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REVIEW ARTICLE

Cancer stem-like cells: the dark knights of clinical hematology and oncology

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Summary

According to recent epidemiological studies, malignant diseases represent the second cause of mortality worldwide and metastasis is the main cause of morbidity and mortality in most cancers. Even if the concept of "cancer stem cells" (CSCs) was anticipated by the genius of Rudolph Virchow, the father of modern pathology, more than 150 years ago, it is only in last few years that that scientists have begun to develop strategies aimed at inhibiting CSCs at a molecular level, the only way cancer can truly be attacked, by crossing the border between histology and molecular biology. The current concise review aims at emphasizing the main characteristics of tumor initiating cells, bridging the basic science to clinical hematology and oncology.

Key words: *cancer stem cells, clinical hematology, clinical oncology*

Cancer stem cells in malignant initiation and metastasis

According to recent epidemiological studies, malignant diseases represent the second cause of mortality worldwide and metastasis is the main cause of morbidity and mortality in most cancers. The words "cancer" (Latin for "crab") and "metastasis" (Greek for "change in position") refer to cell movement, the crab-like invasion of the healthy tissue by cancer and the migration of cancer cell to distant sites from the primary tumor. Since the work of Paget in the XIXth century, pathologists have recognized that the spread of cancer cells follow a well-established pattern and that different types of cancers have different destinations. What was at the moment called the "soil and seed theory" states that different organs provide optimal growth conditions for specific cancers.

From a darwinistic point of view, metastasis is the end product of an evolutionary process in which diverse interactions between cancer cells and their microenvironment yield alterations that allow these cells to transcend their programmed behavior. Tumor cells thus populate and flourish in new tissue habitats and ultimately cause organ dysfunction and death. Understanding the many molecular elements involved in metastasis will lead to effective targeted approaches to prevent and treat neoplastic diseases [1-4]. Evidence supports that many, if not all tumors depend on a small population of CXCR4+ CSCs for their continuous growth, a concept postulated by oncologists and recently experimentally documented for human leukemia, brain, breast, prostate, liver, bone, skin or pancreatic cancer [5-7].

Mesenchymal stem cells and CSCs share many characteristics, the most important of which being the capacity of self-renewal. Both types of cells have long telomeres, high activity of tel-

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omerase and high expression of the efflux pump ATP-binding cassette transporter. The ABC transporter explains why some types of cancers are relatively resistant to certain types of anticancer drugs. At the molecular level, the cells share similar pathways involved in self-renewal and proliferation, including Wnt, Sonic Hedgehog, Notch signaling, Polycomb genes BMI-1 and EZH2.

Last but not least, CSCs and normal stem cells share similar surface antigens, including CXCR4, potentially employed in addition to other antigens, like Sca-1 in mice and CD133 in humans, as markers used to identify tumor stem cells from growing solid cancers or leukemias. The SDF-1-CXCR4 axis influences metastasis by chemoattracting cancer cells to organs that highly express SDF-1, such as lymph nodes, lungs, liver or bone tissue and this is the very reason why breast cancer, ovarian cancer, rhabdomyosarcoma or neuroblastoma metastasize especially to bones and lymph nodes. The axis is also responsible for the retention in the bone marrow of acute lymphoid leukemia and acute myeloid leukemia cells. Facilitating VLA-4-VCAM-1 interactions of cells increases their survival and accounts for anticancer drug failure. Also, SDF-1 is responsible for deregulated adhesion and integrin-dependent bone marrow retention of Philadelphia (Ph+) CD34+ cells in chronic myeloid leukemia. Elevated levels of SDF-1 are associated with increased osteoclast activity and osteolytic bone disease in patients with multiple myeloma [8,9].

Even if the concept of CSCs was anticipated by the genius of Rudolph Virchow, the father of modern pathology, more than 150 years ago, who along with Julium Connheim proposed the idea of "lost" embryonic remnants during developmental organogenesis that lie dormant and may give rise to malignancies [10], it is only in the last few years that scientists have begun to develop strategies aimed at inhibiting CSCs at a molecular level, the only way cancer can truly be attacked, by crossing the border between histology and molecular biology.

