

Cancer and Transdifferentiation Study Literatures

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Abstract: Transdifferentiation is a process where one mature somatic cell transforms into another mature somatic cell without undergoing an intermediate pluripotent state or progenitor cell type. It is a type of metaplasia, which includes all cell fate switches, including the interconversion of stem cells. Current uses of transdifferentiation include disease modeling and drug discovery and in the future may include gene therapy and regenerative medicine. Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent reports as references in the related studies.

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1. Introduction

Transdifferentiation is a process where one mature somatic cell transforms into another mature somatic cell without undergoing an intermediate pluripotent state or progenitor cell type. It is a type of metaplasia, which includes all cell fate switches, including the interconversion of stem cells. Current uses of transdifferentiation include disease modeling and drug discovery and in the future may include gene therapy and regenerative medicine. Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

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

Ansieau, S. "EMT in breast cancer stem cell generation." *Cancer Lett.* 2013 Sep 10;338(1):63-8. doi: 10.1016/j.canlet.2012.05.014. Epub 2012 May 22.

The concept of cancer stem cells (CSCs) has been proposed to explain the ability of single disseminated cancer cells to reconstitute tumours with heterogeneity similar to that of the primary tumour they arise from. Although this concept is now commonly accepted, the origin of these CSCs remains

a source of debate. First proposed to arise through stem/progenitor cell transformation, CSCs might also or alternatively arise from differentiated cancer cells through epithelial to mesenchymal transition (EMT), an embryonic transdifferentiation process. Using breast carcinomas as a study model, I propose revisiting the role of EMT in generating CSCs and the debate on potential underlying mechanisms and biological significance.

Arthur-Farraj, P. J., M. Latouche, et al. "c-Jun reprograms Schwann cells of injured nerves to generate a repair cell essential for regeneration." *Neuron.* 2012 Aug 23;75(4):633-47. doi: 10.1016/j.neuron.2012.06.021.

The radical response of peripheral nerves to injury (Wallerian degeneration) is the cornerstone of nerve repair. We show that activation of the transcription factor c-Jun in Schwann cells is a global regulator of Wallerian degeneration. c-Jun governs major aspects of the injury response, determines the expression of trophic factors, adhesion molecules, the formation of regeneration tracks and myelin clearance and controls the distinctive regenerative potential of peripheral nerves. A key function of c-Jun is the activation of a repair program in Schwann cells and the creation of a cell specialized to support regeneration. We show that absence of c-Jun results in the formation of a dysfunctional repair cell, striking failure of functional recovery, and neuronal death. We conclude that a single glial transcription factor is essential for restoration of damaged nerves, acting to control the transdifferentiation of myelin and Remak

Schwann cells to dedicated repair cells in damaged tissue.

Baer, R., C. Cintas, et al. "Pancreatic cell plasticity and cancer initiation induced by oncogenic Kras is completely dependent on wild-type PI 3-kinase p110alpha." *Genes Dev.* 2014 Dec 1;28(23):2621-35. doi: 10.1101/gad.249409.114.

Increased PI 3-kinase (PI3K) signaling in pancreatic ductal adenocarcinoma (PDAC) correlates with poor prognosis, but the role of class I PI3K isoforms during its induction remains unclear. Using genetically engineered mice and pharmacological isoform-selective inhibitors, we found that the p110alpha PI3K isoform is a major signaling enzyme for PDAC development induced by a combination of genetic and nongenetic factors. Inactivation of this single isoform blocked the irreversible transition of exocrine acinar cells into pancreatic preneoplastic ductal lesions by oncogenic Kras and/or pancreatic injury. Hitting the other ubiquitous isoform, p110beta, did not prevent preneoplastic lesion initiation. p110alpha signaling through small GTPase Rho and actin cytoskeleton controls the reprogramming of acinar cells and regulates cell morphology in vivo and in vitro. Finally, p110alpha was necessary for pancreatic ductal cancers to arise from Kras-induced preneoplastic lesions by increasing epithelial cell proliferation in the context of mutated p53.

Barcena, C., M. Stefanovic, et al. "Angiogenin secretion from hepatoma cells activates hepatic stellate cells to amplify a self-sustained cycle promoting liver cancer." *Sci Rep.* 2015 Jan 21;5:7916. doi: 10.1038/srep07916.

Hepatocellular carcinoma (HCC) frequently develops in a pro-inflammatory and pro-fibrogenic environment with hepatic stellate cells (HSCs) remodeling the extracellular matrix composition. Molecules secreted by liver tumors contributing to HSC activation and peritumoral stromal transformation remain to be fully identified. Here we show that conditioned medium from HCC cell lines, Hep3B and HepG2, induced primary mouse HSCs transdifferentiation, characterized by profibrotic properties and collagen modification, with similar results seen in the human HSC cell line LX2. Moreover, tumor growth was enhanced by coinjection of HepG2/LX2 cells in a xenograft murine model, supporting a HCC-HSC crosstalk in liver tumor progression.

Barneda-Zahonero, B., L. Roman-Gonzalez, et al. "HDAC7 is a repressor of myeloid genes whose downregulation is required for transdifferentiation of pre-B cells into macrophages." *PLoS Genet.* 2013

May;9(5):e1003503. doi: 10.1371/journal.pgen.1003503. Epub 2013 May 16.

B lymphopoiesis is the result of several cell-commitment, lineage-choice, and differentiation processes. Every differentiation step is characterized by the activation of a new, lineage-specific, genetic program and the extinction of the previous one. To date, the central role of specific transcription factors in positively regulating these distinct differentiation processes to acquire a B cell-specific genetic program is well established. However, the existence of specific transcriptional repressors responsible for the silencing of lineage inappropriate genes remains elusive. Here we addressed the molecular mechanism behind repression of non-lymphoid genes in B cells. We report that the histone deacetylase HDAC7 was highly expressed in pre-B cells but dramatically down-regulated during cellular lineage conversion to macrophages. Microarray analysis demonstrated that HDAC7 re-expression interfered with the acquisition of the gene transcriptional program characteristic of macrophages during cell transdifferentiation; the presence of HDAC7 blocked the induction of key genes for macrophage function, such as immune, inflammatory, and defense response, cellular response to infections, positive regulation of cytokines production, and phagocytosis. Moreover, re-introduction of HDAC7 suppressed crucial functions of macrophages, such as the ability to phagocytose bacteria and to respond to endotoxin by expressing major pro-inflammatory cytokines.

Bronckaers, A., P. Hilkens, et al. "Mesenchymal stem/stromal cells as a pharmacological and therapeutic approach to accelerate angiogenesis." *Pharmacol Ther.* 2014 Aug;143(2):181-96. doi: 10.1016/j.pharmthera.2014.02.013. Epub 2014 Mar 1.

Mesenchymal stem cells or multipotent stromal cells (MSCs) have initially captured attention in the scientific world because of their differentiation potential into osteoblasts, chondroblasts and adipocytes and possible transdifferentiation into neurons, glial cells and endothelial cells. This broad plasticity was originally hypothesized as the key mechanism of their demonstrated efficacy in numerous animal models of disease as well as in clinical settings. However, there is accumulating evidence suggesting that the beneficial effects of MSCs are predominantly caused by the multitude of bioactive molecules secreted by these remarkable cells. Numerous angiogenic factors, growth factors and cytokines have been discovered in the MSC secretome, all have been demonstrated to alter endothelial cell behavior in vitro and induce angiogenesis in vivo.

Bullock, M. D., K. M. Pickard, et al. "Pleiotropic actions of miR-21 highlight the critical role of deregulated stromal microRNAs during colorectal cancer progression." Cell Death Dis. 2013 Jun 20;4:e684. doi: 10.1038/cddis.2013.213.

The oncogene microRNA-21 (miRNA; miR-21) is overexpressed in most solid organ tumours; however, a recent examination of stage II colorectal cancer (CRC) specimens suggests this may be a stromal phenomenon and not only a feature of cancer cells. In vitro and in vivo studies show that miR-21 has potent pro-metastatic effects in various malignant carcinoma cell lines. The tumour microenvironment has also been identified as a key actor during the metastatic cascade; however to date the significance of deregulated miR-21 expression within the cancer-associated stroma has not been examined. In the present study, a quantitative RT-PCR-based analysis of laser microdissected tissue confirmed that miR-21 expression is associated with a four-fold mean increase in CRC stroma compared with normal tissue. In situ hybridisation using locked nucleic acid probes localised miR-21 expression predominantly to fibroblasts within tumour-associated stroma. To study the molecular and biological impact of deregulated stromal miR-21 in CRC, stable ectopic expression was induced in immortalised fibroblasts.

Burke, Z. D. and D. Tosh "Barrett's metaplasia as a paradigm for understanding the development of cancer." Curr Opin Genet Dev. 2012 Oct;22(5):494-9. doi: 10.1016/j.gde.2012.08.001. Epub 2012 Sep 11.

The conversion of one cell type to another is defined as metaplasia (or sometimes it is referred to as transdifferentiation or cellular reprogramming). Metaplasia is important clinically and may predispose to the development of cancer. Barrett's metaplasia is one such example and is the focus of the present review. Barrett's is a pathological condition in which the normal oesophageal stratified squamous epithelium is replaced by intestinal-type columnar epithelium and is associated with gastro-oesophageal reflux disease. The appearance of columnar epithelium in the oesophagus predisposes to the development of adenocarcinoma. Herein we review the latest evidence on the cellular origin of Barrett's metaplasia. Until recently it was thought that the cellular origin of the columnar epithelium was from a pre-existing cell within the oesophagus. However, recent evidence suggests that this may not be the case. Instead two recent publications indicate that the columnar cells may migrate from a site distal to the oesophagus. These new data contravene our current understanding of metaplasia and raise important questions about the cellular origin of cancer.

Buser, L., M. Bihl, et al. "Unique composite hematolymphoid tumor consisting of a pro-T lymphoblastic lymphoma and an indeterminate dendritic cell tumor: evidence for divergent common progenitor cell differentiation." Pathobiology. 2014;81(4):199-205. doi: 10.1159/000365396. Epub 2014 Sep 11.

Until recently, hematopoietic neoplasms were considered monoclonal proliferations belonging to one cell lineage. In the last years, evidence for transdifferentiation from one cell lineage to another or divergent common progenitor cell differentiation has accumulated, mainly based on composite hematolymphoid tumors, sharing common genetic abnormalities. We report the case of a 59-year-old woman with a composite pro-T lymphoblastic lymphoma (LBL) and indeterminate dendritic cell tumor infiltrating the lymph nodes, bone marrow and stomach. Genetic analyses revealed that both cell populations bore +21, while a G13D mutation of the NRAS gene and monosomy 18 were detected only in the pro-T LBL. The synchronous appearance of two distinct uncommon hematolymphoid tumors in the same patient, recurrent at three different anatomic locations, with an identifiable common genetic denominator, namely +21, but also with unique genetic anomalies in the pro-T LBL raises the hypothesis of a divergent common progenitor cell differentiation.

Cadranel, J., A. M. Ruppert, et al. "Therapeutic strategy for advanced EGFR mutant non-small-cell lung carcinoma." Crit Rev Oncol Hematol. 2013 Dec;88(3):477-93. doi: 10.1016/j.critrevonc.2013.06.009. Epub 2013 Jul 31.

Activating mutation in exons 19 or 21 of epidermal growth factor receptor (EGFR) in non-small-cell lung cancers (NSCLC) are associated with increased sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib. Cancer patients harboring activating EGFR mutations benefit from first-line TKI therapy. Yet 10% of patients present a primary TKI resistance, while 50% of the others develop a secondary resistance within 9-12 months after starting TKI. The RECIST's definition of progression appears flawed when applied to EGFR-mutated NSCLC patients. Most often, tumor volume shrinking widely exceeds 30% during TKI response and kinetics of growth is low during relapse.

Corbett, J. L. and D. Tosh "Conversion of one cell type into another: implications for understanding organ development, pathogenesis of cancer and generating cells for therapy." Biochem Soc Trans. 2014 Jun;42(3):609-16. doi: 10.1042/BST20140058.

