Stem Cell and Evolution 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 and evolution related studies.
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1. Introduction

There are many methods to deliver the transcription factors into target cells to generate iPSCs. The first method is retrovirus or lentivirus transduction. The problem of this technique is the genome integration of virus DNA which could possibly alter differentiation potential or other malignant transformation. The second method is adenoviral vectors to induce iPSC. The advantage of adenovirus vector based expression is that the transgenes will not integrate into the house genome, thus reduces the risk of tumorogenesis. The third one is a plasmid based transfection that can avoid the genome integration also. Recently, the Cre-recombinase excisable systems are used in iPSC induction and subsequent transgene removal making the iPSC technology closer to clinic applications.

The following introduces recent reports as references in the related studies.

Baker, A. M., B. Cereser, et al. "Quantification of crypt and stem cell evolution in the normal and neoplastic human colon." Cell Rep. 2014 Aug 21;8(4):940-7. doi: 10.1016/j.celrep.2014.07.019. Epub 2014 Aug 7.

Human intestinal stem cell and crypt dynamics remain poorly characterized because transgenic lineage-tracing methods are impractical in humans. Here, we have circumvented this problem by quantitatively using somatic mtDNA mutations to trace clonal lineages. By analyzing clonal imprints on the walls of colonic crypts, we show that human intestinal stem cells conform to one-dimensional neutral drift dynamics with a "functional" stem cell number of five to six in both normal patients and individuals with familial adenomatous polyposis (germline APC(-/+)). Furthermore, we show that, in adenomatous crypts (APC(-/-)), there is a proportionate increase in both functional stem cell number and the loss/replacement rate. Finally, by analyzing fields of mtDNA mutant crypts, we show that a normal colon crypt divides around once every 30-40 years, and the division rate is increased in adenomas by at least an order of magnitude. These data provide in vivo quantification of human intestinal stem cell and crypt dynamics.

Barritta de Defranchi, R. L., A. Bordalejo, et al. "Evolution of nutritional status in patients with autologous and allogeneic hematopoietic stem cell transplant." Support Care Cancer. 2015 May;23(5):1341-7. doi: 10.1007/s00520-014-2473-z. Epub 2014 Oct 28.

PURPOSE: To describe the nutritional status in patients undergoing hematopoietic stem cell transplant (HSCT) in three different defined moments: at admission to the Bone Marrow Transplant Unit (BMTU), at discharge from the BMTU and at follow-up. We hypothesized that nutrition status declines during hospitalization and recovers at follow-up. METHODS: Prospective cohort study. Nutritional status was determined using the patient-generated subjective global assessment (PG-SGA) at three different defined moments: T1, defined as the time of admission to the BMTU; T2, at the time of discharge from the BMTU; and T3, at follow-up appointment 10 days after discharge. PG-SGA score differences were described among T1, T2, and T3. Participants were adults admitted for any type of HSCT to our BMTU from March 2010 to July 2013. One hundred and twenty-three patients were included. RESULTS: Subjects (94.3 %) were well nourished at T1, but 59.7 % were classified as malnourished at T2. PG-SGA score was 3.39 (+/-3.47) at T1, 12.3 (+/-5.6) at T2, and 6.54 (+/-4.57) at T3 ($p < 0.001$). During

hospitalization, nutritional status deteriorated more in men than women (10.59 vs. 7.93; p = 0.002), in patients with length of hospital stay greater than 21 days (10.64 vs. 8.45, p = 0.034), in patients younger than 60 years (10.7 vs. 6.42; p = 0.0007), and those individuals with allogeneic transplant (12.45 vs. 8.74; p = 0.0152). CONCLUSIONS: Patients undergoing HSCT were well nourished upon admission to the BMTU. Nutritional status significantly declined during hospitalization and improved at follow-up. However, nutritional intervention may still be required.

Blanco, Y., A. Saiz, et al. "Evolution of brain-derived neurotrophic factor levels after autologous hematopietic stem cell transplantation in multiple sclerosis." Neurosci Lett. 2005 May 20-27;380(1-2):122-6. Epub 2005 Feb 1.

A neuroprotective role of inflammation has been suggested based on that immune cells are the main source of brain-derived neurotrophic factor (BDNF). We investigated the 3-year evolution of BDNF levels in serum, CSF and culture supernatant of peripheral blood mononuclear cells (PBMC), unstimulated and stimulated with anti-CD3 and soluble anti-CD28 antibodies, in 14 multiple sclerosis patients who underwent an autologous hematopoietic stem cell transplantation (AHSCT). BDNF levels were correlated with previously reported MRI measures that showed a reduction of T2 lesion load and increased brain atrophy, mainly at first year post-transplant. A significant decrease of serum BDNF levels was seen at 12 months post-transplant. BDNF values were found significantly lower in stimulated but not in unstimulated PBMC supernatants during the follow-up, supporting that AHSCT may induce a down-regulation of BDNF production. The only significant correlation was found between CSF BDNF levels and T2 lesion load before and 1 year after AHSCT, suggesting that BDNF reflects the past and ongoing inflammatory activity and demyelination of these highly active patients. Our study suggests that AHSCT can reduce BDNF levels to values associated with lower activity. This decrease does not seem to correlate with the brain atrophy measures observed in the MRI.

Busardo, F. P., M. Gulino, et al. "The evolution of legislation in the field of Medically Assisted Reproduction and embryo stem cell research in European union members." Biomed Res Int. 2014;2014:307160. doi: 10.1155/2014/307160. Epub 2014 Jul 24.

Medically Assisted Reproduction (MAR), involving in vitro fertilisation (IVF), and research on embryos have created expectation to many people affected by infertility; at the same time it has generated a surplus of laws and ethical and social debates. Undoubtedly, MAR represents a rather new medical field and constant developments in medicine and new opportunities continue to defy the attempt to respond to those questions. In this paper, the authors reviewed the current legislation in the 28 EU member states trying to evaluate the different legislation paths adopted over the last 15 years and highlighting those EU countries with no specific legislation in place and MAR is covered by a general health Law and those countries in which there are no laws in this field but only "guidelines." The second aim of this work has been to compare MAR legislation and embryo research in EU countries, which derive from different origins ranging from an extremely prohibitive approach versus a liberal one, going through a cautious regulatory approach.

Cabezas-Wallscheid, N., V. Eichwald, et al. "Instruction of haematopoietic lineage choices, evolution of transcriptional landscapes and cancer stem cell hierarchies derived from an AML1-ETO mouse model." EMBO Mol Med. 2013 Dec;5(12):1804-20. doi: 10.1002/emmm.201302661. Epub 2013 Oct 4.

The t(8;21) chromosomal translocation activates aberrant expression of the AML1-ETO (AE) fusion protein and is commonly associated with core binding factor acute myeloid leukaemia (CBF AML). Combining a conditional mouse model that closely resembles the slow evolution and the mosaic AE expression pattern of human t(8;21) CBF AML with global transcriptome sequencing, we find that disease progression was characterized by two principal pathogenic mechanisms. Initially, AE expression modified the lineage potential of haematopoietic stem cells (HSCs), resulting in the selective expansion of the myeloid compartment at the expense of normal erythro- and lymphopoiesis. This lineage skewing was followed by a second substantial rewiring of transcriptional networks occurring in the trajectory to manifest leukaemia. We also find that both HSC and lineage-restricted granulocyte macrophage progenitors (GMPs) acquired leukaemic stem cell (LSC) potential being capable of initiating and maintaining the disease. Finally, our data demonstrate that long-term expression of AE induces an indolent myeloproliferative disease (MPD)-like myeloid leukaemia phenotype with complete penetrance and that acute inactivation of AE function is a potential novel therapeutic option.

