World J Surg (2011) 35:1738–1745
DOI 10.1007/s00268-010-0941-2

World Journal of Surgery

Defining the Cancer Master Switch

Courtney J. Balentine · David H. Berger · Shi-He Liu · Changyi Chen · John Nemunaitis · F. Charles Brunicardi

Published online: 1 February 2011

Abstract
Background Recent research has focused on signaling cascades and their interactions yielding considerable insight into which genetic pathways are targeted and how they tend to be altered in tumors. Therapeutic interventions now can be designed based on the knowledge of pathways vital to tumor growth and survival. These critical targets for intervention, master switches for cancer, are termed so because the tumor attempts to "flip the switch" in a way that promotes its survival, whereas molecular therapy aims to "switch off" signals important for tumor-related processes.
Methods Literature review.
Conclusions Defining useful targets for therapy depends on identifying pathways that are crucial for tumor growth, survival, and metastasis. Because not all signaling cascades are created equal, selecting master switches or targets for intervention needs to be done in a systematic fashion. This discussion proposes a set of criteria to define what it means to be a cancer master switch and provides examples to illustrate their application.

C. J. Balentine · D. H. Berger · C. Chen
Michael E. DeBakey Veterans Affairs Hospital, Houston, TX, USA

C. J. Balentine · D. H. Berger
Houston Veterans Affairs Health Services Research & Development Center of Excellence, Houston, TX, USA

C. J. Balentine · D. H. Berger · S.-H. Liu · C. Chen · F. C. Brunicardi (✉)
Michael E. DeBakey Department of Surgery, Baylor College of Medicine, 1709 Dryden Street, Suite 1500, Houston, TX 77030, USA
e-mail: cbrunica@bcm.tmc.edu

J. Nemunaitis
Mary Crowley Cancer Research Centers, Dallas, TX, USA

J. Nemunaitis
Gradalis, Inc, Dallas, TX, USA

Introduction

Advances in technology for assessing genomic changes have resulted in the rapid expansion of our understanding of tumor biology [1–3]. Research interest currently is shifting away from the study of individual genes toward that of pathways and networks because of the increased ability to conduct rapid and unbiased surveys of the genome for mutations, chromosomal rearrangement, epigenetic phenomenon, and other changes affecting gene expression [4–7]. Focusing on signaling cascades and their interactions rather than individual genes has yielded considerable insight into which genetic pathways are targeted and how they tend to be altered in tumors [8–10]. Therapeutic interventions can be designed based on the knowledge of pathways vital to tumor growth and survival. These critical targets for intervention can be thought of as master switches for cancer, with the tumor attempting to "flip the switch" in a way that promotes its survival, whereas molecular therapy aims to "switch off" signals important for tumor-related processes. Defining useful targets for therapy depends on identifying pathways that are crucial for tumor growth, survival, and metastasis. Because not all signaling cascades are created equal, selecting master switches or targets for intervention needs to be performed in a systematic fashion. Toward this end, we propose a set of criteria to define what it means to be a cancer master switch and provide a few examples to illustrate their application.

Defining criteria for a master switch

Figure 1 illustrates our conceptual model for the different ways in which molecular pathways can function as a master switch for cancer. Although there are multiple ways in which a tumor can develop and spread, there are certain commonalities that persist across tumor type. A pathway initiated by the binding of ligand and receptor can promote tumor growth and invasion through activation of downstream transcription factors and regulatory proteins that modulate multiple pathways. The sum total of these interactions promotes processes important to tumor development, survival, and metastasis. The balance of stimulatory and inhibitory crosstalk between pathways is a delicate balance that the tumor upsets by carefully targeted genetic and epigenetic changes. Generally, a single change is inadequate to upset this balance so tumors tend to deregulate multiple processes involving signal activation and downstream regulation.

When determining the significance of a particular pathway, we believe it is important to demonstrate that disruption of its component signaling occurs in vivo and does not represent only an in vitro artifact. Consequently, a master switch is more than a promising mutation found in a petri dish or animal model, and must have demonstrated relevance in human disease. Tumor-induced changes can take the form of alterations in gene sequence or structure as well as epigenetic silencing through methylation or histone modification [6, 7]. A pathway constituting a master switch ought to be altered at a high frequency, because this reflects its importance in tumor evolution [5]. Moreover, these changes should have some connection to tumor genesis, survival, or metastasis. Additionally, because tumor development involves significant crosstalk between signaling cascades rather than single molecules acting in isolation, a master switch ought to communicate with other pathways that are significant for tumor development. Relationships with other important pathways can take the form of physical interaction between components of each cascade as well as transcriptional and translational regulation. Alternatively, a master switch can be involved in global regulation of mutation or transcription so that multiple pathways are simultaneously affected by changes in the master switch. To clarify the application of these criteria for their identification and targeting as cancer master switches, we offer three examples of master switch candidates.

