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Deregulation of Cell Signaling in Cancer

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Summary

Oncogenic mutations disrupt the regulatory circuits that govern cell function, enabling tumor cells to undergo de-regulated mitogenesis, to resist to proapoptotic insults, and to invade through tissue boundaries. Cancer cell biology has played a crucial role in elucidating the signaling mechanisms by which oncogenic mutations sustain these malignant behaviors and thereby in identifying rational targets for cancer drugs. The efficacy of such targeted therapies illustrate the power of a reductionist approach to the study of cancer.

Introduction

Oncogenic mutations disrupt the signaling systems that govern cell fate, endowing tumor cells with several attributes that sustain their malignant behavior. About a decade ago, it has been argued that six enabling traits (“hallmarks”) underlie the development of a malignant tumor: self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, evasion of apoptosis, sustained angiogenesis, and tissue invasion [1]. Since then, it has become clear that metabolic fitness and genomic instability also contribute to tumor malignancy, suggesting the existence of two additional traits [2,3]. Furthermore, a large body of evidence has established that tumor cells must evade immune recognition [4] and recruit both angiogenic and non-angiogenic normal cells, such as macrophages, activated fibroblasts, and inflammatory cells, and mould a permissive microenvironment – the tumor microenvironment – in order to progress to full malignancy [5] (Fig. 1).

Modern cell biologists do not view cell biology as an approach or group of approaches, but rather as a discipline that integrates multiple approaches to study cell function. From this expanded vantage point, it is possible to appreciate the contribution of cell biology to our current understanding of tumorigenesis and, viceversa, the contribution of studies on cancer to our current understanding of normal cell function. In this Review, I will focus on how cell biological investigations have shed light into the mechanisms by which oncogenic mutations endow tumor cells with three cardinal aberrations: de-regulated mitogenesis, resistance to apoptotic insults and other forms of cell attrition, and ability to invade through tissue

boundaries. My choice is informed by three considerations: 1) These three major aberrations encapsulate all previously described tumor cell-intrinsic hallmarks and are the defining features of malignantly transformed cells (“driver functions”). In contrast, genomic instability and recruitment of a tumor microenvironment foster tumor progression by enabling and sustaining one or more of the tumor cell-intrinsic hallmarks (“Fostering functions”) (Fig. 1); 2) Studies on cell signaling have revealed the mechanisms by which oncogenic mutations induce and maintain these cardinal aberrations; and 3) Blockage of oncogenic signaling results in tumor regression in mouse models and, increasingly so, in the clinic, validating the usefulness of a mechanistic approach to the cell biology of cancer.

Loss-of-function mutation and epigenetic silencing of tumor suppressor genes are prevalent driver alterations in cancer. My intent is to provide an overview of the signaling networks in which the proteins they encode operate and thereby introduce the individual Reviews that comprise this special issue of FEBS Letters.

Cancer as a Disorder of Cell Signaling

During development and tissue repair, individual cells or population of cells undergo expansion in response to contextual cues that regulate their ability to enter into and progress through the cell cycle, to migrate, and to survive within provisional microenvironments [6]. Cell biological studies have revealed that these processes are governed by multiple signaling systems, which operate - often in a tissue and cell-type specific manner - to govern the cell cycle, anti-apoptotic, and pro-migratory machineries [7,8]. In parallel, studies on retroviral oncogenes, on transforming genes isolated by transfection of cancer genomes into normal cells, and on genes identified as mutated in human cancer have indicated most oncogenic mutations can be mapped onto nine distinct signaling systems [9]. Prevalent oncogenic mutations disrupt the normal operation of these pathways leading to deregulated mitogenesis, resistance to pro-apoptotic insults, and a gain in motility [1]. Although biochemical and genetic analyses have played an indispensable role in elucidating the molecular underpinnings, and thereby shaping our understandings, of the signaling systems altered in cancer, additional approaches, such as advanced imaging and computational modeling, have helped to place the linear pathways defined by biochemistry and genetics within spatially organized signaling networks regulated by cross-talk and positive and negative feedback loops [10,11]. Such an integrated approach to cell biology has been instrumental to the development of our current model of cancer development and to the design of therapies interfering with the operation of cancer-causing genes.