Calabrese, P., S. Tavare, et al. "Pretumor progression: clonal evolution of human stem cell populations." Am J Pathol. 2004 Apr;164(4):1337-46.

Multistep carcinogenesis through sequential cycles of mutation and clonal succession is usually described as tumor progression, or the clonal evolution of tumor cell populations. However, many mutations found in cancers are also compatible with normal appearing phenotypes and therefore genetic progression may precede tumor progression. To better characterize such pretumor progression (mutations in the absence of visible phenotypic changes), a quantitative model was developed that postulates most oncogenic cancer mutations first accumulate in normal appearing colon crypt niche stem cells. Each crypt contains multiple stem cells, and random niche stem cell loss with replacement eventually leads to the loss of all stem cell lineages except one. This niche succession or crypt clonal evolution is similar to the clonal succession of tumor progression except it does not require selection or change visible phenotype. Mutations may sequentially accumulate during stem cell clonal evolution either through drift (passenger mutations) or selection. To determine the feasibility of pretumor progression, mutation rates sufficient to recreate the epidemiology of colorectal cancer were estimated. Pretumor progression may completely substitute for visible tumor progression because it is theoretically possible for all cancer mutations to first accumulate in normal appearing colon with normal replication fidelity. Elevated mutation rates or tumorigenesis may be unnecessary for early progression.

Caulfield, T., C. Rachul, et al. "The evolution of policy issues in stem cell research: an international survey." Stem Cell Rev. 2012 Dec;8(4):1037-42. doi: 10.1007/s12015-012-9404-5.

Stem cell research remains a tremendously promising yet controversial field of study. It continues to attract considerable public interest and generate discussion and debate. However, while the high profile of this field has endured, the tone and nature of the discourse that drives this profile appears to be changing. In order to get a better sense of how these potential shifts are perceived by individuals directly embedded in the field, we conducted an international internet survey of members of the stem cell research community. Our participants included individuals publishing on both scientific and ethical, legal and social issues topics. We explored the degree to which participants perceived that key policy issues were becoming more or less contentious over time. We queried views regarding the effect of regulatory frameworks on emerging stem cell research technologies and the extent to which participants experience pressure related to clinical translation. We also explored participants' relationships with industry, experience with patents and perceptions regarding the emphasis placed on the potential economic benefits of stem cell research. Our results suggest that while traditional debates such as those surrounding the moral status of the embryo remain, other issues more closely associated with clinical translation and commercialization are perceived as becoming increasingly contentious. This survey provides useful insight into the perspectives of a sample of active researchers working in countries around the world as well as an opportunity to reflect on the likely direction of future stem cell policy debates.

Chen, S., X. Huang, et al. "The evolution of malignant and reactive gammadelta + T cell clones in a relapse T-ALL case after allogeneic stem cell transplantation." Mol Cancer. 2013 Jul 12;12:73. doi: 10.1186/1476-4598-12-73.

BACKGROUND: To improve the outcome of patients with T-cell acute lymphoblastic leukemia (T-ALL), characterization of the biological features of T-ALL blast cells and the immune status of patients with T-ALL is needed to identify specific therapeutic strategies. FINDINGS: Using a novel approach based on the combination of fine-tiling comparative genomic hybridization (FT-CGH) and ligation-mediated PCR (LM-PCR), we molecularly identified a malignant gammadelta + T cell clone with a Vdelta5Ddelta2Jdelta1 rearrangement that was paired with a T cell receptor (TCR) VgammaI and comprised a Vgamma1Vdelta5 T cell clone in a relapse T-ALL patient. This malignant Vdelta5 T cell clone disappeared after chemotherapy, but the clone was detected again when disease relapsed post allogeneic hematopoietic stem cell transplantation (allo-HSCT) at 100 weeks. Using PCR and GeneScan analyses, the distribution and clonality of the TCR Vgamma and Vdelta subfamilies were examined before and after allo-HSCT in the patient. A reactive T cell clone with a Vdelta4Ddelta3Jdelta1 rearrangement was identified in all samples taken at different time points (i.e., 4, 8, 68, 100 and 108 weeks after allo-HSCT). The expression of this Vdelta4+ T cell clone was higher in the patient during complete remission (CR) post allo-HSCT and at disease relapse. CONCLUSIONS: This study established a sensitive methodology to detect T cell subclones, which may be used to monitor minimal residual disease and immune reconstitution.

Choi, J. Y. and C. F. Aquadro "The coevolutionary period of Wolbachia pipientis infecting Drosophila ananassae and its impact on the evolution of the host germline stem cell regulating genes." Mol Biol Evol. 2014 Sep;31(9):2457-71. doi: 10.1093/molbev/msu204. Epub 2014 Jun 28.

The endosymbiotic bacteria Wolbachia pipientis is known to infect a wide range of arthropod

species yet less is known about the coevolutionary history it has with its hosts. Evidence of highly identical W. pipientis strains in evolutionary divergent hosts suggests horizontal transfer between hosts. For example, Drosophila ananassae is infected with a W. pipientis strain that is nearly identical in sequence to a strain that infects both D. simulans and D. suzukii, suggesting recent horizontal transfer among these three species. However, it is unknown whether the W. pipientis strain had recently invaded all three species or a more complex infectious dynamic underlies the horizontal transfers. Here, we have examined the coevolutionary history of D. ananassae and its resident W. pipientis to infer its period of infection. Phylogenetic analysis of D. ananassae mitochondrial DNA and W. pipientis DNA sequence diversity revealed the current W. pipientis infection is not recent. In addition, we examined the population genetics and molecular evolution of several germline stem cell (GSC) regulating genes of D. ananassae. These studies reveal significant evidence of recent and long-term positive selection at stonewall in D. ananassae, whereas pumillio showed patterns of variation consistent with only recent positive selection. Previous studies had found evidence for adaptive evolution of two key germline differentiation genes, bag of marbles (bam) and benign gonial cell neoplasm (bgcn), in D. melanogaster and D. simulans and proposed that the adaptive evolution at these two genes was driven by arms race between the host GSC and W. pipientis. However, we did not find any statistical departures from a neutral model of evolution for bam and bgcn in D. ananassae despite our new evidence that this species has been infected with W. pipientis for a period longer than the most recent infection in D. melanogaster. In the end, analyzing the GSC regulating genes individually showed two of the seven genes to have evidence of selection. However, combining the data set and fitting a specific population genetic model significant proportion of the nonsynonymous sites across the GSC regulating genes were driven to fixation by positive selection. Clearly the GSC system is under rapid evolution and potentially multiple drivers are causing the rapid evolution.

delaCruz, J. and K. Pursell "BK Virus and Its Role in Hematopoietic Stem Cell Transplantation: Evolution of a Pathogen." Curr Infect Dis Rep. 2014 Aug;16(8):417. doi: 10.1007/s11908-014-0417-x.

