Stem Cell Origin Research Literatures

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Abstract: The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the stem cell origin related studies.
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Key words: stem cell; origin; life; research; literature

1. Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

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Researchers identify stem cell origin of AML, Cancer Discov. 2014 May;4(5):500-1. doi: 10.1158/2159-8290.CD-NB2014-040. Epub 2014 Mar 13.

Akashi, K., S. Taniguchi, et al. "B-lymphoid/myeloid stem cell origin in Ph-positive acute leukemia with myeloid markers." Leuk Res. 1993 Jul;17(7):549-55.

We report two cases of Philadelphia chromosome (Ph)-positive acute leukemia with definite myeloid markers. Ph was the sole chromosomal abnormality at presentation, and neither eosinophilia, basophilia, thrombocytosis nor hepatosplenomegaly was present. In both cases, Ph+ myeloblasts showed positive stain for myeloperoxidase and naphthol ASD chloroacetate esterase, which fulfilled the FAB criteria of acute myelogenous leukemia (AML). Ph+ myeloblasts co-expressed myeloid and B-lymphoid antigens (CD10, CD13, CD19 and CD33). In case 1, myeloblasts rearranged M-BCR, and the expression of M-BCR/ABL chimeric RNA was demonstrated by using the reverse transcription polymerase chain reaction (RT-PCR). They also clonally rearranged IGH. Ph clone disappeared on cytogenetic analysis in remission, and granulocytes in remission did not have rearranged M-BCR. In case 2, morphocytochemically distinct myeloid and lymphoid blast populations were seen. Myeloblasts and lymphoblasts were enriched > 96% as CD19-/CD33+ and CD19+/CD33- populations, respectively. Both of them possessed the identical rearrangement of IGH and M-BCR, indicating a common leukemic progenitor cell origin. Furthermore, m-BCR/ABL was detected in addition to M-BCR/ABL on RT-PCR. Accordingly, both cases were diagnosed as de novo Ph+ acute leukemia rather than as chronic myelogenous leukemia in blastic crisis. Their mixed B-lymphoid/myeloid characteristics strongly suggest that so-called 'Ph+ AML' is derived from Ph+ myeloid/B-lymphoid stem cells.

Buschle, M., J. W. Janssen, et al. "Evidence for pluripotent stem cell origin of idiopathic myelofibrosis: clonal analysis of a case characterized by a N-ras gene mutation." Leukemia. 1988 Oct;2(10):658-60.

Three cases of idiopathic myelofibrosis were screened for the presence of mutations at codon 12, 13, or 61 of the ras gene family by a rapid method based on polymerase chain reaction and hybridization to mutation-specific oligonucleotides. PB cells of one patient showed a point mutation at codon 12 of the N-ras oncogene. This molecular genetic hallmark was used to investigate the clonal relationship of different cell lineages by cell separation analysis. Presence of the N-ras 12 mutation in granulocytes, monocytes, B cells, and T lymphocytes, as well as erythroblasts, indicates that idiopathic myelofibrosis originates from a pluripotent stem cell, at least in this patient.

Chakraborti, S., A. Mahadevan, et al. "Rosette-forming glioneuronal tumor -- evidence of stem cell origin with biphenotypic differentiation." Virchows Arch. 2012 Nov;461(5):581-8. doi: 10.1007/s00428-012-1313-0. Epub 2012 Sep 13.

Rosette-forming glioneuronal tumor (RGNT) of the fourth ventricle is a new addition to the WHO classification of central nervous system tumors. To date, 72 cases have been described in literature. In the present study, we report the clinical and imaging features, with detailed histopathological and immunohistochemical profile, of eight cases. Confocal microscopic evidence of stem cell origin with biphenotypic, glial and neurocytic differentiation is presented with a comprehensive review of literature.

Chung, S. S., E. Kim, et al. "Hematopoietic stem cell origin of BRAFV600E mutations in hairy cell leukemia." Sci Transl Med. 2014 May 28;6(238):238ra71. doi: 10.1126/scitranslmed.3008004.

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder characterized by somatic BRAFV600E mutations. The malignant cell in HCL has immunophenotypic features of a mature B cell, but no normal counterpart along the continuum of developing B lymphocytes has been delineated as the cell of origin. We find that the BRAFV600E mutation is present in hematopoietic stem cells (HSCs) in HCL patients, and that these patients exhibit marked alterations in hematopoietic stem/progenitor cell (HSPC) frequencies. Quantitative sequencing analysis revealed a mean BRAFV600E-mutant allele frequency of 4.97% in HSCs from HCL patients. Moreover, transplantation of BRAFV600E-mutant HSCs from an HCL patient into immunodeficient mice resulted in stable engraftment of BRAFV600E-mutant human hematopoietic cells, revealing the functional self-renewal capacity of HCL HSCs. Consistent with the human genetic data, expression of BRafV600E in murine HSPCs resulted in a lethal hematopoietic disorder characterized by splenomegaly, anemia, thrombocytopenia, increased circulating soluble CD25, and increased clonogenic capacity of B lineage cells-all classic features of human HCL. In contrast, restricting expression of BRafV600E to the mature B cell compartment did not result in disease. Treatment of HCL patients with vemurafenib, an inhibitor of mutated BRAF, resulted in normalization of HSPC frequencies and increased myeloid and erythroid output from HSPCs. These findings link the pathogenesis of HCL to somatic mutations that arise in HSPCs and further suggest that chronic lymphoid malignancies may be initiated by aberrant HSCs.

Daidone, M. G., A. Costa, et al. "Correspondence re: T. Zhang et al., Evidence that APC regulates survivin expression: a possible mechanism contributing to the stem cell origin of colon cancer. Cancer Res., 61: 8664-8667, 2001." Cancer Res. 2004 Jan 15;64(2):776-7; author reply 777-9.

Elias, H. K., C. Schinke, et al. "Stem cell origin of myelodysplastic syndromes." Oncogene. 2014 Oct 30;33(44):5139-50. doi: 10.1038/onc.2013.520. Epub 2013 Dec 16.

Myelodysplastic syndromes (MDS) are common hematologic disorders that are characterized by decreased blood counts due to ineffective hematopoiesis. MDS is considered a 'preleukemic' disorder linked to a significantly elevated risk of developing an overt acute leukemia. Cytopenias can be observed in all three myeloid lineages suggesting the involvement of multipotent, immature hematopoietic cells in the pathophysiology of this disease. Recent studies using murine models of MDS as well as primary patient-derived bone marrow samples have provided direct evidence that the most immature, self-renewing hematopoietic stem cells (HSC), as well as lineage-committed progenitor cells, are critically altered in patients with MDS. Besides significant changes in the number and distribution of stem as well as immature progenitor cells, genetic and epigenetic aberrations have been identified, which confer functional changes to these aberrant stem cells, impairing their ability to proliferate and differentiate. Most importantly, aberrant stem cells can persist and further expand after treatment, even upon transient achievement of clinical complete remission, pointing to a critical role of these cells in disease relapse. Ongoing preclinical and clinical studies are particularly focusing on the precise molecular and functional characterization of aberrant MDS stem cells in response to therapy, with the goal to develop stem cell-targeted strategies for therapy and disease monitoring that will allow for achievement of longer-lasting remissions in MDS.

