Iraqi JMS

Published by Al-Nahrain College of Medicine
P-ISSN 1681-6579
E-ISSN 2224-4719
Email: iraqijms@colmed.nahrainuniv.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net
Iraqi JMS 2023; Vol. 21(2)

Molecular Pathways That Involved in The Regulation of Some Cancer Initiating Cells: A Review

Afraa M. Mamoori[1] *PhD*, **Iqbal G. Farhood**[2] *FICMS, D&V*

[1]Dept. of Pathology and Forensic Medicine, College of Medicine, University of Babylon, Iraq, [2]Dept. of Medicine, College of Medicine, Al-Nahrain University, Baghdad, Iraq

Abstract

There are emerging data shows that different types of malignancies arising from cells called cancer initiating cells, which have self-renewal and tumorgenesity properties. Acquiring these properties make them able to initiate and transmit cancer. These cells are identified in different types of malignancies like stomach, colon, brain, breast and others. This review aims to identify the signaling pathways, which are involved in emerging these cells. Highly impact research papers regarding this subject were collected from trusted data base for analyzing. Analyzing these data identified that Notch, Hedgehog, high mobility group A2 (HMGA2), wingless/Int (Wnt)/B-catenin and epithelial mesenchymal transition (EMT) are the main signaling pathways, which are involved in this process. Targeting these signaling pathways will be a great technique to inhibit the formation of these cells. This will apply clinically as a treatment in different types of cancers and will be of great importance in treatment of cancers resisting chemotherapy.

Keywords Cancer stem cells (CSC), epithelial mesenchymal transition (EMT), chemotherapeutic, notch, hedgehog

Citation Mamoori AM, Farhood IG. Molecular pathways that involved in the regulation of some cancer initiating cells: A review. Iraqi JMS. 2023; 21(2): 166-171. doi: 10.22578/IJMS.21.2.3

List of abbreviations: CSC = Cancer stem cells, EMT = Epithelial mesenchymal transition, HMGA2 = High mobility group A2, MFCM = Myofibroblast-conditioned medium, TGFB = Tumor growth factor B, Wnt = Wingless/Int

Introduction

The concept of cancer initiating cells or what is called cancer stem cells (CSCs) and their role in initiation and progression of cancer become widely accepted in the area of cancer research. Stem cells, which initiate cancer, can be defined as "the cells, which have both self-renewal and differentiation capability" [(1)]. Identification of these cells were proved in different types of cancers like brain cancer, colorectal cancer, gastric cancer, and bronchogenic carcinoma. CSCs are similar to the normal stem cells in main properties, which include self-renewal and differentiation and differ from these cells by their ability to initiate and metastasis cancer [(2)]. Glycosylation is another new feature that can differentiate CSCs from normal stem cells, which proved by recent research [(3)]. In addition, CSCs can be identified and isolated from cancerous tissues by expression of their specific cell surface markers like CD24, CD29, CD44, CD 13, CD133, CD117, CD90 [(4)].

There are two different explanations to the origin of CSCs and both of them are accepted in the area of cancer research. Stem/progenitor cells can be the source of CSCs, also these cells can be derived from terminally differentiated

cells by acquiring several genetic lesions [5]. For last decades, researchers focused on studying these cells and try to uncover their role in different types of cancers, identifying their target genes and the way by which these cells exert their pathological roles.

This review aims to identify the signaling pathways, which are involved in initiating and regulating the function of cancer stem cells. To achieve this aim, Academic published papers related to this subject were collected from PubMed data base and analyzed to identify the most involved signaling pathways. The target transcripts were published between (2009-2022). Identifying these signaling will assist the scientists to develop treatments that antagonize the genes that involved in each pathway, subsequently inhibit this system and recover the patients with different types of cancers.

Signaling pathways of CSCs

There are growing evidences support that normal stem cells and CSCs act through the same signaling pathway, which is ultimately lead to the regulation of tumorigenic and metastatic properties of these cells [6]. Notch, Hedgehog, HMGA2, Wnt/B-catenin, Bcl-2, Bmil-1 signaling all are involved in this pathway [7]. On normal mammary stem cells, Notch signaling have been implicated in promote self-renewal so that participate in development of breast tissue [8]. Studies on cancer tissues showed that this pathway is upregulated in breast cancer [9] and colonic cancer [10] (Figure 1).