We reviewed the literature regarding disease induced by BK virus (BKV) in the hematopoietic stem cell transplant (HSCT) population, particularly hemorrhagic cystitis (HC) and nephritis. The association between BKV and HC has been reported over the past four decades. BKV has been clinically implicated and widely accepted as an etiologic agent of HC and nephritis in HSCT and nephropathy in renal transplant patients. We discuss the potential benefit of early initiation of therapy in patients who fail supportive care alone as well as the different treatment strategies for HC induced by BKV. Treatments that have been used such as cidofovir and leflunomide are accompanied by risks, and the benefits are not as concrete as with other viral illness in the HSCT population.

Desai, N., P. Rambhia, et al. "Human embryonic stem cell cultivation: historical perspective and evolution of xeno-free culture systems." Reprod Biol Endocrinol. 2015 Feb 22;13:9. doi: 10.1186/s12958-015-0005-4.

Human embryonic stem cells (hESC) have emerged as attractive candidates for cell-based therapies that are capable of restoring lost cell and tissue function. These unique cells are able to self-renew indefinitely and have the capacity to differentiate in to all three germ layers (ectoderm, endoderm and mesoderm). Harnessing the power of these pluripotent stem cells could potentially offer new therapeutic treatment options for a variety of medical conditions. Since the initial derivation of hESC lines in 1998, tremendous headway has been made in better understanding stem cell biology and culture requirements for maintenance of pluripotency. The approval of the first clinical trials of hESC cells for treatment of spinal cord injury and macular degeneration in 2010 marked the beginning of a new era in regenerative medicine. Yet it was clearly recognized that the clinical utility of hESC transplantation was still limited by several challenges. One of the most immediate issues has been the exposure of stem cells to animal pathogens, during hESC derivation and during in vitro propagation. Initial culture protocols used co-culture with inactivated mouse fibroblast feeder (MEF) or human feeder layers with fetal bovine serum or alternatively serum replacement proteins to support stem cell proliferation. Most hESC lines currently in use have been exposed to animal products, thus carrying the risk of xeno-transmitted infections and immune reaction. This mini review provides a historic perspective on human embryonic stem cell culture and the evolution of new culture models. We highlight the challenges and advances being made towards the development of xeno-free culture systems suitable for therapeutic applications.

Glazko, T. T., L. M. Mezhevikina, et al. "["Chain" karyotypic evolution of embryonic stem cell line R1 in vitro]." Tsitologiia. 2005;47(8):679-85.

Cytogenetic anomaly frequencies were analysed in three sublines of ES R1 line in its five

clonal sublines, obtained from two cell colonies after transformation of ES R1 cells by plasmid with gene lif. Cell transformation did not increase cytogenic anomalies, however, the initial sublines of ES R1 line, as well as its transformed clonal descendants bore a redundant quantity of the chromosome 8 material within the structure of various Robertsonian translocations even in cells with diploid chromosome quantity (2n = 40). In the initial sublines ES R1 and its clonal descendants a common Rb (8; 15) was revealed. It was supposed that selection for the increase in ES cell sensitivity to cytokines (in particular, LIF) under cultural conditions was accompanied by an increase in chromosomal copies, carrying genes of mapk andjak/stat, through which downstream effectors of cytokine signals for preservation of cell pluripotention and propagation are realized. Genes of chromatid separation and chromosome segregation control (for example, separase gene Esp1 in chromosome 15) may be passively involved in this process, thus promoting acceleration of karyotype evolution in ES cells.

Gratwohl, A., H. Baldomero, et al. "Evolution of hematopoietic stem cell transplantation in Eastern and Western Europe from 1990 to 2003. A report from the EBMT activity survey." Croat Med J. 2004 Dec;45(6):689-94.

Transplantation of hematopoietic stem cells (HSCT) has seen rapid expansion during the last decade. It is evident that there are differences between eastern and western European countries when this high cost procedure is concerned. In order to obtain more insight into the mechanisms associated with these differences, we compared the transplant rates (number of transplants per 10 million population) for allogeneic and autologous HSCT between selected eastern and western European countries and looked for factors associated with their differences. Data were obtained by the annual European Group for Blood and Marrow Transplantation (EBMT) activity survey for the period from 1990 to 2003. Transplant rates were substantially lower in eastern European countries for autologous, allogeneic, and unrelated HSCT throughout the observation period. The rapid increase in transplant rates during the 1990s occurred later in eastern European countries. Transplant rates continued to rise during the last three years in eastern European countries in contrast to a plateau in transplant rates in western European countries. There was a clear correlation between economic factors, measured as gross national income per capita, and transplant rates for low-income countries. There was also a clear correlation between team density (number of teams per 10 million population) and transplant rates. These data document that economic factors explain the differences in transplant rates between eastern and western European countries only in part. Another important factor seems to be the access to the therapeutic procedure. These data provide a basis for health care planning.

Gratwohl, A. and D. Niederwieser "History of hematopoietic stem cell transplantation: evolution and perspectives." Curr Probl Dermatol. 2012;43:81-90. doi: 10.1159/000335266. Epub 2012 Feb 17.

Hematopoietic stem cell transplantation (HSCT) has evolved over the last half century from experimental bone marrow transplantation for patients with incurable leukemia or bone marrow failure to standard of care for a broad range of patients with congenital or acquired disorders of the hematopoietic system or radio-, chemo- or immune-sensitive malignancies. More than 60,000 such transplants are currently carried out annually worldwide with increasing frequency. HSCT has always been closely linked to Dermatology from its very beginning through its main and most devastating complication graft-versus-host disease. Treatment complications of HSCT have provided a great deal of insight into basic mechanisms of immunology, clinical medicine and networking in general. It remains a challenge to turn this knowledge from the two disciplines into benefit for the future patients with disturbed immune function and skin diseases.

Henig, I. and T. Zuckerman "Hematopoietic stem cell transplantation-50 years of evolution and future perspectives." Rambam Maimonides Med J. 2014 Oct 29;5(4):e0028. doi: 10.5041/RMMJ.10162. eCollection 2014 Oct.

Hematopoietic stem cell transplantation is a highly specialized and unique medical procedure. Autologous transplantation allows the administration of high-dose chemotherapy without prolonged bone marrow aplasia. In allogeneic transplantation, donor-derived stem cells provide alloimmunity that enables a graft-versus-tumor effect to eradicate residual disease and prevent relapse. The first allogeneic transplantation was performed by E. Donnall Thomas in 1957. Since then the field has evolved and expanded worldwide. New indications beside acute leukemia and aplastic anemia have been constantly explored and now include congenital disorders of the hematopoietic system, metabolic disorders, and autoimmune disease. The use of matched unrelated donors, umbilical cord blood units, and partially matched related donors has dramatically extended the availability of allogeneic transplantation. Transplant-related mortality has decreased due to improved supportive care, including better strategies to prevent severe infections and with the incorporation of reduced-intensity conditioning protocols that lowered the toxicity and allowed for

transplantation in older patients. However, disease relapse and graft-versus-host disease remain the two major causes of mortality with unsatisfactory progress. Intense research aiming to improve adoptive immunotherapy and increase graft-versus-leukemia response while decreasing graft-versus-host response might bring the next breakthrough in allogeneic transplantation. Strategies of graft manipulation, tumor-associated antigen vaccinations, monoclonal antibodies, and adoptive cellular immunotherapy have already proved clinically efficient. In the following years, allogeneic transplantation is likely to become more complex, more individualized, and more efficient.