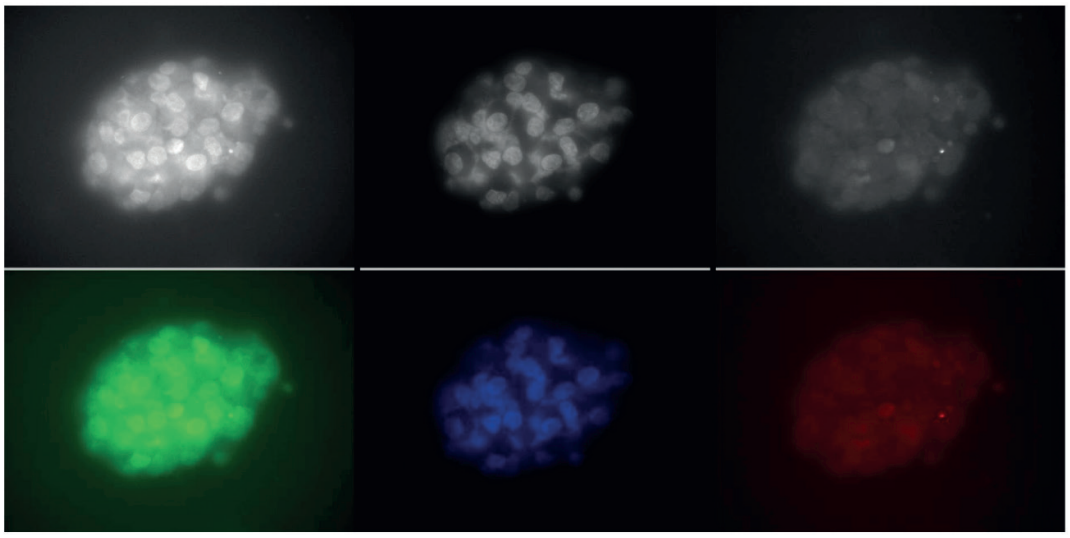
From normal histology and physiology to cancer

The goal to elucidate cellular mechanisms that link genetic changes to the development of cancer is a formidable task because it involves a complex process that occurs in the local niche, it develops over a long period of time and involves a multitude of causes, contributory elements and risk factors. Cancer is initiated by Wnt-pathway-activating mutations in genes such as adenomatous polyposis coli (APC) and as in many cancers, the cell of origin remains relatively elusive.

The anatomy of the crypts is uniquely suited to study adult stem cells and their niche. Each crypt contains long lived stem cells intermingled with Paneth cells in the small intestine and with goblet cells in the colon. These cells divide every day, being called crypt base columnar cells, and their daughter cells constitute the transit-amplifying crypt compartment. Transit amplifying cells divide every 12 to 16 hrs, reside within the crypts and undergo several rounds of cell division while migrating upwards. When a transit amplifying cell reaches the crypt-villous junction, it differentiates while continuing its upward migration and initiating mutations in colorectal malignancies targeting Wnt pathway components, most frequently the negative regulator APC. This will result in the constitutive activation of a Wnt target gene that drives the formation of bening adenomas [11,12].

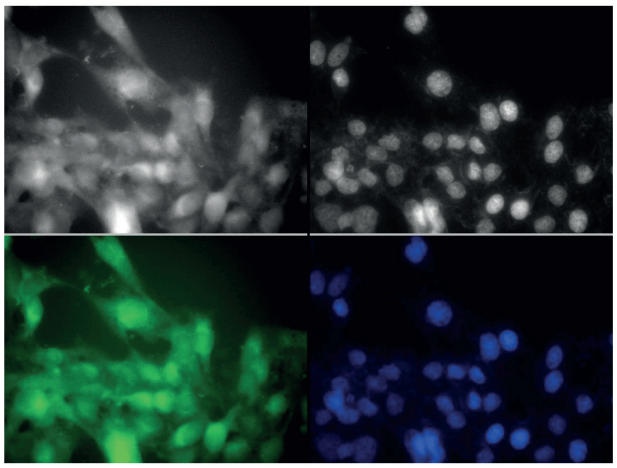
The Vogeltein's theory, first developed at the Johns Hopkins Hospital in the United States, was improved by later research, especially by the hypothesis of stem cell overpopulation and adenoma development. Morphologically, adenomatous crypts are wider and longer than normal ones, indicating that the total crypt cell population has expanded. Adenomatous epithelium has a relatively immature, undifferentiated phenotype that resembles the proliferative epithelium found in the bottom of normal crypts. This proves that the proliferative cell population expands to replace the entire crypt population and that the distribution of S-phase cells is shifted upward to the luminal surface of adenomatous crypts [13,14]. A further displacement of the rapidly proliferating cell population and a further shift in the distribution of S-phase cells toward the crypt top is testable by immunohistochemical staining of colon tissue sections using antibodies against available colonic markers, such as CD133 (Figure 1), CD44 (Figure 2) or Lgr5 (Figure 3), and against rapidly proliferating cells (i.e. Ki67) [15].