Metaplasia is the irreversible conversion of one differentiated cell or tissue type into another. Metaplasia usually occurs in tissues that undergo regeneration, and may, in a pathological context, predispose to an increased risk of disease. Studying the conditions leading to the development of metaplasia is therefore of significant clinical interest. In contrast, transdifferentiation (or cellular reprogramming) is a subset of metaplasia that describes the permanent conversion of one differentiated cell type into another, and generally occurs between cells that arise from neighbouring regions of the same germ layer. Transdifferentiation, although rare, has been shown to occur in Nature. New insights into the signalling pathways involved in normal tissue development may be obtained by investigating the cellular and molecular mechanisms in metaplasia and transdifferentiation, and additional identification of key molecular regulators in transdifferentiation and metaplasia could provide new targets for therapeutic treatment of diseases such as cancer, as well as generating cells for transplantation into patients with degenerative disorders. In the present review, we focus on the transdifferentiation of pancreatic cells into hepatocyte-like cells, the development of Barrett's metaplasia in the oesophagus, and the cellular and molecular mechanisms underlying both processes.

De Waele, E., E. Wauters, et al. "Conversion of human pancreatic acinar cells toward a ductal-mesenchymal phenotype and the role of transforming growth factor beta and activin signaling." *Pancreas*. 2014 Oct;43(7):1083-92. doi: [10.1097/MPA.0000000000000154](https://doi.org/10.1097/MPA.0000000000000154).

OBJECTIVE: Epithelial-mesenchymal transition may interfere with the differentiation of cultured pancreatic acinar cells toward endocrine cells. Therefore, it will be important to investigate into detail the reprogramming of human pancreatic acinar cells toward a mesenchymal phenotype: the association with acinoductal transdifferentiation, the influence of cell adhesion, and the regulation behind this process. **METHODS:** Human exocrine cells, isolated from donor pancreata, were cultured in suspension or as monolayers. Non-genetic lineage tracing, using labeled ulex europaeus agglutinin 1 lectin, was performed, and the role of the transforming growth factor (TGF-beta) superfamily was investigated. **RESULTS:** After 7 days in monolayer culture, the human acinar cells coexpressed the mesenchymal marker vimentin and the ductal marker Sox9. However, when the human exocrine cells were cultured in suspension, epithelial-mesenchymal transition was not observed. The spontaneous transition of the human acinar cells toward a ductal and mesenchymal phenotype was decreased by inhibition of the TGF-beta and activin

signaling pathways. **CONCLUSIONS:** The human acinar cells spontaneously undergo TGF-beta-regulated reprogramming in the monolayer culture. These observations are helpful to develop culture methods for the in vitro reprogramming of pancreatic exocrine to endocrine cells. They are also of potential interest for studies on exocrine acinar cells in the development of pancreatic cancer.

Delk, N. A. and M. C. Farach-Carson "Interleukin-6: a bone marrow stromal cell paracrine signal that induces neuroendocrine differentiation and modulates autophagy in bone metastatic PCa cells." *Autophagy*. 2012 Apr;8(4):650-63. doi: [10.4161/autophagy.19226](https://doi.org/10.4161/autophagy.19226). Epub 2012 Apr 1.

Autophagy reallocates nutrients and clears normal cells of damaged proteins and organelles. In the context of metastatic disease, invading cancer cells hijack autophagic processes to survive and adapt in the host microenvironment. We sought to understand how autophagy is regulated in the metastatic niche for prostate cancer (PCa) cells where bone marrow stromal cell (BMSC) paracrine signaling induces PCa neuroendocrine differentiation (NED). In PCa, this transdifferentiation of metastatic PCa cells to neuronal-like cells correlates with advanced disease. Because autophagy provides a survival advantage for cancer cells and promotes cell differentiation, we hypothesized that autophagy mediates PCa NED in the bone. Thus, we determined the ability of paracrine factors in conditioned media (CM) from two separate BMSC subtypes, HS5 and HS27a, to induce autophagy in C4-2 and C4-2B bone metastatic PCa cells by characterizing the autophagy marker, LC3. Unlike HS27a CM, HS5 CM induced LC3 accumulation in PCa cells, suggesting autophagy was induced and indicating that HS5 and HS27a secrete a different milieu of paracrine factors that influence PCa autophagy.

Denlinger, C. E. and R. K. Thompson "Molecular basis of esophageal cancer development and progression." *Surg Clin North Am*. 2012 Oct;92(5):1089-103. doi: [10.1016/j.suc.2012.07.002](https://doi.org/10.1016/j.suc.2012.07.002). Epub 2012 Aug 17.

This article discusses the molecular basis of esophageal cancer development and subsequent progression of disease. Differing epidemiologic factors are associated with esophageal adenocarcinoma and squamous cell carcinoma. These 2 different histologic types have differing putative underlying mechanisms of transdifferentiation from normal esophageal mucosa to malignant histologies via gene dysregulation, biochemical modifications, and altered cell signaling pathways. Our developing understanding of the molecular events underlying esophageal cancer is

leading to the establishment of identifiable biomarkers and the clinical use of molecularly targeted treatment agents. The identification of driving genetic mutations and altered signaling pathways has also had favorable outcomes.

Derynck, R., B. P. Muthusamy, et al. "Signaling pathway cooperation in TGF-beta-induced epithelial-mesenchymal transition." *Curr Opin Cell Biol.* 2014 Dec;31:56-66. doi: 10.1016/j.ceb.2014.09.001. Epub 2014 Sep 18.

Transdifferentiation of epithelial cells into cells with mesenchymal properties and appearance, that is, epithelial-mesenchymal transition (EMT), is essential during development, and occurs in pathological contexts, such as in fibrosis and cancer progression. Although EMT can be induced by many extracellular ligands, TGF-beta and TGF-beta-related proteins have emerged as major inducers of this transdifferentiation process in development and cancer. Additionally, it is increasingly apparent that signaling pathways cooperate in the execution of EMT. This update summarizes the current knowledge of the coordination of TGF-beta-induced Smad and non-Smad signaling pathways in EMT, and the remarkable ability of Smads to cooperate with other transcription-directed signaling pathways in the control of gene reprogramming during EMT.

Dey, P., S. Rachagani, et al. "PD2/Paf1 depletion in pancreatic acinar cells promotes acinar-to-ductal metaplasia." *Oncotarget.* 2014 Jun 30;5(12):4480-91.

Pancreatic differentiation 2 (PD2), a PAF (RNA Polymerase II Associated Factor) complex subunit, is overexpressed in pancreatic cancer cells and has demonstrated potential oncogenic property. Here, we report that PD2/Paf1 expression was restricted to acinar cells in the normal murine pancreas, but its expression increased in the ductal cells of KrasG12D/Pdx1Cre (KC) mouse model of pancreatic cancer with increasing age, showing highest expression in neoplastic ductal cells of 50 weeks old mice. PD2/Paf1 was specifically expressed in amylase and CK19 double positive metaplastic ducts, representing intermediate structures during pancreatic acinar-to-ductal metaplasia (ADM). Similar PD2/Paf1 expression was observed in murine pancreas that exhibited ADM-like histology upon cerulein challenge. In normal mice, cerulein-mediated inflammation induced a decrease in PD2/Paf1 expression, which was later restored upon recovery of the pancreatic parenchyma. In KC mice, however, PD2/Paf1 mRNA level continued to decrease with progressive dysplasia and subsequent neoplastic transformation. Additionally, knockdown of PD2/Paf1 in pancreatic acinar cells resulted in the abrogation of

Amylase, Elastase and Lipase (acinar marker) mRNA levels with simultaneous increase in CK19 and CAII (ductal marker) transcripts. In conclusion, our studies indicate loss of PD2/Paf1 expression during acinar transdifferentiation in pancreatic cancer initiation and PD2/Paf1 mediated regulation of lineage specific markers.

Di Stefano, B., J. L. Sardina, et al. "C/EBPalpha poises B cells for rapid reprogramming into induced pluripotent stem cells." *Nature.* 2014 Feb 13;506(7487):235-9. doi: 10.1038/nature12885. Epub 2013 Dec 15.

CCAAT/enhancer binding protein-alpha (C/EBPalpha) induces transdifferentiation of B cells into macrophages at high efficiencies and enhances reprogramming into induced pluripotent stem (iPS) cells when co-expressed with the transcription factors Oct4 (Pou5f1), Sox2, Klf4 and Myc (hereafter called OSKM). However, how C/EBPalpha accomplishes these effects is unclear. Here we find that in mouse primary B cells transient C/EBPalpha expression followed by OSKM activation induces a 100-fold increase in iPS cell reprogramming efficiency, involving 95% of the population. During this conversion, pluripotency and epithelial-mesenchymal transition genes become markedly upregulated, and 60% of the cells express Oct4 within 2 days. C/EBPalpha acts as a 'path-breaker' as it transiently makes the chromatin of pluripotency genes more accessible to DNase I. C/EBPalpha also induces the expression of the dioxygenase Tet2 and promotes its translocation to the nucleus where it binds to regulatory regions of pluripotency genes that become demethylated after OSKM induction. In line with these findings, overexpression of Tet2 enhances OSKM-induced B-cell reprogramming. Because the enzyme is also required for efficient C/EBPalpha-induced immune cell conversion, our data indicate that Tet2 provides a mechanistic link between iPS cell reprogramming and B-cell transdifferentiation. The rapid iPS reprogramming approach described here should help to fully elucidate the process and has potential clinical applications.

Enescu, A. S., C. L. Margaritescu, et al. "The involvement of growth differentiation factor 5 (GDF5) and aggrecan in the epithelial-mesenchymal transition of salivary gland pleomorphic adenoma." *Rom J Morphol Embryol.* 2013;54(4):969-76.

Pleomorphic adenoma is the most common salivary gland tumor with annual incidence of 2-3.5/100 000 in population. The histogenesis of salivary gland pleomorphic adenoma is still unclear. One concept sustains the existence of an epithelial-mesenchymal transitions (EMT) process in

pleomorphic adenomas by which neoplastic epithelial cells transdifferentiate into mesenchymal cells and leading to tissue heterogeneity from this salivary gland neoplasia. Here we investigate by immunohistochemistry the expression of growth differentiation factor 5 (GDF5) and aggrecan in 15 cases of salivary gland pleomorphic adenomas. We found that both markers were present in normal salivary gland, mainly in the cells that line striated and intercalated ducts suggesting their involvement in the morphogenesis of this duct system.

Frontini, A., A. Vitali, et al. "White-to-brown transdifferentiation of omental adipocytes in patients affected by pheochromocytoma." Biochim Biophys Acta. 2013 May;1831(5):950-9. doi: [10.1016/j.bbaliip.2013.02.005](https://doi.org/10.1016/j.bbaliip.2013.02.005). Epub 2013 Feb 20.

In all mammals, white adipose tissue (WAT) and brown adipose tissue (BAT) are found together in several fat depots, forming a multi-depot organ. Adrenergic stimulation induces an increase in BAT usually referred to as "browning". This phenomenon is important because of its potential use in curbing obesity and related disorders; thus, understanding its cellular mechanisms in humans may be useful for the development of new therapeutic strategies. Data in rodents have supported the direct transformation of white into brown adipocytes. Biopsies of pure white omental fat were collected from 12 patients affected by the catecholamine-secreting tumor pheochromocytoma (pheo-patients) and compared with biopsies from controls. Half of the omental fat samples from pheo-patients contained uncoupling protein 1 (UCP1)-immunoreactive-(ir) multilocular cells that were often arranged in a BAT-like pattern endowed with noradrenergic fibers and dense capillary network. Many UCP1-ir adipocytes showed the characteristic morphology of paucilocular cells, which we have been described as cytological marker of transdifferentiation. Electron microscopy showed increased mitochondrial density in multi- and paucilocular cells and disclosed the presence of perivascular brown adipocyte precursors. Brown fat genes, such as UCP1, PR domain containing 16 (PRDM16) and beta3-adrenoreceptor, were highly expressed in the omentum of pheo-patients and in those cases without visible morphologic rearrangement.