Hermiston, M. L. and J. I. Gordon "Organization of the crypt-villus axis and evolution of its stem cell hierarchy during intestinal development." Am J Physiol. 1995 May;268(5 Pt 1):G813-22.

The small intestinal crypt of the adult mouse represents a model system for studying cell renewal. One or more functionally equivalent stem cells located within the crypt fuel a continuous regeneration of the gut's four principal epithelial cell lineages. These lineages differentiate during a geographically well-organized migration along the crypt-villus axis. This axis does not complete its morphogenetic program until the third postnatal week. We examined the organization of the crypt-villus axis and its stem cell hierarchy in postnatal day 1 (P1) to P28 transgenic mice. These mice contained transcriptional regulatory elements from the liver fatty acid binding protein gene linked to a human growth hormone (hGH) reporter. Adult male and female animals exhibit a striped pattern of hGH accumulation in their villus-associated epithelial cells: vertical coherent bands of wholly hGH-positive epithelial cells derived from a monoclonal crypt and vertical coherent stripes of wholly hGH-negative epithelial cells derived from an adjacent crypt extend to the apical extrusion zone of their common villus. Villus striping develops in a proximal-to-distal wave that extends from the duodenum to the jejunum by P7 and to the ileum by P14. Striping occurs as a result of a loss in the ability to support transgene expression. The decision appears to affect all cells within a stripe, irrespective of their position along the basilar-to-apical axis of a villus, suggesting that it is programmed by the nascent crypt's multipotent stem cell(s). Suppression of transgene expression traverses the crypt-villus axis more rapidly than the rate of epithelial cell migration. The boundary between stripes is very sharp and does not contain cells with transitional levels of the hGH reporter, indicating that the epithelial components of the crypt-villus axis have a higher degree of organization at this stage of development than appreciated previously.

Huntly, B. J. and D. G. Gilliland "Leukaemia stem cells and the evolution of cancer-stem-cell research." Nat Rev Cancer. 2005 Apr;5(4):311-21.

Many cancers seem to depend on a small population of 'cancer stem cells' for their continued growth and propagation. The leukaemia stem cell (LSC) was the first such cell to be described. The origins of these cells are controversial, and their biology - like that of their normal-tissue counterpart, the haematopoietic stem cell (HSC) - is still not fully elucidated. However, the LSC is likely to be the most crucial target in the treatment of leukaemias, and a thorough understanding of its biology - particularly of how the LSC differs from the HSC - might allow it to be selectively targeted, improving therapeutic outcome.

Ji, J., R. Shimizu, et al. "Analyses of WOX4 transgenics provide further evidence for the evolution of the WOX gene family during the regulation of diverse stem cell functions." Plant Signal Behav. 2010 Jul;5(7):916-20. doi: 10.1104/pp.109.149641. Epub 2010 Jul 1.

The WOX (WUSCHEL-related homeobox) gene family of Arabidopsis comprises fifteen plant-specific transcriptional factors that play important development roles. Genetic, phylogenetic, and genomic analyses suggest that WOX genes generally act non-autonomously to organize stem-cell and initial-cell populations within plant meristems and organ anlagen. Previous cross-complementation analyses indicate that the functional diversification of distinct WOX paralogs may be explained largely by promoter evolution, although paralog-specific protein::protein interactions are also implicated. A recent report described WOX4 function during development of the procambium, which comprises the meristematic tissues of the plant vasculature. Here we show that WOX4 fails to complement PRS1/WOX3 function, when driven from the PRS1/WOX3 native promoter. These data suggest that WOX4 identifies different DNA targets and/or interacting proteins during development of the vasculature procambium than does PRS1/WOX3 during the specification of lateral organ initial cells. The identification of super-compound leaf phenotypes induced by overexpression of the SlWOX4 ortholog in tomato suggests a functional link between vascular patterning and leaf complexity.

Korbling, M. and T. M. Fliedner "The evolution of clinical peripheral blood stem cell transplantation." Bone Marrow Transplant. 1996 May;17(5):675-8.

Our growing physiological understanding of hematopoietic progenitor cells has led to the clinical

use of circulating progenitor cells, including stem cells, for either reconstitution of hematopoietic function, up to the transduction of functional genes into a self-renewing cell system. In the following, an attempt has been made to recollect the major steps in the evolution of clinical blood stem transplantation, from the morphological description of small lymphocytes circulating in the blood up to somatic gene therapy covering a time period of 87 years.

Kreso, A. and J. E. Dick "Evolution of the cancer stem cell model." Cell Stem Cell. 2014 Mar 6;14(3):275-91. doi: 10.1016/j.stem.2014.02.006.

Genetic analyses have shaped much of our understanding of cancer. However, it is becoming increasingly clear that cancer cells display features of normal tissue organization, where cancer stem cells (CSCs) can drive tumor growth. Although often considered as mutually exclusive models to describe tumor heterogeneity, we propose that the genetic and CSC models of cancer can be harmonized by considering the role of genetic diversity and nongenetic influences in contributing to tumor heterogeneity. We offer an approach to integrating CSCs and cancer genetic data that will guide the field in interpreting past observations and designing future studies.

Langeveld, D., M. Jansen, et al. "Aberrant intestinal stem cell lineage dynamics in Peutz-Jeghers syndrome and familial adenomatous polyposis consistent with protracted clonal evolution in the crypt." Gut. 2012 Jun;61(6):839-46. doi: 10.1136/gutjnl-2011-300622. Epub 2011 Sep 22.

OBJECTIVE: Genetic predisposition to cancer in Peutz-Jeghers syndrome (PJS) and the role of germline serine-threonine kinase (LKB1) mutations are poorly understood. The authors studied the effect of germline LKB1 mutations on intestinal stem cell dynamics in unaffected flat PJS mucosa. Recent research has documented that the intestinal crypt houses multiple equipotent stem cell lineages. Lineages continuously compete through random drifts, while somatically inherited methylation patterns record clonal diversity. DESIGN: To study the effect of germline LKB1 mutations on clonal expansion, the authors performed quantitative analyses of cardiac-specific homeobox methylation pattern diversity in crypts isolated from unaffected colonic mucosa obtained from archival PJS patient material. The authors compared methylation density and methylation pattern diversity in patients with PJS to those in patients with familial adenomatous polyposis and age-matched controls. RESULTS: The percentage of total methylation is comparable between groups, but the number of unique methylation patterns is significantly increased for patients with familial adenomatous polyposis and patients with PJS compared to control subjects. CONCLUSIONS: Monoallelic LKB1 loss is not silent and provokes a protracted clonal evolution in the crypt. The increased methylation pattern diversity observed in unaffected PJS mucosa predicts that premalignant lesions will arise at an accelerated pace compared to the general population.