Colorectal cancer and Wnt signaling

One of the earliest mutational events occurring in colorectal cancer is loss of adenomatosis polyposis coli (APC) expression, and this change is found in the majority of sporadic colorectal cancers [11]. APC mutation also is seen in familial adenomatous polyposis (FAP) with both point mutations and deletions playing a role [12–16]. It is not uncommon, however, to see a combination of inherited mutations in some form giving rise to the loss of most, but not all, APC expression. The concept that total loss of APC expression actually is counterproductive for tumor growth has been called the just-right signaling model that proposes that a certain level of APC expression actually is advantageous for tumor growth [17]. Moreover, there is some evidence to suggest that when mutation of the APC gene does not occur, methylation of the locus results in decreased expression [18]. APC is an important element in the Wnt-signaling pathway that plays an important role in tumor development. In canonical Wnt signaling, the transcription factor beta-catenin is bound in a cytoplasmic destruction complex involving APC, axin, GSK3β, and CK1γ [19]. In the absence of a Wnt ligand, beta-catenin is maintained in the destruction complex where it is phosphorylated by GSK3β and CK1γ [19–21]. Phosphorylated beta-catenin is targeted for proteasome degradation, and Wnt signaling remains in an inactive state. Activation of the canonical Wnt pathway involves Wnt ligand binding to Frizzled (Fz) receptors in the presence of lipoprotein receptor-related protein (LRP)5/6 and is inhibited by binding of sclerostin (SOST) or soluble Fz protein [22–27]. After the binding of Wnt to the Fz receptor complex, phosphorylation of beta-catenin via the destruction complex is inhibited. Beta-catenin is then free to translocate to the nucleus where it interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to trigger gene expression [28–30]. In addition to the previously mentioned mutations in APC, there are several other alterations utilized by colorectal cancers to affect Wnt signaling. Mutations in beta-catenin exon 3 have been found in patients with hereditary nonpolyposis colorectal cancer, and AXIN1 mutations at GSK3β binding sites have been described as well [31–33]. When wild-type AXIN1 is present, mutations in AXIN2 have been described [34]. Additionally, epigenetic changes, including hypermethylation as well as somatic mutations of various Fz proteins, also have been found [35–37].

Elements of Wnt signaling interact with other pathways that play important roles in colorectal cancer. These pathways include transforming growth factor beta (TGF-β), mitogen-activated protein kinases (MAPK), phosphatase and tensin homolog (PTEN), and phosphatidylinositol 3-kinase (PI3 K)/Akt, which are responsible for regulating cell growth and survival [38]. These relationships tend to be exceedingly complex and are context-dependent. In some instances, Wnt signaling negatively regulates factors in the TGF or bone morphogenetic protein (BMP) pathway, but they also can cooperate to increase transcription of