While a few tumors develop very rapidly, most develop over many years or even decades. A malignant tumor requires mutations that confer a tumor cell the ability to overcome the multiple intrinsic and extrinsic mechanisms that the human body possesses to prevent the breakdown of homeostasis. Mutations that cause aberrant cell proliferation are key aspects of oncogenesis and still, most DNA damage is quickly repaired. Also,



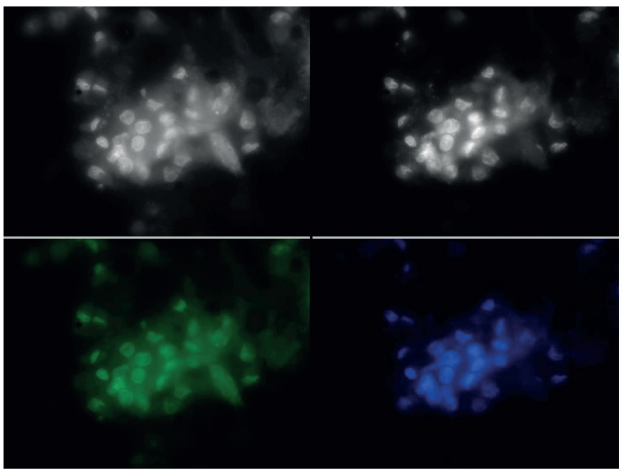
A B C

Figure 1. Immunocytochemistry for CD133 (x20). Upper row: white light microscopy. **A:** positive nuclear staining with green fluorescent protein (GFP). **B:** positive staining of nuclei with dihydroxyphenyl indole (DAPI). **C:** positive control with Texas Red staining.



A B

Figure 2. Immunocytochemistry for CD44 (x40). Upper row: white light microscopy. **A:** positive nuclear staining for CD44 with green fluorescent protein (GFP). **B:** positive nuclear staining with dihydroxyphenyl indole (DAPI).



A B

Figure 3. Immunocytochemistry for Lgr5 (x40). Upper row: white light microscopy. **A:** positive nuclear staining for Lgr5 with green fluorescent protein (GFP). **B:** positive nuclear staining with dihydroxyphenyl indole (DAPI).

because somatic cells are dependent on homeostatic signals, the mutation that disrupts an epithelial cells' interaction with the basal lamina can trigger apoptosis or replicative senescence. Considering that the immune system also plays a role in cancer progression, we might say that all the anti-cancer initiation and progression systems act as a selective force that promotes somatic evolution of different clonal subspecies [16].

Cancer can be considered a phenotypic selection of multiple advantageous traits by a specific environment rather than an expansion of individual mutant genotypes. In tumor cell biology, as well as in evolutionary biology, selection is applied at the phenotypic level and cellular phenotypes in tumors are the result of the integration of the genotype with the microenvironment. Tumor cells acquire a number of traits as the neoplasm

progresses to malignancy, as described by Baylin and Pupa et al. [17,18], include self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, angiogenesis, limitless replicative potential and the ability to invade the surrounding tissues.

A rather unconventional but as close to reality as possible way to see cancer is the "game theory", a ecological mathematical tool used by ecologists to address cancer, evolution of cooperation between the tumor cell and the surrounding environment and the network of metastasis. The game theory, initially introduced by the Nobel laureate John Nash in the 1950s to study human behavior and economy [19], was expanded to study interactions between individuals in the same species to determine the evolutionary dynamics of the population. In the past decade mathematical oncologists have started using the evolutionary game theory to study somatic evolution in cancer, which requires formally defining the relevant cell phenotypes present during invasion and metastasis and the interplay between these elements in relation to a fitness payoff. The theory has successfully demonstrated the emergence of phenotypes capable of unconstrained growth, avoiding apoptosis, acidifying the microenvironment, and promoting angiogenesis and invasion [20-22].

Stem cell niche and metastasis

The undifferentiated cells in a niche are a cell population undergoing a constant process of regeneration. In order to strictly regulate this process, there has to be a balance between proliferation, differentiation, senescence and apoptosis, a central role being played by the stem cells located at this level [23], as cancer stem-like cells have a very high proliferation rate. Figures 4A and B show the proliferation rate of the cells within 48 hours.