Le, R. Q., J. J. Melenhorst, et al. "Evolution of the donor T-cell repertoire in recipients in the second decade after allogeneic stem cell transplantation." Blood. 2011 May 12;117(19):5250-6. doi: 10.1182/blood-2011-01-329706. Epub 2011 Mar 18.

After allogeneic stem cell transplantation (SCT), T lymphocyte function is reestablished from the donor's postthymic T cells and through thymic T-cell neogenesis. The immune repertoire and its relation to that of the donor have not been characterized in detail in long-term adult SCT survivors. We studied 21 healthy patients in their second decade after a myeloablative SCT for hematologic malignancy (median follow-up, 12 years). Immune profiles were compared with donor samples cryopreserved at transplant and beyond 10 years from SCT. Only one recipient was on continuing immunosuppression. Compared with the donor at transplant, there was no significant difference in CD4, CD8, natural killer, and B-cell blood counts. However, compared with donors, recipients had significantly fewer naive T cells, lower T-cell receptor excision circle levels, fewer CD4 central memory cells, more effector CD8(+) cells, and more regulatory T cells. TCR repertoire analysis showed no significant difference in complexity of TCRVbeta spectratype between recipients and donors, although spectratype profiles had diverged with both gain and loss of donor repertoire peaks in the recipient. In conclusion, long-term allogeneic SCT survivors have subtle defects in their immune profile consistent with defective thymic function but compatible with normal health. This study is registered at http://www.clinicaltrials.gov as NCT00106925.

Li, C. G., C. Zagarrigo, et al. Evolution of sequential bortezomib-dexamethasone treatment followed by autologous hematopoietic stem cell transplantation in hemodialysis treatment, Chin Med J (Engl). 2013;126(9):1795.

Lin, C. K. and Y. C. Sung "Newly diagnosed multiple myeloma in Taiwan: the evolution of therapy, stem cell transplantation and new treatment agents." Hematol Oncol Stem Cell Ther. 2009;2(3):385-93.

Multiple myeloma is a clonal plasma cell dyscrasia with clinical heterogeneity. As of now, two key questions need to be answered before starting to

treat a newly diagnosed myeloma patient. One is whether the patient is a candidate for high-dose chemotherapy with stem cell support and the other is risk stratification. As novel therapeutics have emerged, it is increasingly important to introduce a risk-adapted approach. The heterogeneity of the disease is established, for the most part, by disease biology, predominantly genetics. Cytogenetic analysis by either banding technique or fluorescent in situ hybridization is able to identify high-risk subpopulations. The new international staging system based on beta2-microglobulin and albumin levels in serum is also very helpful in defining the high-risk group (stage 3). This group of patients may not respond well to high-dose chemotherapy and require early introduction of newer treatments such as the bortezomib-containing regimen. The main factor in determining the eligibility for stem cell transplants is age. Based on the current literature and situation in Taiwan, we suggest stem cell transplantation if the patient is younger than 55 years of age. Each case should be considered individually if the age of the patient is between 55 and 70 years. Finally, we have also reviewed the status and the treatment of multiple myeloma in Taiwan. Fortunately, there has been an improvement in awareness, diagnosis and treatment. Cytogenetic studies have been applied in risk evaluations, but are limited in a few centers due to lack of availability. With the exception of the agent lenalidomide, new novel agents are available for treating of myeloma in Taiwan.

Merckaert, I., Y. Libert, et al. "Impact of life-threatening risk information on the evolution of patients' anxiety and risk recall: the specific context of informed consent for experimental stem cell transplant." Patient Educ Couns. 2009 May;75(2):192-8. doi: 10.1016/j.pec.2008.09.013. Epub 2008 Nov 21.

OBJECTIVE: This study examines risk recall and evolution of patients' anxiety after transmission of life-threatening risk information in an informed consent procedure for experimental HSCT. METHODS: Informed consent interviews were audio-recorded and transcribed. Patient risk recall was obtained through comparing information provided in the interview to information recalled by patients following the interview. The evolution of patients' anxiety was assessed through comparing patients' post- to patients' pre-interview anxiety using the STAI-State. Physicians' communication skills and risk framing were analyzed. RESULTS: Twenty patients were included. Patients recalled on average 4 risks (S.D.=1.6) out of 9 different risks transmitted (S.D.=2) which corresponds to a recall rate of 44% (S.D.=15.5). Patients' anxiety remained on average stable (Mean=0.4; S.D.=9.1). Linear regression analysis showed that risk recall was predicted positively by the number of risks transmitted (B=.30; P=.032) and by patients' problem-focused coping (B=.21; P=.008). The evolution of anxiety was predicted positively by the number of times benefits were transmitted (B=.83; P=.003) and negatively by the level of anxiety before the interview (B=-.50; P=.001). CONCLUSION: Results show the limits of patients' risk recall in the context of informed consent for a life-threatening procedure. PRACTICE IMPLICATIONS: This study highlights the necessity to develop strategies allowing tailoring of risk transmission to every patient's needs.

Mosquna, A., A. Katz, et al. "Regulation of stem cell maintenance by the Polycomb protein FIE has been conserved during land plant evolution." Development. 2009 Jul;136(14):2433-44. doi: 10.1242/dev.035048.

The Polycomb group (PcG) complex is involved in the epigenetic control of gene expression profiles. In flowering plants, PcG proteins regulate vegetative and reproductive programs. Epigenetically inherited states established in the gametophyte generation are maintained after fertilization in the sporophyte generation, having a profound influence on seed development. The gametophyte size and phase dominance were dramatically reduced during angiosperm evolution, and have specialized in flowering plants to support the reproductive process. The moss Physcomitrella patens is an ideal organism in which to study epigenetic processes during the gametophyte stage, as it possesses a dominant photosynthetic gametophytic haploid phase and efficient homologous recombination, allowing targeted gene replacement. We show that P. patens PcG protein FIE (PpFIE) accumulates in haploid meristematic cells and in cells that undergo fate transition during dedifferentiation programs in the gametophyte. In the absence of PpFIE, meristems overproliferate and are unable to develop leafy gametophytes or reach the reproductive phase. This aberrant phenotype might result from failure of the PcG complex to repress proliferation and differentiation of three-faced apical stem cells, which are designated to become lateral shoots. The PpFIE phenotype can be partially rescued by FIE of Arabidopsis thaliana, a flowering plant that diverged >450 million years ago from bryophytes. PpFIE can partially complement the A. thaliana fie mutant, illustrating functional conservation of the protein during evolution in regulating the differentiation of meristematic cells in gametophyte development, both in bryophytes and angiosperms. This mechanism was harnessed at the onset of the evolution of alternating generations, facilitating the establishment of sporophytic developmental programs.

Nardmann, J. and W. Werr "The shoot stem cell niche in angiosperms: expression patterns of WUS

orthologues in rice and maize imply major modifications in the course of mono- and dicot evolution." Mol Biol Evol. 2006 Dec;23(12):2492-504. Epub 2006 Sep 20.