Fialkow, P. J. "Stem cell origin of human myeloid blood cell neoplasms." Verh Dtsch Ges Pathol. 1990;74:43-7.

Studies with G6PD and molecular probes indicate that the myeloid leukemias and the chronic myeloproliferative disorders are clonal diseases. The G6PD data indicate that chronic myelogenous leukemia, polycythemia vera and essential thrombocythemia involve stem cells pluripotent for granulocytes, erythrocytes, megakaryocytes and lymphocytes. Agnogenic myeloid metaplasia is also a clonal disease that involves multipotent hematopoietic stem cells. However, myelofibrosis, the predominant

clinical manifestation, occurs secondarily and is not a component of the abnormal clonal proliferation. Acute nonlymphocytic leukemia is a clonal disease, but G6PD studies suggest that there are at least two forms of this leukemia. In one type of ANL, the involved stem cells exhibit pluripotent differentiative expression. In another type of ANL, differentiative expression is largely restricted to the granulocytic pathway. The heterogeneity of ANL has both clinical and pathogenetic implications.

Fialkow, P. J., J. W. Singer, et al. "Acute nonlymphocytic leukemia: heterogeneity of stem cell origin." Blood. 1981 Jun;57(6):1068-73.

Four patients with acute nonlymphocytic leukemia who were heterozygous for the X-chromosome-linked enzyme glucose-6-phosphate dehydrogenase (G6PD) were studied to determine the numbers and types of progenitor cells in which the disease arose. Both forms of enzyme were found in normal tissues, but the malignant blast cells showed only one G6PD, indicating that the disease was clonal at the time of testing. The observations that normal erythroid cells were present in two young patients at diagnosis and relapse indicate that the clone suppressed expression of normal granulopoiesis but did not prevent normal erythroid differentiation. In contrast to this situation, in two elderly patients, the disease involved stem cells multipotent for granulocytes, red cells, and platelets. These results indicate that acute nonlymphocytic leukemia is heterogeneous. In some patients, the disease is expressed in cells with differentiation restricted to the granulocyte-monocyte pathway; in others, it involves stem cells capable of differentiating to granulocytes-monocytes, platelets, and erythrocytes. This heterogeneity may reflect differences in causation and could have prognostic and therapeutic importance.

Glinsky, G. V. "Stem cell origin of death-from-cancer phenotypes of human prostate and breast cancers." Stem Cell Rev. 2007 Jan;3(1):79-93.

In clinical terms, all human cancers diagnosed in individuals can be divided in two major categories: malignant tumors that will be cured with the existing cancer therapies and tumors that have therapy-resistant phenotypes and will return after initial treatment as incurable metastatic disease. These tumors manifesting clinically lethal death-from-cancer phenotypes represent the most formidable challenge of experimental, translational, and clinical cancer research. Clinical genomics data demonstrate that gene expression signatures associated with the "stemness" state of a cell are informative as molecular predictors of cancer therapy outcome and can help to identify cancer patients with therapy-resistant tumors. Here, we present experimental and clinical evidence in support of the BMI1 pathway rule indicating a genetic link between the stemness state and therapy-resistant death-from-cancer phenotypes. Our analysis demonstrates that therapy-resistant and therapy-responsive cancer phenotypes manifest distinct patterns of association with stemness/differentiation pathways, suggesting that therapy-resistant and therapy-responsive tumors develop within genetically distinct stemness/differentiation programs. These differences can be exploited for development of prognostic and therapy selection genetic tests utilizing a microarray-based cancer therapy outcome predictor algorithm. One of the major regulatory pathways manifesting distinct patterns of association with therapy-resistant and therapy-responsive cancer phenotypes is the Polycomb group proteins chromatin silencing pathway.

Govindan, A., A. Mahadevan, et al. "Papillary glioneuronal tumor-evidence of stem cell origin with biphenotypic differentiation." J Neurooncol. 2009 Oct;95(1):71-80. doi: 10.1007/s11060-009-9893-5. Epub 2009 Apr 30.

Papillary glioneuronal tumors are newly recognized seizure producing tumors. We report two such cases with immunohistochemical characterization of glial and neuronal components and briefly review literature. Co-localization of glial and neuronal markers was demonstrable on confocal microscopy with expression of stem cell markers (Nestin and CD133) suggesting possible origin from neuroepithelial stem cell with biphenotypic differentiation.

Hassan, R., I. Otazu, et al. "A child with Philadelphia positive (Ph+)-acute leukemia with myeloid morphology: one case of stem cell origin." Leuk Lymphoma. 2004 Sep;45(9):1925-9.

Philadelphia positive (Ph+) acute myeloid leukemia (AML) is a rare and heterogeneous condition, mainly reported in adults, associated to poor prognosis and unfavorable response to therapy. Here we report clinical and laboratory findings in an 8-year-old patient diagnosed with Ph+ acute leukemia with myeloid (FAB M4) morphology. The patient consistently expressed variable levels of m-bcr, e1a2 transcripts during a 42-month follow-up after two different stem cell transplantation protocols. An immunophenotypic switch was documented, from a mixed, myeloid-lymphoid lineage to a full lymphoid phenotype following stem cell transplants, in association with an immature B-cell gene rearrangement profile and clonal instability during clinical progression. This report indicates a stem cell origin as previously suggested for Ph+ AML.

Hayashi, Y., N. Watanabe, et al. "The "replacement hypothesis": corneal stem cell origin epithelia are replaced by limbal stem cell origin epithelia in mouse cornea during maturation." Cornea. 2012 Nov;31 Suppl 1:S68-73. doi: 10.1097/ICO.0b013e318269c83f.

PURPOSE: Previous studies have shown that the stem cells of corneal epithelia are located at the limbal basal layer. Limbal stem cells are believed to be the source of corneal epithelial cell proliferation and differentiation. This study tested the replacement hypothesis, which suggests that corneal stem cell origin epithelia may be replaced by limbal stem cell origin epithelia after 2 weeks of age in mice. METHODS: The cytokeratin 12 expression pattern in the cornea was examined using K12 IRES-Cre and Cre reporter mice. RESULTS: Before 2 weeks of age, K12 expression in corneal epithelia showed a mosaic pattern. After 2 weeks of age, centripetal K12 IRES-Cre expression gradually elongated from the limbal area. Around 12 weeks of age, the mosaic expression pattern disappeared from the center of the cornea. Temporal and spatial observations of K12 IRES-Cre expression patterns suggested that the mosaic pattern cells proliferated and amassed at the same position from day 15.5 of the embryonic stage at the latest. CONCLUSIONS: Therefore, these cells were considered corneal stem cell origin epithelia. In contrast, centripetal pattern cell populations were considered limbal stem cell origin epithelia because they originated from the limbal area and moved to the center of the cornea. These observations suggest that corneal stem cell origin epithelia are replaced by limbal stem cell origin epithelia after 2 weeks of age in mice.

Hellmen, E., M. Moller, et al. "Expression of different phenotypes in cell lines from canine mammary spindle-cell tumours and osteosarcomas indicating a pluripotent mammary stem cell origin." Breast Cancer Res Treat. 2000 Jun;61(3):197-210.