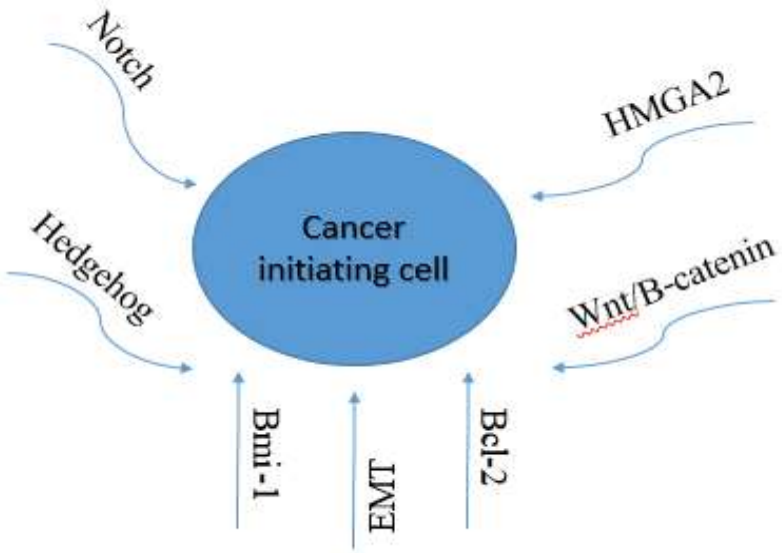

Figure 1. Signaling pathways that involved in regulation cancer initiating cells

Hedgehog signaling has implicated in self-renewal and the evidence, which shows the importance of this pathway in normal stem cells, appears when Drosophila ovarian stem cells cannot proliferate in vitro without Hedgehog signaling [11]. Studies on cancerous tissues reveal that this pathway is up regulated in colon cancer [12], pancreatic cancer [13]. Furthermore, studies showed that the upregulation of these pathways is not the same all over the cancerous tissues and it appear significantly upregulated in CSCs [14]. The upregulation of Hedgehog signaling pathway is more in pancreatic CSCs than in the other

surrounding tumor tissue [14]. Moreover, researchers state that Hedgehog pathway plays essential role in self-renewal properties of both normal and CSCs of breast tissue [15].

Wnt/B-catenin pathway is essential for normal stem cells development [16]. Study stated that this pathway is necessary for normal colonic stem cells [17]. In addition, the same study demonstrated that the Wnt pathway is upregulated in colonic cancer tissue and colonic cancer stem cells showed more expression to this pathway than the surrounding malignant tissues [17]. This study also concluded that CSCs of colonic cancer can be created from more differentiated tumor cells by enhancing Wnt activity [17]. Its role is also documented in breast cancer stem cells; it plays a crucial role in stemness by targeting the microenvironment [18].

Bcl-2 has been investigated in both normal stem cells and CSCs. Studies revealed that the Bcl-2 protein family is essential to maintain the balance between cells survival and apoptosis [19]. Bcl-2 is a crucial for survival of hematopoietic stem cells, renal epithelial progenitors, melanocyte progenitors [20]. Research demonstrated that leukemic CD34+ progenitor cells are highly expressed Bcl-2 and the level of expression is much higher than in more differentiated malignant cells [21]. Furthermore, data revealed the higher expression for this protein family in breast CSCs than other breast cancer tissue [22].

Another regulator of stemness is Bmi-1, which is belong to the Polycomb group of transcriptional suppressors, it is also one of epigenetic factors [23]. Its role in maintain self-renewal feature of stem cells has been widely understood in different types of normal and malignant tissue. Self-renewal and maintenance of stem cells have been strongly related to stabilizing the level of Bmi-1 [24]. Suppression the level of Bmi-1 inhibits the ability of colorectal CSCs to self-renewal and lead eventually to block their tumorigenicity [25]. Moreover, exposure of colorectal cancer xenografts to the BMI-I inhibitor result in long term cancer free graft [26]. It is clear that the signaling pathways, which regulate the stemness features of stem cells will enhance tumor formation and even lead to develop CSCs from more differentiated cells.

Epithelial-mesenchymal transition (EMT) is a new pathway to generate cancer cells with stem cell-like properties

Involving of EMT in tumor development, metastasis and resistance to the therapeutic treatment extends to include its ability to create cells with stem like properties from more differentiated tumor cells. EMT can be defined as "the ability of some cancer epithelial cells to lose their differentiated properties and instead have the mesenchymal features, which include liability to motile, invade and a resist apoptosis" [27]. Several studies focused on impacts of this complex system on the several types of the tumors. Researchers demonstrated that the patients with non-small cell lung cancer who showed bad prognosis is due to promoting tumor EMT [28]. Furthermore, proved data demonstrated that EMT promotes invasiveness and metastasis of nasopharyngeal carcinoma both in-vitro and in-vivo [29]. Other evidences start to accumulate regarding the crucial role of EMT in development of CSCs from more differentiated cells. For example, EMT generates CSCs from more differentiated tumor cells by promoting factors Snail or Twist and this process will revert when EMT signaling are not sustained [30]. In addition, restoration of clonogenic potential of differentiated colonic cancer cells and re expression of CSCs markers in these cells is achieved by exposure of these terminally differentiated cells to myofibroblast-conditioned medium myofibroblast-conditioned medium (MFCM) [31]. Moreover, data verified that non-stem cells are liable to convert to stem cells under several circumstances [31].