In Arabidopsis, stem cell homeostasis in the shoot apical meristem (SAM) is controlled by a feedback loop between WUS and CLV functions. We have identified WUS orthologues in maize and rice by a detailed phylogenetic analysis of the WOX gene family and subsequent cloning. A single WUS orthologue is present in the rice genome (OsWUS), whereas the allotetraploid maize genome contains 2 WUS paralogues (ZmWUS1 and ZmWUS2). None of the isolated grass WUS orthologues displays an organizing center-type expression pattern in the vegetative SAM as in Arabidopsis. In contrast, the grass-specific expression patterns relate to the specification of new phytomers consistent with the transcriptional expression patterns of TD1 and FON1 (CLV1 orthologues of maize and rice, respectively). Moreover, the grass WUS and CLV1 orthologues are coexpressed in all reproductive meristems, where fasciation and supernumerary floral organs occur in td1 or fon1 loss-of-function mutants. The expression patterns of WUS orthologues in both grass species compared with those of dicots imply that major changes in WUS function, which are correlated with changes in CLV1 signaling, have occurred during angiosperm evolution and raise doubts about the uniqueness of the WUS/CLV antagonism in the maintenance of the shoot stem cell niche in grasses.

Parichy, D. M. and J. E. Spiewak "Origins of adult pigmentation: diversity in pigment stem cell lineages and implications for pattern evolution." Pigment Cell Melanoma Res. 2015 Jan;28(1):31-50. doi: 10.1111/pcmr.12332. Epub 2014 Dec 16.

Teleosts comprise about half of all vertebrate species and exhibit an extraordinary diversity of adult pigment patterns that function in shoaling, camouflage, and mate choice and have played important roles in speciation. Here, we review studies that have identified several distinct neural crest lineages, with distinct genetic requirements, that give rise to adult pigment cells in fishes. These lineages include post-embryonic, peripheral nerve-associated stem cells that generate black melanophores and iridescent iridophores, cells derived directly from embryonic neural crest cells that generate yellow-orange xanthophores, and bipotent stem cells that generate both melanophores and xanthophores. This complexity in adult chromatophore lineages has implications for our understanding of adult traits, melanoma, and the evolutionary diversification of pigment cell lineages and patterns.

Puissant-Lubrano, B., A. Huynh, et al. "Evolution of peripheral blood T lymphocyte subsets after allogenic or autologous hematopoietic stem cell transplantation." Immunobiology. 2014 Aug;219(8):611-8. doi: 10.1016/j.imbio.2014.03.012. Epub 2014 Mar 21.

With the aim to search for differences in T cell reconstitution after allogenic or autologous hematopoietic stem cell transplantation (HSCT), we characterized peripheral blood T-cell subsets by means of flow cytometry, in adult patients who had undergone either allogenic (n=23) or autologous (n=29) HSCT for the treatment of hematological malignancies. The patients were followed every 3 months for 21 months after HSCT. Compared to healthy controls (n=20 blood donors), the two transplanted groups displayed (i) a CD4 lymphopenia, (ii) a low percentage of naive T cells, (iii) high percentages of memory T cells and of activated T cells (HLA-DR+, CD25+) and high percentages of CD4 T cells with a high expression of CD25. The levels of TRECs (TCR rearrangement excision circles) were not significantly different between the two groups. In total, the differences of the nature and the speed of T lymphocyte reconstitution observed between the two patient groups were minor. This leads us to conclude that in allografted patients, lymphocyte activation as well as many other disturbances of subpopulations of peripheral blood lymphocytes are probably not related to the allogenicity of the graft, but are due to the expansion of T cells transfused with HSC and slow differentiation of T lymphocytes in the thymus progressively colonized by bone marrow-derived T-cell precursors.

Reekmans, K., N. De Vocht, et al. "Spatiotemporal evolution of early innate immune responses triggered by neural stem cell grafting." Stem Cell Res Ther. 2012 Dec 14;3(6):56. doi: 10.1186/scrt147.

INTRODUCTION: Transplantation of neural stem cells (NSCs) is increasingly suggested to become part of future therapeutic approaches to improve functional outcome of various central nervous system disorders. However, recently it has become clear that only a small fraction of grafted NSCs display long-term survival in the (injured) adult mouse brain. Given the clinical invasiveness of NSC grafting into brain tissue, profound characterisation and understanding of early post-transplantation events is imperative to claim safety and efficacy of cell-based interventions. METHODS: Here, we applied in vivo bioluminescence imaging (BLI) and post-mortem quantitative histological analysis to determine the localisation and survival of grafted NSCs at early time points post-transplantation. RESULTS: An initial dramatic cell loss (up to 80% of grafted cells) due to apoptosis could be observed within the first 24 hours

post-implantation, coinciding with a highly hypoxic NSC graft environment. Subsequently, strong spatiotemporal microglial and astroglial cell responses were initiated, which stabilised by day 5 post-implantation and remained present during the whole observation period. Moreover, the increase in astrocyte density was associated with a high degree of astroglial scarring within and surrounding the graft site. During the two-week follow up in this study, the NSC graft site underwent extensive remodelling with NSC graft survival further declining to around 1% of the initial number of grafted cells. CONCLUSIONS: The present study quantitatively describes the early post-transplantation events following NSC grafting in the adult mouse brain and warrants that such intervention is directly associated with a high degree of cell loss, subsequently followed by strong glial cell responses.

Romero Fernandez, E., G. M. Bravo, et al. "Lymphocyte recovery and infused CD34+ cells dose: Effect on the evolution after stem cell autotransplantation." Leuk Res Rep. 2013 Jul 15;2(2):54-7. doi: 10.1016/j.lrr.2013.06.002. eCollection 2013.

BACKGROUND AND OBJECTIVE: The number of infused CD34+cells (CD34+i) has been associated with absolute lymphocyte count (ALC) and the outcome undergoing autologous hematopoietic stem cell transplantation (HSCT) in patients with hematologic malignancies. The study's aim was to analyze the relationship between CD34+i, ALC and prognosis in this patients. PATIENTS AND METHOD: Medical records of 163 patients receiving HSCT between 2005 and 2012 were reviewed. RESULTS: We found significant and inversely proportional relationship between the CD34+i and the days required to reach ALC>/=500/mul according to the regression line: days=-0.981xnumber of CD34+i+18.09. CONCLUSIONS: We have obtained a predictive model of lymphocyte recovery based recovery of CD34+i.

Rush, S. M. "Trinity Evolution: mesenchymal stem cell allografting in foot and ankle surgery." Foot Ankle Spec. 2010 Jun;3(3):140-3. doi: 10.1177/1938640010369638.

Biologic augmentation of orthopaedic procedures is a time-tested useful adjunct. The ability to predictably heal all fractures and arthrodesis procedures is still elusive because of multiple factors. The next frontier in musculoskeletal medicine and surgery will involve increasing biologic manipulation of the healing environment. Mesenchymal stem cell allograft is viable living biologic material that is capable of new bone formation and osteointegration at the implantation site.

Smith, A. M., M. J. Sanchez, et al. "A novel mode of enhancer evolution: the Tal1 stem cell enhancer recruited a MIR element to specifically boost its activity." Genome Res. 2008 Sep;18(9):1422-32. doi: 10.1101/gr.077008.108. Epub 2008 Aug 7.