Mammary spindle-cell tumours and sarcomas seem to be restricted to dogs and humans. Two cell lines from spontaneous primary canine mammary spindle-cell tumours (CMT-U304 and CMT-U309) and two cell lines from spontaneous primary canine mammary osteosarcomas (CMT-U334 and CMT-U335) were established to study the mesenchymal phenotypes of mammary tumours in the female dog. The cells from the spindle-cell tumours expressed cytokeratin, vimentin and smooth muscle actin filaments. When these cells were inoculated subcutaneously into female and male nude mice they formed different types of mesenchymal tumours such as spindle-cell tumours, fibroma and rhabdomyoid tumours (n = 6/8). The cells from the osteosarcomas expressed vimentin filaments and also formed different types of mesenchymal tumours such as chondroid, rhabdomyoid, smooth muscle-like and spindle-cell tumours (n = 6/10). The cell lines CMT-U304, CMT-U309 and CMT-U335 had receptors for progesterone but none of the four cell lines had receptors for estrogen. All four cell lines and their corresponding primary tumours showed identical allelic patterns in microsatellite analysis. By in situ hybridization with genomic DNA we could verify that all formed tumours but one were of canine origin. Our results support the hypothesis that canine mammary tumours are derived from pluripotent stem cells.

Horn, L. C., C. Hanel, et al. "Mixed serous carcinoma of the endometrium with trophoblastic differentiation: analysis of the p53 tumor suppressor gene suggests stem cell origin." Ann Diagn Pathol. 2008 Feb;12(1):1-3. doi: 10.1016/j.anndiagpath.2007.01.004. Epub 2007 Oct 29.

The pathogenesis of mixed endometrial adenocarcinoma with trophoblastic differentiation is quite unclear at times. The present study examines a serous carcinoma with choriocarcinomatous differentiation. p53 staining was seen in the serous component and the cytotrophoblastic cells of the choriocarcinomatous component, but not in the syncytiotrophoblastic cells. p53 mutational analysis showed a heterozygotic mutation at exon 8 for the choriocarcinomatous component and a homozygote deletion at exon 7 for the serous component. These alterations suggest that the multidirectional tumor differentiation might occur from a common stem cell in these malignancies.

Hubbard, S. A. and C. E. Gargett "A cancer stem cell origin for human endometrial carcinoma?" Reproduction. 2010 Jul;140(1):23-32. doi: 10.1530/REP-09-0411. Epub 2010 Jan 20.

Endometrial cancer (EC) is the most common gynaecological malignancy affecting women in the western world. Cancer stem cells (CSCs) are defined as a subset of tumour cells with the capacity to self-renew and give rise to the differentiated cells that comprise the bulk of the tumour. Given that a rare population of epithelial stem/progenitor cells has been identified in human endometrium, it is possible that these cells or their progeny may be the source of the putative CSCs that may initiate and maintain EC. Studies have shown that some cells within EC have the capacity to initiate clones that undergo self-renewing cell division and form tumours in vivo that can be serially passaged, demonstrating self-renewal, proliferation and differentiation abilities of the potential EC stem cells (ECSCs). These potential

ECSCs may be located within the tumour cell population expressing CD133 and/or within the side population. With the discovery of markers for ECSCs, it is hoped that ECSCs can be isolated and characterised, and that their role in the development of human EC will be further investigated. This knowledge opens the way for the development of new treatment modalities that target the CSCs, but spares normal endometrial stem/progenitor cells and other cells. Such treatments will be particularly useful for early-stage and pre-menopausal EC candidates where the uterus may be conserved, and for late-stage cases where hysterectomy is not curative and current treatments target the bulk tumour cells rather than CSCs.

Huels, D. J. and O. J. Sansom "Stem vs non-stem cell origin of colorectal cancer." Br J Cancer. 2015 Jun 25. doi: 10.1038/bjc.2015.214.

Colorectal cancer (CRC) is one of the most common cancers in the western world and is characterised by deregulation of the Wnt signalling pathway. Mutation of the adenomatous polyposis coli (APC) tumour suppressor gene, which encodes a protein that negatively regulates this pathway, occurs in almost 80% of CRC cases. The progression of this cancer from an early adenoma to carcinoma is accompanied by a well-characterised set of mutations including KRAS, SMAD4 and TP53. Using elegant genetic models the current paradigm is that the intestinal stem cell is the origin of CRC. However, human histology and recent studies, showing marked plasticity within the intestinal epithelium, may point to other cells of origin. Here we will review these latest studies and place these in context to provide an up-to-date view of the cell of origin of CRC.British Journal of Cancer advance online publication, 25 June 2015; doi:10.1038/bjc.2015.214 www.bjcancer.com.

Inagaki, T., M. Nagata, et al. "Carcinosarcoma with rhabdoid features of the urinary bladder in a 2-year-old girl: possible histogenesis of stem cell origin." Pathol Int. 2000 Dec;50(12):973-8.

A case of carcinosarcoma of the urinary bladder in a 2-year-old girl is reported. The tumor, measuring 34 x 20 x 18 mm, was located in the peri-trigone area of the urinary bladder with polypoid features. Histologic examination revealed transitional cell carcinoma at the tumor surface with downward invasion. Concurrently, a sarcomatous area was found beneath the carcinoma, with these two different malignant components sharing on apparent transition without distinct boundaries. Sarcomatous components included immature round cells focally showing rhabdoid features. No rhabdomyomatous component was observed. Immunohistochemistry disclosed vimentin and cytokeratin-double positive cells at the transposition between carcinoma and sarcomatous components. In addition, ultrastructural analysis revealed that the epithelial cells had a distinct junctional complex, and the sarcomatous cells occasionally had a meshwork of cytoplasmic intermediate filaments, indicating bidirectional cytodifferentiation to epithelial and mesenchymal elements. The extremely young age at which this case of carcinosarcoma occurred suggests that the tumor may be of mesodermal stem cell origin.

Ishikawa, K., A. Sasaki, et al. "A case of an alpha-fetoprotein-producing intrahepatic cholangiocarcinoma suggests probable cancer stem cell origin." Oncologist. 2007 Mar;12(3):320-4.

Recent evidence suggests that some cancers may originate from cancer stem cells, which may derive from carcinogenesis of normal stem cells. A hepatic progenitor cell population, which gives rise to hepatocytes and cholangiocytes, has been suggested in humans, though whether these cells can give rise to malignant tumors has not been confirmed. We report here a case of an alpha-fetoprotein (AFP)-producing intrahepatic cholangiocarcinoma (ICC) in an 81-year-old woman with chronic hepatitis C viral infection, suggesting malignant transformation of hepatic stem cells as a mechanism for hepatic neoplasia. Abdominal computed tomography revealed a low-density mass with surrounding enhancement measuring 5 cm x 5 cm in segments IV and VIII of the liver. The preoperative serum levels of tumor markers were 1.7 ng/ml of carcinoembryonic antigen, 22 mAU/ml of protein induced by vitamin K absence or antagonist II, 43.4 U/ml of carbohydrate antigen 19-9, and 1,560 ng/ml of AFP. Following central bisegmentectomy of the liver, serum AFP levels decreased dramatically. Histologically, the tumor cells showed indistinct glandular structures with abundant fibrous stroma. Immunohistochemical analysis demonstrated that the neoplastic cells reacted strongly to antibodies against AFP and cytokeratin (CK) 7. In addition, cancer cells showed partially positive reaction to anti-CK14, a liver stem cell marker, and to anticluster designation (CD) 133, a hematopoietic stem cell marker, and negative reaction to antihepatocyte paraffin (HepPar) 1. These data may indicate that the tumor was derived from a normal liver stem cell that underwent oncogenic transformation.

