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Pro-oncogenic and anti-oncogenic pathways: opportunities and challenges of cancer therapy

Jiao Zhang, MD,
Department of Anatomy & Cell Biology, The Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA

Yan-Hua Chen, PhD, and
Department of Anatomy & Cell Biology, Leo Jenkins Cancer Center, The Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA

Qun Lu, PhD[†]
Associate Professor, Department of Anatomy & Cell Biology, Leo Jenkins Cancer Center, The Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA, Tel.: +1 252 744 2844, Fax: +1 252 744 2850, luq@ecu.edu

Abstract

Carcinogenesis is the uncontrolled growth of cells gaining the potential to invade and disrupt vital tissue functions. This malignant process includes the occurrence of 'unwanted' gene mutations that induce the transformation of normal cells, for example, by overactivation of pro-oncogenic pathways and inactivation of tumor-suppressive or anti-oncogenic pathways. It is now recognized that the number of major signaling pathways that control oncogenesis is not unlimited; therefore, suppressing these pathways can conceivably lead to a cancer cure. However, the clinical application of cancer intervention has not matched up to scientific expectations. Increasing numbers of studies have revealed that many oncogenic-signaling elements show double faces, in which they can promote or suppress cancer pathogenesis depending on tissue type, cancer stage, gene dosage and their interaction with other players in carcinogenesis. This complexity of oncogenic signaling poses challenges to traditional cancer therapy and calls for considerable caution when designing an anticancer drug strategy. We propose future oncology interventions with the concept of integrative cancer therapy.

Keywords

cell signaling; cell survival; integrative cancer therapy; oncogene; tumor suppressor

Goal of cancer therapy

Carcinogenesis includes 'unwanted' gene mutations that induce the transformation of normal cells, for example, by overactivation of protooncogenes, such as *ras*, *src* or *abl*, and inactivation

[†]Author for correspondence: Department of Anatomy & Cell Biology, Leo Jenkins Cancer Center, The Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA, Tel.: +1 252 744 2844, Fax: +1 252 744 2850, luq@ecu.edu.

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of tumor suppressors, such as *p53* and *PTEN* (Table1) [1–5]. Tumorigenic gene mutations can also be induced by harmful environmental factors, such as tobacco overusage and UV exposure [6–8]. On the other hand, cancer development can be viewed from the point of evolution, in which case, genetic drifting followed by selection acting upon growth-control genes by chance may be sufficient to introduce oncogenic mutations that cause malignant transformation [9, 10]. During the repetitive repairing of damaged tissues by stem cells, deviation from recapitulation of normal developmental processes may drive cells towards malignancy [11, 12]. Regardless of the underlying causes, the consequence is the same: the activation of pro-oncogenic signaling pathways and the downregulation of anti-oncogenic pathways that normally keep cellular behaviors in check. The outcome of the overgrowth of cells capable of metastasizing to vital organs is the disruption of normal functions of the body, ultimately resulting in death. The goal of cancer therapy is to suppress or eliminate the cancer growth and metastasis by reversing oncogenic signaling pathways. However, increasing amounts of literature have demonstrated considerable complexities in the regulation of pro- and anti-oncogenic pathways, which pose huge challenges for traditional cancer therapies.

Progresses in detecting & treating cancers

Early detection

In 2007, the steepest decline in cancer deaths in the USA was recorded. This significant milestone reflects the outcome of many years of investment in cancer research and care, and it is one of the most encouraging signs of progress since the war on cancer began in the 1970s. It is clear that early detection saves lives and increases treatment options. For example, mammography can detect breast cancer at an early stage when treatment can be more effective and survival is more likely. Clinical data indicate that, on average, mammography can detect approximately 80–90% of breast cancers in women without alarming symptoms [13,14]. Indeed, the recent decline in breast cancer mortality rates among women can be attributed to a combination of early detection and improvements in treatments. Another good example is the early detection of prostate cancer in men.

Although there are insufficient data to recommend for or against prostate cancer screening in men at average risk of developing the disease, the American Cancer Society recommends the prostate-specific antigen (PSA) blood test and the digital rectal examination for men at average risk, beginning at the age of 50 years. Individuals at higher risk of developing prostate cancer (e.g., African–Americans or men with a strong family history) are encouraged to begin screening at the age of 45 years. Despite the controversial clinical trial outcomes regarding PSA reliability and utility, and the clear need to provide additional viable biomarkers in prostate cancer diagnosis and prognosis, over the past 20 years the availability of the PSA test has led to significant advances in the early detection of many prostate cancers [15,16].

Effective therapies

There have been remarkable successes in the treatment of certain cancers. Pioneering chemotherapy drugs, such as platinum compounds are good examples. Cisplatin suppresses cancer cell proliferation by disrupting DNA synthesis and is extremely effective in inhibiting germ-cell-derivative cancers. It was originally found to elicit anticancer properties in tumor-bearing mice in 1968 [17–19]. The results from the preliminary studies were so promising that patients were treated with cisplatin for the first time in 1971, and cisplatin received US FDA approval shortly thereafter [20,21]. Before cisplatin was available, metastatic testicular cancer had a mortality rate of 95%. Cisplatin-based regimens resulted in a 60% cure rate for this disease [22,23].