In the colon for example, these cells are situated in the basal compartment of the crypts. Just like the other adult stem cells, it is assumed that these cells are surrounded by a niche consisting of mesenchymal structures, which ensure the preservation of their characteristic properties as stem cells [24]. The studies conducted in the attempt to determine the clonal origin of colonic crypts have indicated that although during their embryological development the cells that constitute the crypts are polyclonal, in a later stage they become monoclonal, possibly through the positive selection of a dominant clone or following the segregation of the cell lines caused by the fission of the crypts, which occurs quite frequently during the development of the colon. This observation has led to the notion of a crypt cycle. Thus, crypts have a limited lifespan which, in the case of mice, has been established at two years [25,26]. Because the fission of the crypts begins at the base, where we also find the colonic stem cells, it is assumed that they play a major role in this process. Thus, customarily, the cell population generated by one stem cell would lead to the formation of an entire colonic crypt. Normally, competition between the cell populations coming from different stem cells is moderate and leads to an increase in the number of niches. In the case of a malignant transformation, the increased proliferation of the cells coming from the tumor stem cell leads to an aggressive, unbalanced competition with the other cells, which come from normal stem cells. This time, the consequence is not the formation of other stem cells, but an anarchic formation of a malignant niche, leading to architecture typical of malignant tumors [27-30].

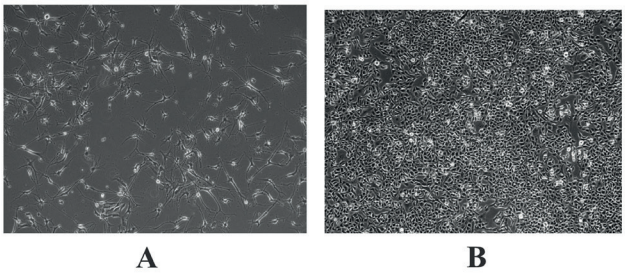


Figure 4. White light microscopy for the stem-like phenotype of hepatocellular-derived cancer cells (x40). Stem-like cells have a very high proliferation rate due to asymmetric division. **A:** stem-like cells population and **B:** the same culture flask after several hours. This Figure clearly proves the aggressiveness of the hepatocellular carcinoma stem-like cells.

This behavior can explain the architecture of colonic metastases in which crypts were identified, provided that the migrated cell has properties similar to those of the colonic stem cells capable of generating an entire crypt [31]. One of the important characteristics that define a stem cell is asymmetrical division. In this case, the division of a stem cell generates a cell identical to the original one and a cell that would differentiate. Following this division, one of the cells would take the place of the initial cell in the niche, and the other would leave the niche and differentiate [32], as shown in Figure 5.

