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DEVELOPMENT OF CANCER, ITS THERAPY AND PROGRESSION

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Abstract:
The uncontrolled cell growth, knows as carcinogenesis, following the activation of oncogenes along with deactivation of cancer suppression genes. Down-regulation of cell adhesion receptors that are important for the tissue-specific, attachment of cell-to-cell just as up-regulation of receptors that improve motility, is required in metastasis.
The epigenetic changes, including modification of histone, methylation and hydro methylation of DNA, help to modify these characteristics. Focuses for these changes incorporate signaling pathways, which control apoptosis and autophagy, just as micro-RNA. We say that the normal predisposed cells, converts to cancerous progenitor cell, which, after growing, go through an epithelial-mesenchymal conversion. This cycle, which is commonly under the control of epigenetic changes, can make a metastatic type of both progenitor and full-fledged cancer cells, after which metastasis to a removed place may happen. Potential therapeutic avenues have been provided by the recognition of epigenetic regulatory process. The action of traditional therapeutics was potentiated more specifically due to these epigenetic drugs. These epigenetic drugs inhibit the formation and development of cancer progenitor cells. Hence, it represses the recurrence of cancer. Receiving epigenetic adjustment as another sign of malignancy is an intelligent and vital advance that will additionally empower the improvement of novel epigenetic biomarkers and therapeutics.

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1. INTRODUCTION:

As identified by the first hallmarks of disease, six unique capacities lead to cancer development and its progression. [1] Development of cancer as a conceptual understanding in biology in the past ten years has provided spectacular suggestion in reprogramming the metabolism and avoidance of immune destruction to be considered as additional signs. [2] We suggest studying the epigenetic changes for the next generation or upcoming cancer therapies because it is considered to be another hallmark of cancer.

Cancer is the uncontrolled growth of cell and accession of metastatic characteristics. Mostly, the uncontrolled progression of the cell cycle and the apoptotic mechanism inactivation is due to the oncogene's activation and tumor suppressor genes deactivation. Instead of benign tumors, threatening malignant tumor growths gain metastasis, down-regulation of cell adhesion receptors that are important for the tissue-specific, attachment of cell-to-cell just as up-regulation of receptors that improve motility. In addition, initiation of layer metalloproteases gives an actual pathway to metastatic malignancy cells to spread. There are various instruments by which these genetic and cellular changes happen. The sanctioned mechanisms are transformation, chromosomal movement, and dysregulated articulation or action of signaling pathways. The dysregulated process of cell and inactive apoptotic pathways are promoted by the genes activated in this process. These occasions may enact qualities that advance dysregulated cell cycling as well as inactivate apoptotic pathways. These cycles are very much portrayed in the current writing, and various fantastic surveys are accessible on every subject. [3, 4] These events may activate genes that promote dysregulated cell cycling and/or inactivate apoptotic pathways. These processes are well introduced in the existing literature, and various other reviews are available on each of these topics. [3, 4]

The part of epigenetics in carcinogenesis are less well known. Ongoing examinations propose that epigenetic adjustment might be another sign of malignant growth because of its function in the development of disease progenitor cells and resulting inception of carcinogenesis. Such alterations are covalent, and may influence histones or DNA buildups. We as of late recommended another worldview for malignant growth movement in which epigenetic changes assume a vital function in the improvement of this clinically critical cell highlights. [5] Epigenetic changes can initiate supportive of malignancy qualities in even transformation free cells. [6] In this survey, we will underline the function of epigenetics in carcinogenesis and the potential therapeutics got from this viewpoint. We likewise estimate a model for the improvement of metastatic malignant growth of progenitor cells from non-metastatic ones.

1. DNA Methylation

Epigenetic changes are the changes in gene expression without changing DNA sequence. The epigenetic changes, including modification of histone, methylation and hydro methylation of DNA help to modify these characteristics. DNA methylation by interfering with the transcriptional machinery at CpG islands, has been appearing to silence gene expression. [7, 8]

For the past many years, tumor development was thought to be a purely genetic process, but now, there are evidences revealing much of its complexity depends upon epigenetics. [9] Cell cycle controllers, for example, p16, p21, p27, and p53, are hushed by methylation in numerous diseases [10–12]. RAR-β2, one of the significant initiators of separation, is additionally quieted in numerous types of malignancy. [9-12]

2. Hydroxymethylation

The recent revelation of "5-hydroxymethylcytosine (5hmC)" in human tissue has resulted in significant interest in the various possible functions of this new DNA modification. [13] The mechanism by which 5hmC is generated has uncovered through computational searches: "TET-mediated hydroxylation of 5-methylcytosine (5mC) to 5hmC." [14] The TET family comprises of TET1, TET2, and TET3; all of them contain an alpha-ketoglutarate- and Fe (II) -dependent dioxygenase. Only TET1 and TET3 possess an intrinsic CXXC DNA binding domain. The TET2 CXXC domain seems to have been isolated from TET2 by chromosomal rearrangement and is expressed separately as IDAX, which binds to unmethylated CpG-rich regions and negatively regulates TET2. [15]