Janssen, J. W., M. Buschle, et al. "Clonal analysis of myelodysplastic syndromes: evidence of multipotent stem cell origin." Blood. 1989 Jan;73(1):248-54.

Restriction fragment length polymorphisms (RFLPs) of the X-chromosome genes hypoxanthine phosphoribosyl transferase (HPRT) and

phosphoglycerate kinase (PGK) were studied in 34 female patients with primary myelodysplastic syndromes (MDS). Twelve patients (35%) were heterozygous at the HPRT or PGK loci for BamHI or BglI RFLPs, respectively. In eight patients showing PGK polymorphisms, clonality was determined by X-chromosome inactivation analysis. These included patients from different morphologic subtypes: four with refractory anemia (RA), two with RA and ring sideroblasts (RARS), one patient with RA with excess of blasts (RAEB), and one with chronic myelomonocytic leukemia (CMML). A monoclonal pattern of X-chromosome inactivation was observed in seven cases. In a further case characterized by bone marrow hypoplasia, peripheral blood (PB) leukocytes were polyclonal in origin. Following low-dose cytarabine therapy, reversion to polyclonal hematopoiesis was observed in a case of RAEB indicating the presence of residual normal hematopoietic stem cells with the capacity for marrow reconstitution. The clonal relation of lymphoid and granulocyte/monocyte lineages was studied directly in two cases of CMML exhibiting somatic mutations of N-ras or Ki-ras oncogenes. By selective oligonucleotide hybridization to ras gene sequences amplified in vitro by the polymerase chain reaction, a mutated ras allele was demonstrated in PB granulocytes, monocytes, and B and T lymphocytes of both patients. We conclude that MDS arise from a multipotent hematopoietic stem cell with the potential for myeloid and lymphoid differentiation.

Kaye, F. J., V. Najfeld, et al. "Confirming evidence for the clonal development and stem cell origin of Philadelphia chromosome-negative chronic myelogenous leukemia." Am J Hematol. 1984 Jul;17(1):93-6.

A 74-year old woman with Ph1-negative chronic myelogenous leukemia (CML) and heterozygous for glucose-6-phosphate dehydrogenase (G6PD) was studied. Both A and B types of G6PD were found in skin. In contrast, white blood cells and platelets showed only a single G6PD type A. These results provide further evidence that Ph1-negative CML has a stem cell origin and develops clonally.

Lafferty-Whyte, K., C. J. Cairney, et al. "A gene expression signature classifying telomerase and ALT immortalization reveals an hTERT regulatory network and suggests a mesenchymal stem cell origin for ALT." Oncogene. 2009 Oct 29;28(43):3765-74. doi: 10.1038/onc.2009.238. Epub 2009 Aug 17.

Telomere length is maintained by two known mechanisms, the activation of telomerase or alternative lengthening of telomeres (ALT). The molecular mechanisms regulating the ALT phenotype are poorly understood and it is unknown how the decision of which pathway to activate is made at the cellular level. We have shown earlier that active repression of telomerase gene expression by chromatin remodelling of the promoters is one mechanism of regulation; however, other genes and signalling networks are likely to be required to regulate telomerase and maintain the ALT phenotype. Using gene expression profiling, we have uncovered a signature of 1305 genes to distinguish telomerase-positive and ALT cell lines. By combining this with the gene expression profiles of liposarcoma tissue samples, we refined this signature to 297 genes. A network analysis of known interactions between genes within this signature revealed a regulatory signalling network consistent with a model of human telomerase reverse transcriptase (hTERT) repression in ALT cell lines and liposarcomas. This network expands on our existing knowledge of hTERT regulation and provides a platform to understand differential regulation of hTERT in different tumour types and normal tissues. We also show evidence to suggest a novel mesenchymal stem cell origin for ALT immortalization in cell lines and mesenchymal tissues.

Li, C. "Toward understanding the stem-cell origin and molecular regulation of rice tillering." J Genet Genomics. 2015 Feb 20;42(2):47-8. doi: 10.1016/j.jgg.2015.01.002. Epub 2015 Jan 24.

Liu, C., J. Wang, et al. "Possible stem cell origin of human cholangiocarcinoma." World J Gastroenterol. 2004 Nov 15;10(22):3374-6.

AIM: To investigate the expression of CD34 and c-kit (receptor of stem cell factor) in cholangiocarcinoma. METHODS: Fifteen cases of intrahepatic cholangiocarcinoma and 17 cases of extrahepatic cholangiocarcinoma were studied in this experiment. Using Envision detection system, paraffin-embedded sections of the resected cholangiocarcinoma tissue were stained with antibodies against CD34 and c-kit, respectively. The sections were counterstained with hematoxylin, and the results were examined under light microscope. Normal tonsil and mammary tissues were used as positive controls for CD34 and c-kit, respectively. RESULTS: CD34 was positive in all sections, but only in capillary endothelial cells of tumor tissue. No cholangiocarcinoma cells were positive for CD34. In one case of extrahepatic cholangiocarcinoma, a few tumor cells (about 5%) were immunoreactive with c-kit. CONCLUSION: CD34 or c-kit positive cells in liver tissue may represent liver stem cells, as they can differentiate into mature biliary cells in vitro. The expression of c-kit by some cholangiocarcinoma cells suggests that cholangiocarcinoma might originate from

liver stem cells. However, other mechanisms of hepatocarcinogenesis, such as de-differentiation of mature cholangiocytes, may also exist.

Maher, V. E., L. Gill, et al. "Simultaneous chronic lymphocytic leukemia and chronic myelogenous leukemia. Evidence of a separate stem cell origin." Cancer. 1993 Mar 15;71(6):1993-7.

The authors studied a patient with the simultaneous occurrence of chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). The coexistence of these two hematologic malignancies leads to questions about their cell of origin. Through analysis of this patient's DNA, the authors studied the derivation of the two malignancies. They separated the blood into a myeloid-rich fraction and a fraction containing the malignant lymphocytes. JH and bcr probes were used to study these loci in the myeloid and lymphoid fractions and in unfractionated white blood cells. The authors found that the unfractionated leukocytes contained the bcr and JH rearrangements. Conversely, the lymphoid fraction contained only the JH rearrangement, and the myeloid fraction contained only the bcr rearrangement, suggesting that these malignancies arose from separate stem cells. This is the first reported patient with simultaneously occurring CML and CLL definitively shown to arise from distinct progenitors, and this report raises questions about the origin of these two cell lines.

Marsh, J. C., A. J. Will, et al. ""Stem cell" origin of the hematopoietic defect in dyskeratosis congenita." Blood. 1992 Jun 15;79(12):3138-44.