During a malignant transformation, this nor-

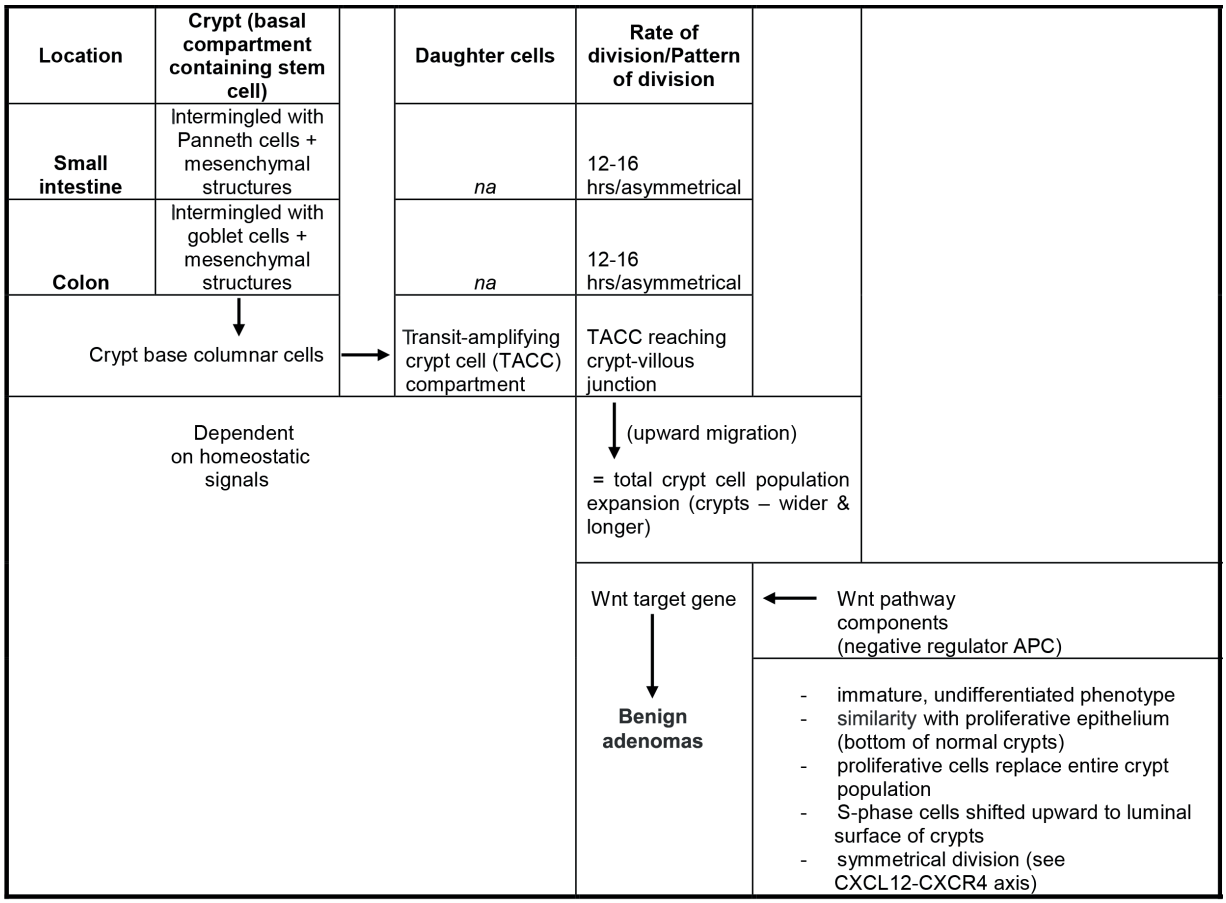


Figure 5. The natural history of stem-like cells of the gastrointestinal tract, showing the property of asymmetric cell division, as well as the pathophysiology of malignant transformation.

mal process of asymmetrical division can turn into a process of symmetrical division, with the consecutive increase in the number of stem cells and without the possibility for the microenvironment to provide a niche for these cells, which would be absolutely necessary for the preservation of their properties [33]. This could lead, in some of these cells, to the activation of certain mechanisms that would allow them to migrate towards other areas in the body, where they could find a suitable microenvironment. The molecular mechanisms involved in this migration process seem to be the same as the ones employed by the normal stem cells, best investigated among them being the CXCL12-CXCR4 axis [34-36].

The activation of this axis determines the cells to move towards areas in the body where previous cellular damage triggered the release of CXCL12, a chemoattractant for normal or tumor stem cells whose surface shows an expression of CXCR4. After reaching this level, displaying increased proliferation properties following the disturbance in the cellular cycle, the tumor cells will begin to generate structures with architecture similar to that of the original tumor from which they migrated [37-40].

Targeted molecular therapies

A key focus of cancer research is the understanding of molecular changes that underlie tumor initiation and progression. One of the most promising pathways to targeting CSCs is the induction of differentiation with the loss of self-renewal capacity. This is the case of acute promyelocytic leukemia, where retinoic acid has significantly increased the efficacy of chemotherapy. This proof principle is that differentiation agents may be the most promising path to developing effective, non-toxic therapies. Inhibitors of Wnt signaling, such as ICG-001, particularly the CREB-Binding Protein (CBP) pathway, show promising in vivo and *in vitro* efficacy without toxicity, as well as arsenic trioxide that sensitizes CSCs to standard chemotherapy [41,42].

CD44 is a widely expressed protein with an important role in cell-to-cell and cell-to-matrix interactions. Though normally expressed at the base of dividing crypts in the proliferative zone, during inflammation and malignant proliferation the distribution of CD44 expression extends to the luminal surface. In a mouse model of acute myeloid leukemia, Jin et al. used a CD44-activat-

ing antibody and resulted in reversal of differentiation blockade [43]. Todaro et al. have recently described the autocrine production of IL-4 by CD133+ colon cancer stem-like cells [44]. Even if the cell isolates were resistant to 5-FU or oxaliplatin, the ability to decrease tumorigenic growth was increased when cells were first treated with anti-IL-4 monoclonal antibodies. Colon CSCs may also be targeted by natural products, such as curcumin (diferuloylmethane) – the major active ingredient of Curcuma longa. Curcumin inhibits the growth of transformed cells, and suppresses initiation, promotion and progression of colon carcinogenesis in combination with either 5-FU or FOLFOX [45].

Cancers are extremely heterogeneous in terms of the frequency and types of mutations, and the high degree of diversity among human colorectal cancers suggests that individualized treatment strategies hold great promise in future clinical experiments. Radioimmunotherapy is an emerging approach with only two FDA-approved protocols thus far, both targeted against non-Hodgkin's lymphoma. Abraham et al. reported a set of 9 different decapeptides which, when labeled with the β-emitter ^{32}P, bound to cell lines derived from a panel of different colorectal adenocarcinomas [46]. The most efficient ^{32}P-labeled decapeptide resulted in permanent incorporation of radioisotope into colon adenocarcinoma cellular proteins at a rate over 100 times greater than in cell lines derived from other cancers.