3. Autophagy and Apoptosis

The inhibition of cancer cell apoptosis is resulted from the silencing of tumor suppressor genes. These genes hinder the tumor progression, which is inhibited by epigenetic silencing. Apoptosis is a regulated phenomenon of cell death. The normal maintenance and development of cells in the normal and natural organisms depends upon the phenomenon of apoptosis. In cancer, the deregulation of normal genes occurs. There are two pathways of apoptosis, one is intrinsic pathway and the other is extrinsic pathway. In intrinsic pathway, the imbalance between Bcl2 and BAX occurs. A large amount of

BAX enters the mitochondrial membrane to cytochrome c through Apaf-1 pathway. [16] Cytochrome-c then, activates the caspase 3 through caspase 9. Which triggers the proteolysis of proteins and as a result cell-death occurs. This whole path is managed by some regulators known as Bcl-2 and XIAP. The Bcl-2 is anti-apoptotic by nature. It is up-regulated in the case of cancer. [17] The extrinsic pathway is started by some cell surface death receptors. The ligands of these receptors are of the family of TNF-α through Jun-Kinase (JNK) to create apoptosis. This process is oppositely regulated by $FLIP_L$ and $FLIP_s$.[18]

4. MicroRNA

These are non-coding types of RNA. It is comprised of about 20 nucleic acids. Their function is to regulate the messenger RNA by attaching with 3' un-translated region of mRNA. They trigger the degradation and stopping the translation. In both manners, the opposing relationship occurs among miRNA and its expression of the targeted mRNA. In spite of the specificity in the attachment to the 3' UTR, any miRNA can aim various mRNAs. [19] The down-streaming of the targets of miRNAs is a highly researched area now-a-day.

5. Epithelial Mesenchymal Transition

The epithelial cancers propagation from the beginner cells to mature cells is done by an Epithelial-Mesenchymal Transition (EMT). It is categorized by a reduction in cell-cell attachment and greater cell motility. The cell-cell adhesion receptors are down-regulated while the opposite occurs for cell motility receptors. [20, 21] For example ligands, integrins and E-cadherin. The EMT is associated with overexpression of surface metalloprotease. They degrade the matrix and allow the motility of cells having mesenchymal features. This process is essential for metastasis. [20, 21]

6. Model for Epigenetics in Progression, Carcinogenesis and Metastasis

New research shows that the expansion of cancer happens from the stem cells. Weinberg *et al.* states that, a small number of stem cells in the population of tumor cells, get the metastatic potential by intrinsic manner. [22] This way to spread occurs through reactive stroma. These cells then move to the different organs. It is hypothesized that the metastatic progenitor cells and metastatic cancer cells move to various areas. The manner of spread of such cells is also reviewed. It is believed that the progression and acquisition of cancer cells require differentiation. The epigenetic changes help in the development of progenitor cells from depositing cancer cells. These epigenetic changes are responsible for the epithelial mesenchymal transition.

7. Clinical Features of Cancer and Therapeutics

The formation of cancer is very challenging for inter as well as intra patient heterogeneity. The therapies which target on the specific market like Her-2 in the case breast cancer or fused BCR-ABL in the case of CML, effects until the resistant cell become dominant. The novel drug development includes targeting of more than one target. It is hypothesized that the exposure to lower doses of non-epigenetic and epigenetic drugs should stimulate the tumor cells as compared to traditional drugs. [5]

For example, HDACi stimulates the ovarian and breast tumor cell underlines to calpeptin, TRAIL or other homolog oligonucleotides. [23-25] The demethylating chemicals treat the ovarian tumor cells as compared to traditional platinum-based chemical agents. [26]

8. CONCLUSION:

The role of epigenetics changes on various cancers is being observed in this article. The mechanism of formation of metastatic progenitor cancer cells from the novel cancer progenitor cells is also discussed. Some processes like "hypomethylation of oncogenes," "hypermethylation of tumor suppressor genes," "depletion of hydroxy methylation," "changes of histone acetylation and methylation patterns," and "miRNA expression level" are attached with numerous cancers. Some studies show that how these changes are initiated and how they affect the development of "metastatic tumor progenitor cells." This information is necessary for understanding the cancer cell transformation and getting the resistance of chemotherapy. This will help in designing of the new and potent drugs. The new drugs along with traditional drugs are effective in the treatment of cancers. The main aim of this article is to analyze the main targets of drugs and reduction of mortality rate of cancer patients.

9. REFERENCES:

1. Hanahan D., Weinberg R.A. The hallmarks of cancer. Cell. 2000;100:57–70. [PubMed] [Google Scholar]
2. Hanahan D., Weinberg R.A. Hallmarks of cancer: The next generation. Cell. 2011;144:646–674. [PubMed] [Google Scholar]
3. Fearon E.R., Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759–767. [PubMed] [Google Scholar]
4. Vogelstein B., Kinzler K.W. Cancer genes and the pathways they control. Nat.