Powering the Engine

Receptor Tyrosine Kinases—The ability of normal cells to survive and proliferate depends on engagement of growth factor receptors endowed with tyrosine kinase activity (Receptor Tyrosine Kinases; RTKs) [12]. The biochemical reactions that underlie RTK signaling have been elucidated and placed in the context of core pathways through a combination of genetics and biochemistry. Ligand binding and the ensuing oligomerization of RTKs leads to phosphorylation of tyrosine residues within the receptor tails or on surrogate proteins (such as IRS, Gab, and FRS) creating docking sites for signaling adaptors containing phosphotyrosine-binding domains [8] (Fig. 2a). Shc and Grb2 are two of such

adaptors and play an essential role in recruiting the guanine-nucleotide exchange factor SOS and thereby activating Ras. This process is facilitated by inactivation of the GTPase-activating proteins p120 and neurofibromin, which is encoded by the *NF1* gene. GTP-bound Ras engages multiple target-effectors [13,14] (Fig. 2b). Whereas Raf commands activation of the MEK-ERK cascade, PI(3)K, which is initially recruited to the plasma membrane by tyrosine-phosphorylated receptors or surrogate adaptors, enables conversion of PIP2 to PIP3 on the inner leaflet of the membrane. PIP3 in turn attracts Akt, which upon activation by PDK phosphorylates and inactivates multiple effectors, including TSC2, GSK3- β , the CDK inhibitors p21 and p27, BAD, and FOXO transcription factors [15,16] (Fig. 2c). Akt signaling is opposed by PTEN, which dephosphorylates PIP3, dampening recruitment to the membrane and thereby activation of Akt [17]. Through these and additional mechanisms, receptor tyrosine kinases promote cell survival, progression through the G1 phase of the cell division cycle, and cell migration (Fig. 2b, c).

Oncogenic mutations causing deregulated activation of receptor tyrosine kinases or their downstream signaling components are prevalent in human cancer. *HER2* is amplified in approximately 30% of breast cancers and *HER1*, encoding the EGFR, in a slightly larger fraction of glioblastomas. Furthermore, activating mutations in *HER1* have been identified in the 10% or so of non small cell lung cancer (NSCLC) patients that responds to EGFR kinase inhibitors, and similar and therefore potentially activating intragenic mutations in *HER2* have been found in about 4% of NSCL patients [12,18]. Activating mutations of *KIT* and *PDGFRA* are commonly found in gastrointestinal sarcomas [19]. In addition, PDGF and its receptor are overproduced in a subset of glioblastomas, although the underlying mechanisms are unclear [12]. *KRAS* and *BRAF* mutations occur frequently in multiple tumor types and are prevalent in melanoma, pancreatic adenocarcinoma, colorectal carcinoma, and Non-Squamous Cell Lung Carcinoma (NSCLC) [20,21]. Activating mutations in *PIK3CA*, encoding a catalytic subunit of PI-3K, occur frequently in breast, ovarian, and colorectal cancer, and loss of heterozygosity of *PTEN* is one of the most common genetic alterations observed in multiple tumor types [15,17]. More recently, activating mutations in the *JAK2* kinase have been found in myeloproliferative neoplasms, *KIT* mutations have been identified in mucosal melanoma, and *FGFR2* mutations in endometrial carcinoma [18]. Moreover, *DDR2*, encoding a collagen-binding RTK, has been found mutationally activated in a small fraction (~4%) of squamous carcinoma of the lung [22]. These findings confirm the view that deregulated mitogenic signaling is a major driver of cancer development.

Cell Adhesion Receptors—Normal cells respond to mitogens only if they not restrained by the inhibitory action of cadherin-mediated contact inhibition and are attached to a supportive matrix via integrins. In contrast, neoplastic cells are largely insensitive to these control mechanisms [23,24]. Cell biological studies have shed light on the major mechanisms by which integrins and cadherins function as key, antithetic regulators of mitogenic signaling in normal cells. Whereas most integrins activate Focal Adhesion Kinase and thereby Src family kinases, certain integrins also combine with RTKs and promote their activation. Through these and additional mechanisms, integrins buttress mitogenic signaling via Ras and PI-3K and regulate Rho family GTPases during cell adhesion and migration [25,26] (Fig. 3). In agreement with the hypothesis that deregulated integrin signaling

contributes to tumorigenesis. FAK is amplified in a subset of breast tumors [27], Src family kinases are often overactivated in colorectal cancer [28], and *DLC1*, encoding a Rho-GAP, is frequently deleted in hepatocellular carcinoma [29].

Although the membrane-proximal signals generated by cadherin engagement remain poorly defined, recent studies have revealed that cadherin engagement inhibits proliferation by promoting accumulation of the de-phosphorylated, growth inhibitory form of the tumor suppressor Merlin in the nucleus [30] as well as phosphorylation and nuclear extrusion of the transcriptional co-activator and oncoprotein YAP [31] (Fig. 3). Studies in *Drosophila* have suggested the existence of a linear growth inhibitor pathway involving the Hippo kinase, the adaptor Salvador, and the Warts kinase, which impinges on the transcriptional co-activator Yorkie (the fly ortholog of YAP) [32,33]. Although genetic analysis in the same organism suggests that Merlin combines with Expanded at the cell cortex to activate the Hippo pathway [34], studies in mammalian cells, which lack a clear ortholog of Expanded, indicate that Merlin mediates contact inhibition and suppresses tumorigenesis through inhibition of the recently identified CRL4^{DCAF1} E3 ligase in the nucleus [30]. Since CRL4^{DCAF1} induces a tumor suppressive gene expression program that includes the repression of a large fraction of YAP target genes [30], it seems likely that Merlin regulates YAP as well as other target genes through CRL4^{DCAF1}. Additional events that may contribute to contact inhibition are a consequence of the assembly of cell junctions, which immobilize β -catenin, prohibiting its participation in Wnt signaling [35], and attenuate the activation of receptor tyrosine kinases [36] (Fig. 3).