Telomerase, the research of which has won Blackburn, Greider and Szostak the 2009 Nobel Prize in Physiology or Medicine, is a ribonucleoprotein considered as a potential target of cancer therapy because of its preferential expression in tumors. Telomerase, whose activity is generally underdetectable in normal somatic cells and expressed in most tumors, has two major components and several associated proteins essential for proper cell function. The first major component is the human telomerase RNA (hTER) that serves as the template on which telomeric repeats are added to the ends of the chromosomes, and the second component is the human telomerase reverse transcriptase (hTERT) catalytic sub-unit. In anticancer therapy, the promoter of the hTERT gene is used to restrict the expression of suicide gene or toxin to telomerase positive tumor cells. Using hTERT-derived peptides or hTERT RNA, cytotoxic T cell responses and tumor immunity are elicited. Due to the fact that normal cells lack telomerase activity they are kept intact and adverse effects are minimal [47,48].

Gene-based therapeutics based on the concept on oncolytic virus therapy also hold considerable promise. Viruses have adapted through millennia of evolution to effectively invade and affect cells through various mechanisms. The research team lead by Galanis at Mayo Clinic in Rochester uses strains of the attenuated measles virus Edmonton (MV-Edm) vaccine lineage that can preferentially infect and destroy cancer cells while sparing the healthy tissue. To facilitate monitoring of the viral gene expression and replication, the oncolytic strains are engineered to express soluble marker peptides, such as the human carcinoembryonic antigen [49,50].

Another approach that has been introduced recently in the clinic to reduce primary tumor and metastasis load is targeting the angiogenesis process. As neovascularization depends largely on VEGF signaling, several strategies have been developed to disrupt this signaling pathway. Small molecule tyrosin kinase inhibitors and antibodies against VEGF receptors can block activation. A phase III clinical trial showed that blocking VEGF with a humanized anti-VEGF antibody in combination with standard chemotherapy will increase overall and progression-free survival of patients with metastatic colorectal cancer [51].

Plerixafor, also known as AMD3100, is a bicyclam molecule which binds reversibly to CXCR4. Even though initially developed as a potential therapeutic agent against HIV, preclinical data have shown that AMD3100 blocks CXCL12 binding of CXCR4 and as a result it inhibits SDF-1α-induced calcium flux and chemotaxis. Clinical trials have demonstrated that Plerixafor is effective for the mobilization of peripheral blood stem cells for use in autologous haematopoietic stem cell transplantation, but blocking the same CXCR4-CXCL12 axis can also play an important role in the control of CSC dissemination from the primary prostate cancer lesion and metastasis. New drugs, such as CTCE-9908, are currently undergoing preclinical confirmation in this setting [52].

Conclusion

Although the treatment of cancer has seen considerable progress during the past few years, the mortality associated with this disease remains high. The integration of paradigms coming from various fields, such as evolutionary dynamics and mathematical oncology, has increased our understanding of the manner in which tissues are organized and operate. This has opened new perspectives in what concerns the genesis of various

pathological processes, especially of malignant tumors. Nowadays we are witnessing a new approach to treatment, and this time the target is a small cell population – tumor stem cells – deemed responsible for the resistance to treatment and for metastasis. That is why current efforts are directed towards the understanding of the biology of this type of cells and of the differences between them and normal stem cells, in an attempt to find more effective treatments that would also have less significant side-effects.