Unlike cisplatin, Gleevec® (imatinib mesylate; Novartis, Basel, Switzerland) is effective for the treatment of certain cancer types by interfering with cell-signaling pathways [24–26]. By blocking the abnormal protein tyrosine kinase BCR-ABL, Gleevec induces leukemia cells to undergo apoptosis. The FDA approved Gleevec in 2001 for the treatment of chronic myeloid leukemia (CML) and for the treatment of a rare form of stomach cancer, gastrointestinal stromal tumor in 2002 [27,28]. The outcome of Gleevec clinical trials was remarkable. In 1999, a small-scale clinical study demonstrated that with an effective daily dose, all patients had their blood counts return to normal with minimal side effects. Such dramatic results were uncommon in any early clinical cancer study [29]. A 2001 study further reported that Gleevec restored normal blood counts in 53 out of 54 chemotherapy-resistant CML patients, a response rate rarely seen in oncology trials with a single antineoplastic agent [30]. Almost all of the patients were still doing well after 1 year on Gleevec, and few complained about side effects. Before Gleevec, efforts on the discovery of anticancer drugs by targeting tyrosine kinases were largely futile. The success of Gleevec and the newer generation inhibitors renewed hopes that inhibition of specific signaling elements of carcinogenesis can produce effective drugs.

Challenges on most fronts of anticancer efforts

Lack of reliable cancer biomarkers

Despite the successes in certain areas of cancer diagnosis and therapy, we still face tremendous challenges in treating most cancer types. In colorectal cancers, when cancers are detected at an early, localized stage, the 5-year survival rate is 90%; however, fewer than half of all colorectal cancer cases are diagnosed at this stage, mostly owing to low screening rates [31]. After the cancer has spread regionally to involve adjacent organs or lymph nodes, the 5-year survival rate for the disease drops to 68%. For patients with distant metastases, the 5-year survival rate drops precipitously to only 10%. For lung cancers, the 5-year survival rate for all stages combined is only 15%. The survival rate is 49% for cases detected when the disease is still localized; however, only 16% of lung cancer cases are diagnosed at this early stage. For pancreatic cancer, at the present time, there is still no method for early detection at all, and fewer than 10% of cases are diagnosed at an early stage. For all stages combined, the 1- and 5-year relative survival rates are only 24 and 5%, respectively. Even for patients diagnosed with local disease occurrence, the 5-year survival rate for pancreatic cancer is only 20% [301]. Additional frustration at the inability to detect and combat these types of cancers is exemplified because the diseases are not uncommon among the working-age population when productivity is high.

From the previous discussions, it is clear that despite the billions of dollars invested in research and development, we are still far from achieving the mission: a cure for cancer. What are the modern strategies for drug discovery against cancer? Most anticancer strategies focus on attacking specific elements of a given biological pathway of cancer cells to achieve target specificity with minimized toxicity. This approach, although it has clear merits, has not produced the desired numbers of viable drugs because most drug leads that are successful *in vitro* or in animal studies do not show the same efficacy in human trials. Some leads, even when proven to be effective in human trials, either encounter resistance during treatment or lose efficacy owing to mutations of the target genes. Other potential leads may be abandoned during early discovery stages owing to low efficacy seen in selected screening models *in vitro*, while they could be effective in human trials. Consequently, few viable cancer drugs have entered the market in recent years, leading to skyrocketing research and development costs. Clearly, we should re-examine our anticancer drug-discovery approaches in current literature and re-evaluate our strategies for future anticancer therapy.

Complex roles of pro- & anti-oncogenic pathways

As we further explored cancer cell-signaling events dictated by pro- and anti-oncogenic pathways, more and more surprising research results were found [32,33]. When oncogenes were first identified in the 1970s, the perception was that if we inhibited the functions of certain oncogenes, we could stop the disease. It was also thought that we could increase the function of tumor suppressors to inhibit disease progression [34–36]. However, we now know that many genes and signaling pathways can be pro-oncogenic under one context but anti-oncogenic under a different context, at different stages or in different tissue types of cancer development [37–42]. In this article, we will discuss some common examples (for additional review, see Lu *et al.* [43]).