Increasing evidence indicates that loss of contact inhibition contributes to the invasive growth of neoplastic cells. E-cadherin is frequently inactivated in diffuse gastric and lobular breast cancers [37], *NF2*, which encodes for Merlin, is inactivated in the cancer predisposition syndrome Type II Neurofibromatosis and in about half of malignant mesotheliomas [36], and *LATS2* is deleted in some of the remaining malignant mesotheliomas [38]. Finally, *YAP* is amplified in hepatocellular carcinomas [39].

Fueling Growth

The TOR Pathway—Among downstream target-effectors of Akt, mTORC1 has emerged as a key mediator of RTK signaling as well as a major sensor of metabolic fitness [40,41]. Following growth factor stimulation, Akt phosphorylates the TSC2 subunit of the Tuberosclerosis complex, thus inhibiting the GAP activity of this complex toward Rheb. GTP-loaded Rheb governs the activation of mTORC1, which in turn phosphorylates 4E-BP1 and S6K. Through these two targets, mTORC1 promotes translation of mRNAs encoding proteins that regulate cell growth (i.e. increase in cell mass), cell survival, and cell cycle progression [42]. In addition, mTORC1 suppresses autophagy (see below) and indirectly activates transcription factors, such as SREBP, PPAR γ and PCG1 α , which promote lipid biosynthesis and mitochondrial function [40,41] (Fig. 4).

Various mechanisms prevent RTK-mediated activation of mTORC1 if the extracellular or intracellular conditions are not favorable to cell growth and cell division. Low levels of nutrients induce a drop in the intracellular concentration of amino acids, which is sensed by the RAG proteins, which in turn inactivate mTORC1. In addition, decreased glycolysis and

the attendant slow down of the mitochondrial respiratory chain lead to a steep decline in the level of ATP, causing activation of AMPK, which phosphorylates and thereby inactivates mTORC1. Finally, whereas DNA damage-induced activation of p53 inhibits mTORC1 through activation of AMPK, hypoxia exerts this effect through the HIF1 target gene REDD1 [40,41] (Fig. 4). Elucidation of these signaling connections has firmly placed mTORC1 at the center of a signaling network that governs cell survival, cell growth, and mitogenesis in response to growth factor stimulation.

Signaling studies have also revealed that a second TOR kinase, mTORC2, also activated by RTKs, performs a distinct function [40,41]. In addition to regulating the cytoskeleton through Rho proteins, mTORC2 phosphorylates Akt at Ser 473, priming it for further phosphorylation by the PIP3-regulated kinase PDK1 (Fig. 4). The realization that inhibition of mTORC1 by rapamycin or rapalogs attenuates the negative feedback loop mediated by S6K, allowing activation of mTORC2 and thereby Akt and other SGK kinases has provided the impetus for the development of dual TOR-PI-3K inhibitors, which are showing promise in early clinical trials in gliomas, breast cancers carrying *PIK3CA* mutations, and T-cell leukemias [41]. These inhibitors should also prevent release of a recently identified additional negative feedback loop involving mTORC1-mediated phosphorylation and stabilization of Grb10, which opposes activations of RTKs [43,44] (Fig. 4, inset).

Metabolic Reprogramming—Although it has been known for long that cancer cells utilize predominantly anaerobic glycolysis [45], recent studies have revealed that oncogenic mutations lead to a substantial reprogramming of metabolism that diverts energy from aerobic glycolysis to the synthesis of aminoacids, lipids, and nucleotides required to fuel growth [2,46] (Fig. 5). As mentioned above, RTK signaling through Akt activates mTORC1, which exerts an overarching effect on metabolism by stimulating protein and lipid biosynthesis. In order to implement these changes, Akt promotes the utilization of glucose by increasing translocation of membrane transporters, such as Glut4, to the plasma membrane, and by phosphorylating and activating key glycolytic enzymes, such as hexokinase and phosphofructokinase [2]. Deregulated Myc promotes alternative splicing of pyruvate kinase, leading to prevalent expression of the less efficient M2 isoform (PK M2), which is further debilitated by binding to phosphotyrosine containing proteins. The net result is increased production of lactate at the expense of mitochondrial utilization of pyruvate as well as induction of the hypoxiainducible transcription factor HIF1. In addition, Myc increases the expression of genes that promote mitochondrial utilization of glutamine and it collaborates with HIF1 to increase expression of glucose transporters and glycolytic enzymes. On its own, HIF1 induces inactivation of the pyruvate dehydrogenase complex, reducing the flow of pyruvate into the tricarboxylic acid (TCA) cycle [47]. Finally, loss of p53 reduces the expression of TIGAR, which decreases glycolysis, SCO2, which is required for the assembly of cytochrome c oxidase complex and therefore electron transport in mitochondria, and PTEN, which opposes activation of Akt. One of the key results of this metabolic reprogramming is increased production of NADPH and thereby of both TRX and GSH, which buffer the reactive oxygen species (ROS) produced by oncogenic mitogenic signaling [2,46] (Fig. 5).