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References

1. Müller A, Homey B, Soto H et al. Involvement of chemokine receptors in breast cancer metastasis. Nature 2001;410:50-56.
2. Liota L. An attractive force in metastasis. Nature 2001;410:24-25.
3. Chiang AC, Massagué J. Molecular basis of metastasis. N Engl J Med 2008;359:2814-2823.
4. Barbieri F, Bajetto A, Porcile C et al. CXC receptor and chemokine expression in human meningioma: SDF1/CXCR4 signaling activates ERK1/2 and stimulates meningioma cell pro- liferation. Ann N Y Acad Sci 2006;1090:332-343.
5. Tang CH, Tan TW, Fu WM, Yang RS. Involvement of matrix metalloproteinase-9 in stromal cell-derived factor-1/CXCR4 pathway of lung cancer metastasis. Carcinogenesis 2008;29:35-43.
6. Zagzag D, Krishnamachary B, Yee H et al. Stromal cell derived factor 1α and CXCR4 expression in hemangioblastoma and clear cell-renal cell carcinoma: von Hippel-Lindau loss of function induces expression of a ligand and its receptor. Cancer Res 2005;65:6178-6188.
7. Ehtesham M, Mapara KY, Stevenson VB, Thompson RC. CXCR4 mediates the proliferation of glioblastoma progenitor cells. Cancer Lett 2009;274:307-312.
8. Libura J, Drukala J, Majka T et al. CXCR4-SDF-1 signaling is active in rhabdomyosarcoma cells and regulates locomotion, chemotaxis and adhesion. Blood 2002;100:2597-2606.
9. Peled A, Hardan I, Trakhtenbrot L et al. Immature leukemic CD34+CXCR4+ cells from CML patients have lower integrin dependent migration and adhesion in response to the chemokine SDF-1. Stem Cells 2002;20:259-266.
10. Virchow R. Editorial archive für pathologische. Anat Physiol Klin Med 1855; 8:23-54.
11. Barker N, van de Wetering M, Clevers H. The intestinal stem cell. Genes Dev 2008;22:1856-1864.
12. Jones S, Chen WD, Parmigiani G et al. Comparative lesion sequencing provides insights into tumor evolution. Proc Natl Acad Sci U S A 2008;105:4283-4288.
13. Boman BM, Fields JZ, Cavanaugh KL, Guetter A, Runquist OA. How dysregulated colonic crypt dynamics cause stem cell overpopulation and initiate colon cancer. Cancer Res 2008;68:3304-3313.
14. Clevers H. At the crossroads of inflammation and cancer. Cell 2004;118:671-674.
15. Choi D, Lee HW, Hur KY et al. Cancer stem cell markers CD133 and CD24 correlate with invasiveness and differentiation in colorectal adenocarcinoma. World J Gastroenterol 2009;15:2258-2264.
16. Mori Y, Yin J, Sato F et al. Identification of genes uniquely involved in frequent microsatellite instability colon carcinogenesis by expression profiling combined with epigenetic scanning. Cancer Res 2004;64:2434-2438.
17. Susman S, Tomuleasa C, Soritau O et al. The colorectal cancer stem-like cell hypothesis: a pathologist's point of view. J BUON 2012;17:230-236.
18. Pupa SM, Ménard S, Forti S, Tagliabue E. New insights into the role of extracellular matrix during tumor onset and progression. J Cell Physiol 2002;192:259-267.
19. Nash JF. Equilibrium Points in N-Person Games. Proc Natl Acad Sci U S A 1950;36:48-49.
20. Vincent TL, Gatenby RA. An evolutionary model for initiation, promotion, and progression in carcinogenesis. Int J Oncol 2008;32:729-737.
21. Basanta D, Simon M, Hatzikirou H, Deutsch A. Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion. Cell Prolif 2008;41:980-987.
22. Strand DW, Franco OE, Basanta D, Anderson AR, Hayward SW. Perspectives on tissue interactions in development and disease. Curr Mol Med 2010;10:95-112.
23. Tse JC, Kalluri R. Mechanisms of metastasis: epithelial-to-mesenchymal transition and contribution of tumor microenvironment. J Cell Biochem 2007;101:816-829.
24. Dalerba P, Dylla SJ, Park IK et al. Phenotypic characterization of human colorectal cancer stem cells. Proc Natl Acad Sci U S A 2007;104:10158–10163.
25. Ricci-Vitiani L, Lombardi DG, Pilozzi E et al. Identification and expansion of human colon-cancer initiating cells. Nature 2007;445:111–115.