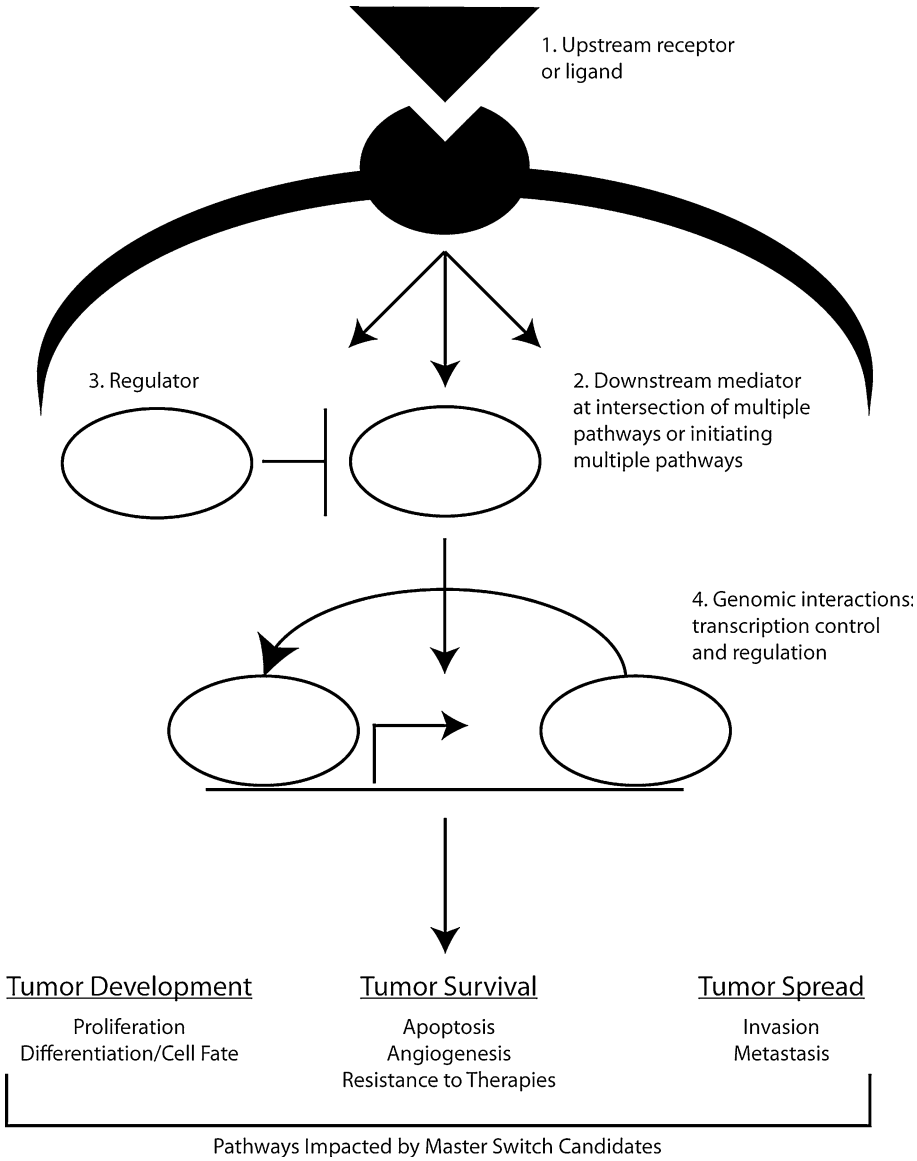

Fig. 1 Mechanisms for a cancer master switch

common targets [39–42]. A similarly complicated interaction is observed with other pathways modulated by Wnt signaling, which makes it difficult to generalize results from one model system to another [43, 44]. Moreover, although mutations in the Wnt pathway have long been recognized as an important early event in the genesis of colorectal cancer, recent work has linked downstream products of Wnt signaling with metastasis, resistance to apoptosis, and decreased survival [45–47]. Recent evaluation of the Wnt pathway using ribonucleic acid interference (RNAi) also has shown promise in identifying potential for intervening in various cancer processes [48–55]. In short, Wnt signaling plays an integral role in the development and progression of colorectal cancer through direct activation of downstream factors and via interaction with other pathways that lead to deregulation of cell growth and survival. Therefore, the Wnt pathway represents an ideal candidate to be targeted for therapeutic and diagnostic measures.

Lung cancer and EGFR

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase with three other family members: ErbB-2/HER2/neu, ErbB-3/HER3, and ErbB-4/HER4 [56]. Like most tyrosine kinase receptors, ligand binding to EGFR induces hetero- or homodimerization and subsequent autophosphorylation, which leads to recruitment of downstream proteins for signaling [56–58]. Interestingly, EGFR heterodimerization with HER2 leads to stronger activation than homodimerization and this has

important therapeutic implications. One of the important pathways activated by EGFR is the Ras/Erk signaling cascade, which is involved in cell proliferation and survival [59]. Once activated, Ras leads to Raf phosphorylation and subsequent stimulation of the MAPK pathway, which also plays a critical role in cell proliferation and survival [60, 61]. The ability of human Raf to activate the MAPK pathway differs depending on each isoform [61]. Additionally, EGF signaling can activate the MAPK pathway via PKC and also can stimulate the PI3 K/Akt pathway, which is frequently altered in human tumors [62, 63]. Finally, EGF signaling promotes expression of vascular endothelial growth factor (VEGF), which is involved in angiogenesis. Overall, abnormalities in EGF signaling have been implicated in tumor proliferation, invasion, angiogenesis, and metastasis [58, 64, 65]. As one might expect from a signaling cascade that intersects with so many other pathways, overexpression of EGFR is quite common in human tumors, including lung cancer and glioblastoma [66, 67]. EGFR mutations also are common in the tyrosine kinase domain, and EGFR expression has been correlated with both disease-free and overall survival rates in lung cancer [68–70].

EGF signaling in lung cancer has become an important therapeutic target. Tyrosine kinase inhibitors, such as gefitinib, have demonstrated efficacy in clinical trials when used in combination with standard chemotherapy [71]. These agents have proven particularly effective in the presence of kinase domain mutations and in lung cancers overexpressing both EGFR and human epidermal growth factor receptor-2 (HER2) [72, 73]. Another approach targeting EGFR involves the use of monoclonal antibodies, such as Erbitux/cetuximab, that lead to receptor internalization and degradation [56]. These agents also have shown the ability to improve survival in selected patients with tumors expressing EGFR [74]. Because the EGF pathway influences a multitude of processes in tumor development and is a promising target for intervention, we believe that it should be included in any discussion of tumor master switches.

PDX-1, embryologic transcription factors, and pancreatic cancer

Pancreatic and duodenal homeobox 1 (PDX-1), a member of the homeodomain-containing transcription factor family, plays a crucial role in the development of the pancreas as well as maintaining normal endocrine function of the adult pancreas [75–79]. The absence of PDX-1 results in pancreatic agenesis in mice and a compound heterozygous mutation in the PDX-1 homeodomain causes human pancreatic agenesis [80, 81]. In the adult pancreas, PDX-1 regulates multiple genes' expression (e.g., insulin, islet amyloid polypeptide, glucokinase, and glucose transporter) [82–85]. PDX-1 also is a critical factor in mediating cell dedifferentiation [86, 87], transdifferentiation [88–91], and cell metaplasia [92, 93]. Most importantly, re-expression of PDX-1 has been found in a variety of human tumors, including those of pancreatic cancer, breast cancer, gastric cancer, and prostate cancer as well as a genetically engineered murine tumor model [93–104]. PDX-1 is capable of inducing cell proliferation, invasion, and transformation in vitro and promoting tumor development and growth in vivo, demonstrating its oncogenic properties [105]. These characteristics meet the criteria for classification as a cancer master switch [106].