Despite the fact that the initiation and maintain the EMT involve a network of interactions in which tumor growth factor B

(TGFB) is critical inducer of such process, Notch, Wnt and Hedgehog signaling can induce and regulate the EMT through complex processes [32]. TGFB can induce EMT by producing multiple signaling, which are finally led to phosphorylate suppressor of mothers against decapentaplegic (SMAD) transcription factors and certain cytoplasmic proteins which are involved in maintain cells polarity and cells adhesion properties [33]. Enhancement of nuclear factor-KB (NF-KB) pathway or activation of TGFB is the way in which Notch signaling pathway induce EMT [7]. Wnt signaling pathway act by inducing specific genes' crucial role to induce EMT, this happens by increasing the level of B-catenin, which consequently translocate to the nucleus [34]. Sonic Hedgehog pathway, controls EMT by knockdown E-cadherin expression [35]. It is obvious that the signaling pathway, which regulates the cancer stem cells properties, can also regulate the EMT program.

Applying the signaling pathways in colonic CSCs development as an example

Studies on both mice and human being demonstrated that Wnt and Notch signaling are involved more than other signaling pathways in both normal and CSCs of colonic tissue [36]. Pathway involving canonical Wnt signaling is involved extensively in regulation normal intestinal stem cells and more recently colonic CSCs [36]. Wnt exert its effect on intestinal hemostasis via regulation of stem cell loop [37]. In addition, Wnt is involved in the development, maintenance and proliferation of intestinal crypts [37]. This pathway involved in colon cancer by implication of adenomatous polyposis colorectal (APC) gene as the main cause of familial adenomatous polyposis syndrome, this disease, which is in turn predispose to the colon cancer [17].

Other pathway, which participate in regulation of intestinal stem cells is Notch; its role is proved in research, for example, specifying the lineage differentiation and promoting the self-renewal of colonic stem cells are attributed to Notch signaling pathway [38]. Moreover, stimulation of progenitor cells proliferation and division occur due to activation of this pathway [٣٨]. Furthermore, over expression of this pathway raise the clonogenicity and minimize the programmed cell death in colonic cancer [39]. Wnt and Notch signaling pathways can interact with each other to exert more regulatory process on colorectal cancer stem cells [7] (Figure 2).

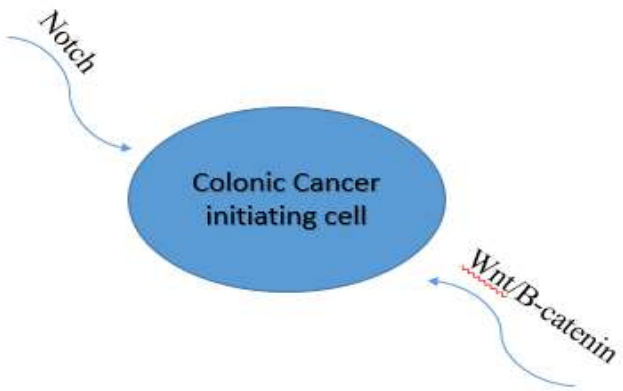

Figure 2. The main signaling pathways that involved in regulation of colonic cancer initiating cells

Conclusion

It is clear that CSCs developed and act via Notch, Hedgehog, HMGA2, Wnt/B-catenin, Bcl-2, Bmil-1 and EMT. These signaling are involved in normal stem cells formation and function too. From above published data, it is clear that Wnt and Notch signaling pathways are the most studied pathways in mechanism of colon cancer stem cells regulation. Understanding the pathways that lead to develop CSCs is very essential to target these cells as treatment for different types of malignancies especially those with resistance to chemotherapeutic treatment.