26. Polyak K, Hahn WC. Roots and stems: stem cells in cancer. Nat Med 2006;12:296-300.
27. Ballinger AB, Anggiansah C. Colorectal cancer. BMJ 2007;335:715-718.
28. Mareel M, Leroy A. Clinical, cellular, and molecular aspects of cancer invasion. Physiol Rev 2003;83:337-376.
29. Subramaniam V, Gardner H, Jothy S. Soluble CD44 secretion contributes to the acquisition of aggressive tumor phenotype in human colon cancer cells. Exp Mol Pathol 2007;83:34134-346.
30. Murphy PM. Chemokines and the molecular basis of cancer metastasis. N Engl J Med 2001;345:833-835.
31. Duffy MJ, van Dalen A, Haglund C et al. Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. Eur J Cancer 2007;43:1348-1360.
32. Ogino S, Brahmandam M, Cantor M et al. Distinct molecular features of colorectal carcinoma with signet ring cell component and colorectal carcinoma with mucinous component. Mod Pathol 2006;19:59-68.
33. Debruyne PR, Bruyneel EA, Karaguni IM et al. Bile acids stimulate invasion and haptotaxis in human colorectal cancer cells through activation of multiple oncogenic signaling pathways. Oncogene 2002;21:6740-6750.
34. Zeelenberg IS, Ruuls-Van Stalle L, Roos E. The chemokine receptor CXCR4 is required for outgrowth of colon carcinoma micrometastases. Cancer Res 2003;3:3833-3839.
35. Koshiba T, Hosotani R, Miyamoto Y et al. Expression of stromal cell-derived factor 1 and CXCR4 ligand receptor system in pancreatic cancer: a possible role for tumor progression. Clin Cancer Res 2000;6:3530-3535.
36. Taichman RS, Cooper C, Keller ET, Pienta KJ, Taichman NS, McCauley LK. Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone. Cancer Res 2002;62:1832-1837.
37. Liang Z, Yoon Y, Votaw J, Goodman MM, Williams L, Shim H. Silencing of CXCR4 blocks breast cancer metastasis. Cancer Res 2005;65:967-971.
38. Ottaiano A, Franco R, Aiello Talamanca A et al. Overexpression of both CXC chemokine receptor 4 and vascular endothelial growth factor proteins predicts early distant relapse in stage II–III colorectal cancer patients. Clin Cancer Res 2006;12:2795-2803.
39. Kim J, Takeuchi H, Lam ST et al. Chemokine receptor CXCR4 expression in colorectal cancer patients increases the risk for recurrence and for poor survival. J Clin Oncol 2005;23:2744-2753.
40. Schimanski CC, Schwald S, Simiantonaki N et al. Effect of chemokine receptors CXCR4 and CCR7 on the metastatic behavior of human colorectal cancer. Clin Cancer Res 2005;11:1743-1750.
41. Emami KH, Nguyen C, Ma H et al. A small molecule inhibitor of beta-catenin/CREB-binding protein transciption. Proc Natl Acad Sci U S A 2004;101:12682-12687.
42. Tomuleasa C, Soritau O, Fischer-Fodor E et al.. Arsenic trioxide plus cisplatin/ interferon α-2b/ doxorubicin/ capecitabine in vitro combination chemotherapy for hepatocellular carcinoma. Hematol Oncol Stem Cell Ther 2011;4:60-66.
43. Jin L, Hope KJ, Zhai Q, Smadja-Joffe F, Dick JE. Targeting of CD44 eradicates human acute myeloid leukemic cells. Nat Med 2006;12:1167-1174.
44. Todaro M, Alea MP, Di Stefano AB et al. Colon cancer stem cells dictate tumor growth and resist cell death by production of interleukin-4. Stem Cell 2007;1:389-402.
45. Yu Y, Kanwar SS, Patel BB, Nautiyal J, Sarkar FH, Majumdar AP. Elimination of colon cancer stem-like cells by the combination of curcumin and FOLFOX. Transl Oncol 2009;2:321-328.
46. Abraham JM, Cheng Y, Hamilton JP et al. Generation of small 32P-labeled peptides as a potential approach to colorectal cancer therapy. PloS One 2008;3(6):e2508-e2514.
47. Koga S, Hirohata S, Kondo Y et al. A novel telomerase-specific gene therapy: gene trasnfer of caspase-8 utilizing the human telomerase catalytic subunit gene promoter. Hum Gene Ther 2000;11:1397-1406.
48. Komata T, Kanzawa T, Kondo Y, Kondo S. Telomerase as a therapeutic target for malignant gliomas. Oncogene 2002;21:656-663.
49. Galanis E, Hartmann LC, Cliby WA et al. Phase I trial of intraperitoneal administration of an oncolytic measles virus strain engineered to express carcinoembryonic antigen for recurrent ovarian cancer. Cancer Res 2010;70:875-882.
50. Msaouel P, Dispenzieri A, Galanis E. Clinical testing of engineered oncolytic measles virus strains in the treatment of cancer: an overview. Curr Opin Mol Ther 2009;11:43-53.
51. Ivy SP, Wick JY, Kaufman BM. An overview of small-molecule inhibitors of VEGFR signaling. Nat Rev Clin Oncol 2009;6:569-579.
52. Matsusue R, Kubo H, Hisamori S et al. Hepatic stellate cells promote liver metastasis of colon cancer cell by the action of SDF-1/CXCR4 axis. Ann Surg Oncol 2009;16:2645-2653.