Med. 2004;10:789–799. [PubMed] [Google Scholar]
5. Sarkar S., Goldgar S., Byler S., Rosenthal S., Heerboth S. Demethylation and re-expression of epigenetically silenced tumor suppressor genes: Sensitization of cancer cells by combination therapy. Epigenomics. 2013;5:87–94. [PubMed] [Google Scholar]
6. Gal-Yam E.N., Saito Y., Egger G., Jones P.A. Cancer epigenetics: Modifications, screening, and therapy. Annu. Rev. Med. 2008;59:267–280. [PubMed] [Google Scholar]
7. Bird A.P. CpG-rich islands and the function of DNA methylation. Nature. 1986;321:209–213. [PubMed] [Google Scholar]
8. Merlo A., Herman J.G., Mao L., Lee D.J., Gabrielson E., Burger P.C., Baylin S.B., Sidransky D. 5′ CpG island methylation is associated with transcriptional silencing of the tumour suppressor p16/CDKN2/MTS1 in human cancers. Nat. Med. 1995;1:686–692. [PubMed] [Google Scholar]
9. Taby R., Issa J.P. Cancer epigenetics. CA Cancer J. Clin. 2010;60:376–392. [PubMed] [Google Scholar]
10. Issa J.P. Cancer prevention: Epigenetics steps up to the plate. Cancer Prev. Res. (Phila.) 2008;1:219–222. [PubMed] [Google Scholar]
11. Ren M., Pozzi S., Bistulfi G., Somenzi G., Rossetti S., Sacchi N. Impaired retinoic acid (RA) signal leads to RARβ2 epigenetic silencing and RA resistance. Mol. Cell. Biol. 2005;25:10591–10603. [PMC free article] [PubMed] [Google Scholar]
12. Jones P.A., Baylin S.B. The fundamental role of epigenetic events in cancer. Nat. Rev. Genet. 2002;3:415–428. [PubMed] [Google Scholar]
13. Kriaucionis S., Heintz N. The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. Science. 2009;324:929–930. [PMC free article] [PubMed] [Google Scholar]
14. Tahiliani M., Koh K.P., Shen Y., Pastor W.A., Bandukwala H., Brudno Y., Agarwal S., Iyer L.M., Liu D.R., Aravind L., et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science. 2009;324:930–935. [PMC free article] [PubMed] [Google Scholar]
15. Ko M., An J., Bandukwala H.S., Chavez L., Aijo T., Pastor W.A., Segal M.F., Li H., Koh K.P., Lahdesmaki H., et al. Modulation of TET2 expression and 5-methylcytosine oxidation by the CXXC domain protein IDAX. Nature. 2013;497:122–126. [PMC free article] [PubMed] [Google Scholar]
16. Adams J.M., Cory S. The Bcl-2 protein family: Arbiters of cell survival. Science. 1998;281:1322–1326. [PubMed] [Google Scholar]
17. Kaufmann T., Strasser A., Jost P.J. Fas death receptor signalling: Roles of Bid and XIAP. Cell Death Differ. 2012;19:42–50. [PMC free article] [PubMed] [Google Scholar]
18. Subramaniam K., Hirpara J.L., Tucker-Kellogg L., Tucker-Kellogg G., Pervaiz S. FLIP: A flop for execution signals. Cancer Lett. 2013;332:151–155. [PubMed] [Google Scholar]
19. Krek A., Grun D., Poy M.N., Wolf R., Rosenberg L., Epstein E.J., MacMenamin P., da Piedade I., Gunsalus K.C., Stoffel M., et al. Combinatorial microRNA target predictions. Nat. Genet. 2005;37:495–500. [PubMed] [Google Scholar]
20. Thiery J.P. Epithelial-mesenchymal transitions in tumour progression. Nat. Rev. Cancer. 2002;2:442–454. [PubMed] [Google Scholar]
21. 87. Wendt M.K., Allington T.M., Schiemann W.P. Mechanisms of the epithelial-mesenchymal transition by TGF-β Future Oncol. 2009;5:1145–1168. [PMC free article] [PubMed] [Google Scholar]
22. Chaffer C.L., Weinberg R.A. A perspective on cancer cell metastasis. Science. 2011;331:1559–1564. [PubMed] [Google Scholar]
23. Sarkar S., Faller D.V. Telomere-homologous G-rich oligonucleotides sensitize human ovarian cancer cells to TRAIL-induced growth inhibition and apoptosis. Nucleic Acid Ther. 2013;23:167–174. [PMC free article] [PubMed] [Google Scholar]
24. Sarkar S., Faller D.V. T-oligos inhibit growth and induce apoptosis in human ovarian cancer cells. Oligonucleotides. 2011;21:47–53. [PMC free article] [PubMed] [Google Scholar]
25. Frew A.J., Lindemann R.K., Martin B.P., Clarke C.J., Sharkey J., Anthony D.A., Banks K.M., Haynes N.M., Gangatirkar P., Stanley K., et al. Combination therapy of established cancer using a histone deacetylase inhibitor and a TRAIL receptor agonist. Proc. Natl. Acad. Sci. USA. 2008;105:11317–11322. [PMC free article] [PubMed] [Google Scholar]
26. Matei D.E., Nephew K.P. Epigenetic therapies for chemoresensitization of epithelial ovarian cancer. Gynecol. Oncol. 2010;116:195–201. [PMC free article] [PubMed] [Google Scholar].