We have used the long-term bone marrow culture (LTBMC) system to analyze hematopoiesis in three patients with dyskeratosis congenita (DC), two of whom had aplastic anemia, and the third had a normal blood count (apart from mild macrocytosis) and normal BM cellularity. Hematopoiesis was severely defective in all three patients, as measured by a low incidence of colony-forming cells and a low level of hematopoiesis in LTBMC. The function of the marrow stroma was normal in its ability to support the growth of hematopoietic progenitors from normal marrows seeded onto them in all three cases, but the generation of hematopoietic progenitors from patients marrow cells inoculated onto normal stromas was reduced, thus suggesting the defect to be of stem cell origin. The parents and unaffected brother of one of the families have also been studied in LTBMC and all showed normal hematopoietic and stromal cell function. From this study we speculate that there are some similarities between DC and the defect in the W/Wv mouse.

Mayumi, M., T. Tsutsui, et al. "Erythroleukemia with myelofibrosis--pediatric case report and discussion of possible stem cell origin of the disorder." Nihon Ketsueki Gakkai Zasshi. 1985 Sep;48(6):1414-22.

Najfeld, V., D. Zucker-Franklin, et al. "Evidence for clonal development and stem cell origin of M7 megakaryocytic leukemia." Leukemia. 1988 Jun;2(6):351-7.

Previous studies have shown that acute nonlymphocytic leukemias are clonal diseases in which there is heterogeneity in the pattern of stem cell differentiative expression. To determine whether M7 megakaryocytic leukemia is a clonal disease and to evaluate the differentiative expression of the cells involved by the leukemia we studied a patient with megakaryocytic leukemia who was heterozygous for the X-chromosome-linked glucose-6-phosphate dehydrogenase (G6PD). The diagnosis of megakaryocytic leukemia was based on results obtained with the immunogold method and ultrastructural studies with the monoclonal anti-Gplla/IIIb antibody, 10E5. Direct testing of blood and marrow mononuclear cells and blood platelets demonstrated only A-type G6PD, whereas skin exhibited both B and A enzymes. The results indicate that the megakaryocytic leukemia in this patient was clonal at the time of study. To determine the differentiative expression of the stem cells, granulocyte/macrophage colony forming units and erythroid burst forming units were cultured and the resultant colonies were tested for G6PD. The results indicate that the stem cells involved by the leukemia exhibited differentiative expression multipotent for the megakaryocytic and granulocytic pathways, but no definitive conclusion could be made regarding the erythroid lineage.

Nilsson, L., P. Eden, et al. "The molecular signature of MDS stem cells supports a stem-cell origin of 5q myelodysplastic syndromes." Blood. 2007 Oct 15;110(8):3005-14. Epub 2007 Jul 6.

Global gene expression profiling of highly purified 5q-deleted CD34+CD38(-)Thy1+ cells in 5q-myelodysplastic syndromes (MDSs) supported that they might originate from and outcompete normal CD34+CD38(-)Thy1+ hematopoietic stem cells. Few but distinct differences in gene expression distinguished MDS and normal stem cells. Expression of BMI1, encoding a critical regulator of self-renewal, was up-regulated in 5q- stem cells. Whereas multiple previous MDS genetic screens failed to identify altered expression of the gene encoding the myeloid transcription factor CEBPA, stage-specific and extensive down-regulation of CEBPA was specifically observed in MDS progenitors. These studies establish

the importance of molecular characterization of distinct stages of cancer stem and progenitor cells to enhance the resolution of stage-specific dysregulated gene expression.

Odoux, C., H. Fohrer, et al. "A stochastic model for cancer stem cell origin in metastatic colon cancer." Cancer Res. 2008 Sep 1;68(17):6932-41. doi: 10.1158/0008-5472.CAN-07-5779.

Human cancers have been found to include transformed stem cells that may drive cancer progression to metastasis. Here, we report that metastatic colon cancer contains clonally derived tumor cells with all of the critical properties expected of stem cells, including self-renewal and the ability to differentiate into mature colon cells. Additionally, when injected into mice, these cells initiated tumors that closely resemble human cancer. Karyotype analyses of parental and clonally derived tumor cells expressed many consistent (clonal) along with unique chromosomal aberrations, suggesting the presence of chromosomal instability in the cancer stem cells. Thus, this new model for cancer origin and metastatic progression includes features of both the hierarchical model for cancerous stem cells and the stochastic model, driven by the observation of chromosomal instability.

Ogawa, M., A. C. Larue, et al. "Hematopoietic stem cell origin of connective tissues." Exp Hematol. 2010 Jul;38(7):540-7. doi: 10.1016/j.exphem.2010.04.005. Epub 2010 Apr 20.

Connective tissue consists of "connective tissue proper," which is further divided into loose and dense (fibrous) connective tissues and "specialized connective tissues." Specialized connective tissues consist of blood, adipose tissue, cartilage, and bone. In both loose and dense connective tissues, the principal cellular element is fibroblasts. It has been generally believed that all cellular elements of connective tissue, including fibroblasts, adipocytes, chondrocytes, and bone cells, are generated solely by mesenchymal stem cells. Recently, a number of studies, including those from our laboratory based on transplantation of single hematopoietic stem cells, strongly suggested a hematopoietic stem cell origin of these adult mesenchymal tissues. This review summarizes the experimental evidence for this new paradigm and discusses its translational implications.

Ogawa, M., A. C. Larue, et al. "Hematopoietic stem cell origin of mesenchymal cells: opportunity for novel therapeutic approaches." Int J Hematol. 2010 Apr;91(3):353-9. doi: 10.1007/s12185-010-0554-4. Epub 2010 Mar 26.

There has been a general belief that there are two types of adult stem cells, i.e., hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), each with distinctly different functions. According to this dogma, HSCs produce blood cells, while MSCs are thought to generate a number of non-hematopoietic cells including fibroblasts, adipocytes, chondrocytes and bone cells. Recently, a number of studies, including those in our laboratory based on single HSC transplantation, blurred the clear distinction between HSCs and MSCs and strongly suggested an HSC origin of the adult mesenchymal tissues. This review summarizes the experimental evidence for this new paradigm and the literature pointing out the vagary in the stem cell nature of MSCs. The concept of the HSC origin of mesenchymal cells will have many immediate and long-term impacts on the therapies of diseases and injuries of the connective tissues.

Ondrejka, S. L., A. G. Jegalian, et al. PDGFRB-rearranged T-lymphoblastic leukemia/lymphoma occurring with myeloid neoplasms: the missing link supporting a stem cell origin, Haematologica. 2014 Sep;99(9):e148-51. doi: 10.3324/haematol.2014.105452. Epub 2014 Jun 20.

Persson, A. I., C. Petritsch, et al. "Non-stem cell origin for oligodendroglioma." Cancer Cell. 2010 Dec 14;18(6):669-82. doi: 10.1016/j.ccr.2010.10.033.

Malignant astrocytic brain tumors are among the most lethal cancers. Quiescent and therapy-resistant neural stem cell (NSC)-like cells in astrocytomas are likely to contribute to poor outcome. Malignant oligodendroglial brain tumors, in contrast, are therapy sensitive. Using magnetic resonance imaging (MRI) and detailed developmental analyses, we demonstrated that murine oligodendroglioma cells show characteristics of oligodendrocyte progenitor cells (OPCs) and are therapy sensitive, and that OPC rather than NSC markers enriched for tumor formation. MRI of human oligodendroglioma also suggested a white matter (WM) origin, with markers for OPCs rather than NSCs similarly enriching for tumor formation. Our results suggest that oligodendroglioma cells show hallmarks of OPCs, and that a progenitor rather than a NSC origin underlies improved prognosis in patients with this tumor.