Elucidation of the regulatory network of PDX-1 provides a better understanding of PDX-1 as a master switch. PDX-1 is reported to directly regulate *insulin* gene expression as well as the expression of the genes encoding glucose transporter 2 (*Slc2a2*), islet amyloid polypeptide precursor, Pax4, synaptotagmin 1, and *Pdx-1* itself [82–85]. PDX-1 also negatively regulates expression of glucagon [107], which is normally expressed in pancreatic alpha cells and Keratin 19, a member of the cytokeratin family which is critical for maintenance of cellular architecture and organization [108]. In beta cells, PDX-1 binds several groups of newly identified targets to regulate gene expression, therefore, regulating cell metabolism, proliferation, and apoptosis [109]. One target is the transcription factor p53, a master regulator of cell growth arrest and cell death. In addition, micro-RNAs are targets for PDX-1. In pancreatic cancer cells, knockdown of PDX-1 expression stimulates apoptosis through a blockade of NFkB signaling, as well as arrest of the cell cycle by downregulation of cyclins. Decreased gene expression related to angiogenesis (vascular endothelial growth factor) and invasion were also demonstrated [105]. Indirect evidence also supports the suggestion that PDX-1 may be involved in many signaling pathways, such as those involving Stat3, MAPK, and PI3 K/Akt/mTOR [92]. Our group has demonstrated that overexpression of PDX-1 in pancreatic cancer cell lines resulted in disruption of the cell cycle, which caused increased cell proliferation and invasion emphasizing a critical feature of PDX-1 as the master switch in pancreatic carcinogenesis [97, 105]. Similar to PDX-1 are the sonic hedgehog homolog (SHH) [110, 111] and Notch [112] signaling pathways that belong to a set of genes required for embryogenesis. Notch and SHH have been demonstrated to be oncogenes because of their involvement in tumorigenesis and progression. It has been suggested that both Notch and SHH are cancer master switches.

In addition to its relationship with the pathways listed above, PDX-1 also interacts with the somatostatin pathway which also plays a key role in pancreatic cancer. The somatostatin signaling pathway has been shown to downregulate the growth of pancreatic cancer [113–116].

Somatostatin receptors are G-protein-coupled receptors that control pathways responsible for cell growth and proliferation, with both SSTR1 and SSTR2 transfection into pancreatic cancer cells leading to decreased cell growth [117–119]. Somatostatin receptors also may play an important role in regulating apoptosis in combination with tumor necrosis factors (TNFs) [120, 121]. Activation of the somatostatin pathway has shown potential for use as adjuvant therapy in pancreatic cancer and has inhibited tumor growth in animal models [114, 122]. Moreover, transfection of pancreatic cancer cells with somatostatin receptor (SSTR)-1 or SSTR-2 inhibits proliferation and increases susceptibility to treatment with somatostatin analogues [117, 118]. SSTR-2 overexpression also may block pancreatic cancer metastasis [123]. PDX-1 is a downstream transcription factor involved in somatostatin expression in adult islet cells as well as pancreatic development and insulin regulation [79, 124]. A molecular network involving SST/SSTRs and endocrine regulation, as well as SST/SSTRs, PDX-1, cell proliferation and cycle regulation strongly suggest a central role of SSTRs in the regulatory network, further implying a master switch.

Conclusions

Defining what it means to be a cancer master switch is important to clarify the discussion regarding optimal targets for intervention in a variety of human cancers. Research efforts should focus on the pathways most likely to have an impact on patient outcomes and on targeting pathways that sit at the center of a network involved in tumor promotion, which are most likely to yield beneficial results. This new paradigm represents a fundamental shift from the previous focus on identifying individual mutations or changes in transcription. It is through the better understanding of how multiple cascades interact to promote tumor development that we will enhance the ability to target them appropriately and move toward improving patient outcomes.

Acknowledgments This work was supported in part by the Houston VA HSR&D Center of Excellence (HFP90-020), by National Institutes of Health grants R01-DK46441 from the National Institute of Diabetes, Digestive and Kidney Disease and R01–CA095731 from the National Cancer Institute, the Vivian L. Smith Foundation, and the M. D. Anderson Foundation. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