Geraud, C., C. Mogler, et al. "Endothelial transdifferentiation in hepatocellular carcinoma: loss of Stabilin-2 expression in peri-tumorous liver correlates with increased survival." Liver Int. 2013 Oct;33(9):1428-40. doi: [10.1111/liv.12262](https://doi.org/10.1111/liv.12262). Epub 2013 Jul 21.

Hepatocellular carcinoma (HCC) is a malignant tumour that is characterized by extensive vascular remodelling and responsiveness to treatment with the anti-angiogenic multikinase inhibitor sorafenib. The aim was to study endothelial remodelling in HCC. METHODS: The murine inducible albumin-SV40-large T-antigen model and two tissue microarrays (TMA) with 295 tumourous and 83 peri-tumourous samples of 296 patients with HCC were analysed for expression of liver sinusoidal endothelial cell (LSEC)-specific marker proteins, stabilin-1 and stabilin-2, LYVE-1 and CD32b. RESULTS: LSEC marker proteins were sequentially lost during HCC progression in the murine HCC model being absent from tumour nodules larger than 800 µm in diameter. Similarly, the TMA analysis of human HCCs revealed loss of all four marker proteins in the majority of tumourous tissue samples. Preservation of LYVE-1 expression showed a significant correlation with low grading (G1). In corresponding peri-tumourous liver tissue, loss of all marker proteins was seen in a minor proportion of cases (34%) while the majority of cases retained expression of at least one of the marker proteins. Loss of stabilin-2 expression in peri-tumourous liver tissue of patients with HCC was significantly less likely to occur (38%) than loss of the other marker proteins (63-95%) and it was associated with significantly longer tumour-specific ($P = 0.0523$) and overall ($P = 0.0338$) survival.

Giordano, A., A. Smorlesi, et al. "White, brown and pink adipocytes: the extraordinary plasticity of the adipose organ." Eur J Endocrinol. 2014 Apr 10;170(5):R159-71. doi: [10.1530/EJE-13-0945](https://doi.org/10.1530/EJE-13-0945). Print 2014 May.

In mammals, adipocytes are lipid-laden cells making up the parenchyma of the multi-depot adipose organ. White adipocytes store lipids for release as free fatty acids during fasting periods; brown adipocytes burn glucose and lipids to maintain thermal homeostasis. A third type of adipocyte, the pink adipocyte, has recently been characterised in mouse subcutaneous fat depots during pregnancy and lactation. Pink adipocytes are mammary gland alveolar epithelial cells whose role is to produce and secrete milk. Emerging evidence suggests that they derive from the transdifferentiation of subcutaneous white adipocytes. The functional response of the adipose organ to a range of metabolic and environmental challenges highlights its extraordinary plasticity. Cold exposure induces an increase in the 'brown' component of the organ to meet the increased thermal demand; in states of positive energy balance, the 'white' component expands to store excess nutrients; finally, the 'pink' component develops in subcutaneous depots

during pregnancy to ensure litter feeding. At the cell level, plasticity is provided not only by stem cell proliferation and differentiation but also, distinctively, by direct transdifferentiation of fully differentiated adipocytes by the stimuli that induce genetic expression reprogramming and through it a change in phenotype and, consequently function.

Goldsmith, E. C., A. D. Bradshaw, et al. "Cellular mechanisms of tissue fibrosis. 2. Contributory pathways leading to myocardial fibrosis: moving beyond collagen expression." Am J Physiol Cell Physiol. 2013 Mar 1;304(5):C393-402. doi: 10.1152/ajpcell.00347.2012. Epub 2012 Nov 21.

While the term "fibrosis" can be misleading in terms of the complex patterns and processes of myocardial extracellular matrix (ECM) remodeling, fibrillar collagen accumulation is a common consequence of relevant pathophysiological stimuli, such as pressure overload (PO) and myocardial infarction (MI). Fibrillar collagen accumulation in both PO and MI is predicated on a number of diverse cellular and extracellular events, which include changes in fibroblast phenotype (transdifferentiation), posttranslational processing and assembly, and finally, degradation. The expansion of a population of transformed fibroblasts/myofibroblasts is a significant cellular event with respect to ECM remodeling in both PO and MI. The concept that this cellular expansion within the myocardial ECM may be due, at least in part, to endothelial-mesenchymal transformation and thereby not dissimilar to events observed in cancer progression holds intriguing future possibilities. Studies regarding determinants of procollagen processing, such as procollagen C-endopeptidase enhancer (PCOLCE), and collagen assembly, such as the secreted protein acidic and rich in cysteine (SPARC), have identified potential new targets for modifying the fibrotic response in both PO and MI. Finally, the transmembrane matrix metalloproteinases, such as MMP-14, underscore the diversity and complexity of this ECM proteolytic family as this protease can degrade the ECM as well as induce a profibrotic response.

Gurlevik, E., B. Fleischmann-Mundt, et al. "Adjuvant gemcitabine therapy improves survival in a locally induced, R0-resectable model of metastatic intrahepatic cholangiocarcinoma." Hepatology. 2013 Sep;58(3):1031-41. doi: 10.1002/hep.26468. Epub 2013 Jul 29.

Complete surgical tumor resection (R0) for treatment of intrahepatic cholangiocarcinoma (ICC) is potentially curative, but the prognosis remains dismal due to frequent tumor recurrence and metastasis after surgery. Adjuvant therapies may improve the outcome,

but clinical studies for an adjuvant approach are difficult and time-consuming for rare tumor entities. Therefore, animal models reflecting the clinical situation are urgently needed to investigate novel adjuvant therapies. To establish a mouse model of resectable cholangiocarcinoma including the most frequent genetic alterations of human ICC, we electroporated Sleeping Beauty-based oncogenic transposon plasmids into the left liver lobe of mice. KRas-activation in combination with p53-knockout in hepatocytes resulted in formation of a single ICC nodule within 3-5 weeks. Lineage tracing analyses confirmed the development of ICC by transdifferentiation of hepatocytes. Histologic examination demonstrated that no extrahepatic metastases were detectable during primary tumor progression. However, formation of tumor satellites close to the primary tumor and vascular invasion were observed, indicating early invasion into normal tissue adjacent to the tumor.

Halley-Stott, R. P., V. Pasque, et al. "Nuclear reprogramming." Development. 2013 Jun;140(12):2468-71. doi: 10.1242/dev.092049.

There is currently particular interest in the field of nuclear reprogramming, a process by which the identity of specialised cells may be changed, typically to an embryonic-like state. Reprogramming procedures provide insight into many mechanisms of fundamental cell biology and have several promising applications, most notably in healthcare through the development of human disease models and patient-specific tissue-replacement therapies. Here, we introduce the field of nuclear reprogramming and briefly discuss six of the procedures by which reprogramming may be experimentally performed: nuclear transfer to eggs or oocytes, cell fusion, extract treatment, direct reprogramming to pluripotency and transdifferentiation.

Hardee, M. E. and D. Zagzag "Mechanisms of glioma-associated neovascularization." Am J Pathol. 2012 Oct;181(4):1126-41. doi: 10.1016/j.ajpath.2012.06.030. Epub 2012 Aug 2.

Glioblastomas (GBMs), the most common primary brain tumor in adults, are characterized by resistance to chemotherapy and radiotherapy. One of the defining characteristics of GBM is an abundant and aberrant vasculature. The processes of vascular co-option, angiogenesis, and vasculogenesis in gliomas have been extensively described. Recently, however, it has become clear that these three processes are not the only mechanisms by which neovascularization occurs in gliomas. Furthermore, it seems that these processes interact extensively, with potential overlap among them. At least five

mechanisms by which gliomas achieve neovascularization have been described: vascular co-option, angiogenesis, vasculogenesis, vascular mimicry, and (the most recently described) glioblastoma-endothelial cell transdifferentiation. We review these mechanisms in glioma neovascularization, with a particular emphasis on the roles of hypoxia and glioma stem cells in each process. Although some of these processes are well established, others have been identified only recently and will need to be further investigated for complete validation. We also review strategies to target glioma neovascularization and the development of resistance to these therapeutic strategies. Finally, we describe how these complex processes interlink and overlap. A thorough understanding of the contributing molecular processes that control the five modalities reviewed here should help resolve the treatment resistance that characterizes GBMs.

Hawinkels, L. J., M. Paauwe, et al. "Interaction with colon cancer cells hyperactivates TGF-beta signaling in cancer-associated fibroblasts." *Oncogene*. 2014 Jan 2;33(1):97-107. doi: 10.1038/onc.2012.536. Epub 2012 Dec 3.

The interaction between epithelial cancer cells and cancer-associated fibroblasts (CAFs) has a major role in cancer progression and eventually in metastasis. In colorectal cancer (CRC), CAFs are present in high abundance, but their origin and functional interaction with epithelial tumor cells has not been elucidated. In this study we observed strong activation of the transforming growth factor-beta (TGF-beta)/Smad signaling pathway in CRC CAFs, accompanied by decreased signaling in epithelial tumor cells. We evaluated the TGF-beta1 response and the expression of target genes including matrix metalloproteinases (MMPs) and plasminogen activator inhibitor (PAI)-1 of various epithelial CRC cell lines and primary CAFs in vitro. TGF-beta1 stimulation caused high upregulation of MMPs, PAI-1 and TGF-beta1 itself. Next we showed that incubation of CAFs with conditioned medium (CM) from epithelial cancer cells led to hyperactivation of the TGF-beta signaling pathway, enhanced expression of target genes like PAI-1, and the expression of alpha-smooth muscle actin (alpha-SMA).

Hemminger, J., A. Satoskar, et al. "Unique pattern of renal kappa light chain amyloid deposition with histiocytic transdifferentiation of tubular epithelial cells." *Am J Surg Pathol*. 2012 Aug;36(8):1253-7. doi: 10.1097/PAS.0b013e31825b845e.

Monoclonal gammopathies can cause renal tubular epithelial damage through multiple mechanisms, the most common manifestation being

myeloma cast nephropathy. Amyloid light chain amyloidosis rarely affects the renal tubular epithelium directly and usually causes glomerular injury. Amyloid deposition can also be seen within vessel walls and in the renal tubulointerstitium. Herein, we describe a unique pattern of kappa light chain amyloid deposition involving the proximal tubule epithelium in a patient with multiple myeloma, characterized by intracellular amyloid globule formation with concomitant phenotypic changes suggestive of histiocytic differentiation of tubular epithelial cells. Amyloid pathogenesis is thought to be closely associated with the reticuloendothelial system, more specifically macrophages, and histiocytic differentiation of mesangial cells seems to be an integral step in glomerulopathic amyloid production. Our report proposes a similar mechanism of amyloidogenesis in the renal tubular epithelium.

Kallin, E. M., J. Rodriguez-Ubreva, et al. "Tet2 facilitates the derepression of myeloid target genes during CEBPalpha-induced transdifferentiation of pre-B cells." *Mol Cell*. 2012 Oct 26;48(2):266-76. doi: 10.1016/j.molcel.2012.08.007. Epub 2012 Sep 13.

The methylcytosine hydroxylase Tet2 has been implicated in hematopoietic differentiation and the formation of myeloid malignancies when mutated. An ideal system to study the role of Tet2 in myelopoiesis is CEBPalpha-induced transdifferentiation of pre-B cells into macrophages. Here we found that CEBPalpha binds to upstream regions of Tet2 and that the gene becomes activated. Tet2 knockdowns impaired the upregulation of macrophage markers as well as phagocytic capacity, suggesting that the enzyme is required for both early and late stage myeloid differentiation. A slightly weaker effect was seen in primary cells with a Tet2 ablation. Expression arrays of transdifferentiating cells with Tet2 knockdowns permitted the identification of a small subset of myeloid genes whose upregulation was blunted. Activation of these target genes was accompanied by rapid increases of promoter hydroxy-methylation. Our observations indicate that Tet2 helps CEBPalpha rapidly derepress myeloid genes during the conversion of pre-B cells into macrophages.

Keenan, J. I. and F. A. Frizelle "Bacteria flying under the radar: linking a bacterial infection to colon carcinogenesis." *Infect Agent Cancer*. 2014 Sep 11;9:31. doi: 10.1186/1750-9378-9-31. eCollection 2014.