Retinoblastoma/E2F pathway—Cancer cells often contain mutations that lead to the loss of retinoblastoma (Rb) tumor suppressor function and the activation of E2F-dependent transcription (Table 1). As a result, cell proliferation is deregulated, and the sensitivity of responses to apoptotic stimuli is increased. Rb protein regulates cell proliferation and cell death. Animal model studies suggest that Rb tumor-suppressor function, that is, inhibition of proliferation, is inactivated by phosphorylation, whereas Rb tumor-promoting function, that is, inhibition of apoptosis, is inactivated by caspase cleavage [44]. On the other hand, Johnson showed that *E2F1* can function as both an oncogene and a tumor suppressor gene, and both positive and negative effects on tumorigenesis can be observed depending on whether E2F1 is absent or overexpressed [42]. In a prostate tissue-recombination model, homozygous deletion of *Rb* elicited increased E2F activity, activation of E2F-target genes and susceptibility to hormonal carcinogenesis [45]. A closer tissue microarray examination of E2F1 expression in human specimens found that E2F1 levels were low in benign and localized prostate cancer, modestly elevated in metastatic lymph nodes from hormone-naive patients, and significantly elevated in metastatic tissues from hormone-resistant prostate cancer patients [46]. By contrast, strong androgen receptor expression was detected in benign prostate, localized prostate cancer and lymph node metastasis, but decreased in metastatic hormone-resistant prostate cancer. Since E2F1 can repress androgen receptor transcription, elevated E2F1 levels may contribute to the progression of hormone-refractory prostate cancer [47]. These studies suggest that in the early stages of prostate cancer development, E2F1 levels are low, probably to allow its oncogenic effects to be best exerted with the cooperation of other oncogenic mutations, such as Ras, to avoid its potential tumor suppressive effects. Therefore, E2F1 is equally capable of inducing cell proliferation and apoptosis [48–50].

TGF pathway—TGF-β1 is a cytokine that displays context-dependent tumor suppressive and tumor-promoting activity in carcinogenesis. For most normal epithelial cells and at the early stages of tumor development, TGF-β1 is believed to function as a tumor suppressor [51]. This process occurs largely through the activation of surface TGF-β1 receptor complex and phosphorylation of Smads, although other signaling pathways are also involved [52]. By contrast, elevated expression of TGF-β1 may enhance the malignant properties of tumor cells through effects on cell invasion, metastasis, epithelial to mesenchymal transition or antitumor immunity. This alteration in the functions of TGF-β1 in cancer development is probably due to its interaction with other signaling pathways, such as *ras* oncogene, that becomes activated during tumor progression [53]. Indeed, oncogenic Ras and TGF-β1 can perhaps cooperate to promote epithelial to mesenchymal transition and the invasive behavior of neoplastic cells [54–55].

Two-stage chemical carcinogenesis of the mouse epidermis is a widely used model to study the interaction of TGF-β1 and oncogenic Ras. TGF-β signaling can suppress squamous tumor formation and progression initiated by an activated cellular or viral *ras* oncogene [56–59]. However, other studies showed that overexpression of TGF-β1 in normal skin can lead to the

formation of highly malignant spindle cell carcinomas, as well as enhancing a metastatic phenotype of benign squamous tumor cells [60,61]. It is suggested that the different roles of TGF-β1 in skin carcinogenesis may depend on the interaction of Smad2 and Smad3 with Ras signaling. Smad2 and Smad3 expression are lost during progression of chemically induced tumors, and the expression of *v-ras* in Smad3-null mouse epidermal keratinocytes causes rapid progression to squamous cell carcinoma in a skin graft system [62,63]. Studies have shown that Smad3 is required for tumor formation in the two-stage carcinogenesis model, suggesting that context-dependent interactions between Ras and Smads are critical for tumor suppression or progression in this tissue model [64].

Cadherin/catenin pathway—Recent studies suggested that cell–cell junction proteins, such as $p120^{ctn}$ (*CTNND1*) and δ-catenin/NPRAP/neurojungin (*CTNND2*) may also play pro-oncogenic roles in one context and anti-oncogenic roles in another. δ-catenin, a close member of the $p120^{ctn}$ subgroup of the armadillo/β-catenin superfamily, shares more than 30% amino acid sequence identity in the armadillo domains with $p120^{ctn}$, and binds to the same juxtamembrane region on E-cadherin as $p120^{ctn}$ [65,66]. Unlike $p120^{ctn}$, which is ubiquitously expressed, δ-catenin is primarily expressed in the CNS [67,68]. $p120^{ctn}$ is frequently downregulated in many cancer types, although its expression remains paradoxically high in most cancer-derived cell lines [69]. Accumulating evidence indicates that $p120^{ctn}$ could play the role of tumor suppressor or metastasis promoter depending on whether it is downregulated before or after the loss of E-cadherin. If E-cadherin loss precedes $p120^{ctn}$ loss, $p120^{ctn}$ remains stranded in the cytoplasm and can promote cell invasion and metastasis through the regulation of Rho GTPases [70,71], which control the formation of actin-rich lamellipodia, filopodia, stress fibers and many other structures associated with cell motility, morphology and invasiveness. Thus, $p120^{ctn}$ may function as a metastasis promoter under these conditions. If $p120^{ctn}$ loss precedes E-cadherin loss, then it may become the initial event, ultimately leading to the inactivation of the cadherin complex. This is strongly suggested by studies that the loss of $p120^{ctn}$ destabilizes E-cadherin, which, in turn, may reduce levels of α- and β-catenin at the cell–cell junction [72].