References

1. Wheeler DA, Srinivasan M, Egholm M et al (2008) The complete genome of an individual by massively parallel DNA sequencing. Nature 452:872–876
2. Voidonikolas G, Kreml SS, Chen C et al (2009) Basic principles and technologies for deciphering the genetic map of cancer. World J Surg 33:615–629
3. Gibbs RA, Weinstock GM (2003) Evolving methods for the assembly of large genomes. Cold Spring Harb Symp Quant Biol 68:189–194
4. Wood LD, Parsons DW, Jones S et al (2007) The genomic landscapes of human breast and colorectal cancers. Science 318:1108–1113
5. Sjoblom T, Jones S, Wood LD et al (2006) The consensus coding sequences of human breast and colorectal cancers. Science 314:268–274
6. Issa JP (2004) CpG island methylator phenotype in cancer. Nat Rev Cancer 4:988–993
7. Vogelstein B, Kinzler KW (2004) Cancer genes and the pathways they control. Nat Med 10:789–799
8. Cancer Genome Atlas Research Network (2008) Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 455:1061–1068
9. Ding L, Getz G, Wheeler DA et al (2008) Somatic mutations affect key pathways in lung adenocarcinoma. Nature 455:1069–1075
10. Weir BA, Woo MS, Getz G et al (2007) Characterizing the cancer genome in lung adenocarcinoma. Nature 450:893–898
11. Kinzler KW, Vogelstein B (1996) Lessons from hereditary colorectal cancer. Cell 87:159–170
12. Galiatsatos P, Foulkes WD (2006) Familial adenomatous polyposis. Am J Gastroenterol 101:385–398
13. Fearnhead NS, Britton MP, Bodmer WF (2001) The ABC of APC. Hum Mol Genet 10:721–733
14. Kinzler KW, Nilbert MC, Su LK et al (1991) Identification of FAP locus genes from chromosome 5q21. Science 253:661–665
15. Nakamura Y, Nishisho I, Kinzler KW et al (1992) Mutations of the APC (adenomatous polyposis coli) gene in FAP (familial polyposis coli) patients and in sporadic colorectal tumors. Tohoku J Exp Med 168:141–147
16. Nishisho I, Nakamura Y, Miyoshi Y et al (1991) Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 253:665–669
17. Albuquerque C, Breukel C, van der Luijt R et al (2002) The 'just-right' signaling model: APC somatic mutations are selected based on a specific level of activation of the beta-catenin signaling cascade. Hum Mol Genet 11:1549–1560
18. Esteller M, Sparks A, Toyota M et al (2000) Analysis of adenomatous polyposis coli promoter hypermethylation in human cancer. Cancer Res 60:4366–4371
19. Ilyas M, Tomlinson IP, Rowan A et al (1997) Beta-catenin mutations in cell lines established from human colorectal cancers. Proc Natl Acad Sci USA 94:10330–10334
20. Davidson G, Wu W, Shen J et al (2005) Casein kinase 1 gamma couples Wnt receptor activation to cytoplasmic signal transduction. Nature 438:867–872
21. Zeng X, Tamai K, Doble B et al (2005) A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. Nature 438:873–877
22. Clevers H (2006) Wnt/beta-catenin signaling in development and disease. Cell 127:469–480
23. Bhanot P, Brink M, Samos CH et al (1996) A new member of the frizzled family from *Drosophila* functions as a Wingless receptor. Nature 382:225–230
24. Pinson KI, Brennan J, Monkley S et al (2000) An LDL-receptor-related protein mediates Wnt signalling in mice. Nature 407:535–538
25. Tamai K, Semenov M, Kato Y et al (2000) LDL-receptor-related proteins in Wnt signal transduction. Nature 407:530–535