The emergence of a link between *Helicobacter pylori* infection and an increased risk of gastric cancer has raised an awareness of a possible link between colonic microbiota and colorectal cancer. Perturbation of the colonic epithelium by toxin-

producing strains of *Bacteroides fragilis* may increase the risk of premalignant transdifferentiation. However, like *H. pylori*, *B. fragilis* exhibit an ability to modulate the normal host response to infection. We speculate this may be an underappreciated risk factor in the genesis of colon carcinogenesis in individuals colonised with toxin-producing strains of *B. fragilis*.

Kishi, S., P. E. Bayliss, et al. "A prospective epigenetic paradigm between cellular senescence and epithelial-mesenchymal transition in organismal development and aging." Transl Res. 2015 Jan;165(1):241-9. doi: 10.1016/j.trsl.2014.05.007. Epub 2014 May 21.

Epigenetic states can govern the plasticity of a genome to be adaptive to environments where many stress stimuli and insults compromise the homeostatic system with age. Although certain elastic power may autonomously reset, reprogram, rejuvenate, or reverse the organismal aging process, enforced genetic manipulations could at least reset and reprogram epigenetic states beyond phenotypic plasticity and elasticity in cells, which can be further manipulated into organisms. The question, however, remains how we can rejuvenate intrinsic resources and infrastructures in a noninvasive manner, particularly in a whole complex aging organism. Given inevitable increase of cancer with age, presumably any failure of resetting, reprogramming, or even rejuvenation could be a prominent causative factor of malignancy. Accompanied by progressive deteriorations of physiological functions in organisms with advancing age, aging-associated cancer risk may essentially arise from unforeseen complications in cellular senescence. At the cellular level, epithelial-mesenchymal plasticity (dynamic and reversible transitions between epithelial and mesenchymal phenotypic states) is enabled by underlying shifts in epigenetic regulation. Thus, the epithelial-mesenchymal transition (EMT) and its reversal (mesenchymal-epithelial transition [MET]) function as a key of cellular transdifferentiation programs.

Lamouille, S., J. Xu, et al. "Molecular mechanisms of epithelial-mesenchymal transition." Nat Rev Mol Cell Biol. 2014 Mar;15(3):178-96. doi: 10.1038/nrm3758.

The transdifferentiation of epithelial cells into motile mesenchymal cells, a process known as epithelial-mesenchymal transition (EMT), is integral in development, wound healing and stem cell behaviour, and contributes pathologically to fibrosis and cancer progression. This switch in cell differentiation and behaviour is mediated by key transcription factors, including SNAIL, zinc-finger E-box-binding (ZEB) and basic helix-loop-helix transcription factors, the functions of which are finely

regulated at the transcriptional, translational and post-translational levels. The reprogramming of gene expression during EMT, as well as non-transcriptional changes, are initiated and controlled by signalling pathways that respond to extracellular cues. Among these, transforming growth factor-beta (TGFbeta) family signalling has a predominant role; however, the convergence of signalling pathways is essential for EMT.

Lechuga, S., S. Baranwal, et al. "Loss of gamma-cytoplasmic actin triggers myofibroblast transition of human epithelial cells." Mol Biol Cell. 2014 Oct 15;25(20):3133-46. doi: 10.1091/mbc.E14-03-0815. Epub 2014 Aug 20.

Transdifferentiation of epithelial cells into mesenchymal cells and myofibroblasts plays an important role in tumor progression and tissue fibrosis. Such epithelial plasticity is accompanied by dramatic reorganizations of the actin cytoskeleton, although mechanisms underlying cytoskeletal effects on epithelial transdifferentiation remain poorly understood. In the present study, we observed that selective siRNA-mediated knockdown of gamma-cytoplasmic actin (gamma-CYA), but not beta-cytoplasmic actin, induced epithelial-to-myofibroblast transition (EMyT) of different epithelial cells. The EMyT manifested by increased expression of alpha-smooth muscle actin and other contractile proteins, along with inhibition of genes responsible for cell proliferation. Induction of EMyT in gamma-CYA-depleted cells depended on activation of serum response factor and its cofactors, myocardial-related transcriptional factors A and B. Loss of gamma-CYA stimulated formin-mediated actin polymerization and activation of Rho GTPase, which appear to be essential for EMyT induction.

Liberko, M., K. Kolostova, et al. "Essentials of circulating tumor cells for clinical research and practice." Crit Rev Oncol Hematol. 2013 Nov;88(2):338-56. doi: 10.1016/j.critrevonc.2013.05.002. Epub 2013 Jul 5.

The major cause of death due to cancer is its metastatic deposit in numerous tissues and organs. The metastatic process requires the migration of malignant cells from primary sites to distant environments. Even for tumors initially spreading through lymphatic vessels, hematogenous transport is the most common metastatic pathway. The detachment of cancer cells from a primary tumor into the blood stream is called epithelial-mesenchymal transition (EMT). As these cells circulate further in the bloodstream they are known as circulating tumor cells (CTCs). The CTC population is highly resilient, enabling the cells to colonize a foreign microenvironment. Alternatively,

cancer stem cells (CSCs) may arise from differentiated cancer cells through EMT and an embryonic transdifferentiation process.

Lignitto, L., A. Mattiolo, et al. "Crosstalk between the mesothelium and lymphomatous cells: insight into the mechanisms involved in the progression of body cavity lymphomas." *Cancer Med.* 2014 Feb;3(1):1-13. doi: [10.1002/cam4.159](https://doi.org/10.1002/cam4.159). Epub 2013 Nov 19.

The peculiar localization of body cavity lymphomas implies a specific contribution of the intracavitary microenvironment to the pathogenesis of these tumors. In this study, primary effusion lymphoma (PEL) was used as a model of body cavity lymphoma to investigate the role of mesothelial cells, which line the serous cavities, in lymphoma progression. The crosstalk between mesothelial and lymphomatous cells was studied in cocultures of primary human mesothelial cells (HMC) with PEL cells and a xenograft mouse model of peritoneal PEL. PEL cells were found to induce type 2 epithelial-mesenchymal transition (EMT) in HMC, which converted into a myofibroblastic phenotype characterized by loss of epithelial markers (pan cytokeratin and E-cadherin), expression of EMT-associated transcriptional repressors (Snail1, Slug, Zeb1, Sip1), and acquisition of alpha-smooth muscle actin (alpha-SMA), a mesenchymal protein. A progressive thickening of serosal membranes was observed in vivo, accompanied by loss of cytokeratin staining and appearance of alpha-SMA-expressing cells, confirming that fibrosis occurred during intracavitary PEL development. On the other hand, HMC were found to modulate PEL cell turnover in vitro, increasing their resistance to apoptosis and proliferation.

Martinelli, P., M. Canamero, et al. "Gata6 is required for complete acinar differentiation and maintenance of the exocrine pancreas in adult mice." *Gut.* 2013 Oct;62(10):1481-8. doi: [10.1136/gutjnl-2012-303328](https://doi.org/10.1136/gutjnl-2012-303328). Epub 2012 Sep 21.

OBJECTIVES: Previous studies have suggested an important role of the transcription factor Gata6 in endocrine pancreas, while GATA6 haploinsufficient inactivating mutations cause pancreatic agenesis in humans. We aimed to analyse the effects of Gata6 inactivation on pancreas development and function. **DESIGN:** We deleted Gata6 in all epithelial cells in the murine pancreas at the onset of its development. Acinar proliferation, apoptosis, differentiation and exocrine functions were assessed using reverse transcriptase quantitative PCR (RT-qPCR), chromatin immunoprecipitation, immunohistochemistry and enzyme assays. Adipocyte transdifferentiation was assessed using electron

microscopy and genetic lineage tracing. **RESULTS:** Gata6 is expressed in all epithelial cells in the adult mouse pancreas but it is only essential for exocrine pancreas homeostasis: while dispensable for pancreatic development after e10.5, it is required for complete acinar differentiation, for establishment of polarity and for the maintenance of acinar cells in the adult. Gata6 regulates directly the promoter of genes coding for digestive enzymes and the transcription factors Rbpjl and Mist1. Upon pancreas-selective Gata6 inactivation, massive loss of acinar cells and fat replacement take place. This is accompanied by increased acinar apoptosis and proliferation, acinar-to-ductal metaplasia and adipocyte transdifferentiation. By contrast, the endocrine pancreas is spared. **CONCLUSIONS:** Our data show that Gata6 is required for the complete differentiation of acinar cells through multiple transcriptional regulatory mechanisms. In addition, it is required for the maintenance of the adult acinar cell compartment. Our studies suggest that GATA6 alterations may contribute to diseases of the human adult exocrine pancreas.

McClellan, J. S., C. Dove, et al. "Reprogramming of primary human Philadelphia chromosome-positive B cell acute lymphoblastic leukemia cells into nonleukemic macrophages." *Proc Natl Acad Sci U S A.* 2015 Mar 31;112(13):4074-9. doi: [10.1073/pnas.1413383112](https://doi.org/10.1073/pnas.1413383112). Epub 2015 Mar 16.

BCR-ABL1(+) precursor B-cell acute lymphoblastic leukemia (BCR-ABL1(+) B-ALL) is an aggressive hematopoietic neoplasm characterized by a block in differentiation due in part to the somatic loss of transcription factors required for B-cell development. We hypothesized that overcoming this differentiation block by forcing cells to reprogram to the myeloid lineage would reduce the leukemogenicity of these cells. We found that primary human BCR-ABL1(+) B-ALL cells could be induced to reprogram into macrophage-like cells by exposure to myeloid differentiation-promoting cytokines in vitro or by transient expression of the myeloid transcription factor C/EBPalpha or PU.1. The resultant cells were clonally related to the primary leukemic blasts but resembled normal macrophages in appearance, immunophenotype, gene expression, and function. Most importantly, these macrophage-like cells were unable to establish disease in xenograft hosts, indicating that lineage reprogramming eliminates the leukemogenicity of BCR-ABL1(+) B-ALL cells, and suggesting a previously unidentified therapeutic strategy for this disease. Finally, we determined that myeloid reprogramming may occur to some degree in human patients by identifying primary CD14(+) monocytes/macrophages in BCR-ABL1(+) B-ALL

patient samples that possess the BCR-ABL1(+) translocation and clonally recombined VDJ regions.

Medici, D. and R. Kalluri "Endothelial-mesenchymal transition and its contribution to the emergence of stem cell phenotype." *Semin Cancer Biol.* 2012 Oct;22(5-6):379-84. doi: [10.1016/j.semcancer.2012.04.004](https://doi.org/10.1016/j.semcancer.2012.04.004). Epub 2012 Apr 23.

Vascular endothelial cells can demonstrate considerable plasticity to generate other cell types during embryonic development and disease progression. This process occurs through a cell differentiation mechanism known as endothelial-mesenchymal transition (EndMT). The generation of mesenchymal cells from endothelium is a crucial step in endothelial cell differentiation to several lineages including fibroblasts, myofibroblasts, mural cells, osteoblasts, chondrocytes, and adipocytes. Such differentiation patterns have been observed in systems of cardiac development, fibrosis, diabetic nephropathy, heterotopic ossification and cancer. Here we describe the EndMT program and discuss the current evidence of EndMT-mediated acquisition of stem cell characteristics and multipotent differentiation capabilities.

Meseure, D., K. Drak Alsibai, et al. "Pivotal role of pervasive neoplastic and stromal cells reprogramming in circulating tumor cells dissemination and metastatic colonization." *Cancer Microenviron.* 2014 Dec;7(3):95-115. doi: [10.1007/s12307-014-0158-2](https://doi.org/10.1007/s12307-014-0158-2). Epub 2014 Dec 19.