Regitnig, P., E. Spuller, et al. "Insulinoma of the pancreas with insular-ductular differentiation in its liver metastasis--indication of a common stem-cell origin of the exocrine and endocrine components." Virchows Arch. 2001 Jun;438(6):624-8.

We describe an insulinoma of the pancreas in a 56-year-old patient, which showed insular-ductular differentiation in its liver metastasis. Although the

primary tumor was uniformly endocrine in nature with insulin production, the metastasis contained two distinct cell types in organoid arrangement. One cell type was insulin-positive and was arranged in islet-like structures; the other was insulin-negative but distinctly pan-cytokeratin and cytokeratin 7 positive and arranged in ducts. In the primary tumor and the metastasis, the tumor cells were surrounded by a desmoplastic stroma. As to the histogenesis of the tumor and its metastasis, we discuss the following possibilities: (1) the tumor cells might derive from a common stem cell that matures into two phenotypically different cell lines, resembling the situation in embryogenesis and (2) one tumor cell type originates from the other by transdifferentiation (metaplasia). We conclude that the parallel occurrence of endocrine and ductal differentiation supports the concept that, under certain conditions, islet cells and ductular cells may also originate from islets and that mixed endocrine/exocrine pancreatic tumors do not necessarily arise from totipotent duct cells but might also have a primary endocrine cell origin.

Reis-Filho, J. S., A. Preto, et al. "p63 expression in solid cell nests of the thyroid: further evidence for a stem cell origin." Mod Pathol. 2003 Jan;16(1):43-8.

Solid cell nests of the thyroid are embryonic remnants of endodermal origin that may be difficult to distinguish from squamous metaplasia, metastatic squamous carcinoma, papillary microcarcinoma, medullary carcinoma, and C-cell hyperplasia. These embryonic structures are composed of main cells and C-cells; cystic structures and mixed follicles are sometimes observed intermingled with solid cell nests. Recently, p63, a p53 homologue that is consistently expressed in basal/stem cells of stratified epithelia and plays a major role in triggering the differentiation of some specific cell lineages, has been characterized. We evaluated the immunohistochemical expression of p63, cytokeratins (CAM 5.2, AE1/AE3, 34betaE12, 7, and 20), carcinoembryonic antigen, thyroid transcription factor 1 (TTF-1), thyroglobulin, and calcitonin using the streptavidin-biotin-peroxidase complex technique in 6 bona fide solid cell nests. We observed that main cells of solid cell nests are strongly decorated by p63, while C-cells and all other thyroid structures were consistently negative. Moreover, main cells expressed carcinoembryonic antigen and all cytokeratins but cytokeratin 20 and lacked TTF-1, thyroglobulin and calcitonin. In contrast to this, C-cells of solid cell nests were immunoreactive for calcitonin, CAM 5.2, AE1/AE3, and cytokeratin 7; focal immunoreactivity for TTF-1 was also observed in some C-cells. We conclude that main cells of the solid cell nests display a basal/stem cell phenotype (p63 and basal cytokeratin positivity), whereas C-cells show features of parafollicular differentiation. We conclude, furthermore, that p63 antibodies may help in distinguishing solid cell nests from their mimics.

Ruff, M. R. and C. B. Pert "Small cell carcinoma of the lung: macrophage-specific antigens suggest hemopoietic stem cell origin." Science. 1984 Sep 7;225(4666):1034-6.

Four surface antigens previously recognized only in macrophages are present on human small cell lung carcinoma cells and tumors. Cancerous cells may arise from macrophage precursors in bone marrow, and these precursors migrate to lung to participate in the repair of damaged tissue produced by continuous heavy smoking. The characteristic presence of neuropeptides such as bombesin in small cell carcinoma, when considered along with these findings, presents new possibilities for the role of such peptides in nervous, endocrine, and immune system function.

Samokhvalov, I. M. "Return to the hematopoietic stem cell origin." Cell Regen (Lond). 2012 Dec 20;1(1):9. doi: 10.1186/2045-9769-1-9. eCollection 2012.

Studying embryonic hematopoiesis is complicated by diversity of its locations in the constantly changing anatomy and by the mobility of blood cell precursors. Embryonic hematopoietic progenitors are identified in traditional in vivo and in vitro cell potential assays. Profound epigenetic plasticity of mammalian embryonic cells combined with significant inductive capacity of the potential assays suggest that our understanding of hematopoietic ontogenesis is substantially distorted. Non-invasive in vivo cell tracing methodology offers a better insight into complex processes of blood cell specification. In contrast to the widely accepted view based on the cell potential assays, the genetic tracing approach identified the yolk sac as the source of adult hematopoietic stem cell lineage. Realistic knowledge of the blood origin is critical for safe and efficient recapitulation of hematopoietic development in culture.

Schaub, J. R., Y. Malato, et al. "Evidence against a stem cell origin of new hepatocytes in a common mouse model of chronic liver injury." Cell Rep. 2014 Aug 21;8(4):933-9. doi: 10.1016/j.celrep.2014.07.003. Epub 2014 Aug 14.

Hepatocytes provide most liver functions, but they can also proliferate and regenerate the liver after injury. However, under some liver injury conditions, particularly chronic liver injury where hepatocyte proliferation is impaired, liver stem cells (LSCs) are thought to replenish lost hepatocytes. Conflicting results have been reported about the identity of LSCs and their contribution to liver regeneration. To address

this uncertainty, we followed candidate LSC populations by genetic fate tracing in adult mice with chronic liver injury due to a choline-deficient, ethionine-supplemented diet. In contrast to previous studies, we failed to detect hepatocytes derived from biliary epithelial cells or mesenchymal liver cells beyond a negligible frequency. In fact, we failed to detect hepatocytes that were not derived from pre-existing hepatocytes. In conclusion, our findings argue against LSCs, or other nonhepatocyte cell types, providing a backup system for hepatocyte regeneration in this common mouse model of chronic liver injury.

Sell, S. "On the stem cell origin of cancer." Am J Pathol. 2010 Jun;176(6):2584-494. doi: 10.2353/ajpath.2010.091064. Epub 2010 Apr 29.

In each major theory of the origin of cancer-field theory, chemical carcinogenesis, infection, mutation, or epigenetic change-the tissue stem cell is involved in the generation of cancer. Although the cancer type is identified by the more highly differentiated cells in the cancer cell lineage or hierarchy (transit-amplifying cells), the property of malignancy and the molecular lesion of the cancer exist in the cancer stem cell. In the case of teratocarcinomas, normal germinal stem cells have the potential to become cancers if placed in an environment that allows expression of the cancer phenotype (field theory). In cancers due to chemically induced mutations, viral infections, somatic and inherited mutations, or epigenetic changes, the molecular lesion or infection usually first occurs in the tissue stem cells. Cancer stem cells then give rise to transit-amplifying cells and terminally differentiated cells, similar to what happens in normal tissue renewal. However, the major difference between cancer growth and normal tissue renewal is that whereas normal transit amplifying cells usually differentiate and die, at various levels of differentiation, the cancer transit-amplifying cells fail to differentiate normally and instead accumulate (ie, they undergo maturation arrest), resulting in cancer growth.