Altered cis-regulation is thought to underpin much of metazoan evolution, yet the underlying mechanisms remain largely obscure. The stem cell leukemia TAL1 (also known as SCL) transcription factor is essential for the normal development of blood stem cells and we have previously shown that the Tal1 +19 enhancer directs expression to hematopoietic stem cells, hematopoietic progenitors, and to endothelium. Here we demonstrate that an adjacent region 1 kb upstream (+18 element) is in an open chromatin configuration and carries active histone marks but does not function as an enhancer in transgenic mice. Instead, it boosts activity of the +19 enhancer both in stable transfection assays and during differentiation of embryonic stem (ES) cells carrying single-copy reporter constructs targeted to the Hprt locus. The +18 element contains a mammalian interspersed repeat (MIR) which is essential for the +18 function and which was transposed to the Tal1 locus approximately 160 million years ago at the time of the mammalian/marsupial branchpoint. Our data demonstrate a previously unrecognized mechanism whereby enhancer activity is modulated by a transposon exerting a "booster" function which would go undetected by conventional transgenic approaches.

Stolzel, F., K. Hackmann, et al. "Clonal evolution including partial loss of human leukocyte antigen genes favoring extramedullary acute myeloid leukemia relapse after matched related allogeneic hematopoietic stem cell transplantation." Transplantation. 2012 Apr 15;93(7):744-9. doi: 10.1097/TP.0b013e3182481113.

BACKGROUND: Relapse of acute myeloid leukemia (AML) after allogeneic hematopoietic stem cell transplantation (HSCT) leaves few therapeutic options, and mechanisms of immune escape of recurring leukemic cells remain poorly understood. Recently, acquired loss of mismatched human leukocyte antigen (HLA) was demonstrated in patients with AML undergoing haploidentical allogeneic HSCT and was suggested not to occur in HLA-matched HSCT. We hypothesized that this mechanism applies to extramedullary AML relapse which occurs frequently after allogeneic HSCT and might also not be restricted to haploidentical HSCT. METHODS: DNA from extramedullary AML relapse after HSCT was compared with bone marrow at diagnosis with array comparative genomic hybridization to investigate relapse-specific genomic aberrations in relapsing AML after allogeneic HSCT. Formalin-

fixed, paraffin-embedded tissues from the same points of time were assessed for HLA, major histocompatibility complex class I chain-related gene A, and TAP2 immunohistochemistry staining to assess cell surface expression of deleted loci encoded on chromosome 6p. RESULTS: Array comparative genomic hybridization revealed a partial loss of chromosome 6p in extramedullary myeloid sarcoma relapse of AML after sustained complete remission was achieved through matched related allogeneic HSCT. Among others, a deleted region 6p21.32-p21.33, which included several HLA class I genes, was detected. CONCLUSIONS: These results suggest that the loss of HLA class I haplotype also occurs in AML relapse after HLA-matched related HSCT. Partial loss of several HLA class I genes and subsequent reduced presentation of minor histocompatibility antigens and reduced ligation of activating natural killer-cell receptors may explain the loss of graft-versus-leukemia response and extramedullary AML relapse in tissue with reduced immunologic surveillance.

Stuart, S. A., Y. Minami, et al. "The CML stem cell: evolution of the progenitor." Cell Cycle. 2009 May 1;8(9):1338-43. Epub 2009 May 17.

The success of imatinib mesylate (STI571, Gleevec) in treating chronic myeloid leukemia (CML) is, to date, the crowning achievement of targeted molecular therapy in cancer. Nearly 90% of newly diagnosed patients treated with imatinib in the chronic phase of the disease achieve a complete cytogenetic response. However, more than 95% of these patients retain detectable levels of BCR-ABL mRNA and patients discontinuing imatinib therapy almost invariably relapse, demonstrating that an imatinib insensitive population of leukemia-initiating cells (LICs) persists in nearly all patients. These findings underscore the need for treatments specifically targeting the leukemia-initiating population of CML cells. While mounting evidence suggests that the LIC in the chronic phase of CML is the BCR-ABL positive hematopoietic stem cell, several recent publications suggest that during CML blast crisis, a granulocyte-macrophage progenitor (GMP) population also acquires LIC properties through activation of the beta-catenin pathway. Characterization of these cells and evaluation of their sensitivity to imatinib is critical to our understanding and treatment of CML blast crisis.

Tiu, R., L. Gondek, et al. "Clonality of the stem cell compartment during evolution of myelodysplastic syndromes and other bone marrow failure syndromes." Leukemia. 2007 Aug;21(8):1648-57. Epub 2007 Jun 7.

Clonal hematopoiesis, observed in certain forms of marrow failure including aplastic anemia (AA), may be due to stem cell depletion. Alternatively, oligoclonality may be a result of recruitment of a preexisting defective clone, such as in paroxysmal nocturnal hemoglobinuria (PNH) or myelodysplastic syndromes (MDS). In PNH, exogenous permissive factors may be required for dominance of the abnormal clone, while in MDS, stem cells undergo transformation steps leading to a growth advantage. Stem or multipotent progenitor cell involvement in PNH is evidenced by long-term persistence of a clonal defect and its presence in all blood cells. In MDS, some clonal aberrations may have a 'founder-effect' and additional defects are secondary. Metaphase cytogenetics measures the proportion of clonal cells within dividing progenitor but not mature cells. Owing to low resolution, lesions can be found in only approximately 50% of MDS patients. This shortcoming may be overcome by application of newer technologies such as comparative genomic hybridization and SNP array-based karyotyping (SNP-A). SNP-A facilitates identification of cryptic lesions in bone marrow failure patients with normal or abnormal cytogenetics and allows for detection of loss of heterozygosity as a result of uniparental disomy, a lesion frequently found in MDS.

Ungerer, P., B. J. Eriksson, et al. "Unravelling the evolution of neural stem cells in arthropods: notch signalling in neural stem cell development in the crustacean Daphnia magna." Dev Biol. 2012 Nov 15;371(2):302-11. doi: 10.1016/j.ydbio.2012.08.025. Epub 2012 Sep 1.

The genetic regulatory networks controlling major developmental processes seem to be conserved in bilaterians regardless of an independent or a common origin of the structures. This has been explained by the employment of a genetic toolkit that was repeatedly used during bilaterian evolution to build the various forms and body plans. However, it is not clear how genetic networks were incorporated into the formation of novel structures and how homologous genes can regulate the disparate morphological processes. Here we address this question by analysing the role of Notch signalling, which is part of the bilaterian toolkit, in neural stem cell evolution in arthropods. Within arthropods neural stem cells have evolved in the last common ancestor of insects and crustaceans (Tetraconata). We analyse here for the first time the role of Notch signalling in a crustacean, the branchiopod Daphnia magna, and show that it is required in neural stem cells for regulating the time of neural precursor production and for binary cell fate decisions in the ventral neuroectoderm. The function of Notch signalling has diverged in the ventral neuroectoderm of insects and crustaceans accompanied by changes in the morphogenetic

processes. In the crustacean, Notch controlled mechanisms of neuroblast regulation have evolved that are surprisingly similar to vertebrates and thus present a remarkable case of parallel evolution. These new data on a representative of crustaceans complete the arthropod data set on Notch signalling in the nervous system and allow for reconstructing how the Notch signalling pathway has been co-opted from pre-existing structures to the development of the evolving neural stem cells in the Tetraconata ancestor.