Reciprocal interactions between neoplastic cells and their microenvironment are crucial events in carcinogenesis and tumor progression. Pervasive stromal reprogramming and remodeling that transform a normal to a tumorigenic microenvironment modify numerous stromal cells functions, status redox, oxidative stress, pH, ECM stiffness and energy metabolism. These environmental factors allow selection of more aggressive cancer cells that develop important adaptive strategies. Subpopulations of cancer cells acquire new properties associating plasticity, stem-like phenotype, unfolded protein response, metabolic reprogramming and autophagy, production of exosomes, survival to anoikis, invasion, immunosuppression and therapeutic resistance. Moreover, by inducing vascular transdifferentiation of cancer cells and recruiting endothelial cells and pericytes, the tumorigenic microenvironment induces development of tumor-associated vessels that allow invasive cells to gain access to the tumor vessels and to intravasate. Circulating cancer cells can survive in the blood stream by interacting with the intravascular microenvironment, extravasate through the microvasculature and interact with the metastatic

microenvironment of target organs. In this review, we will focus on many recent paradigms involved in the field of tumor progression.

Mikaelian, I., M. Malek, et al. "Genetic and pharmacologic inhibition of mTORC1 promotes EMT by a TGF-beta-independent mechanism." *Cancer Res.* 2013 Nov 15;73(22):6621-31. doi: [10.1158/0008-5472.CAN-13-0560](https://doi.org/10.1158/0008-5472.CAN-13-0560). Epub 2013 Sep 27.

Epithelial-to-mesenchymal transition (EMT) is a transdifferentiation process that converts epithelial cells into highly motile mesenchymal cells. This physiologic process occurs largely during embryonic development but is aberrantly reactivated in different pathologic situations, including fibrosis and cancer. We conducted a siRNA screening targeted to the human kinome with the aim of discovering new EMT effectors. With this approach, we have identified mTOR complex 1 (mTORC1), a nutrient sensor that controls protein and lipid synthesis, as a key regulator of epithelial integrity. Using a combination of RNAi and pharmacologic approaches, we report here that inhibition of either mTOR or RPTOR triggers EMT in mammary epithelial cells. This EMT was characterized by the induction of the mesenchymal markers such as fibronectin, vimentin, and PAI-1, together with the repression of epithelial markers such as E-cadherin and ZO-3. In addition, mTORC1 blockade enhanced in vivo migratory properties of mammary cells and induced EMT independent of the TGF-beta pathway. Finally, among the transcription factors known to activate EMT, both ZEB1 and ZEB2 were upregulated following mTOR repression. Their increased expression correlated with a marked reduction in miR-200b and miR-200c mRNA levels, two microRNAs known to downregulate ZEB1 and ZEB2 expression.

Minkina, A., C. K. Matson, et al. "DMRT1 protects male gonadal cells from retinoid-dependent sexual transdifferentiation." *Dev Cell.* 2014 Jun 9;29(5):511-20. doi: [10.1016/j.devcel.2014.04.017](https://doi.org/10.1016/j.devcel.2014.04.017). Epub 2014 May 22.

Mammalian sex determination initiates in the fetal gonad with specification of bipotential precursor cells into male Sertoli cells or female granulosa cells. This choice was long presumed to be irreversible, but genetic analysis in the mouse recently revealed that sexual fates must be maintained throughout life. Somatic cells in the testis or ovary, even in adults, can be induced to transdifferentiate to their opposite-sex equivalents by loss of a single transcription factor, DMRT1 in the testis or FOXL2 in the ovary. Here, we investigate what mechanism DMRT1 prevents from triggering transdifferentiation. We find that DMRT1 blocks testicular retinoic acid (RA) signaling from

activating genes normally involved in female sex determination and ovarian development and show that inappropriate activation of these genes can drive sexual transdifferentiation. By preventing activation of potential feminizing genes, DMRT1 allows Sertoli cells to participate in RA signaling, which is essential for reproduction, without being sexually reprogrammed.

Miyazono, K., S. Ehata, et al. "Tumor-promoting functions of transforming growth factor-beta in progression of cancer." Ups J Med Sci. 2012 May;117(2):143-52. doi: 10.3109/03009734.2011.638729. Epub 2011 Nov 24.

Transforming growth factor-beta (TGF-beta) elicits both tumor-suppressive and tumor-promoting functions during cancer progression. Here, we describe the tumor-promoting functions of TGF-beta and how these functions play a role in cancer progression. Normal epithelial cells undergo epithelial-mesenchymal transition (EMT) through the action of TGF-beta, while treatment with TGF-beta and fibroblast growth factor (FGF)-2 results in transdifferentiation into activated fibroblastic cells that are highly migratory, thereby facilitating cancer invasion and metastasis. TGF-beta also induces EMT in tumor cells, which can be regulated by oncogenic and anti-oncogenic signals. In addition to EMT promotion, invasion and metastasis of cancer are facilitated by TGF-beta through other mechanisms, such as regulation of cell survival, angiogenesis, and vascular integrity, and interaction with the tumor microenvironment. TGF-beta also plays a critical role in regulating the cancer-initiating properties of certain types of cells, including glioma-initiating cells. These findings thus may be useful for establishing treatment strategies for advanced cancer by inhibiting TGF-beta signaling.

Moriarity, B. S., E. P. Rahrmann, et al. "Modular assembly of transposon integratable multigene vectors using RecWay assembly." Nucleic Acids Res. 2013 Apr;41(8):e92. doi: 10.1093/nar/gkt115. Epub 2013 Feb 26.

Studying complex biological processes such as cancer development, stem cell induction and transdifferentiation requires the modulation of multiple genes or pathways at one time in a single cell. Herein, we describe straightforward methods for rapid and efficient assembly of bacterial marker free multigene cassettes containing up to six complementary DNAs/short hairpin RNAs. We have termed this method RecWay assembly, as it makes use of both Cre recombinase and the commercially available Gateway cloning system. Further, because RecWay assembly uses truly modular components, it allows for the

generation of randomly assembled multigene vector libraries. These multigene vectors are integratable, and later excisable, using the highly efficient piggyBac (PB) DNA transposon system. Moreover, we have dramatically improved the expression of stably integrated multigene vectors by incorporation of insulator elements to prevent promoter interference seen with multigene vectors. We demonstrate that insulated multigene PB transposons can stably integrate and faithfully express up to five fluorescent proteins and the puromycin-thymidine kinase resistance gene in vitro, with up to 70-fold higher gene expression compared with analogous uninsulated vectors. RecWay assembly of multigene transposon vectors allows for widely applicable modelling of highly complex biological processes and can be easily performed by other research laboratories.

Nam, K. T., R. L. O'Neal, et al. "Spasmolytic polypeptide-expressing metaplasia (SPEM) in the gastric oxyntic mucosa does not arise from Lgr5-expressing cells." Gut. 2012 Dec;61(12):1678-85. doi: 10.1136/gutjnl-2011-301193. Epub 2011 Dec 23.

OBJECTIVE: Metaplastic lineages in the oxyntic mucosa of the stomach are critical preneoplastic precursors of gastric cancer. Recent studies have demonstrated that spasmolytic polypeptide-expressing metaplasia (SPEM) in the mouse oxyntic mucosa arises from transdifferentiation of mature gastric chief cells. Other investigations of intestinal progenitor cells have shown that cells demonstrating transcriptional activity for leucine-rich repeat containing G-protein-coupled receptor 5 (Lgr5) in the intestine, colon and gastric antrum function as adult stem cells. We have now investigated whether cells demonstrating Lgr5 transcriptional activity in the oxyntic mucosa of mice might be responsible for development of metaplasia. DESIGN: Lgr5-EGFP-IRES-Cre(ERT2/+);Rosa26R mice were used to examine the distribution of Lgr5 transcriptionally active cells in the normal oxyntic mucosa as well as after treatment with DMP-777 or L-635 to induce acute SPEM. Lineage mapping was performed to determine if Lgr5-expressing cells gave rise to SPEM. RESULTS: Cells expressing transcriptional activity for Lgr5 in the oxyntic mucosa were present as scattered rare cells only along the lesser curvature of the stomach. These cells also stained for markers of chief cells (intrinsic factor and pepsinogen) but never showed any staining for proliferative markers (Ki-67). In Lgr5-EGFP-IRES-Cre(ERT2/+);Rosa26R mice induced with tamoxifen, treatment with either DMP-777 or L-635 to induce acute oxyntic atrophy caused induction of SPEM, but no lineage mapping into SPEM from Lgr5-expressing cells was observed. CONCLUSION: The results indicate that, while chief

cells with Lgr5 transcriptional activity are present along the lesser curvature of the gastric oxyntic mucosa, they are not responsible for production of metaplasia.

Nilsson, G. M., N. Akhtar, et al. "Loss of E-cadherin expression is not a prerequisite for c-erbB2-induced epithelial-mesenchymal transition." *Int J Oncol.* 2014 Jul;45(1):82-94. doi: 10.3892/ijco.2014.2424. Epub 2014 May 7.

Recent research into the mechanisms of tumour cell invasiveness has highlighted the parallels between carcinogenesis and epithelial-mesenchymal transition (EMT), originally described as a developmental transdifferentiation program but also implicated in fibrosis and cancer. In a model system for mammary carcinogenesis, we previously observed that induced signalling from a homodimer of the c-erbB2 (HER2) receptor tyrosine kinase in an initially non-malignant mammary cell line caused EMT where i) cell scattering occurred before downregulation of the cell-cell adhesion molecule E-cadherin and ii) the progress of EMT was dramatically delayed when cells were grown at high density. Here, we have further analysed these phenomena. Ectopic expression of E-cadherin concomitant with c-erbB2 signalling was unable to impede the progression of EMT, suggesting that E-cadherin downregulation is not required for EMT. Furthermore, fibroblast-like cells isolated after EMT induced in the presence or absence of ectopic E-cadherin expression showed highly similar morphology and vimentin expression. E-cadherin expressed in these fibroblastic cells had a subcellular localisation similar to that found in epithelial cells, but it exhibited a much weaker attachment to the cytoskeleton, suggesting cytoskeletal rearrangements as an important mechanism in EMT-associated cell scattering.

Nouri, M., E. Ratther, et al. "Androgen-targeted therapy-induced epithelial mesenchymal plasticity and neuroendocrine transdifferentiation in prostate cancer: an opportunity for intervention." *Front Oncol.* 2014 Dec 23;4:370. doi: 10.3389/fonc.2014.00370. eCollection 2014.

Androgens regulate biological pathways to promote proliferation, differentiation, and survival of benign and malignant prostate tissue. Androgen receptor (AR) targeted therapies exploit this dependence and are used in advanced prostate cancer to control disease progression. Contemporary treatment regimens involve sequential use of inhibitors of androgen synthesis or AR function. Although targeting the androgen axis has clear therapeutic benefit, its effectiveness is temporary, as prostate tumor cells adapt to survive and grow. The removal of

androgens (androgen deprivation) has been shown to activate both epithelial-to-mesenchymal transition (EMT) and neuroendocrine transdifferentiation (NETD) programs. EMT has established roles in promoting biological phenotypes associated with tumor progression (migration/invasion, tumor cell survival, cancer stem cell-like properties, resistance to radiation and chemotherapy) in multiple human cancer types. NETD in prostate cancer is associated with resistance to therapy, visceral metastasis, and aggressive disease. Thus, activation of these programs via inhibition of the androgen axis provides a mechanism by which tumor cells can adapt to promote disease recurrence and progression.

Novak, D., K. Weina, et al. "From skin to other cell types of the body." *J Dtsch Dermatol Ges.* 2014 Sep;12(9):789-92. doi: 10.1111/ddg.12403. Epub 2014 Aug 1.

Regenerative medicine allows for the customization of tissues and organs which may bring hope to patients with incurable diseases and severe injuries. Therefore, reliable and safe methods for the generation of specific cell types must be established. Recently, different strategies have emerged to convert somatic cells into differentiated cells of interest. One of these strategies is cellular reprogramming, which converts somatic cells into induced pluripotent stem cells (iPSCs). These iPSCs are embryonic stem cell-like cells with almost unlimited developmental potential and can be differentiated into specific lineages. Alternatively, the method of transdifferentiation can be used to directly convert one terminally differentiated cell into another cell type. Both of these methods have proven to have the potential to push the field of cell replacement therapy forward. In this context, the skin is of particular interest because it represents an ideal source of somatic cells for reprogramming to pluripotency as well as transdifferentiation. In this review, we briefly compare both above-mentioned strategies and summarize the latest advances in this highly dynamic field of research.

