating Bmi1 and PTEN/AKT/GSK3beta pathway in human colon cancer. Oncotarget. 2015;6(36):38667–80. doi:10.18632/oncotarget.5484. [PubMed: 26452029]. [PubMed Central: PMC4770728].

Kreso A, Dick JE. Evolution of the cancer stem cell model. Cell Stem Cell. 2014;14(3):275–91. doi:10.1016/j.stem.2014.02.006. [PubMed: 24607043].

Chen J, Wang Y, Zhao L, Liu Z, Zuo Y, Li W, et al. Fas signaling induces stemness properties in colorectal cancer by regulation of Bmi1. Mol Carcinog. 2017;56(10). doi:10.1002/mc.22880. [PubMed: 2853447].

Jones MF, Hara T, Francis P, Li XL, Bilke S, Zhu Y, et al. The CDX1-microRNA-215 axis regulates colorectal cancer stem cell differentiation. Proc Natl Acad Sci U S A. 2015;112(13):41550–8. doi:10.1073/pnas.1503370112. [PubMed: 25775580]. [PubMed Central: PMC4386393].

Doman-Dell C, Schneider A, Moucadel V, Guerin E, Guenet D, Agullion S, et al. Cdt1 homeobox gene during human colon cancer progression. Oncogene. 2003;22(39):7913–21. doi:10.1038/sj.onc.1206756. [PubMed: 12970739].

Soheilifar MH et al. Int J Cancer Manag. 2018;11(9):e82926.