In many carcinomas, $p120^{ctn}$ is downregulated while δ-catenin is overexpressed [73]. It is interesting and also paradoxical that δ-catenin expression levels in cancer-derived cell lines are generally moderate or minimal [74,75]. Its overexpression in prostate cancer cells altered tumor suppressor E-cadherin and $p120^{ctn}$ distribution at the cell–cell junction [73], disrupted the normal monolayer in cell culture [76] and promoted prostate tumorigenesis in mice [76]. Furthermore, a recent study identified the association of δ-catenin specifically with only pathological (but not physiological) angiogenesis, such as with cancer [77]. Thus, it behaves like a cancer-promoting protein. However, in normal fibroblast cells in culture, ectopic expression of δ-catenin results in the cessation of cell division to promote cellular protrusions [78]. Furthermore, in noncancerous mammary epithelial cells, δ-catenin appears to act as a tumor suppressor inhibiting cell-colony formation [79]. These studies raise intriguing possibilities that δ-catenin can exert context-dependent effects on normal epithelial cells as a tumor suppressor while acting as a tumor promoter on certain types of transformed cancer cells.

PI3K/PTEN/Akt pathway—Recent research on a widely studied oncogenic protein family, PI3Ks, indicated that multiple pathways, of which PI3Ks play critical roles, may function in opposite directions in carcinogenesis. The family of PI3Ks regulates signaling for diverse cellular functions, including cell division, migration, apoptosis and angiogenesis [80,81]. Disruption of this tightly regulated pathway by gene loss (*PTEN*), mutation (*PIK3CA*, *AKT1* or, less commonly, *PIK3R1*) or amplification (*PIK3CA*) is one of the most common alterations in human cancers (Table 1) [82]. *PIK3CA* mutations lead to constitutive activation of p110 (the catalytic subunit of PI3K), increasing its lipid kinase activity and resulting in an increase in Akt activation [83–85]. Cultured cells expressing *PIK3CA* mutations exhibit features of cell

transformation, promote cell survival and show increased angiogenesis [80,83,84,86–89]. However, in normal, nontransformed cells, Akt activation has an opposite effect through the induction of cellular senescence [90,91]. In animal models, differences in tumorigenic effects have also been observed. For example, while an increased PIK3CA activity induces tumorigenesis in xenografts [86,88], the expression of activated Akt1 is insufficient to induce tumors in mouse mammary epithelium [92,93]. Furthermore, although p110 expression induces mouse mammary tumors, they are generally microscopic with low frequency [94].

In human breast cancers, the *PIK3CA* mutation frequency ranges variably from 8 to 40% [95–100]. The majority of mutations in breast cancer occur at three hotspots: E542K and E545K at exon 9, which encode the helical domain, and H1047R at exon 20, which encodes the kinase domain [97–99]. In cell-based assays, these rare mutations confer a gain of function as measured by lipid kinase activity, constitutive activation of Akt, and cellular transformation, with a different range of oncogenic potency [83]. Therefore, the frequency of *PIK3CA* mutation is consistent with the significance of PI3Ks in breast cancer pathogenesis.

However, Kalinsky and colleagues recently identified a positive prognostic significance of *PIK3CA* mutations [101], indicating that *PIK3CA* can even be a 'good' activating mutation in breast cancer [102]. They analyzed the prognostic value of *PI3KCA* mutations in paraffin-embedded tumor tissue from 590 breast cancer patients with a median follow-up of 12.8 years. In this large cohort with optimal follow-up, they found *PIK3CA* mutations in 32.5% of invasive breast primary tumors, 24.1% occurring at the three 'hot spot' sites and the remaining 8.5% in the combined rare *PIK3CA* mutations. *PI3KCA* mutations were significantly more likely to occur in postmenopausal patients, aged 60–70 years, with hormone-receptor-positive, HER2-negative, and low-grade and -stage breast cancer at diagnosis. Patients with *PI3KCA*-mutated tumors showed a marginally significant longer progression-free survival and a significantly improved breast cancer-specific and overall survival [101]. Thus, this study proposes the positive prognostic significance of *PIK3CA* mutations and is clinically relevant, because it will significantly affect the design of clinical trials planned for PI3K-targeted therapy [102]. These considerations are also clinically important because the presence of activated *PI3KCA* in cancer has led to the development of PI3K inhibitors as a novel targeted therapeutic strategy. PI3K inhibitors have been demonstrated to be active in preclinical models [88], with many agents currently in the early stages of clinical development. These agents have different degrees of potency and target specificity. Some agents inhibit both PI3K and mTOR, whereas others are PI3K-specific inhibitors. This approach may be fruitful in targeting breast cancer, because a neoadjuvant study using an mTOR inhibitor in combination with an antiestrogen therapy exhibited silencing of the PI3K pathway and reduction in its activity in patients harboring PI3K mutations [90]. These agents also hold promise in combination with chemotherapy and in HER2-amplified breast cancer patients harboring either *PI3KCA* mutations or *PTEN* deletions [91].

Besides PI3K and mTOR inhibitors, targeting of other components of the pathway, such as AKT and Rictor, is also under investigation [103–106]. 17-allyl-aminogeldanamycin is a geldanamycin derivative currently employed in clinical trials [103]. In addition to downregulating Akt expression, 17-allyl-aminogeldanamycin also causes a rapid inhibition of Akt kinase activity prior to proteosomal degradation of HER2 and Akt [104]. CCI-779 and 40-O-(2-hydroxyethyl)-rapamycin are esterified rapamycin derivatives that improve drug solubility and oral bioavailability. Recent data suggest that tumor cell lines or murine tumors lacking PTEN are particularly sensitive to CCI-779 [105]. Phase II/III trials are underway in the treatment of several cancers including prostate cancer. While we cannot conclude for the efficacy for the CCI-779 from these trials, it would not be surprising if the outcomes are variable for different cancer types and cancers at the different stages. In consideration of the current therapeutic strategy with PI3K/AKT pathways, the study by Kalinsky and colleagues thus

cautions that because tumors with *PI3KCA* mutations have a more favorable clinical outcome and these mutations are quite frequent, the presence of *PI3KCA* mutations will need to be taken into consideration when analyzing the effects of hormonal therapy.

