

Review Paper

New Approaches to Colorectal Cancer Treatment; an Overview

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ABSTRACT

Colorectal cancer (CRC) is the third major cause of cancer death globally, with about 694,000 deaths each year. Recent studies have shown that cancer stem cells (CSCs) play an important role in cancer relapse and metastasis. Inhibition of COX-2, Wnt / beta-catenin, HIF-1 alpha, K-Ras, NF- κ B, P53 signaling pathways and activation of TGF- β are amongst proposed strategies against colorectal cancer. Specific markers of CSCs including CD133, CD24, CD29, CD44 and Lgr5 are also of importance in diagnosis and monitoring of the disease. Therefore, the use of nanoparticles can be discussed in two different fields: 1. using nanoparticles in diagnosis and targeting CSCs, 2. targeting the cancer cells directly, where nanoparticles can affect the cell signaling pathways and expression patterns to prevent extension of tumor cells. In addition, nanoparticles can be used as the carriers for anti-cancer drugs and drug delivery, which in turn may enhance effectiveness of treatment. This review covers the novel signaling pathways in colorectal cancer and also gives a brief explanation about the role of some nanostructures that enhance treatment efficiency.

Keywords: Colorectal Cancer, Cancer Stem cell, Cell Signalling, Nanoparticle, CD133, CD24, CD29, CD44, Lgr5

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Cancer is a leading cause of death worldwide. Due to substantial improvements in early detection and treatment, the mortality rate has decreased in recent years, but treatment of many cases remains quite sophisticated (1). Colorectal cancer is the third major cause of cancer deaths in the United States both in men and women. Novel therapeutic strategies are under investigation including using nanoparticles (2). In this brief review different aspects of using nanoparticles in colorectal cancer stem cell are discussed.

Cancer Stem Cell

Cancer stem cells (CSCs) are small subpopulations of tumor cells responsible for the spread of cancer and tumor growth in a very efficient manner (3). Perhaps one of the most important causes of relapse and resistance to treatment is that the CSCs are not affected despite the administration of common therapeutic agents (4). CSCs have the ability of infinite self-renewal and the capacity to differentiate into the various populations of cells that comprise a tumor.

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Self-renewal refers to the ability to create new stem cells with the same properties such as potential proliferation, development, and differentiation, thereby maintaining the stem cell population. Induction of cancer stem cells to differentiate, may result in removal of their ability of self-renewal (5). A niche is a special microenvironment where stem cells are stored and characterized with having different factors that can control stem cell proliferation and determination. In general, the niche is kept in a state of stasis by creating a signal that inhibits the growth and proliferation of stem cells (6). Stem cells can only get activated in presence of the excitation signals which make them start dividing and going into proliferation. Therefore the balance between proliferation and inhibitory signals is the key for stem cell homeostasis. Any disruption increases the risk of developing tumors (7).

Colorectal Cancer Stem Cells and Markers

Several studies identified a subpopulation of colorectal cancer cells that are more resistant to cancer treatment methods (such as chemotherapy and radiation therapy). Effective treatment depends on the elimination of these resistant subpopulations. These cancer stem cells or tumor-initiating cells have several highly expressed markers on their cell surface (8). Important markers in colorectal cancer stem cells are CD24, CD29, LGR5, CD133 and CD44 (9).

CD24 is a cell surface protein that is attached to the outer plasma membrane. CD24⁺ subpopulations have cancer stem cell-like properties such as increased resistance to chemotherapy, self-renewal and potential tumorigenesis both in vitro and in vivo, compared to CD24⁻ cell subpopulations (10).

CD29 (B1- integrin) is a member of the integrin family and contains a large extracellular and a short cytoplasmic domain that acts as a receptor for extracellular matrix proteins. It also activates signaling pathways to regulate cell migration, proliferation, permanence, differentiation and death. CD29 also plays a role in the higher activity of colorectal cancer cell metastasis (11).

LGR5 is a member of the Wnt signaling pathway. Although its ligand is unclear, it is one of the stem cell markers in the intestinal crypts. The findings show that LGR5 could play a key role in the development of CRC and may be considered as a useful marker for identifying and / or targeting colorectal cancer stem cells (11).