Ostrakhovitch, E. A., S. Akakura, et al. "Dedifferentiation of cancer cells following recovery from a potentially lethal damage is mediated by H2S-Nampt." *Exp Cell Res.* 2015 Jan 1;330(1):135-50. doi: 10.1016/j.yexcr.2014.09.027. Epub 2014 Sep 30.

Recently, we reported that cancer cells that recover from a potentially lethal damage gain new phenotypic features comprised of mitochondrial structural remodeling associated with increased glycolytic dependency and drug resistance. Here, we demonstrate that a subset of cancer cells, upon recovery from a potentially lethal damage, undergo

dedifferentiation and express genes, which are characteristic of undifferentiated stem cells. While these cells are competent in maintaining differentiated progeny of tumor, they also exhibit transdifferentiation potential.

Pernicova, Z., E. Slabakova, et al. "The role of high cell density in the promotion of neuroendocrine transdifferentiation of prostate cancer cells." Mol Cancer. 2014 May 20;13:113. doi: 10.1186/1476-4598-13-113.

BACKGROUND: Tumor heterogeneity and the plasticity of cancer cells present challenges for effective clinical diagnosis and therapy. Such challenges are epitomized by neuroendocrine transdifferentiation (NED) and the emergence of neuroendocrine-like cancer cells in prostate tumors. This phenomenon frequently arises from androgen-depleted prostate adenocarcinoma and is associated with the development of castration-resistant prostate cancer and poor prognosis. **RESULTS:** In this study, we showed that NED was evoked in both androgen receptor (AR)-positive and AR-negative prostate epithelial cell lines by growing the cells to a high density. Androgen depletion and high-density cultivation were both associated with cell cycle arrest and deregulated expression of several cell cycle regulators, such as p27Kip1, members of the cyclin D protein family, and Cdk2.

Petersen, C. P., V. G. Weis, et al. "Macrophages promote progression of spasmolytic polypeptide-expressing metaplasia after acute loss of parietal cells." Gastroenterology. 2014 Jun;146(7):1727-38.e8. doi: 10.1053/j.gastro.2014.02.007. Epub 2014 Feb 15.

BACKGROUND & AIMS: Loss of parietal cells causes the development of spasmolytic polypeptide-expressing metaplasia (SPEM) through transdifferentiation of chief cells. In the presence of inflammation, SPEM can advance into a more proliferative metaplasia with increased expression of intestine-specific transcripts. We used L635 to induce acute SPEM with inflammation in mice and investigated the roles of inflammatory cells in the development of SPEM. **METHODS:** To study the adaptive immune system, Rag1 knockout, interferon-gamma-deficient, and wild-type (control) mice received L635 for 3 days. To study the innate immune system, macrophages were depleted by intraperitoneal injection of clodronate liposomes 2 days before and throughout L635 administration. Neutrophils were depleted by intraperitoneal injection of an antibody against Ly6G 2 days before and throughout L635 administration. Pathology and immunohistochemical analyses were used to determine depletion efficiency, metaplasia, and proliferation. To characterize SPEM in

each model, gastric tissues were collected and levels of Cfr, Dmbt1, and Gpx2 mRNAs were measured. Markers of macrophage polarization were used to identify subpopulations of macrophages recruited to the gastric mucosa. **RESULTS:** Administration of L635 to Rag1 knockout, interferon-gamma-deficient, and neutrophil-depleted mice led to development of proliferative SPEM and up-regulation of intestine-specific transcripts in SPEM cells, similar to controls.

Pineda, M., C. J. Weijer, et al. "Modelling cell movement, cell differentiation, cell sorting and proportion regulation in Dictyostelium discoideum aggregations." J Theor Biol. 2015 Apr 7;370:135-50. doi: 10.1016/j.jtbi.2015.01.042. Epub 2015 Feb 7.

Understanding the mechanisms that control tissue morphogenesis and homeostasis is a central goal not only in developmental biology but also has great relevance for our understanding of various diseases, including cancer. A model organism that is widely used to study the control of tissue morphogenesis and proportioning is the Dictyostelium discoideum. While there are mathematical models describing the role of chemotactic cell motility in the Dictyostelium assembly and morphogenesis of multicellular tissues, as well as models addressing possible mechanisms of proportion regulation, there are no models incorporating both these key aspects of development. In this paper, we introduce a 1D hyperbolic model to investigate the role of two morphogens, DIF and cAMP, on cell movement, cell sorting, cell-type differentiation and proportioning in Dictyostelium discoideum. First, we use the non-spatial version of the model to study cell-type transdifferentiation. We perform a steady-state analysis of it and show that, depending on the shape of the differentiation rate functions, multiple steady-state solutions may occur. Then we incorporate spatial dynamics into the model, and investigate the transdifferentiation and spatial positioning of cells inside the newly formed structures, following the removal of prestalk or prespore regions of a Dictyostelium slug.

Polanska, U. M. and A. Orimo "Carcinoma-associated fibroblasts: non-neoplastic tumour-promoting mesenchymal cells." J Cell Physiol. 2013 Aug;228(8):1651-7. doi: 10.1002/jcp.24347.

Cancerous stroma coevolves alongside tumour progression, thereby promoting the malignant conversion of epithelial carcinoma cells. To date, an abundance of data have supported crucial roles of the tumour microenvironment (TME) in providing cancer cells with proliferative, migratory, survival and invasive propensities favouring the processes of tumourigenesis. The cancerous reactive stroma is frequently populated by a large number of

myofibroblasts (MFs), which are activated, non-transformed fibroblasts expressing alpha-smooth muscle actin (alpha-SMA). MFs together with non-MF cells present in the tumour-associated stroma are collectively referred to as carcinoma-associated fibroblasts (CAFs), one of the major stromal cell types recognised in various human carcinomas. Recruitment of fibroblasts and/or their progenitors to a tumour mass and their subsequent transdifferentiation into MFs, as well as ongoing maintenance of their activated state, are believed to be essential processes facilitating tumour progression. However, the complex networks of signalling pathways mediating the phenotypic conversion into CAFs, as well as those underlying their tumour-promoting interactions with other tumour-constituting cells, have yet to be fully explored. Histopathological confirmation of the presence of large numbers of CAF MFs within TME and their altered gene expression profiles are known to be associated with disease progression and to serve as independent negative prognostic factors for a wide range of tumour types.

Rabajante, J. F. and A. L. Babierra Branching and oscillations in the epigenetic landscape of cell-fate determination, *Prog Biophys Mol Biol.* 2015 Jan 30. pii: S0079-6107(15)00007-3. doi: 10.1016/j.pbiomolbio.2015.01.006.

The well-known Waddington's epigenetic landscape of cell-fate determination is not static but varies because of the dynamic gene regulation during development. However, existing mathematical models with few state variables and fixed parameters are inadequate in characterizing the temporal transformation of the landscape. Here we simulate a decision-switch model of gene regulation with more than two state variables and with time-varying repression among regulatory factors. We are able to demonstrate multi-lineage differentiation at different timescales that portrays the branching canals in Waddington's illustration. We also present a repressilator-type system that activates suppressed genes via sustained oscillations in a flattened landscape, hence providing an alternative scheme for cellular reprogramming. The time-dependent parameters governed by gradient-based dynamics regulate cell differentiation, dedifferentiation and transdifferentiation.

Rajput, S., B. N. Kumar, et al. "Thymoquinone restores radiation-induced TGF-beta expression and abrogates EMT in chemoradiotherapy of breast cancer cells." *J Cell Physiol.* 2015 Mar;230(3):620-9. doi: 10.1002/jcp.24780.

Radiotherapy remains a prime approach to adjuvant therapies in patients with early and advanced

breast cancer. In spite of therapeutic success, metastatic progression in patients undergoing therapy, limits its application. However, effective therapeutic strategies to understand the cellular and molecular machinery in inhibiting radiation-induced metastatic progression, which is poorly understood so far, need to be strengthened. Ionizing radiation was known to prompt cancer cell's metastatic ability by eliciting Transforming Growth Factor-beta (TGF-beta), a key regulator in epithelial-mesenchymal transdifferentiation and radio-resistance. In this viewpoint, we employed thymoquinone as a radiosensitizer to investigate its migration and invasion reversal abilities in irradiated breast cancer cell lines by assessing their respective attributes. The role of metastasis regulatory molecules like TGF-beta, E-cadherin, and integrin alphaV and its downstream molecules were determined using RT-PCR, western blotting, immunofluorescence, and extracellular TGF-beta levels affirmed through ELISA assays.

Rapino, F., E. F. Robles, et al. "C/EBPalpha induces highly efficient macrophage transdifferentiation of B lymphoma and leukemia cell lines and impairs their tumorigenicity." *Cell Rep.* 2013 Apr 25;3(4):1153-63. doi: 10.1016/j.celrep.2013.03.003. Epub 2013 Mar 28.

Earlier work demonstrated that the transcription factor C/EBPalpha can convert immature and mature murine B lineage cells into functional macrophages. Testing >20 human lymphoma and leukemia B cell lines, we found that most can be transdifferentiated at least partially into macrophage-like cells, provided that C/EBPalpha is expressed at sufficiently high levels. A tamoxifen-inducible subclone of the Seraphina Burkitt lymphoma line, expressing C/EBPalphaER, could be efficiently converted into phagocytic and quiescent cells with a transcriptome resembling normal macrophages. The converted cells retained their phenotype even when C/EBPalpha was inactivated, a hallmark of cell reprogramming. Interestingly, C/EBPalpha induction also impaired the cells' tumorigenicity. Likewise, C/EBPalpha efficiently converted a lymphoblastic leukemia B cell line into macrophage-like cells, again dramatically impairing their tumorigenicity.

Rodriguez-Ubreva, J., L. Ciudad, et al. "C/EBPalpha-mediated activation of microRNAs 34a and 223 inhibits Lef1 expression to achieve efficient reprogramming into macrophages." *Mol Cell Biol.* 2014 Mar;34(6):1145-57. doi: 10.1128/MCB.01487-13. Epub 2014 Jan 13.

MicroRNAs (miRNAs) exert negative effects on gene expression and influence cell lineage choice during hematopoiesis. C/EBPalpha-induced pre-B cell-to-macrophage transdifferentiation provides an excellent

model to investigate the contribution of miRNAs to hematopoietic cell identity, especially because the two cell types involved fall into separate lymphoid and myeloid branches. In this process, efficient repression of the B cell-specific program is essential to ensure transdifferentiation and macrophage function. miRNA profiling revealed that upregulation of miRNAs is highly predominant compared with downregulation and that C/EBPa directly regulates several upregulated miRNAs. We also determined that miRNA 34a (miR-34a) and miR-223 sharply accelerate C/EBPa-mediated transdifferentiation, whereas their depletion delays this process. These two miRNAs affect the transdifferentiation efficiency and activity of macrophages, including their lipopolysaccharide (LPS)-dependent inflammatory response. miR-34a and miR-223 directly target and downregulate the lymphoid transcription factor Lef1, whose ectopic expression delays transdifferentiation to an extent similar to that seen with miR-34a and miR-223 depletion. In addition, ectopic introduction of Lef1 in macrophages causes upregulation of B cell markers, including CD19, Pax5, and Ikzf3. Our report demonstrates the importance of these miRNAs in ensuring the erasure of key B cell transcription factors, such as Lef1, and reinforces the notion of their essential role in fine-tuning the control required for establishing cell identity.

Saegusa, M., M. Hashimura, et al. "Sox4 functions as a positive regulator of beta-catenin signaling through upregulation of TCF4 during morular differentiation of endometrial carcinomas." Lab Invest. 2012 Apr;92(4):511-21. doi: 10.1038/labinvest.2011.196. Epub 2012 Jan 9.

Sox factors function as either activators or repressors of beta-catenin/TCF transcription depending on the cellular context and associated interacting proteins. Our previous study provided evidence that alteration in beta-catenin signaling is an essential event during transdifferentiation toward the morular phenotype of endometrial carcinomas (Em Cas). Here, we focused on related functional roles of Sox factors. Of eight Sox factors investigated, Sox4 could enhance beta-catenin/TCF4 transcription, through upregulation of TCF4 at the transcription level, without any direct beta-catenin association. Cells stably overexpressing Sox4 showed significant decreases in proliferation rate, along with increases in expression of p21(WAF1), as well as TCF4, in contrast to increased cell growth observed with knockdown.