MAPK pathway—The current consensus is that tumorigenesis requires the deregulation of at least six cellular processes [107], and cancer cells must acquire the following capabilities [108]:

- Independence of proliferation signals;
- Evasion of apoptosis;
- Insensitivity to antigrowth signals;
- Unlimited replicative potential;
- The ability to invade and metastasize;
- The ability to attract and sustain angiogenesis for nutrient supply.

Abnormalities in MAPK signaling impinge on most of these processes and play a critical role in the development and progression of cancer [109,110]. To date, six distinct groups of MAPKs have been characterized in mammals; ERK1/2, ERK3/4, ERK5, ERK7/8, JNK1/2/3 and the p38 isoforms α/β/γ(ERK6)/δ [111–114].

ERK is a downstream component of an evolutionarily conserved signaling module that is activated by the Raf serine/threonine kinase. Raf activates the MEK1/2 dual-specificity protein kinases, which then activate ERK1/2 [115]. The mutational activation of Raf plays important roles in human oncogenesis (Table 1) [116]. In addition, the Raf–MEK–ERK pathway is a key downstream effector of the Ras small GTPase, which is the most frequently mutated oncoprotein in human cancers. Ras is a key downstream effector of EGF receptor (EGFR), which is mutationally activated and/or overexpressed in a wide variety of human cancers [117,118]. ERK activation also promotes upregulation of EGFR ligands, promoting an autocrine growth loop critical for tumor growth. In addition, MAPK signaling pathway often plays key roles in the response of tumor cells to cancer therapies [119]. Thus, the EGFR–Ras–Raf–MEK–ERK signaling network has been the subject of intense research and pharmaceutical scrutiny to identify novel target-based approaches for cancer treatment.

For example, second-generation MEK inhibitors, such as PD184352 (also known as CI1040), have been developed and are currently in clinical trials [120–123]. However, how the activation of Ras/Raf/MEK/ERK leads to a cellular decision to proliferate or differentiate remains highly context dependent. A classical example is the neuronal differentiation of pheochromocytoma (PC12) cells. It is well documented that EGF-mediated activation of Ras/Raf/MEK/ERK signaling promotes cell proliferation, while NGF activates the same pathway to induce neuronal differentiation [124–126]. It was found that EGF stimulation actually results in a transient activation of ERK, while NGF elicits a sustained ERK activation, which leads to a neuronal differentiation program. However, this model may not be simply extended to other cancer cells under cytotoxic treatment. For example, the anticancer activity of ethyl-4-isothiocyanatobutanoate can lead to a rapid activation of the ERK signaling pathway coupled with delayed transition through the cell cycle and cell cycle arrest, which results in diminished mitochondrial membrane potential, culminating in apoptosis in leukemic HL-60 cells [127].

The role of the Ras/Raf/MEK/ERK pathway in the development of specific cancer is also not without controversy [128]. Take Raf activation as an example; overexpression of activated Raf proteins is associated with cell growth, cell cycle arrest or even apoptosis [129–131]. However, the fate of the cells depends on the expression level and isoform of Raf kinase. Overexpression

of Raf proteins is associated with proliferation in hematopoietic cells [129], erythroid progenitor cells [132] and A10 smooth muscle cells [133]. However, overexpression of activated Raf proteins is also associated with cell cycle arrest in Schwann cells, PC12 cells, HL-60 cells, small-cell lung cancer cells and some hematopoietic cells [134–136]. Depending on the Raf isoform, overexpression of Raf can either lead to cell proliferation (A-Raf or Raf-1) or cell-growth arrest (B-Raf) in NIH-3T3 fibroblasts and FDC-P1 hematopoietic cells [129, 137,138]. It is not clear why overexpression of the *Raf* gene can lead to such diverse and conflicting results. One possibility is that the opposite outcomes may be determined by the amount or activity of the particular Raf oncoprotein [138,139]. Therefore, cancer therapies targeted at the inhibition of Raf kinase expression and/or activity should consider the potential off-target effects in different types of cancer cells.