References

1. Nassar D, Blanpain C. Cancer stem cells: Basic concepts and therapeutic implications. Annu Rev Pathol. 2016 May 23; 11: 47-76. doi: 10.1146/annurev-pathol-012615-044438.
2. Lathia JD, Liu H. Overview of cancer stem cells and stemness for community oncologists. Target Oncol. 2017; 12(4): 387-99. doi: 10.1007/s11523-017-0508-3.
3. Barkeer S, Chugh S, Batra SK, et al. Glycosylation of Cancer stem cells: function in stemness, tumorigenesis, and metastasis. Neoplasia. 2018; 20(8): 813-25. doi: 10.1016/j.neo.2018.06.001.
4. Kim WT, Ryu CJ. Cancer stem cell surface markers on normal stem cells. BMB Rep. 2017; 50(6): 285-98. doi: 10.5483/bmbrep.2017.50.6.039.
5. Walcher L, Kistenmacher AK, Suo H, et al. Cancer stem cells-origins and biomarkers: Perspectives for targeted personalized therapies. Front Immunol. 2020; 11: 1280. doi: 10.3389/fimmu.2020.01280.
6. Matsui WH. Cancer stem cell signaling pathways. Medicine (Baltimore). 2016; 95(1 Suppl 1): S8-S19. doi: 10.1097/MD.0000000000004765.
7. Kumar V, Vashishta M, Kong L, et al. The role of Notch, Hedgehog, and Wnt signaling pathways in the resistance of tumors to anticancer therapies. Front Cell Dev Biol. 2021; 9: 650772. doi: 10.3389/fcell.2021.650772.
8. Wang Z, Li Y, Banerjee S, Sarkar FH. Emerging role of Notch in stem cells and cancer. Cancer Lett. 2009; 279(1): 8-12. doi: 10.1016/j.canlet.2008.09.030.
9. Edwards A, Brennan K. Notch signaling in breast development and cancer. Front Cell Dev Biol. 2021; 9: 692173. doi: 10.3389/fcell.2021.692173.
10. Vinson KE, George DC, Fender AW, et al. The Notch pathway in colorectal cancer. Int J Cancer. 2016; 138(8): 1835-42. doi: 10.1002/ijc.29800.
11. Jia Y, Wang Y, Xie J. The Hedgehog pathway: Role in cell differentiation, polarity and proliferation. Arch Toxicol. 2015; 89(2): 179-91. doi: 10.1007/s00204-014-1433-1.
12. Wu C, Zhu X, Liu W, et al. Hedgehog signaling pathway in colorectal cancer: function, mechanism, and therapy. Onco Targets Ther. 2017; 10: 3249-59. doi: 10.2147/OTT.S139639.
13. Lee JJ, Perera RM, Wang H, et al. Stromal response to Hedgehog signaling restrains pancreatic cancer progression. Proc Natl Acad Sci U S A. 2014; 111(30): E3091-100. doi: 10.1073/pnas.1411679111.
14. Onishi H, Katano M. Hedgehog signaling pathway as a new therapeutic target in pancreatic cancer. World J Gastroenterol. 2014; 20(9): 2335-42. doi: 10.3748/wjg.v20.i9.2335.
15. Zhang T, Zhou H, Wang K, et al. Role, molecular mechanism and the potential target of breast cancer stem cells in breast cancer development. Biomed Pharmacother. 2022; 147: 112616. doi: 10.1016/j.biopha.2022.112616.
16. Nusse R, Clevers H. Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. Cell. 2017; 169(6): 985-99. doi: 10.1016/j.cell.2017.05.016.
17. Zhao H, Ming T, Tang S, et al. Wnt signaling in colorectal cancer: pathogenic role and therapeutic target. Mol Cancer. 2022; 21(1): 144. doi: 10.1186/s12943-022-01616-7.
18. Xu X, Zhang M, Xu F, et al. Wnt signaling in breast cancer: biological mechanisms, challenges and opportunities. Mol Cancer. 2020; 19(1): 165. doi: 10.1186/s12943-020-01276-5.
19. Shamas-Din A, Kale J, Leber B, et al. Mechanisms of action of Bcl-2 family proteins. Cold Spring Harb Perspect Biol. 2013; 5(4): a008714. doi: 10.1101/cshperspect.a008714.
20. Kelly PN, Strasser A. The role of Bcl-2 and its pro-survival relatives in tumourigenesis and cancer therapy. Cell Death Differ. 2011; 18(9): 1414-24. doi: 10.1038/cdd.2011.17.
21. Konopleva M, Zhao S, Hu W, et al. The anti-apoptotic genes Bcl-X(L) and Bcl-2 are over-expressed and contribute to chemoresistance of non-proliferating leukaemic CD34+ cells. Br J Haematol. 2002; 118(2): 521-34. doi: 10.1046/j.1365-2141.2002.03637.x.
22. Zhou QM, Sun Y, Lu YY, et al. Curcumin reduces mitomycin C resistance in breast cancer stem cells by regulating Bcl-2 family-mediated apoptosis. Cancer Cell Int. 2017; 17: 84. doi: 10.1186/s12935-017-0453-3.
23. Sahasrabuddhe AA. BMI1: A Biomarker of Hematologic Malignancies. Biomark Cancer. 2016; 8: 65-75. doi: 10.4137/BIC.S33376.
24. Jiang L, Li J, Song L. Bmi-1, stem cells and cancer. Acta Biochim Biophys Sin (Shanghai). 2009; 41(7): 527-34. doi: 10.1093/abbs/gmp040.
25. Xu J, Li L, Shi P, et al. The crucial roles of Bmi-1 in cancer: Implications in pathogenesis, metastasis, Drug resistance, and targeted therapies. Int J Mol Sci. 2022; 23(15): 8231. doi: 10.3390/ijms23158231.
26. Kreso A, van Galen P, Pedley NM, et al. Self-renewal as a therapeutic target in human colorectal cancer. Nat Med. 2014; 20(1): 29-36. doi: 10.1038/nm.3418.