Sell, S. "Stem cell origin of cancer and differentiation therapy." Crit Rev Oncol Hematol. 2004 Jul;51(1):1-28.

Our forefathers in pathology, on observing cancer tissue under the microscope in the mid-19th century, noticed the similarity between embryonic tissue and cancer, and suggested that tumors arise from embryo-like cells [Recherches dur le Traitement du Cancer, etc. Paris. (1829); Editoral Archiv fuer pathologische Anatomie und Physiologie und fuer klinische Medizin 8 (1855) 23]. The concept that adult tissues contain embryonic remnants that generally lie dormant, but that could be activated to become cancer was later formalized by Cohnheim [Path. Anat. Physiol. Klin. Med. 40 (1867) 1-79; Virchows Arch. 65 (1875) 64] and Durante [Arch. Memori ed Osservazioni di Chirugia Practica 11 (1874) 217-226], as the "embryonal rest" theory of cancer. An updated version of the embryonal rest theory of cancer is that cancers arise from tissue stem cells in adults. Analysis of the cellular origin of carcinomas of different organs indicates that there is, in each instance, a determined stem cell required for normal tissue renewal that is the most likely cell of origin of carcinomas [Lab. Investig. 70 (1994) 6-22]. In the present review, the nature of normal stem cells (embryonal, germinal and somatic) is presented and their relationships to cancer are further expanded. Cell signaling pathways shared by embryonic cells and cancer cells suggest a possible link between embryonic cells and cancer cells. Wilm's tumors (nephroblastomas) and neuroblastomas are presented as possible tumors of embryonic rests in children. Teratocarcinoma is used as the classic example of the totipotent cancer stem cell which can be influenced by its environment to differentiate into a mature adult cell. The observation that "promotion" of an epidermal cancer may be accomplished months or even years after the initial exposure to carcinogen ("initiation"), implies that the original carcinogenic event occurs in a long-lived epithelial stem cell population. The cellular events during hepatocarcinogenesis illustrate that cancers may arise from cells at various stages of differentiation in the hepatocyte lineage. Examples of genetic mutations in epithelial and hematopoietic cancers show how specific alterations in gene expression may be manifested as maturation arrest of a cell lineage at a specific stage of differentiation. Understanding the signals that control normal development may eventually lead us to insights in treating cancer by inducing its differentiation (differentiation therapy). Retinoid acid (RA) induced differentiation therapy has acquired a therapeutic niche in treatment of acute promyelocytic leukemia and the ability of RA to prevent cancer is currently under examination.

Sell, S. and H. A. Dunsford "Evidence for the stem cell origin of hepatocellular carcinoma and cholangiocarcinoma." Am J Pathol. 1989 Jun;134(6):1347-63.

A review of the morphologic, autoradiographic, and phenotypic analysis of the cellular changes seen during induction of cancer of the liver in rats by chemical carcinogens is used to develop an alternative to the established hypothesis that chemically induced hepatocellular carcinoma arises from premalignant nodules. The authors propose that hepatocellular and ductular carcinomas arise from

a pluripotent liver stem cell and that enzyme-altered foci and nodular changes are adaptive non-oncogenic responses to the toxic effects of carcinogens. It is further postulated that persistent nodules may provide an environment that nurtures development of neoplastic cells other than the altered hepatocytes that originally form the nodule. It is possible, however, that there may be more than one cellular lineage to hepatocellular cancer and that persistent nodules contain these different lineages.

Sera, Y., A. C. LaRue, et al. "Hematopoietic stem cell origin of adipocytes." Exp Hematol. 2009 Sep;37(9):1108-20, 1120.e1-4. doi: 10.1016/j.exphem.2009.06.008. Epub 2009 Jul 2.

OBJECTIVE: It has generally been believed that adipocytes are derived from mesenchymal stem cells via fibroblasts. We recently reported that fibroblasts/myofibroblasts in a number of tissues and organs are derived from hematopoietic stem cells (HSCs). In the present study, we tested the hypothesis that HSCs also give rise to adipocytes. MATERIALS AND METHODS: Using transplantation of a single enhanced green fluorescent protein-positive (EGFP(+)) HSC and primary culture, we examined generation of adipocytes from HSCs. RESULTS: Adipose tissues from clonally engrafted mice showed EGFP(+) adipocytes that stained positive for leptin, perilipin, and fatty acid binding protein 4. A diet containing rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, significantly enhanced the number of EGFP(+) adipocytes. When EGFP(+) bone marrow cells from clonally engrafted mice were cultured under adipogenic conditions, all of the cultured cells stained positive with Oil Red O and Sudan Black B and exhibited the presence of abundant mRNA for adipocyte markers. Finally, clonal culture- and sorting-based studies of Mac-1 expression of hematopoietic progenitors suggested that adipocytes are derived from HSCs via progenitors for monocytes/macrophages. CONCLUSION: Together, these studies clarify the current controversy regarding the ability of HSCs to give rise to adipocytes. Furthermore, our primary culture method that generates adipocytes from uncommitted hematopoietic cells should contribute to the studies of the mechanisms of early adipocytic differentiation and may lead to development of therapeutic solutions for many general obesity issues.

Shirai, K., Y. Sera, et al. "Hematopoietic stem cell origin of human fibroblasts: cell culture studies of female recipients of gender-mismatched stem cell transplantation and patients with chronic myelogenous leukemia." Exp Hematol. 2009 Dec;37(12):1464-71. doi: 10.1016/j.exphem.2009.09.008. Epub 2009 Sep 26.

OBJECTIVE: Our series of studies using transplantation of single hematopoietic stem cells (HSCs) demonstrated that mouse fibroblasts/myofibroblasts are derived from HSCs. In order to determine the origin of human fibroblasts, we established a method for culturing fibroblasts from human peripheral blood (PB) mononuclear cells and studied fibroblasts from gender-mismatched HSC transplant recipients and patients with untreated Philadelphia chromosome-positive chronic myelogenous leukemia (CML). MATERIALS AND METHODS: We cultured PB cells from three female subjects who showed near-complete hematopoietic reconstitution from transplantation of granulocyte-colony stimulating factor-mobilized male PB cells and examined the resulting fibroblasts using fluorescent in situ hybridization for Y chromosome. Because the mobilized PB cells may contain mesenchymal stem cells, we could not determine the HSC or mesenchymal stem cell origin of the fibroblasts seen in culture. To further document the HSC origin of human fibroblasts, we next examined fibroblasts from two patients with untreated CML, a known clonal disorder of HSCs. RESULTS: All cultured fibroblasts from female recipients of male cells showed the presence of Y chromosome, indicating the donor origin of fibroblasts. Cultured fibroblasts from the CML patients revealed the presence of BCR-ABL translocation. This demonstration provided strong evidence for the HSC origin of human fibroblasts because CML is a clonal disorder of the HSC. CONCLUSIONS: These studies strongly suggest that human fibroblasts are derived from HSCs. In addition, the results suggest that fibrosis seen in patients with CML may be a part of the clonal process.

Shupe, T. and B. E. Petersen "Evidence regarding a stem cell origin of hepatocellular carcinoma." Stem Cell Rev. 2005;1(3):261-4.