Villa-Diaz, L. G., A. M. Ross, et al. "Concise review: The evolution of human pluripotent stem cell culture: from feeder cells to synthetic coatings." Stem Cells. 2013 Jan;31(1):1-7. doi: 10.1002/stem.1260.

Current practices to maintain human pluripotent stem cells (hPSCs), which include induced pluripotent stem cells and embryonic stem cells, in an undifferentiated state typically depend on the support of feeder cells such as mouse embryonic fibroblasts (MEFs) or an extracellular matrix such as Matrigel. Culture conditions that depend on these undefined support systems limit our ability to interpret mechanistic studies aimed at resolving how hPSCs interact with their extracellular environment to remain in a unique undifferentiated state and to make fate-changing lineage decisions. Likewise, the xenogeneic components of MEFs and Matrigel ultimately hinder our ability to use pluripotent stem cells to treat debilitating human diseases. Many of these obstacles have been overcome by the development of synthetic coatings and bioreactors that support hPSC expansion and self-renewal within defined culture conditions that are free from xenogeneic contamination. The establishment of defined culture conditions and synthetic matrices will facilitate studies to more precisely probe the molecular basis of pluripotent stem cell self-renewal and differentiation. When combined with three-dimensional cultures in bioreactors, these systems will also enable large-scale expansion for future clinical applications.

Villadsen, R. "In search of a stem cell hierarchy in the human breast and its relevance to breast cancer evolution." APMIS. 2005 Nov-Dec;113(11-12):903-21.

By deliberate analogy with the well-established concept of hematopoiesis, the term "mammopoiesis" is occasionally used to describe the development of the different cellular lineages and functional units in the mammary gland. The use of this term signifies a strong bias towards the idea that tissue homeostasis during mammary development, pregnancy, lactation and involution is brought about by the action of somatic stem cells characterized by longevity and multipotency. The progenies hereof eventually differentiate into structurally and functionally well-defined ductal-lobular units. During the past two decades evidence of such a notion in the mouse has developed from being largely circumstantial based on non-clonal in vivo experiments to a quite elaborate characterization of individual candidate stem cells by a number of different properties. Within tumor biology this has led to a renaissance of the concept of tumors as caricatures of tissue renewal. Thus, recent molecular classification of breast cancer based on genome wide expression analysis operates with different subtypes with specific reference to the normal luminal epithelial and myoepithelial/basal lineages in the breast. Apparently some tumors are lineage restricted and others differentiate more broadly as if they have preserved some stem-like properties. This holds promise for the existence of a stem cell hierarchy, the understanding of which may prove to be instrumental in further dissecting the histogenesis of breast cancer evolution. Most attention has been devoted to the question of different cellular origins of cancer subtypes and different susceptibilities of possible stem cells to gain or loss of oncogenes and tumor suppressor genes, respectively. Invaluable progress has been made over the past two decades in culture technology not only in terms of population doubling and clonal growth, but also the availability of lineage specific markers, cell sorting, and three-dimensional functional assays for tissue specific morphogenesis. Transcriptional profiling of stem cell zones has unraveled a hitherto unknown preservation of signaling pathways for maintenance of stem cell properties across tissue boundaries and species. Somatic stem cells have therefore been narrowed down to specific anatomic locations not only in rapidly renewing tissues such as skin and skin derivatives, but also in tissues with slower turnover times, such as lung, kidney and prostate. It is therefore now possible to integrate this information in a search for similar cells within the breast. Even if cell turnover after birth is provided exclusively by dividing lineage-restricted cells, more information about the robustness of breast differentiation programs during tumor progression is still very much required. Complete knowledge of the primary cell of origin of breast cancer and the mechanisms that influence differentiation programs during tumor initiation, promotion and progression may be crucial for the development of novel non-toxic therapies that influence tumor cell behaviour. The scope of this review is to discuss reports that have begun to elucidate the topographic location, key cellular type and lineage fidelity in culture and xenograft models of candidate human breast stem cells and their differentiated progenies with particular

emphasis on comparison with the differentiation programs of tumor subtypes.

Wong, W. S., K. C. Cheng, et al. "Clonal evolution of 8p11 stem cell syndrome in a 14-year-old Chinese boy: a review of literature of t(8;13) associated myeloproliferative diseases." Leuk Res. 2007 Feb;31(2):235-8. Epub 2006 Jun 13.

We describe a case of coexisting BCR-ABL negative myeloproliferative disorder and precursor T-cell lymphoblastic lymphoma associated with t(8;13) involving FGFR1 at 8p11 in a 14-year-old boy who presented with generalized lymphadenopathy and an abdominal mass. JAK2 mutation and FIP1L1-PDGFRalpha were not detected. RT-PCR revealed the ZNF198-FGFR1 fusion transcript in both the bone marrow (BM) and lymph node (LN) of the patient at diagnosis. Of interest, reciprocal FGFR1-ZNF198 fusion transcript was demonstrated in the BM but not LN. Also differential clonal TcRgamma gene rearrangements in the BM and LN samples were observed. These findings provide novel insights into the genetic pathogenesis.

Yoshimi, A. and M. Kurokawa "[Leukemia stem cell and clonal evolution]." Nihon Rinsho. 2014 Jun;72(6):1012-7.

The introduction of next generation sequencing technology has greatly broadened our view on the genetic landscape of hematological malignancies. The first comprehensive experiment of acute myeloid leukemia(AML) using genome-wide analysis has also shed light on the clonal evolution of AML, which seems to have been underestimated. It is now possible to precisely define clonal size and selection at different stages. This approach demonstrated that AML at diagnosis is either monoclonal or oligoclonal, harboring a selected number of genetically defined subclones. Furthermore, targeted deep sequencing of diagnosis and relapse pairs revealed that founding clones or subclones present at diagnosis obtain some additional mutations that contribute to clonal expansion and/or chemoresistance. Some subclones may be eradicated by treatment, whereas others are resistant to chemotherapeutic agents and ultimately grow out. The molecular heterogeneity in AML will have a great impact on the development of targeted therapies.

Zhou, H. and S. Ding "Evolution of induced pluripotent stem cell technology." Curr Opin Hematol. 2010 Jul;17(4):276-80. doi: 10.1097/MOH.0b013e328339f2ee.

PURPOSE OF REVIEW: Induced pluripotent stem cell (iPSC) technology, which uses defined transcription factors to reprogram somatic cells to become pluripotent cells, offers a significant technical simplicity and enables generation of patient-specific pluripotent stem cells with reduced ethical concerns. This review will focus on recent progresses in understanding of iPSCs and improved methods of generating iPSCs. RECENT FINDINGS: Whereas iPSCs generated from a variety of cell sources were found to be nearly identical functionally to embryonic stem cells, some differences were also identified and remain to be characterized. Meanwhile, new methods of generating iPSCs with minimal or no exogenous genetic modifications to cells have advanced rapidly. SUMMARY: iPSC technology provides unprecedented opportunities in biomedical research and regenerative medicine. However, there remain a great deal to learn about iPSC safety, the reprogramming mechanisms, and better ways to direct a specific reprogramming process. The iPSC field will flourish on its mechanistic studies, iPSC-based disease modeling, and identification of new small molecules that modulate reprogramming.

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