While the metabolic rewiring observed in cancer is mostly adaptive, recent studies suggest that mutations in metabolic enzymes can be oncogenic. A large fraction of acute myeloid leukemias, gliomas, and glioblastomas harbor heterozygous mutations in one of the two genes encoding isocitrate dehydrogenase (*IDH1* and *IDH2*), which converts isocitrate to alpha-ketoglutarate [48-50]. Interestingly, these mutations cause a gain-of-function phenotype: the neomorphic enzymes can convert the α -ketoglutarate produced by the wild-type allele to 2-hydroxyglutarate [51,52]. Studies of the hematopoietic system suggest that the ensuing accumulation of 2-hydroxyglutarate drives deregulated activation of TET2, which induces global DNA hypermethylation and provokes neoplastic transformation of stem cells [53-55].

Autophagy—Studies in yeast and mammalian cells have uncovered the core molecular machinery that controls macro-autophagy (here referred to as autophagy), the major catabolic process that governs the degradation of long-lived proteins and organelles, providing an essential housekeeping function [56,57]. Hormonal and metabolic deprivation signals, which are sensed through inactivation of the mTORC1 pathway, lead to activation of a Ser/Thr kinase complex comprised of mATG13, ULK1/2, and the scaffold protein FIP200. Subsequently, a lipid kinase complex comprising the class III PI-3K mVps34, Beclin 1 (Atg6), UVRAG, and other components mediate nucleation of a flat vesicle, the phagophore. Two ubiquitin-like conjugation systems, LC3-II (Atg8) and Atg12 (Atg12-5-16L), function downstream of the lipid kinase complex to promote expansion of the phagophore, which eventually surrounds cytoplasm and organelles destined for disposal and encloses them in the autophagosome. Fusion of the autophagosome with lysosomes allows degradation of the organelles and release of amino acids and fatty acids that can be used by the TCA cycle to generate ATP. Whereas mTORC1 suppresses initiation of autophagy by phosphorylating and inactivating mATG13, additional regulatory inputs are provided by the antiapoptotic proteins Bcl2 and Bcl-X_L, which bind to Beclin and suppress mVps34 catalytic activity. This inhibitory interaction is alleviated by pro-apoptotic proteins, such as BH3-only proteins, DAPK, and JNK, which disrupt the association of Bcl2 and Bcl-X_L with Beclin, thus promoting autophagy. Although autophagy and apoptosis are induced by largely overlapping subsets of stimuli, the existence of different thresholds for the activation of the two processes and of reciprocal negative regulation between them explains why weak stress stimuli induce autophagy, allowing eventual recovery, but stronger stimuli induce apoptosis and why inhibition of apoptosis leads to autophagic death (self-cannibalism) under conditions of stress, whereas inhibition of autophagy accelerates apoptosis under similar conditions [56].

Since autophagy serves a metabolic protective function under conditions of low oxygen or nutrient availability, it may sustain the expansion of incipient tumors that have not yet recruited a neo-vasculature. In addition, it can promote further growth of established tumors that have expanded beyond the functional capacity of their defective vasculature. In agreement with this hypothesis, Ras-dependent tumorigenesis appears to depend on the ability of autophagy to remove defective mitochondria and thereby prevent both oxidative damage and metabolic impairment [58,59]. On the other side, complete loss of autophagy, such as in cells and mice lacking Beclin, favors tumor initiation, suggesting that autophagy

may suppress tumorigenesis [56]. Autophagy may prevent normal cells from becoming cancerous because it removes defective mitochondria, preventing a build up of reactive oxygen species, which can damage the DNA. In addition, autophagy disposes of centrosomes and other components of the mitotic apparatus that have become defective, ensuring correct completion of mitosis. Therefore, although autophagy can sustain tumor growth under conditions of metabolic stress, its complete loss may predispose normal cells to acquire oncogenic mutations [60].