The cellular origin of tumors remains as one of the unanswered, fundamental questions of cancer biology. The notion that tumors may arise from tissue stem cells is supported by phenotypic similarities between these two cell types, such as proliferative potential and expression of onco-fetal proteins. Liver stem cells, or oval cells, have been put forth as a possible target for hepatocarcinogens. Genetically modified and in vitro transformed oval cells have been shown to form tumors in transplantation to animals. Chemical carcinogenesis models in the liver demonstrate varying degrees of oval cell proliferation. There is also preliminary evidence that hepatocellular carcinoma may maintain a bipotential phenotype consistent with an oval cell origin. Whereas definitive

proof of an oval cell origin of hepatocellular has yet to be presented, the current circumstantial evidence justifies continued research on this subject.

Simon, L. L., J. R. Kateley, et al. "Congenital leukemia of possible stem cell origin--multiparameter analysis." Am J Pediatr Hematol Oncol. 1984 Summer;6(2):217-20.

Som, A., S. Wen, et al. "Stem cell origin of testicular seminoma." Clin Genitourin Cancer. 2013 Dec;11(4):489-94. doi: 10.1016/j.clgc.2013.04.015. Epub 2013 Jul 10.

INTRODUCTION: A major question concerning cancer is its cells of origin. We hypothesized that distinct cancer subtypes arise from unique cancer-initiating cells. By performing a microarray meta-analysis of seminomas and spermatogonial stem cells, we investigated a putative cell of origin for seminoma. MATERIALS AND METHODS: We obtained published microarray data for 6 human adult germ cell lines, 16 embryonic stem cell lines, 3 normal testicular tissue samples, and 40 seminomas from the Gene Expression Omnibus database. By assessing correlations between various tissue microarrays, we determined the number of transitional events and the distance between seminomas and human spermatogonial stem cells. RESULTS: Our meta-analysis showed that spermatogonial stem cells correlated similarly with seminoma (95% CI of Spearman rho, 0.33-0.44) and with normal somatic testicular tissue cells (95% CI, 0.39-0.40), which suggests parallel paths of cellular origins. CONCLUSION: Analysis of our results suggests that a unique cancer subtype, namely seminoma, may have originated from an undifferentiated cell with stemness features rather than from a differentiated cell that acquired stemness features.

Terrin, B. N., E. J. Studer, et al. "Childhood leukemia with simultaneously expressed myeloid and lymphoid markers suggesting stem cell origin." Am J Hematol. 1985 Oct;20(2):175-81.

A case study is presented of a leukemic patient whose cells express markers of both myeloid and lymphoid cells. Cells were identified from bone marrow which expressed either myeloid antigens, lymphoid antigens, or both myeloid and lymphoid antigens, indicating a possible common stem cell capable of differentiating along either a lymphoid or myeloid cell lineage. Using specific monoclonal antibodies, 40-70% of the cells were reactive with anti-T-cell antibodies, 50% of the cells were reactive with antibodies to the common ALL antigen (CALLA), and 80-90% of the cells were reactive with antibodies directed against myeloid antigens. Using double staining techniques, some cells were found to demonstrate only myeloid markers; others, only lymphoid markers; and others, both myeloid and lymphoid markers. These results suggest that a common stem cell is capable of differentiating along both lymphoid and myeloid lineages.

Tez, M. and Y. A. Kilic Stem cell origin theory of the inguinal hernia, Med Hypotheses. 2006;66(5):1042-3. Epub 2006 Jan 30.

Tsukamoto, N., K. Morita, et al. "Clonality in myelodysplastic syndromes: demonstration of pluripotent stem cell origin using X-linked restriction fragment length polymorphisms." Br J Haematol. 1993 Apr;83(4):589-94.

Restriction fragment length polymorphisms (RFLP) of the X-chromosome genes phosphoglycerate kinase (PGK) and hypoxanthine phorphoribosyltransferase (HPRT) were used to determine the clonal nature of myelodysplastic syndromes (MDS) in 22 patients. These included eight with refractory anaemia (RA), four with RA with ring sideroblasts (RARS), six with RA with an excess of blasts (RAEB), three with RAEB in transformation (RAEB-T), and one with chronic myelomonocytic leukaemia (CMML). Monoclonal X-inactivation patterns were observed in 19/22 patients. The remaining three cases, one each with RA, RARS and RAEB, were of polyclonal composition. Separated T-lymphocyte and granulocyte fraction analyses in six patients of the former cases revealed that T-lymphocyte as well as granulocyte fractions showed a monoclonal pattern of X-inactivation. These results support the view that the majority of MDS arise from a pluripotent stem cell capable of myeloid and lymphoid differentiation.

Tu, S. M., S. H. Lin, et al. "Stem-cell origin of metastasis and heterogeneity in solid tumours." Lancet Oncol. 2002 Aug;3(8):508-13.

An explanation for the inherently metastatic and heterogeneous nature of cancers may be their derivation from distinct stem cells. The type of stem cell from which a neoplasm arises determines both the metastatic potential and the phenotypic diversity of that neoplasm. Hence, tumours originating from an early stem cell or its progenitor cells metastasise readily and have a more heterogeneous phenotype, whereas tumours originating from a later stem cell or its progenitor cells have limited metastatic potential and a more homogeneous phenotype. Further investigation of the role of stem cells in the development of cancer may lead to the discovery of

novel diagnostic tools, prognostic markers, and therapeutic targets in the battle against cancer.

Turner, J. D. and N. Sanai A brain tumor stem cell origin for glioblastoma endothelium, World Neurosurg. 2011 May-Jun;75(5-6):574-5. doi: 10.1016/j.wneu.2011.03.030.

Waters, D., B. Newman, et al. "Stem cell origin of brain tumors." Adv Exp Med Biol. 2010;671:58-66.

The biology of both normal and tumor development clearly possesses overlapping and parallel features. Oncogenes and tumor suppressors are relevant not only in tumor biology, but also in physiological developmental regulators of growth and differentiation. Conversely, genes identified as regulators of developmental biology are relevant to tumor biology. This is particularly relevant in the context of brain tumors, where recent evidence is mounting that the origin of brain tumors, specifically gliomas, may represent dysfunctional developmental neurobiology. NSCs are increasingly being investigated as the cell type that originally undergoes malignant transformation--the cell of origin--and the evidence for this is discussed.

Zhang, T., T. Otevrel, et al. "Evidence that APC regulates survivin expression: a possible mechanism contributing to the stem cell origin of colon cancer." Cancer Res. 2001 Dec 15;61(24):8664-7.

Because colorectal cancers (CRCs) frequently display APC mutation, inhibition of apoptosis, and increased expression of the antiapoptotic protein survivin, we hypothesized that APC mutation inhibits apoptosis by allowing constitutive survivin expression. Using HT-29 CRC cell lines having inducible wild-type APC (wt-APC) or transfected dominant-negative TCF-4, we show that wt-APC down-regulates survivin expression via APC/beta-catenin/TCF-4 signaling. Using normal colonic epithelium, we found survivin by immunostaining/reverse transcription-PCR to be preferentially expressed in the lower crypt (which inversely correlates with wt-APC's expression pattern). Thus, wt-APC, by progressively decreasing survivin and increasing apoptosis from crypt bottom to top, may limit the population size of stem cells and other proliferative cells in the lower crypt; mutant APC may allow expansion of these populations, thereby initiating tumorigenesis.

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