26. Semenov M, Tamai K, He X (2005) SOST is a ligand for LRP5/LRP6 and a Wnt signaling inhibitor. J Biol Chem 280:26770–26775
27. Hoang B, Moos M Jr, Vukicevic S et al (1996) Primary structure and tissue distribution of FRZB, a novel protein related to Drosophila frizzled, suggest a role in skeletal morphogenesis. J Biol Chem 271:26131–26137
28. Behrens J, von Kries JP, Kuhl M et al (1996) Functional interaction of beta-catenin with the transcription factor LEF-1. Nature 382:638–642
29. Molenaar M, van de Wetering M, Oosterwegel M et al (1996) XTcf-3 transcription factor mediates beta-catenin-induced axis formation in Xenopus embryos. Cell 86:391–399
30. van de Wetering M, Sancho E, Verweij C et al (2002) The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. Cell 111:241–250
31. Shimizu Y, Ikeda S, Fujimori M et al (2002) Frequent alterations in the Wnt signaling pathway in colorectal cancer with microsatellite instability. Gene Chromosom Cancer 33:73–81
32. Johnson V, Volikos E, Halford SE et al (2005) Exon 3 beta-catenin mutations are specifically associated with colorectal carcinomas in hereditary non-polyposis colorectal cancer syndrome. Gut 54:264–267
33. Webster MT, Rozycka M, Sara E et al (2000) Sequence variants of the axin gene in breast, colon, and other cancers: an analysis of mutations that interfere with GSK3 binding. Gene Chromosom Cancer 28:443–453
34. Liu W, Dong X, Mai M et al (2000) Mutations in AXIN2 cause colorectal cancer with defective mismatch repair by activating beta-catenin/TCF signalling. Nat Genet 26:146–147
35. Suzuki H, Watkins DN, Jair KW et al (2004) Epigenetic inactivation of SFRP genes allows constitutive WNT signaling in colorectal cancer. Nat Genet 36:417–422
36. Caldwell GM, Jones C, Gensberg K et al (2004) The Wnt antagonist sFRP1 in colorectal tumorigenesis. Cancer Res 64:883–888
37. Caldwell GM, Jones CE, Taniere P et al (2006) The Wnt antagonist sFRP1 is downregulated in premalignant large bowel adenomas. Br J Cancer 94:922–927
38. Guo X, Wang XF (2009) Signaling cross-talk between TGF-beta/BMP and other pathways. Cell Res 19:71–88
39. Hussein SM, Duff EK, Sirard C (2003) Smad4 and beta-catenin co-activators functionally interact with lymphoid-enhancing factor to regulate graded expression of Msx2. J Biol Chem 278:48805–48814
40. Kim JS, Crooks H, Dracheva T et al (2002) Oncogenic beta-catenin is required for bone morphogenetic protein 4 expression in human cancer cells. Cancer Res 62:2744–2748
41. Labbe E, Letamendia A, Attisano L (2000) Association of Smads with lymphoid enhancer binding factor 1/T cell-specific factor mediates cooperative signaling by the transforming growth factor-beta and Wnt pathways. Proc Natl Acad Sci USA 97:8358–8363
42. Nishita M, Hashimoto MK, Ogata S et al (2000) Interaction between Wnt and TGF-beta signalling pathways during formation of Spemann's organizer. Nature 403:781–785
43. Lee JY, Kang MB, Jang SH et al (2009) Id-1 activates Akt-mediated Wnt signaling and p27(Kip1) phosphorylation through PTEN inhibition. Oncogene 28:824–831
44. Marsh V, Winton DJ, Williams GT et al (2008) Epithelial Pten is dispensable for intestinal homeostasis but suppresses adenoma development and progression after Apc mutation. Nat Genet 40:1436–1444
45. Fritzmann J, Morkel M, Besser D et al (2009) A colorectal cancer expression profile that includes transforming growth factor beta inhibitor BAMBI predicts metastatic potential. Gastroenterology 137:165–175
46. Yu J, Tao Q, Cheng YY et al (2009) Promoter methylation of the Wnt/beta-catenin signaling antagonist Dkk-3 is associated with poor survival in gastric cancer. Cancer 115:49–60
47. De Toni EN, Thieme SE, Herbst A et al (2008) OPG is regulated by beta-catenin and mediates resistance to TRAIL-induced apoptosis in colon cancer. Clin Cancer Res 14:4713–4718
48. Lock FE, Underhill-Day N, Dunwell T et al (2010) The RASSF8 candidate tumor suppressor inhibits cell growth and regulates the Wnt and NF-kappaB signaling pathways. Oncogene 29:4307–4316
49. Tang W, Dodge M, Gundapaneni D et al (2008) A genome-wide RNAi screen for Wnt/beta-catenin pathway components identifies unexpected roles for TCF transcription factors in cancer. Proc Natl Acad Sci USA 105:9697–9702
50. Xiang Y, Lin G, Zhang Q et al (2008) Knocking down Wnt9a mRNA levels increases cellular proliferation. Mol Biol Rep 35:73–79
51. Feng Y, Bommer GT, Zhai Y et al (2007) Drosophila split ends homologue SHARP functions as a positive regulator of Wnt/beta-catenin/T-cell factor signaling in neoplastic transformation. Cancer Res 67:482–491
52. Bjorklund M, Taipale M, Varjosalo M et al (2006) Identification of pathways regulating cell size and cell-cycle progression by RNAi. Nature 439:1009–1013
53. Katoh M (2005) WNT/PCP signaling pathway and human cancer (review). Oncol Rep 14:1583–1588
54. Brown AM (2005) Canonical Wnt signaling: high-throughput RNAi widens the path. Genome Biol 6:231
55. He B, You L, Uematsu K et al (2004) A monoclonal antibody against Wnt-1 induces apoptosis in human cancer cells. Neoplasia 6:7–14
56. Bianco R, Gelardi T, Damiano V et al (2007) Rational bases for the development of EGFR inhibitors for cancer treatment. Int J Biochem Cell Biol 39:1416–1431
57. Lemmon MA, Schlessinger J (1994) Regulation of signal transduction and signal diversity by receptor oligomerization. Trends Biochem Sci 19:459–463
58. Yarden Y, Sliwkowski MX (2001) Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2:127–137
59. Waters SB, Chen D, Kao AW et al (1996) Insulin and epidermal growth factor receptors regulate distinct pools of Grb2-SOS in the control of Ras activation. J Biol Chem 271:18224–18230
60. Marais R, Marshall CJ (1996) Control of the ERK MAP kinase cascade by Ras and Raf. Cancer Surv 27:101–125
61. Voice JK, Klemke RL, Le A et al (1999) Four human ras homologs differ in their abilities to activate Raf-1, induce transformation, and stimulate cell motility. J Biol Chem 274:17164–17170
62. Samuels Y, Ericson K (2006) Oncogenic PI3 K and its role in cancer. Curr Opin Oncol 18:77–82
63. McClellan M, Kievit P, Auersperg N et al (1999) Regulation of proliferation and apoptosis by epidermal growth factor and protein kinase C in human ovarian surface epithelial cells. Exp Cell Res 246:471–479
64. Herbst RS, Shin DM (2002) Monoclonal antibodies to target epidermal growth factor receptor-positive tumors: a new paradigm for cancer therapy. Cancer 94:1593–1611
65. Mendelsohn J (2004) EGF receptors as a target for cancer therapy. Trans Am Clin Climatol Assoc 115:249–253
66. Ohgaki H (2005) Genetic pathways to glioblastomas. Neuropathology 25:1–7
67. Nicholson RI, Gee JM, Harper ME (2001) EGFR and cancer prognosis. Eur J Cancer 37(Suppl 4):S9–S15