Shekhani, M. T., A. S. Jayanthi, et al. "Cancer stem cells and tumor transdifferentiation: implications for

novel therapeutic strategies." Am J Stem Cells. 2013 Mar 8;2(1):52-61. Print 2013.

Highly malignant tumors mostly consist of rapidly proliferating cells. However, tumors also contain a few cells in a quiescent state that can be characterized as slow-cycling, expressing markers of stem cells and possessing the ability to initiate new tumors. These quiescent cells, now generally termed 'cancer stem cells' (CSC) (or 'cancer initiating cells'), are capable of regenerating the entire tumor--as it occurs in metastatic spread. This process of tumor initiation by stem-like cells presumably involves differentiation of quiescent CSC into rapidly proliferating tumor cells. An important implication of the presence of slow cycling, quiescent stem-like cells in the tumor and their ability to initiate tumors is that they contribute to the resistance to treatments by conventional chemo- and radiotherapy directed toward killing rapidly dividing cells. However, similar to normal stem cells, the CSC could also potentially transdifferentiate into cell lineages other than the original lineage from which the tumor arose. Therefore, transdifferentiation of CSC offers a possible therapeutic strategy which has not yet been fully exploited. In this article, we provide a comprehensive review of the concepts in tumor cell transdifferentiation and discuss the mechanisms of transdifferentiation with emphasis on their relevance to potential novel treatment strategies.

Shoshani, O. and D. Zipori Stress as a fundamental theme in cell plasticity, Biochim Biophys Acta. 2015 Apr;1849(4):371-377. doi: 10.1016/j.bbagr.2014.07.006. Epub 2014 Jul 16.

Over a decade of intensive investigation of the possible plasticity of mammalian cells has eventually substantiated that mammalian species are endowed with a remarkable capacity to change mature cell fates. We review below the evidence for the occurrence of processes such as dedifferentiation and transdifferentiation within mammalian tissues in vivo, and in cells removed from their protective microenvironment and seeded in culture under conditions poorly resembling their physiological state in situ. Overall, these studies point to one major conclusion: stressful conditions, whether due to in vivo tissue damage or otherwise to isolation of cells from their in vivo restrictive niches, lead to extreme fate changes. Some examples of dedifferentiation are discussed in detail showing that rare cells within the population tend to turn back into less mature ones due to severe cell damage. It is proposed that cell stress, mechanistically sensed by isolation from neighboring cells, leads to dedifferentiation, in an attempt to build a new stem cell reservoir for subsequent regeneration of the damaged tissue. This article is part of a Special

Issue entitled: Stress as a fundamental theme in cell plasticity.

Solaimani Kartalaei, P., T. Yamada-Inagawa, et al. "Whole-transcriptome analysis of endothelial to hematopoietic stem cell transition reveals a requirement for Gpr56 in HSC generation." *J Exp Med.* 2015 Jan 12;212(1):93-106. doi: [10.1084/jem.20140767](https://doi.org/10.1084/jem.20140767). Epub 2014 Dec 29.

Hematopoietic stem cells (HSCs) are generated via a natural transdifferentiation process known as endothelial to hematopoietic cell transition (EHT). Because of small numbers of embryonal arterial cells undergoing EHT and the paucity of markers to enrich for hemogenic endothelial cells (ECs [HECs]), the genetic program driving HSC emergence is largely unknown. Here, we use a highly sensitive RNAseq method to examine the whole transcriptome of small numbers of enriched aortic HSCs, HECs, and ECs. Gpr56, a G-coupled protein receptor, is one of the most highly up-regulated of the 530 differentially expressed genes. Also, highly up-regulated are hematopoietic transcription factors, including the "heptad" complex of factors. We show that Gpr56 (mouse and human) is a target of the heptad complex and is required for hematopoietic cluster formation during EHT. Our results identify the processes and regulators involved in EHT and reveal the surprising requirement for Gpr56 in generating the first HSCs.

Stoecker, M. M. and E. Wang "Histiocytic/dendritic cell transformation of B-cell neoplasms: pathologic evidence of lineage conversion in differentiated hematolymphoid malignancies." *Arch Pathol Lab Med.* 2013 Jun;137(6):865-70. doi: [10.5858/arpa.2012-0104-RS](https://doi.org/10.5858/arpa.2012-0104-RS).

B-cell lymphomas, such as low-grade follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma, can transform to histiocytic/dendritic cell sarcoma (H/DS) in rare cases. The diagnosis of this unconventional neoplastic evolution relies on a combination of immunophenotypic analysis and genotypic studies. A genotype identical to that of the primary B-cell neoplasm in a secondary neoplasm with H/DS immunophenotype supports the lineage conversion to H/DS. Putative mechanisms for this unusual phenomenon include dedifferentiation, common immature progenitor, and transdifferentiation models, the latter of which is suggested by clinical laboratory data at the present time. Elucidation of the molecular mechanisms governing this lineage conversion may facilitate the understanding of carcinogenesis of not only hematopoietic but also nonhematolymphoid neoplasms. The clinical outcome of secondary H/DS is

dismal, as observed in sporadic cases, and the optimal treatment remains to be determined.

Streppel, M. M., E. A. Montgomery, et al. "New advances in the pathogenesis and progression of barrett's esophagus." *Curr Mol Med.* 2014 Jan;14(1):58-68.

Barrett's esophagus (BE) is a premalignant condition in the esophagus, with a rising incidence rate among Caucasians, and an established risk factor for the subsequent progression to esophageal adenocarcinoma (EAC). In contrast to the stratified squamous epithelium that normally lines the distal esophagus, BE is characterized by columnar epithelium that to some extent resembles the mucosa of the lower intestinal tract. The mechanism of intestinalization of the esophagus is still uncertain. For many years, it was postulated that either abnormal differentiation of resident progenitor cells in the esophagus, or transdifferentiation of mature esophageal keratinocytes provoked by reflux-induced genetic alterations, resulted in the BE phenotype. However, more recent studies suggest that indigenous progenitor cells at the gastro-esophageal junction might, under unfavorable conditions such as TP63 loss or an activated inflammatory response, migrate to the esophagus and initiate columnar cell differentiation. In this review, we discuss the competing theories of the origins of BE, as well as the role of developmental signaling pathways such as Notch, Hedgehog, and Wnt/beta-catenin signaling that have been implicated in the molecular pathogenesis of BE and EAC. Additionally, we provide an overview of the mutational landscapes of BE and EAC, derived from the results of recently published next generation sequencing (NGS) studies. Future research should elucidate whether NGS on endoscopic mucosal biopsies can help in identifying BE patients at highest risk for EAC development, and whether some of the prevalent mutations are "actionable", leading to improvements in current therapeutic strategies for BE and EAC.

Takahashi, E. and S. Nakamura "Histiocytic sarcoma : an updated literature review based on the 2008 WHO classification." *J Clin Exp Hematop.* 2013;53(1):1-8.

Histiocytic sarcoma (HS) is an extremely rare malignant neoplasm showing morphologic and immunophenotypic evidence of histiocytic differentiation. The vast majority of previously reported HSs are now generally recognized to be misdiagnosed examples of non-Hodgkin lymphomas, predominantly diffuse large B-cell lymphoma or anaplastic large cell lymphoma. The recognition of such tumors parallels the development and widespread use of immunohistochemical techniques, along with

the development of molecular genetic methods to detect immunoglobulin (IG) or T-cell receptor (TCR) gene rearrangement. The 2001 World Health Organization (WHO) definition of HS requires the absence of clonal B/T-cell receptor gene rearrangements. However, the 2008 WHO classification no longer strictly requires the absence of clonal immunoglobulin heavy chain (IGH) or TCR gene rearrangement for the diagnosis of HS. Recent studies demonstrated that HSs that occur subsequent to or concurrent with B- or T-lymphoblastic lymphoma/leukemia or mature B-cell neoplasms generally show clonal IgH and/or TCR gene rearrangement.

Tawadros, T., F. Alonso, et al. "Release of macrophage migration inhibitory factor by neuroendocrine-differentiated LNCaP cells sustains the proliferation and survival of prostate cancer cells." *Endocr Relat Cancer*. 2013 Feb 18;20(1):137-49. doi: [10.1530/ERC-12-0286](https://doi.org/10.1530/ERC-12-0286). Print 2013 Feb.

The acquisition of neuroendocrine (NE) characteristics by prostate cancer (PCa) cells is closely related to tumour progression and hormone resistance. The mechanisms by which NE cells influence PCa growth and progression are not fully understood. Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine involved in oncogenic processes, and MIF serum levels correlate with aggressiveness of PCa. Here, we investigated the regulation and the functional consequences of MIF expression during NE transdifferentiation of PCa cells. NE differentiation (NED) of LNCaP cells, initiated either by increasing intracellular levels of cAMP or by culturing cells in an androgen-depleted medium, was associated with markedly increased MIF release. Yet, intracellular MIF protein and mRNA levels and MIF gene promoter activity decreased during NED of LNCaP cells, suggesting that NED favours MIF release despite decreasing MIF synthesis. Adenoviral-mediated forced MIF expression in NE-differentiated LNCaP cells increased cell proliferation without affecting the expression of NE markers. Addition of exogenous recombinant MIF to LNCaP and PC-3 cells stimulated the AKT and ERK1/2 signalling pathways, the expression of genes involved in PCa, as well as proliferation and resistance to paclitaxel and thapsigargin-induced apoptosis.

Terry, S., P. Maille, et al. "Cross modulation between the androgen receptor axis and protocadherin-PC in mediating neuroendocrine transdifferentiation and therapeutic resistance of prostate cancer." *Neoplasia*. 2013 Jul;15(7):761-72.

Castration-resistant prostate cancers (CRPCs) that relapse after androgen deprivation therapies

(ADTs) are responsible for the majority of mortalities from prostate cancer (PCa). While mechanisms enabling recurrent activity of androgen receptor (AR) are certainly involved in the development of CRPC, there may be factors that contribute to the process including acquired neuroendocrine (NE) cell-like behaviors working through alternate (non-AR) cell signaling systems or AR-dependent mechanisms. In this study, we explore the potential relationship between the AR axis and a novel putative marker of NE differentiation, the human male protocadherin-PC (PCDH-PC), in vitro and in human situations. We found evidence for an NE transdifferentiation process and PCDH-PC expression as an early-onset adaptive mechanism following ADT and elucidate AR as a key regulator of PCDH-PC expression. PCDH-PC overexpression, in turn, attenuates the ligand-dependent activity of the AR, enabling certain prostate tumor clones to assume a more NE phenotype and promoting their survival under diverse stress conditions. Acquisition of an NE phenotype by PCa cells positively correlated with resistance to cytotoxic agents including docetaxel, a taxane chemotherapy approved for the treatment of patients with metastatic CRPC. Furthermore, knockdown of PCDH-PC in cells that have undergone an NE transdifferentiation partially sensitized cells to docetaxel. Together, these results reveal a reciprocal regulation between the AR axis and PCDH-PC signals, observed both in vitro and in vivo, with potential implications in coordinating NE transdifferentiation processes and progression of PCa toward hormonal and chemoresistance.

Tucci, M., S. Stucci, et al. "Immature dendritic cells in multiple myeloma are prone to osteoclast-like differentiation through interleukin-17A stimulation." *Br J Haematol*. 2013 Jun;161(6):821-31. doi: [10.1111/bjh.12333](https://doi.org/10.1111/bjh.12333). Epub 2013 Apr 18.