Furthermore, crosstalks between Ras/Raf/MEK/ERK and PI3K/PTEN/AKT signaling pathways can be observed in some advanced prostate cancer cells. These cells express increased levels of activated Akt [140,141], which may suppress Raf activation. Introduction of activated forms of Akt increased the drug resistance of advanced prostate cancer cells. However, introduction of activated forms of Raf did not increase the drug resistance of the prostate cancer cells. In contrast to the results observed in hematopoietic cells, Raf may normally promote differentiation in prostate cells, which is suppressed in advanced prostate cancer owing to increased expression of activated Akt, resulting from *PTEN* mutation. Thus in advanced prostate cancer, it may be advantageous to induce Raf expression to promote differentiation, while in hematopoietic cancers, it may be better to inhibit Raf/MEK/ERK-induced proliferation to achieve optimal effects [128].

p53 functions—Mutations in *p53* are found in most tumor types and contribute to the complex network of molecular events leading to tumor formation (Table 1). p53 is perhaps one of the most consistent players performing roles as a tumor suppressor and is called the ‘guardian of the genome’ [142]. Wild-type p53 is believed to be continuously monitoring the integrity of the DNA molecule. When changes in the DNA are detected, p53 protein binds to a gene to promote the transcription of $p21^{cip1}$, which, in turn, enters the metabolic process of the cell to shut down the cell cycle at the G1 phase [143]. This block of cell cycle progression allows time for the cell to repair the damaged DNA before it enters the DNA replication phase. If repair is not possible, p53 stimulates the cell to enter a pathway leading to apoptosis. In total, p53 targets approximately 150 genes to prevent the proliferation of damaged cells [144,145]. In carcinogenesis, p53 is mutated and can no longer bind DNA in an effective way. As a consequence, the $p21^{cip1}$ protein is not available to act as the ‘stop signal’ for cell division. With the DNA structure now unprotected against defects, mutations accumulate, checks and balances on the cell cycle fail to operate, and cell growth proceeds unchecked, which result in tumorigenesis. Recent studies showed that mutant p53 proteins not only represent the loss of wild-type p53 tumor suppressor activity, but also gain new oncogenic properties favoring the insurgence, maintenance, spreading and chemoresistance of malignant tumors [146].

There have been hundreds of clinical trials targeted at restoring p53 function [147]. Gene therapy involves restoring the function of a defective gene by the addition of a normal gene into the DNA structure. Roth *et al.* attached wild-type *p53* gene to an adenovirus and injected it directly into tumors, which led to tumor regression [148]. The function of p53 protein is completely dependent upon maintaining the correct 3D conformation of the molecule. Pfizer conducted studies in which they inserted small synthetic molecules into the DNA-binding region of mutated p53 protein [149]. This technique stabilized the active conformation of newly synthesized mutated p53, and has the ability to inhibit tumor growth in mice. In addition, studies have shown that some components, such as resveratrol or vitamin A, activate or increase the expression of p53, leading to cell cycle arrest and apoptosis [150–152].

Notch/γ-secretase pathway—The diverse roles that Notch signaling plays during the development and maintenance of normal tissues are recapitulated and associated with both tumor-suppressive and oncogenic functions in different forms of cancer. Depending on the tumor type, Notch can variously promote or limit tumor growth through either cell-autonomous or -nonautonomous effects on differentiation, cellular metabolism, cell cycle progression, angiogenesis, and possibly self-renewal and immune function.

The first data describing the oncogenic consequences of aberrant Notch signaling in solid tumors was derived from animal studies characterizing a frequent insertion site, named int3, in the mouse mammary tumor virus (Table 1) [153]. Studies showed that aberrant Notch signaling is significant for human solid cancers, such as breast cancer, medulloblastoma, colorectal cancer and pancreatic cancer, as well as melanoma and leukemia [154–160].

Notch can also act as a tumor suppressor in certain contexts. Instead of maintaining progenitor cells in an undifferentiated state or influencing their cell fate decisions, Notch can induce differentiation in some tissues, which is associated with growth suppression. The best-studied example is the role of Notch in the skin. Conditional *Notch1* knockout mice develop cutaneous basal cell carcinoma-like lesions that have increased levels of Hedgehog and Wnt signaling [161]. *In vitro* data from both human and mouse keratinocytes suggest that Notch signaling induces differentiation, which is accompanied by cell cycle arrest. Negative crosstalk between Notch and p63 regulates the balance between self-renewal and differentiation, and the dysregulation of this Notch function could contribute to keratinocyte transformation [162–164]. Another property of Notch1 activation is the induction of early differentiation markers, including Keratin1/10 and involucrin, and the downmodulation of integrin expression [164]. Conditional inactivation of signaling components of the Notch cascade in mouse skin results in hyperproliferation of the skin and epidermal cyst formation. Over time, Notch1-deficient animals develop spontaneous, highly vascularized basal cell carcinoma-like tumors [161, 165].

Another feature of the complex nature of Notch signaling in cancer can be reflected by the opposite outcomes of the Notch-activated downstream elements, such as Hairy and enhancer of split (HES)1 protein, the human homolog of *Drosophila* Hes1 and a basic helix–loop–helix transcriptional repressor. The Notch–HES1 axis in signaling is intricately modulated to control proliferation, differentiation and apoptosis [166]. Notch activation involves its proteolytic cleavage by γ-secretase and the generation of an intracellular Notch fragment to enter nuclei and activate transcriptions. HES1 is a target of Notch1 signaling that is aberrantly activated in a variety of human cancers, including prostate, lung, colorectal, osteogenic and breast carcinomas [167–171]. HES1 expression is downregulated in the nonmetastatic cancer cell line LNCaP compared with that in metastatic cancer cells (C4-2B) and, in this case, may act as a tumor suppressor for primary prostate tumorigenesis [172,173]. In breast and pancreatic endocrine tumors, HES1 is also downregulated [174,175]. However, in some tumors, HES1 is upregulated during tumorigenesis, such as osteosarcomas [167,176]. As the tumorigenesis is further underway, gene expression in cancer cells is deregulated and seems to be very complex and multifaceted in nature. HES1 may thus act as a tumor suppressor in one context and as an oncogene in another depending on the tumor type and the stage of cancer progression.