CD133 (or prominin-1) is a glycoprotein which is encoded by the PROM1 gene in humans. While the accurate function of CD133 is not clear yet, it appears to act as an organizer of the cell membrane topology. However, the findings indicate that CD133 plays a key role in the initiation and progression of colorectal cancer and can be used as a marker of prognosis and diagnosis of CRC (10, 12).

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assembly of growth factors on the cell surface. Research has shown that CD44 could have a more decisive role in the tumorigenesis of colorectal cancer cells. Furthermore, active participation in many cellular activities, such as survival, differentiation, and migration are some other properties of CD44 (10, 13).

An effective treatment should be able to target all the different microenvironments of colon cancer stem cells in tumours to inhibit primary tumor growth, metastasis and recurrence of cancer. A promising method for increasing the efficiency of the treatment, is the use of nanoparticles in the diagnosis and treatment process. Biocompatible nanoparticles are conjugated with specific monoclonal antibodies against CCSC markers and also are capable of carrying drugs or small selectively directed RNAs to silence fundamental molecules for CCSC survival (14).

There are monoclonal antibodies such as specific anti-human CD133 mAb, anti human CD29 monoclonal antibody-clone 12G10, SWA11 mAb and KM4056 mAb for CD133, CD29, CD24 and LGR5 antigens respectively. For a more effective and specific drug delivery, it is suggested to target colorectal cancer stem cells with specific antibody conjugated with nanoparticles which contain loaded drug (15).

Inhibition of the expression of P53, HIF-1 α and COX-2 genes as well as inhibition of NF-k β , Wnt / β -catenin and K-Ras signaling and also activation of TGF- β are strategies for the treatment of colorectal

cancer (16). Pending strategies for eradication of colorectal cancer stem cells are as follows: PI3K signaling impairment causes inhibition of proliferation and apoptosis induction hedgehog signaling impairment causes proliferation impairment and apoptosis induction Notch signaling impairment causes a decrease in tumor growth and reduction in CCSCs frequency Inhibition of IL-4 signaling causes sensitization to chemotherapy CD44 silencing causes apoptosis induction and tumors growth suppression (17).

Nanotechnology and Gene Expression Regulation

Nano Script is an artificial nanoparticle with similar functional Transcription Factor (TF) protein that in fact is a platform for regulating gene expression. TF is a binding protein to specific sequence of DNA, so regulates the rate of transcription of genetic information from DNA to messenger RNA. Nano Script has two interesting features that make it appropriate platform in the field of stem cells: First, it is non-viral, that is a good alternative to viral vectors. Second, simple arrangement of the sequence of any molecule on Nano Script is possible so they can specifically target and induce differentiation (15).

Liu et al developed a new nanostructure which contains a combination of cross-linked hydrophilic polymers with lipids.

This nanostructure can be used for the delivery of anticancer drug and siRNA, targeting colon cancer stem cells (including CD133 + cells). Using this approach leads to inhibition of the MDR1 activity

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(multidrug-resistant gene) resulting in efficiency of treatment (18).

There have been several other attempts to enhance the efficacy of different anti-cancer drugs. Curcumin is well known for its anti-cancer properties. However, due to the insolubility of this herbal drug in water, its use is limited. Wang et al, have developed the stearic acid-g-chitosan oligosaccharide polymeric micelles (CSO-SA) to overcome such problem. Micelles CSO-SA /

curcumin made in dimensions of 115 nm, has increased the efficiency of anticancer effects of curcumin about 6 times and caused to eliminate colorectal cancer stem cells in-vitro. The ratio of expression CD44 + / CD24 + in the complex CSO-SA-Cur are Less than curcumin only. Also, in intravenous injection, CSO-SA-Cur micelles inhibit tumor growth and suppress enrichment of cancer stem cells (17).

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Conclusion

In this review, we discussed the important role of cancer stem cells in cancer recurrence with a view of the roles of genes and signaling pathways in the progression of colorectal cancer. Use of nanotechnology can help to modulate the expression of genes and signaling pathways in cancer therapy for targeting cancer stem cells to increase efficiency of treatment.