27. Ribatti D, Tamma R, Annese T. Epithelial-mesenchymal transition in cancer: A historical overview. Transl Oncol. 2020; 13(6):100773. doi: 10.1016/j.tranon.2020.100773.

28. Ortiz-Cuaran S, Swalduz A, Foy JP, et al. Epithelial-to-mesenchymal transition promotes immune escape by inducing CD70 in non-small cell lung cancer. Eur J Cancer. 2022; 169: 106-22. doi: 10.1016/j.ejca.2022.03.038.

29. Wang J, Zhong Q, Zhang H, et al. Nogo-B promotes invasion and metastasis of nasopharyngeal carcinoma via RhoA-SRF-MRTFA pathway. Cell Death Dis. 2022; 13(1): 76. doi: 10.1038/s41419-022-04518-0.

30. Huang Y, Hong W, Wei X. The molecular mechanisms and therapeutic strategies of EMT in tumor progression and metastasis. J Hematol Oncol. 2022; 15(1): 129. doi: 10.1186/s13045-022-01347-8.

31. Colak S, Medema JP. Human colonic fibroblasts regulate stemness and chemotherapy resistance of colon cancer stem cells. Cell Cycle. 2016; 15(12): 1531-7. doi: 10.4161/15384101.2014.973321.

32. Zhang J, Tian XJ, Xing J. Signal Transduction Pathways of EMT Induced by TGF-β, SHH, and WNT and Their Crosstalks. J Clin Med. 2016; 5(4): 41. doi: 10.3390/jcm5040041.

33. Derynck R, Muthusamy BP, Saeteurn KY. Signaling pathway cooperation in TGF-β-induced epithelial-mesenchymal transition. Curr Opin Cell Biol. 2014; 31: 56-66. doi: 10.1016/j.ceb.2014.09.001.

34. Liu J, Xiao Q, Xiao J, et al. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther. 2022; 7(1): 3. doi: 10.1038/s41392-021-00762-6.

35. Xiao C, Ogle SA, Schumacher MA, et al. Hedgehog signaling regulates E-cadherin expression for the maintenance of the actin cytoskeleton and tight junctions. Am J Physiol Gastrointest Liver Physiol. 2010; 299(6): G1252-65. doi: 10.1152/ajpgi.00512.2009.

36. Perochon J, Carroll LR, Cordero JB. Wnt signaling in intestinal stem cells: Lessons from mice and flies. Genes (Basel). 2018; 9(3): 138. doi: 10.3390/genes9030138.

37. Walter RJ, Sonnentag SJ, Munoz-Sagredo L, et al. Wnt signaling is boosted during intestinal regeneration by a CD44-positive feedback loop. Cell Death Dis. 2022; 13(2): 168. doi: 10.1038/s41419-022-04607-0.

38. Baulies A, Angelis N, Li VSW. Hallmarks of intestinal stem cells. Development. 2020; 147(15): dev182675. doi: 10.1242/dev.182675.

39. Meisel CT, Porcheri C, Mitsiadis TA. Cancer stem cells, quo vadis? The Notch signaling pathway in tumor initiation and progression. Cells. 2020; 9(8): 1879. doi: 10.3390/cells9081879.

Correspondence to Dr. Iqbal G. Farhood
E-mail: driqbalderma30@gmail.com
driqbalderma30@nahrainuniv.edu.iq

Received Mar. 19th 2023
Accepted Jun. 18th 2023