Inputs into the Cell Division Cycle—Progression through the cell division cycle is governed by the periodic oscillation of cyclins and thereby the activation of their catalytic subunits, the Cdk4s [61,62]. A complex loop of ubiquitin-mediated degradation events coordinate completion of mitosis with entry in S phase, enforcing a gap phase, G1, between the two events [63]. The presence of a G1 phase enables multiple inputs to regulate cell cycle progression. Permissive signals, such as those transmitted jointly by integrins and RTKs, elevate the levels of Cyclin D and thereby activate CDK4/6, which phosphorylates Rb [64]. Liberated from the inhibitory action of Rb, the E2F transcription factors drive expression of Cyclin E and of a myriad of factors necessary for DNA replication [65]. Whereas Ras signaling induces expression of Cyclin D through activation of Myc and Ets transcription factors [66], Akt blocks the ability of GSK3- β to phosphorylate Cyclin D and to mark it for ubiquitin-dependent degradation [64]. In addition to controlling Cyclin D, mitogenic signals inactivate the CDK2 inhibitor p27^{kip1} through multiple mechanisms, including suppression of transcription, inhibition of nuclear accumulation, and sequestration by active Cyclin D-Cdk4/6 complexes [67,68]. Unhindered by p27, Cyclin E-Cdk2 marks p27 for degradation via the CRL1^{Skp2} E3 ligase, ultimately disposing of the inhibitor [69]. Anti-mitogenic signals, such as those activated by engagement of TGF- β receptors, restrict progression through G1 by inhibiting the expression of Myc and ID transcription factors and by elevating the levels of the Cdk inhibitors p21^{Cip1/WAF1} and p15^{Ink4b} [68].

Oncogenic mutations target several elements of this signaling network. Cyclin D1 is overexpressed in a large fraction of breast cancers [70]. Myc is overexpressed as a result of chromosomal translocation in Burkitt lymphoma and as a consequence of other mechanisms in several other cancer types [71]. *RB*, which was originally identified as the tumor suppressor inactivated in familial retinoblastoma, is mutated in a variety of prevalent cancers [64]. The gene encoding p15^{Ink4b} is inactivated as a consequence of deletion of the *INK4* locus in both solid cancers and leukemias [64]. Finally, overexpression of *SKP2* leads to severely diminished levels of p27 in various carcinomas, brain tumors, and lymphomas [67].

Disabling the Brakes—Increasing evidence indicates that the emergence of carcinomas requires avoidance of the anti-mitogenic signals provided by TGF- β . Cell biological studies have revealed that the effects of TGF- β are cell context-dependent: whereas differentiated epithelial and endothelial cells undergo growth arrest in response to TGF- β , other cell types proliferate and then undergo differentiation and yet others may fail to do so or even undergo apoptosis in spite of the presence of the correct inducing factors [72]. The signaling mechanisms that underlie these diverse responses to TGF- β have been elucidated to considerable detail [73]. Upon engagement by TGF- β , the type II receptors phosphorylate

and activate the type I receptors, which initiate downstream signaling by phosphorylating the Smad 2 and 3 transcription factors. These Receptor substrate Smads (RSmads) combine with Smad4 to form RSmad-Smad4 complexes that migrate into the nucleus. In order to bind with high affinity and specificity to the promoters of target genes, the RSmad-Smad4 complexes must associate with cell type-specific transcriptional partners, such as forkhead, homeobox, zinc finger, bLHL, and AP1 proteins. Each RSmad-Smad4-cofactor combination targets a specific set of genes, defining so-called synexpression groups [72,73]. The differential response of different cell types to TGF- β appears to be in large part a consequence of the variegated expression pattern of the Smad cofactors and their modulation by extracellular signals.

Since TGF- β signaling induces a cytostatic program in epithelial cells, it is not surprising that various elements of this pathway function as tumor suppressors in human cancer [72]. Biallelic deletions and frameshift or missense mutations that inactivate the TGF- β type II receptor occur in a variety of carcinomas and in virtually all colon carcinomas with microsatellite instability. Although Smad 2 and 3 are rarely mutated in human cancer, Smad4 is mutated in about half of pancreatic adenocarcinomas and of colorectal cancers without microsatellite instability. Finally, ERK-mediated phosphorylation of the linker region may target Smad proteins for ubiquitin-dependent degradation in cancers carrying amplified or mutationally activated RTKs, mutant *RAS*, or mutant *BRAF*. While the above alterations disable all arms of the TGF- β pathway, enabling tumor cells to evade also the pro-differentiative and pro-apoptotic effect of TGF- β , other mutations, such as the inactivation of *INK4* or the overexpression of Cyclin D1 or Myc, abrogate the effect of TGF- β on CDK inhibitors allowing other TGF- β responses to proceed unadulterated [72]. In fact, inactivation of the cytostatic arm of the TGF- β signaling pathway enables tumor cells to usurp the other arm of the pathway to foster their malignancy, as exemplified by the ability of TGF- β to induce an Epithelial-to-Mesenchymal Transition (EMT) and promote invasion and metastasis in tumor cells that have lost cytostatic responses (see below).