68. Kuan CT, Wikstrand CJ, Bigner DD (2001) EGF mutant receptor vIII as a molecular target in cancer therapy. Endocr Relat Cancer 8:83–96
69. Moscatello DK, Holgado-Madruga M, Godwin AK et al (1995) Frequent expression of a mutant epidermal growth factor receptor in multiple human tumors. Cancer Res 55:5536–5539
70. Scaltriti M, Baselga J (2006) The epidermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res 12:5268–5272
71. Reade CA, Ganti AK (2009) EGFR targeted therapy in non-small cell lung cancer: potential role of cetuximab. Biologics 3:215–224
72. Lynch TJ, Bell DW, Sordella R et al (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129–2139
73. Hirsch FR, Varella-Garcia M, Cappuzzo F (2009) Predictive value of EGFR and HER2 overexpression in advanced non-small-cell lung cancer. Oncogene 28(Suppl 1):S32–S37
74. Pirker R, Pereira JR, Szczesna A et al (2009) Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 373:1525–1531
75. Vaca P, Martin F, Vegara-Meseguer JM et al (2006) Induction of differentiation of embryonic stem cells into insulin-secreting cells by fetal soluble factors Stem. Cells 24:258–265
76. Sander M, German MS (1997) The beta cell transcription factors and development of the pancreas. J Mol Med 75:327–340
77. Hui H, Perfetti R (2002) Pancreas duodenum homeobox-1 regulates pancreas development during embryogenesis and islet cell function in adulthood. Eur J Endocrinol 146:129–141
78. Ber I, Shternhall K, Perl S et al (2003) Functional, persistent, and extended liver to pancreas transdifferentiation. J Biol Chem 278:31950–31957
79. Ashizawa S, Brunicardi FC, Wang XP (2004) PDX-1 and the pancreas. Pancreas 28:109–120
80. Verwest AM, Poelman M, Dinjens WN et al (2000) Absence of a PDX-1 mutation and normal gastroduodenal immunohistology in a child with pancreatic agenesis. Virchows Arch 437:680–684
81. Melloul D, Tsur A, Zangen D (2002) Pancreatic duodenal homeobox (PDX-1) in health and disease. J Pediatr Endocrinol Metab 15:1461–1472
82. Watada H, Kajimoto Y, Kaneto H et al (1996) Involvement of the homeodomain-containing transcription factor PDX-1 in islet amyloid polypeptide gene transcription. Biochem Biophys Res Commun 229:746–751
83. Smith SB, Watada H, Scheel DW et al (2000) Autoregulation and maturity onset diabetes of the young transcription factors control the human PAX4 promoter. J Biol Chem 275:36910–36919
84. Nakajima-Nagata N, Sugai M, Sakurai T et al (2004) Pdx-1 enables insulin secretion by regulating synaptotagmin 1 gene expression. Biochem Biophys Res Commun 318:631–635
85. Gerrish K, Cissell MA, Stein R (2001) The role of hepatic nuclear factor 1 alpha and PDX-1 in transcriptional regulation of the pdx-1 gene. J Biol Chem 276:47775–47784
86. Meivar-Levy I, Sapir T, Gefen-Halevi S et al (2007) Pancreatic and duodenal homeobox gene 1 induces hepatic dedifferentiation by suppressing the expression of CCAAT/enhancer-binding protein beta. Hepatology 46:898–905
87. Jabari S, Meissnitzer M, Quint K et al (2009) Cellular plasticity of trans- and dedifferentiation markers in human hepatoma cells in vitro and in vivo. Int J Oncol 35:69–80
88. Yamada S, Yamamoto Y, Nagasawa M et al (2006) In vitro transdifferentiation of mature hepatocytes into insulin-producing cells. Endocr J 53:789–795
89. Marzioni M, Saccomanno S, Candelaresi C et al (2010) Pancreatic Duodenal homeobox-1 de novo expression drives cholangiocyte neuroendocrine-like transdifferentiation. J Hepatol 53:663–670
90. Koizumi M, Doi R, Toyoda E et al (2004) Hepatic regeneration and enforced PDX-1 expression accelerate transdifferentiation in liver. Surgery 136:449–457
91. Di Gioacchino G, Di Campli C, Zocco MA et al (2005) Transdifferentiation of stem cells in pancreatic cells: state of the art. Transplant Proc 37:2662–2663
92. Miyatsuka T, Kaneto H, Shiraiwa T, Matsuoka TA, Yamamoto K et al (2006) Persistent expression of PDX-1 in the pancreas causes acinar-to-ductal metaplasia through Stat3 activation. Genes Dev 20:1435–1440
93. Leys CMNS, Rudzinski E, Kaminishi M, Montgomery E, Washington MK, Goldenring JR (2006) Expression of PDX-1 in human gastric metaplasia and gastric adenocarcinoma. Hum Pathol 37:1162–1168
94. Wang XP, Li ZJ, Magnusson J et al (2005) Tissue MicroArray analyses of pancreatic duodenal homeobox-1 (PDX-1) in human cancers. World J Surg 29:334–338
95. Quint K, Stintzing S, Alinger B et al (2009) The expression pattern of PDX-1, SHH, Patched and Gli-1 is associated with pathological and clinical features in human pancreatic cancer. Pancreatology 9:116–126
96. Liu T, Gou SM, Wang CY et al (2007) Pancreas duodenal homeobox-1 expression and significance in pancreatic cancer. World J Gastroenterol 13:2615–2618
97. Liu S, Ballian N, Belaguli NS et al (2008) PDX-1 acts as a potential molecular target for treatment of human pancreatic cancer. Pancreas 37:210–220
98. Koizumi M, Doi R, Toyoda E et al (2003) Increased PDX-1 expression is associated with outcome in patients with pancreatic cancer. Surgery 134:260–266
99. Jonmarker S, Glaessgen A, Culp WD et al (2008) Expression of PDX-1 in prostate cancer, prostatic intraepithelial neoplasia and benign prostatic tissue. APMIS 116:491–498
100. Ballian N, Liu SH, Brunicardi FC (2008) Transcription factor PDX-1 in human colorectal adenocarcinoma: a potential tumor marker? World J Gastroenterol 14:5823–5826
101. Sakai HEY, Li XL, Akiyama Y, Miyake S, Takizawa T, Konishi N, Tatematsu M, Koike M, Yuasa Y (2004) PDX-1 homeobox protein expression in pseudopyloric glands and gastric carcinomas. Gut 53:323–330
102. Buettner M, Dimmler A, Magener A et al (2004) Gastric PDX-1 expression in pancreatic metaplasia and endocrine cell hyperplasia in atrophic corpus gastritis. Mod Pathol 17:56–61
103. Du YC, Klimstra DS, Varmus H (2009) Activation of PyMT in beta cells induces irreversible hyperplasia, but oncogene-dependent acinar cell carcinomas when activated in pancreatic progenitors. PLoS One 4:e6932
104. Stanger BZ, Stiles B, Lauwers GY et al (2005) Pten constrains centroacinar cell expansion and malignant transformation in the pancreas. Cancer Cell 8:185–195
105. Liu SH, Patel S, Gingras MC et al (2010) PDX-1: demonstration of oncogenic properties in pancreatic cancer. Cancer Sep 30 (in press)
106. Pocket Oxford American Dictionary, 2nd edn. Oxford University Press, New York, p 1008 (2008)
107. Wang H, Maechler P, Ritz-Laser B et al (2001) Pdx1 level defines pancreatic gene expression pattern and cell lineage differentiation. J Biol Chem 276:25279–25286
108. von Burstin J, Reichert M, Wescott MP et al (2010) The pancreatic and duodenal homeobox protein PDX-1 regulates the ductal specific keratin 19 through the degradation of MEIS1 and DNA binding. PLoS One 5:e12311