As outlined earlier, while a rationale can now be developed for the treatment of several human tumors with Notch inhibitors, and the availability of γ-secretase inhibitors makes this feasible [177], suppression of the Notch and γ-secretase pathways may have unintended effects. Current γ-secretase inhibitors turn off all Notch receptors, which have significant acute toxicities [178], and their long-term effects are yet to be discovered.

Conclusion: integrative cancer therapies

The previously described analyses argue that many oncogenes and tumor suppressors elicit context-dependent effects (sometimes opposite to their definitions) in carcinogenesis. It is conceivable that the signaling pathways that they are responsible for initiating also display complex regulation. To improve the success of anticancer therapy, we propose to develop and implement an integrative treatment strategy (integrative cancer therapy [ICT]). ICT emphasizes the need to not only categorize tumor signatures but also incorporate the stage dimension as well as the personalized care strategy. There is increasing emphasis on personalized medicine to categorize the specific gene signatures in given tumors to guide anticancer treatment. It is also important to develop better cancer biomarkers to assist in categorizing the specific stages of given cancer types to guide stage-dependent anticancer treatment. Additionally, emerging research reveals that there are underinvestigated relationships between stress, low immunity, psychosocial intervention and cancer [179–183]. Some epidemiological evidence suggests a reduced incidence of many common types of nonsmoking-related cancers in individuals with Parkinson's disease [184–186], and an inverse relationship between Alzheimer's disease and cancer [187]. Clearly, further investigation into how the alterations of system physiology affect cancer incidence and treatment outcomes can contribute significantly to the rational strategy of intervention.

Future perspective

The term ‘targeted therapy’ refers to anticancer drugs designed to interfere with a specific molecular target (whether at the RNA or protein level) in a biological pathway that is believed to play a critical role in tumorigenesis or progression. The identification of appropriate targets is based on a detailed understanding of the molecular mechanisms underlying cancer progression [188–191]. This approach is in contrast to the more empirical approach used to develop cytotoxic chemotherapeutics – the mainstay of cancer drug development in past decades. Recent development of target-specific therapy, such as Gleevec [25–27] and the humanized anti-HER2 monoclonal antibody trastuzumab, has the potential to revolutionize cancer therapy by individualizing treatment [192]. With the better understanding of the dichotomy of oncogenic and tumor-suppressive pathways, they can be applied to best exert their anticancer efficacy.

Cytotoxic therapy with protective adjuvants could be effective for symptom relief in advanced cancer [193], although many of these compounds lack tumor selectivity [194]. Cytotoxic therapy, or chemotherapy as it is commonly known, has been the cornerstone of cancer treatment for many years and involves the use of drugs that are toxic to all cells, including normal, non-cancer cells. While relatively effective, this leads to the unpleasant side effects commonly associated with cytotoxic treatment, such as vomiting, nausea, alopecia and fatigue.

Currently as well as for the future, the chemotherapeutic emphasis of oncology is still towards the use of adjuvant drugs to improve patient survival by delaying micrometastasis [195]. This treatment philosophy can be extended by expanding the previously discussed knowledge of the oncogenic pathways underlying tumor progression, as well as by the development of molecularly targeted drugs that modulate these pathways. More and more combined cytotoxic and targeted anticancer drugs have been incorporated into practice and have improved both survival outcomes and quality of life [196,197]. Monoclonal antibodies, which have the capability to bind to specific markers on the surface of tumor cells, offer an attractive therapy that is tumor specific and thus less toxic [194]. For example, pancreatic cancer is a common, highly lethal disease with a rising incidence. Mucin 1 (MUC1) is a tumor-associated antigen that is overexpressed in pancreatic adenocarcinoma. Most recent studies showed that active

immunotherapy that targets MUC1 could have great treatment value and may be used as a new adjuvant strategy against pancreatic cancer [198].

There are many time-proven therapies that have not reached their full potential owing to toxicity; there are also many underexplored areas that may prove promising in cooperation with anticancer therapy. Many existing target-specific therapies can manifest greater potential in limiting cancer if they are applied to the most appropriate stages in carcinogenesis. Future oncology will rely on an integrative approach of applying target-specific cancer therapies and cytotoxic therapies with protective adjuvant, as well as reliable cancer biomarkers for treatment guidance.

Executive summary

Goal of cancer therapy: our progress in detecting & treating cancers

- Early detection and effective therapies:
  - Breast cancer and prostate cancer, two areas in which early detection is possible;
  - Pioneering chemoagent platinum compounds offered earlier hopes for cancer cure;
  - Signaling-targeted anticancer drug Gleevec® (Novartis, Basel, Switzerland) renewed hopes for target-based cancer therapies.