Intrinsic Tumor Suppression

Strong oncogenic mutations, such as those activating Ras, elevating Myc, or inactivating Pten, induce apoptosis or senescence in the majority of normal cells in which they have been acutely introduced. These findings point to the existence of a fail-safe program designed to eliminate incipient neoplastic cells undergoing deregulated mitogenesis [74]. In order to overcome this intrinsic form of tumor suppression, incipient neoplastic cells need to evade apoptosis or senescence through the acquisition of additional oncogenic mutations, most commonly loss-of-function mutations of the Rb or p53 tumor suppressors (Fig. 6).

In addition to providing a formal understanding of oncogene cooperativity and intrinsic tumor suppression, the elucidation of the normal function of the Rb and p53 signaling networks has shed light into the evolutionary advantage of these molecular circuitries and their connection to aging. Whereas, as discussed above, Rb restrains G1 progression in cells that are not exposed to mitogenic signals, the p53 transcription factor can block transit through the cell cycle in response to multiple stress signals, including genotoxic damage, loss of proper adhesion, and hypoxia [75]. Depending on the level and/or quality of the

stress sensed by the cell, p53 can temporarily halt the cell cycle to allow repair or induce apoptosis and thereby eliminates irreparably damaged cells. If the insult is not lethal, p53 activates genes that induce transient cell cycle arrest, such as p21, and allows repair of the damage through additional effectors, such as TIGAR and sestrins, which reduce the levels of intracellular reactive oxygen species, and DRAM and AMP-K, which activate autophagy. If the damage cannot be repaired and is poised to create a deranged cell potentially harmful to the organism, p53 induces apoptosis, through activation of the proapoptotic genes Puma, Noxa, and Bax, or promotes senescence through induction of p21.

Although the mechanisms by which p53 is able to sense the quality and strength of the insult suffered by the cell are incompletely understood, different upstream stimuli decorate p53 with distinct post-translational modifications, resulting in the assembly of distinctive transcriptional complexes at the promoters of target genes [76]. For example, DNA damage is sensed by the ATM and ATR kinases, which in turn activate CHK2 and CHK1, respectively. Whereas CHK1 inhibits the CDC25 phosphatase, inducing phosphorylation and inactivation of G2 CDKs, ATM and CHK2 phosphorylate p53 at Ser 15 in the N-terminal transcriptional activation domain. In response to high levels of DNA damage, signals initiated by ATM and ATR induce phosphorylation and inactivation of the E3 ubiquitin ligase Mdm2, which targets p53 for degradation. In addition to driving stabilization of p53, inhibition of Mdm2 also increases the levels of the homeodomain interacting protein kinase 2 (HIPK2), which phosphorylates Ser 46 in the second transcriptional activation domain of p53.

Suppression of Apoptosis—In order to emerge as neoplastic cells, cells carrying strong oncogenic mutations must evade apoptosis induced by oncogenic stress [74]. In addition, suppression of apoptosis enables tumor cells to survive under a host of stressful circumstances, such as loss of adhesion to a supportive matrix, protracted deprivation of growth and survival factors, and hypoxia [77].

The discovery that the proto-oncogene *BCL2* is brought under control of the Ig promoter by translocation in a subset of B-cell lymphomas and the realization that it promotes cell survival, but not deregulated mitogenesis, set the stage for the elucidation of the apoptotic machinery [78]. Whereas TNF receptors are the major activators of signal-regulated apoptosis, most if not all other death-inducing stimuli operate by activating the so-called intrinsic pathway of apoptosis. In both the extrinsic and the intrinsic pathway, stress signals activate BH3-only proteins, such as Bim, Noxa, Puma, and Bid, and liberate them from stoichiometric inhibition by Bcl2-family members [79,80]. The activated BH3-only proteins undergo a conformational transition that enable them to combine with Bax on the surface of mitochondria and to initiate a series of events culminating in the release of cytochrome c and Smac/Diablo from these organelles [81]. Cytochrome c promotes assembly of the apoptosome complex, which drives activation of caspase 9 and 3, whereas Smac/Diablo blocks the Inhibitory of Apoptosis Proteins (IAPs), which inhibits caspases [82]. Apoptosis is finally executed through regulated, systematic proteolysis of cellular proteins and endonucleolytic degradation of DNA [83].

Neoplastic cells evade apoptosis through multiple mechanisms. Oncogenic signals transmitted through Ras and PI-3K promote cell survival by inactivating Bim and Bad through multiple mechanisms as well as by enhancing the expression of Bcl2 family proteins and IAPs. In contrast, loss of p53 protects tumor cells from apoptosis predominantly by reducing the expression of Puma, Noxa, and Bax [79,80] (Fig. 6).