Interleukin 17A (IL17A), a cytokine involved in allergy, inflammation and osteoclastogenesis, was investigated in multiple myeloma (MM) to assess its role in the osteoclast (OC)-like activity of marrow immature dendritic cells (iDCs). Comparing nine MM patients with control subjects affected by monoclonal gammopathy of undetermined significance, we found high IL17A expression in the marrow plasma of MM patients in parallel with its deposits within the stromal matrix. Increased expression of the IL17A receptor (IL17RA) was also found in primary myeloma iDCs, which underwent OC-like transdifferentiation after IL17A stimulation. To assess the role of IL17A, we measured the activity of the IL17/IL17RA pathway in IL17A-transdifferentiated iDCs and the expression of functional OC genes by Western blotting and real-time polymerase chain reaction. These cells showed increased RNA transcription of genes enrolled in the

maturation of OCs, while NFATC1 and FOS were induced by IL17A, independently of NFKB1 phosphorylation. Moreover, the concurrent phosphorylation of the Lip isoform of CEBPB and the down-regulation of MAFB supported the activation of IL17RA pathway in OC-like transdifferentiated iDCs that was apparently unrelated to TNFRSF11A signalling. These data emphasize the involvement of iDCs in MM hyperactive osteoclastogenesis and suggest that their bone resorption activity is also regulated, at least in vitro, by IL17RA.

Ul-Mulk, J., H. Rasmussen, et al. "A case of collision tumor or transdifferentiation between malignant melanoma and leiomyosarcoma." *Indian J Pathol Microbiol.* 2012 Oct-Dec;55(4):538-9. doi: [10.4103/0377-4929.107806](https://doi.org/10.4103/0377-4929.107806).

A 73-year-old woman was referred to the hospital due to a pigmented, asymptomatic nevus on her right arm that had changed in size and color. The histopathological examination showed a superficial spreading malignant melanoma, Clark level III, 2.26 mm in thickness. Two years later, the patient presented a 10 cm rapidly growing mass in her right axilla. The mass in the axilla measured 12.59cm. It revealed a lymph node metastases with a tumor growth composed of two different contiguous morphological and immunohistochemical components, respectively, melanosomes and leiomyosarcoma. The combination of a melanocytic nevus with other tumor of epidermal or adnexal origin has been described before, but still the co-existence of two different neoplasms within a lesion is still uncommon. The most common combination is basal cell carcinoma and melanocytic nevus or one of them together with a seborrheic keratosis. There have also been occasional reports of rhabdomyosarcomatous differentiation. However, mesenchymal differentiation, and in this case leiomyosarcoma, with formation of heterologous elements in melanocytic tumor is very rare. Another plausible explanation may be that malignant melanoma cells could have transdifferentiated into a leiomyosarcomatoid phenotype with resulting metastases of either type. Malignant melanomas have shown a wide variety of cytological changes and can mimic carcinomas, lymphomas, and sarcomas. Spindle cell melanomas commonly simulate spindle cell carcinomas. It has also been documented that desmoplastic melanomas can change into fibroblastic, Schwannian, and myofibroblastic differentiation.

Vacchio, M. S., L. Wang, et al. "A ThPOK-LRF transcriptional node maintains the integrity and effector potential of post-thymic CD4+ T cells." *Nat Immunol.* 2014 Oct;15(10):947-56. doi: [10.1038/ni.2960](https://doi.org/10.1038/ni.2960). Epub 2014 Aug 17.

The transcription factor ThPOK promotes CD4(+) T cell differentiation in the thymus. Here, using a mouse strain that allows post-thymic gene deletion, we show that ThPOK maintains CD4(+) T lineage integrity and couples effector differentiation to environmental cues after antigenic stimulation. ThPOK preserved the integrity and amplitude of effector responses and was required for proper differentiation of types 1 and 2 helper T cells in vivo by restraining the expression and function of Runx3, a nuclear factor crucial for cytotoxic T cell differentiation. The transcription factor LRF acts redundantly with ThPOK to prevent the transdifferentiation of mature CD4(+) T cells into CD8(+) T cells. As such, the ThPOK-LRF transcriptional module was essential for CD4(+) T cell integrity and responses.

Vainshtein, J. M., R. Kabarriti, et al. "Bone marrow-derived stromal cell therapy in cirrhosis: clinical evidence, cellular mechanisms, and implications for the treatment of hepatocellular carcinoma." *Int J Radiat Oncol Biol Phys.* 2014 Jul 15;89(4):786-803. doi: [10.1016/j.ijrobp.2014.02.017](https://doi.org/10.1016/j.ijrobp.2014.02.017).

Current treatment options for hepatocellular carcinoma (HCC) are often limited by the presence of underlying liver disease. In patients with liver cirrhosis, surgery, chemotherapy, and radiation therapy all carry a high risk of hepatic complications, ranging from ascites to fulminant liver failure. For patients receiving radiation therapy, cirrhosis dramatically reduces the already limited radiation tolerance of the liver and represents the most important clinical risk factor for the development of radiation-induced liver disease. Although improvements in conformal radiation delivery techniques have improved our ability to safely irradiate confined areas of the liver to increasingly higher doses with excellent local disease control, patients with moderate-to-severe liver cirrhosis continue to face a shortage of treatment options for HCC. In recent years, evidence has emerged supporting the use of bone marrow-derived stromal cells (BMSCs) as a promising treatment for liver cirrhosis, with several clinical studies demonstrating sustained improvement in clinical parameters of liver function after autologous BMSC infusion. Three predominant populations of BMSCs, namely hematopoietic stem cells, mesenchymal stem cells, and endothelial progenitor cells, seem to have therapeutic potential in liver injury and cirrhosis.

Vijayan, A., D. Guha, et al. "IGFBP-5 enhances epithelial cell adhesion and protects epithelial cells from TGFbeta1-induced mesenchymal invasion." *Int J*

Biochem Cell Biol. 2013 Dec;45(12):2774-85. doi: 10.1016/j.biocel.2013.10.001. Epub 2013 Oct 11.

TGFbeta1 is a major fibrotic factor and its actions involve induction of epithelial cell death, together with the stimulation and transdifferentiation of fibroblasts into collagen- and fibronectin-secreting myofibroblasts. These actions of TGFbeta1 are also consistent with a pro-metastatic role, by aiding epithelial cell escape through mesenchymal tissues. Recently IGFBP-5 has been described as a pro-fibrotic (pro-metastatic?) agent and the aim of this study was to compare and contrast the actions of IGFBP-5 with TGFbeta1. We used NMuMG cells and cloned stable epithelial and mesenchymal lines from the parent cells. TGFbeta1 induced apoptosis and/or EMT in the epithelial cells, whereas it enhanced mesenchymal cell survival and migration. IGFBP-5, in contrast, enhanced both cell-cell and cell-ECM adhesion and also improved wound closure in epithelial cells whereas, in mesenchymal cells, IGFBP-5 decreased adhesion and migration. Furthermore, IGFBP-5 was able to antagonise the actions of TGFbeta1. In a co-culture model simulating epithelial-mesenchymal boundaries, IGFBP-5 was able to antagonise the disruptive transgressions induced by TGFbeta1.

Vizoso, M. and M. Esteller German-Catalan workshop on epigenetics and cancer, Epigenetics. 2013 Sep;8(9):998-1003. doi: 10.4161/epi.25856. Epub 2013 Jul 24.

In the First German-Catalan Workshop on Epigenetics and Cancer held in Heidelberg, Germany (June 17-19, 2013), cutting-edge laboratories (PEBC, IMPPC, DKFZ, and the Collaborative Research Centre Medical Epigenetics of Freiburg) discussed the latest breakthroughs in the field. The importance of DNA demethylation, non-coding and imprinted genes, metabolic stress, and cell transdifferentiation processes in cancer and non-cancer diseases were addressed in several lectures in a very participative and dynamic atmosphere. The meeting brought together leading figures in the field of cancer epigenetics to present their research work from the last five years. Experts in different areas of oncology described important advances in colorectal, lung, neuroblastoma, leukemia, and lymphoma cancers. The workshop also provided an interesting forum for pediatrics, and focused on the need to improve the treatment of childhood tumors in order to avoid, as far as possible, brain damage and disruption of activity in areas of high plasticity. From the beginning, the relevance of "omics" and the advances in genome-wide analysis platforms, which allow cancer to be studied in a more comprehensive and inclusive way, was very clear. Modern "omics" offer the possibility of identifying metastases of uncertain origin and establishing epigenetic signatures

linked to a specific cluster of patients with a particular prognosis. In this context, invited speakers described novel tumor-associated histone variants and DNA-specific methylation, highlighting their close connection with other processes such as cell-lineage commitment and stemness.

Weissbein, U., U. Ben-David, et al. "Virtual karyotyping reveals greater chromosomal stability in neural cells derived by transdifferentiation than those from stem cells." Cell Stem Cell. 2014 Dec 4;15(6):687-91. doi: 10.1016/j.stem.2014.10.018.

Neural cells can be derived either from pluripotent or adult stem cells via differentiation or by transdifferentiation from other cell types with the aid of tissue regulators. We compared the chromosomal stability of over 500 neural cell samples from human and mouse with virtual karyotyping (e-karyotyping). We detected notable genomic instability in cells derived from pluripotent or adult stem cells, but surprisingly, transdifferentiated cells seemed more chromosomally stable, except if they were reprogrammed using pluripotency factors.

West, D. S., A. Dogan, et al. "Clonally related follicular lymphomas and Langerhans cell neoplasms: expanding the spectrum of transdifferentiation." Am J Surg Pathol. 2013 Jul;37(7):978-86. doi: 10.1097/PAS.0b013e318283099f.

The traditional model of hematopoiesis is based on unidirectional maturation of hematopoietic precursors into lineage-committed cells. However, recent studies indicate that mature B lymphocytes may demonstrate significant lineage plasticity. We and others have reported transdifferentiation of follicular lymphomas (FLs) into clonally related histiocytic/dendritic cell neoplasms. Here, we describe 2 patients with FL who developed clonally related Langerhans cell neoplasms. The first was a 52-year-old man diagnosed with FL, grade 1. He received immunochemotherapy and had stable disease for 8 years. He then developed increasing lymphadenopathy, and lymph node biopsy showed Langerhans cell sarcoma with no evidence of FL. The second patient was a 77-year-old woman who presented with lymphadenopathy, an abdominal mass, and pulmonary nodules. Lymph node biopsy showed both Langerhans cell histiocytosis and minimal involvement by FL, grade 1. In each case, a combination of immunoglobulin gene rearrangement and fluorescence in situ hybridization studies provided evidence to support a clonal relationship between the FL and Langerhans cell neoplasm. These cases provide striking examples of neoplastic transdifferentiation and expand the spectrum of lesions clonally identical to otherwise typical FL. Awareness

of this phenomenon may aid in diagnosis when histologically dissimilar tumors arise synchronously or metachronously in patients with lymphoma.

Ziegler, H., C. Welker, et al. "Human Peripheral CD4(+) Vdelta1(+) gammadeltaT Cells Can Develop into alphabetaT Cells." *Front Immunol.* 2014 Dec 17;5:645. doi: 10.3389/fimmu.2014.00645. eCollection 2014.

The lifelong generation of alphabetaT cells enables us to continuously build immunity against pathogens and malignancies despite the loss of thymic function with age. Homeostatic proliferation of post-thymic naive and memory T cells and their transition into effector and long-lived memory cells balance the decreasing output of naive T cells, and recent research suggests that also alphabetaT-cell development independent from the thymus may occur. However, the sites and mechanisms of extrathymic T-cell development are not yet understood in detail. gammadeltaT cells represent a small fraction of the overall T-cell pool, and are endowed with tremendous phenotypic and functional plasticity. gammadeltaT cells that express the Vdelta1 gene segment are a minor population in human peripheral blood but predominate in epithelial (and inflamed) tissues. Here, we characterize a CD4(+) peripheral Vdelta1(+) gammadeltaT-cell subpopulation that expresses stem-cell and progenitor markers and is able to develop into functional alphabetaT cells ex vivo in a simple culture system and in vivo. The route taken by this process resembles thymic T-cell development. However, it involves the re-organization of the Vdelta1(+) gammadeltaTCR into the alphabetaTCR as a consequence of TCR-gamma chain downregulation and the expression of surface Vdelta1(+)Vbeta(+) TCR components, which we believe function as surrogate pre-TCR. This transdifferentiation process is readily detectable in vivo in inflamed tissue. Our study provides a conceptual framework for extrathymic T-cell development and opens up a new vista in immunology that requires adaptive immune responses in infection, autoimmunity, and cancer to be reconsidered.

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