Challenges on most fronts of anticancer efforts

- Lack of reliable cancer biomarkers:
  - We lack reliable biomarkers for some cancers to reduce false-detection rates;
  - Many cancers are detected at a later stage when there are fewer treatment options.
- Complex roles of pro- and anti-oncogenic pathways:
  - Rb–E2F axis showed both pro-proliferation and pro-apoptosis features;
  - TGF-β1 signaling suppresses tumorigenesis at the earlier stage but promotes tumor progression at the later stage;
  - Cell–cell junction proteins from the $p120^{ctn}$/δ-catenin family can have both oncogenic and tumor-suppressive functions depending on the status of E-cadherin;
  - PI3K signaling activation can be pro-oncogenic as well as anti-oncogenic;
  - Inhibition of the Raf–MEK–ERK pathway at different tumor stages or in different cancer types produces different effects;
  - Hundreds of clinical trials are exploring restoration of wild-type, tumor-suppressive p53 functions or inhibition of mutant, oncogenic p53 functions;
  - Complex Notch signaling pathway with both oncogenic and tumor-suppressive outcomes can now be explored with the availability of γ-secretase inhibitors.

Conclusion: integrative cancer therapies

- It is important to recognize the roles of personalized medicine (e.g., categorize the specific gene signatures in given tumors to guide anticancer treatment).
- It is also important to develop better cancer biomarkers to assist in categorizing the specific stages of given cancer types to guide stage-dependent anticancer treatment to circumvent the unintended effects of targeting given anti- and pro-oncogenic pathways.
- It is important to recognize the underinvestigated relationships between stress, low immunity, psychosocial intervention, Alzheimer's disease, Parkinson's disease and certain cancers. Further investigation into how the alterations of system physiology affect cancer incidence and treatment outcomes can contribute significantly to the rationale of intervention strategy.

Future perspective

- Target-specific cancer therapy, such as monoclonal antibody-based drugs, showed long-term benefits to minimize toxicity towards noncancer cells.
- Cytotoxic therapy with protective adjuvant strategy has the potential to expand and extend the application of existing US FDA-approved drugs. Both strategies in conjunction with reliable, stage-specific biomarkers will provide greater opportunities for cancer management.
- Strategies of applying integrative cancer therapy will have great potential in succeeding in the war against cancer.

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Table 1

Pro- and anti-oncogenic functions of oncogenes and tumor suppressors in carcinogenesis

Name	Functions	Pro-oncogenic	Anti-oncogenic	Mutations†	Ref.
C-myc	Cell proliferation	+	+	ND	[199]
E2F1	Transcription factor	+	+	ND	[45–47,200,201]
K-ras	Kirsten ras oncogene homolog	+	+	Mutations in codons 12 or 13	[202–205]
Src	Tyrosine kinase	+	+	Transformation-defective mutants	[1]
Abl	Tyrosine kinase	+	+	SH3 domain, ATP-binding domain mutation	[206–208]
Rb	Cell proliferation	+	+	C-terminal caspase cleavage site mutation; loss of heterozygosity	[44,209,210]
Aurora A	A serine/threonine kinase in mitotic regulation	+	+	ND	[211,212]
β-*catenin*	Key player in cell–cell adhesion and also in the Wnt signaling pathways	+	+	Mutations in codon 32 or 3	[213–220]
APC	Mitotic regulation	+	+	Truncating mutation; loss of heterozygosity	[210,221–226]
p120^{ctn}	Regulate E-cadherin stability and Rho small GTPases	+	+	ND	[69–72,227,228–233]
δ-catenin	Neural gene misregulated in cancer	+	+	5′-UTR mutation	[66–68,73,75,79,234,235]
Raf	Functions downstream of the Ras family GTPases	+	+	Mutations in codon 600	[129–139]
miRNAs	Function in the negative regulation of gene expression	+	+	ND	[236–248]
EBNA1	Human herpes virus	+	+	ND	[249]
TGF-β	Growth factor initially growth inhibitory and then becoming tumor promoting	+	+	ND	[250–254]
IRF-4	A hematopoietic cell-restricted transcription factor	+	+	ND	[255]
GSK-3	A key serine/threonine kinase in Wnt signaling pathway	+	+	ND	[256]
Notch	Signaling pathway for cell–cell communication and gene regulation	+	+	Int3 (insertion site)	[153–165,177,178]
PI3K	A family of lipid kinases that propagates intracellular signaling cascades	+	+	Somatic mutations in *PIK3CA*	[257–265]
AKT	Serine/threonine-specific protein kinase	+	+	*AKT1 E17K* mutation	[266–270]
p53	Tumor suppressor called the guardian of the genome	+	+	DNA-binding domain mutations	[142–145,147–152,271]
PTEN	Negatively regulates PI3K/AKT signaling pathways	+	+	Gene loss	[82,105,106,128,140,141]

†Here we only show some mutation sites or domains as examples.

+: Literature cited to support the findings; ND: Mutations not discussed in this article; UTR: Untranslated region.