Evasion of Senescence—Incipient tumor cells must also avert cellular senescence in order to outgrow into a neoplastic lesion. While normal cells undergo cellular senescence in response to erosion of their telomeres or to genotoxic damage accumulated over the years, incipient tumor cells succumb to the same fate as a consequence of oncogenic or replicative stress [84]. Oncogenic stress induces senescence through induction of the CDK inhibitor p16 (e.g. Ras) or activation of p19^{ARF} (e.g. Myc). P19^{ARF} in turn blocks Mdm2, allowing accumulation of p53 and thereby induction of the other CDK inhibitor p21. In contrast, replicative stress activates the DNA damage response (DDR) and thereby directly impinges on p53 and thereby p21 (Fig. 6). The relative ability of oncogenic and replicative stress to induce senescence may vary between mouse and human cells [85].

In agreement with the hypothesis that Rb and p53 are the main mediator of intrinsic tumor suppression and must be inactivated for tumor development to occur, *RB* and *TP53* are amongst the most commonly mutated tumor suppressor genes in human cancers [75]. Furthermore, several cancer predisposition syndromes arise from loss-of-function mutations in genes encoding essential components of the DNA damage response pathway, in agreement with the idea that loss of a functional p53 response allows the accumulations of mutations that contribute to tumorigenesis [86,87].

Disrupting the Internal Compass

In order to colonize distant organs, carcinoma cells need to break from adjacent cells, disrupt the underlying basement membrane, and invade through multiple tissue boundaries [88,89]. Cell and developmental studies have shed light on the mechanisms that enable oncogenic mutations to disrupt epithelial adhesion and polarity and to induce a gain in invasive ability.

Apicobasal polarity, the form of polarity that characterizes epithelial cells, arises from the establishment of an apical surface and a basolateral surface, physically separated by the apical junctional complex, consisting of tight junctions and adherens junctions. Once cells have attached to the basal lamina via integrins and formed initial E-cadherin-dependent adhesions, three evolutionarily conserved polarity protein complexes generate the sets of signals that direct the establishment of apicobasal polarity [90]. The Par3/Par6/aPKC (PAR) complex localizes to the maturing apical junctional complex and governs the assembly of tight junctions in response to the activation of Cdc42 and Rac. A second complex, consisting of the transmembrane protein Crumbs and the scaffolding proteins Pals1 and PatJ (CRB complex), localizes to the apical-lateral boundary in response to the PAR complex and regulates the expansion of the apical surface. Finally, a third complex, comprising Scrib, Dlg and Lgl (SCRIB complex), defines the basolateral surface. Whereas a reciprocally reinforcing interaction between the PAR and the CRB complex helps to stabilize the PAR

complex at the apicolateral boundary, a mutually antagonistic interaction between the PAR and the SCRIB complex ensures that these complexes localize underneath opposed membrane domains. In addition, while Par1 (Lkb1) localizes to the basolateral cortex and phosphorylates and inactivates Par3 that has diffused into this domain, the PAR complex phosphorylates and inactivates Par-1 at the apical surface. As apicobasal polarity is being established, vectorial delivery of vesicles containing E-cadherin and other junctional proteins enables final maturation of adherens and tight junctions.

Analyses of epithelial organoids grown in 3-dimensional (3D) matrices, such as Matrigel, have revealed that the establishment of epithelial adhesion and polarity restrains overproliferation and prevents apoptosis [91,92]. Normal cells that have lost contact with the basement membrane undergo apoptosis, contributing to the cavitation of epithelial acini. In order to induce luminal filling, oncogenic mutations need not only to induce hyperproliferation but also to suppress apoptosis. Furthermore, to induce invasive growth, they must disrupt epithelial adhesion and polarity [91].

Oncogenic mutations disrupt epithelial adhesion and polarity by various mechanisms and to varying degrees. Oncogenic RTKs, such as ErbB2 and Met, and activated Src can phosphorylate the cytoplasmic tail of E-cadherin and β -catenin, which tags them for ubiquitin-dependent or lysosomal-mediated degradation. ErbB2 also coopts the β 4 integrin to induce a STAT3-dependent program of gene expression as well as it binds to Par6 to inhibit the Par complex. In addition, activation of PI-3K or inactivation of Pten causes depletion of PIP2, which is required for Cdc42's function upstream of the PAR complex at the apical surface [93]. Finally, epigenetic silencing leads to underexpression of several components of the SCRIB complex in several carcinomas, and inherited mutations impair the polarizing function of LKB1 (Par4) in the familial hamartoma Peutz-Jeghers Syndrome [94,95].