109. Keller DM, McWeeney S, Arsenlis A et al (2007) Characterization of pancreatic transcription factor Pdx-1 binding sites using promoter microarray and serial analysis of chromatin occupancy. J Biol Chem 282:32084–32092
110. Roy S, Qiao T, Wolff C et al (2001) Hedgehog signaling pathway is essential for pancreas specification in the zebrafish embryo. Curr Biol 11:1358–1363
111. Katoh Y, Katoh M (2006) Hedgehog signaling pathway and gastrointestinal stem cell signaling network (review). Int J Mol Med 18:1019–1023
112. Murtaugh LC, Stanger BZ, Kwan KM et al (2003) Notch signaling controls multiple steps of pancreatic differentiation. Proc Natl Acad Sci USA 100:14920–14925
113. Fisher WE, Doran TA, Muscarella P 2nd et al (1998) Expression of somatostatin receptor subtype 1–5 genes in human pancreatic cancer. J Natl Cancer Inst 90:322–324
114. Fisher WE, Muscarella P, Boros LG et al (1998) Gastrointestinal hormones as potential adjuvant treatment of exocrine pancreatic adenocarcinoma. Int J Pancreatol 24:169–180
115. Fisher WE, Muscarella P, O'Dorisio TM et al (1996) Expression of the somatostatin receptor subtype-2 gene predicts response of human pancreatic cancer to octreotide. Surgery 120:234–240
116. Buscail L, Saint-Laurent N, Chastre E et al (1996) Loss of sst2 somatostatin receptor gene expression in human pancreatic and colorectal cancer. Cancer Res 56:1823–1827
117. Li M, Wang X, Li W et al (2008) Somatostatin receptor-1 induces cell cycle arrest and inhibits tumor growth in pancreatic cancer. Cancer Sci 99:2218–2223
118. Li M, Zhang R, Li F et al (2005) Transfection of SSTR-1 and SSTR-2 inhibits Panc-1 cell proliferation and renders Panc-1 cells responsive to somatostatin analogue. J Am Coll Surg 201:571–578
119. Delesque N, Buscail L, Esteve JP et al (1997) SST2 somatostatin receptor expression reverses tumorigenicity of human pancreatic cancer cells. Cancer Res 57:956–962
120. Guillermet-Guibert J, Saint-Laurent N, Davenne L et al (2007) Novel synergistic mechanism for sst2 somatostatin and TNFalpha receptors to induce apoptosis: crosstalk between NF-kappaB and JNK pathways. Cell Death Differ 14:197–208
121. Zhang Z, Huang Y, Newman K et al (2009) Reexpression of human somatostatin receptor gene 2 gene mediated by oncolytic adenovirus increases antitumor activity of tumor necrosis factor-related apoptosis-inducing ligand against pancreatic cancer. Clin Cancer Res 15:5154–5160
122. Carrere N, Vernejoul F, Souque A et al (2005) Characterization of the bystander effect of somatostatin receptor sst2 after in vivo gene transfer into human pancreatic cancer cells. Hum Gene Ther 16:1175–1193
123. Feng Y, Huang T, Gao J et al (2006) Inhibition of metastatic progression of SSTR2 gene transfection mediated by adenovirus in human pancreatic carcinoma cells. J Huazhong Univ Sci Technolog Med Sci 26:68–71
124. Kritzik MR, Krahl T, Good A et al (2000) Transcription factor expression during pancreatic islet regeneration. Mol Cell Endocrinol 164:99–107