In advanced tumors, a fraction of the constituent cells undergo an Epithelial-to-Mesenchymal Transition (EMT), seemingly highjacking the developmental program deployed by normal cells to form the mesoderm, the neural crest, and heart valves during embryogenesis [96,97]. In addition to losing their epithelial features, including their adhesion and polarity, cancer cells undergoing an EMT acquire mesenchymal and invasive traits. Contextual signals present in the tumor microenvironment, such as Wnt and TGF- β family ligands, and hyperactivation of the Ras-ERK cascade constitute the predominant culprits in most cases. These signals produce an EMT by activating a discrete subset of "EMT-inducing" transcription factors [98]. Amongst these, Snail, Slug, Zeb1, and Twist1 repress the expression of E-cadherin and other proteins involved in the establishment and maintenance of epithelial adhesion and polarity (occluding, claudins, Crb, Dlg, Lgl), while FOXC2 promotes mesenchymal differentiation. Negative and positive feed back loops mediated by microRNAs contribute to initiate and stabilize the phenotype induced by the EMT [99]. Interestingly, similar to normal mesenchymal cells, cancer cells that have undergone an EMT become at least in part insensitive to the survival threatening effects of loss of matrix and cell-to-cell adhesion. Furthermore, they acquire stem cell traits, such as increased self-renewal and tumor initiation capacities [100]. It is likely that multiple of the attributes conferred by the EMT contribute to invasion and metastasis.

While loss of cadherin-mediated adhesion facilitates and often is a prerequisite for invasion, cancer cells can also migrate while maintaining some degree of intercellular cohesion under a form of migration referred to as collective cell migration [101]. The elucidation of the signaling mechanisms and cellular machineries that implement normal cellular migration has been instrumental in building models of cancer cell migration. In normal mesenchymal cells, integrins and cytokine receptors coordinate activation of Cdc42 and Rac at the leading edge, promoting actin polymerization and extension of lamellipodia. After these structures have attached firmly to the matrix, Rho activation drives actomyosin contractility, favoring detachment of the cell's rear and promoting translocation of the cell body. Leukocytes can instead undergo an amoeboid form of movement, which is dominated by Rho kinase-mediated contraction of the cortical cytoskeleton [102,103]. Depending on intrinsic signaling and the density and rigidity of the surrounding matrix, cancer cells can undergo mesenchymal or amoeboid migration. Integrin-mediated adhesion, hyperactivation of Rac, and a rigid, dense matrix favor mesenchymal migration, while weak adhesion, hyperactivation of Rho, and a pliable, loose matrix promote amoeboid movement [104]. Whereas the former type of cancer cell migration requires localized proteolysis of the matrix by MMPs and other enzymes, cancer cells can squeeze through intact interstitial matrices when moving by amoeboid movement.

Exploiting Stemness

Increasing evidence indicates that the expansion of both leukemias and solid tumors is driven by a limited number of dedicated stem cells that are capable of self-renewal as well as of partial differentiation [105]. Phenotypic sorting experiments on dissociated tumor cells support the model that the cancer stem cells are the only cells that can initiate secondary tumors upon orthotopic implantation in immunocompatible hosts, suggesting that self-renewal is intimately linked to tumor outgrowth. In contrast, the remaining tumor cells, which comprise rapidly proliferating cells as well as aberrantly differentiated cells, are devoid of significant tumor initiation capacity.

In order to be defined as stem cells, the cancer stem cells do not need to phenocopy all the behaviors exhibited by embryonic or adult stem cells. In fact, the cancer stem cells may differ from embryonic stem cells because they do not appear to give rise to multiple lineages and they are dissimilar from adult stem cells because they divide predominantly in a symmetric fashion. Furthermore, the cancer stem cells do not necessarily need to arise from the transformation of adult stem cells. Although certain oncogenic mutations or combinations of oncogenic mutations may transform adult stem cells, others may transform transient-amplifying cells and confer stem cell properties upon them [106,107]. Interestingly, recent studies have indicated that neoplastic cells undergoing the EMT program acquire stem cell traits, suggesting that tumor cells with transient-amplifying characteristics may be induced to de-differentiate to cancer stem cells. If quantitatively limited, these forms of plasticity are not inconsistent with the hierarchical organization implied by the cancer stem cell model [100].

Cell biology and genetics have played key roles in the identification of signaling networks that sustain the self-renewal of normal adult stem cells and that, when deregulated,

contribute to tumorigenesis. Three signaling pathways, Wnt, Hedgehog (Hh), and Notch, initially defined on the basis of their developmental roles in flies, have emerged as major positive regulators in many adult stem cells [35,108-111] (Fig. 7). In addition, the TGF- β family ligand BMP suppresses self-renewal and promotes differentiation, at least in some adult stem cells, suggesting that inhibition of BMP signaling may contribute to tumor initiation by blocking differentiation [112]. Finally, the gene expression program that underlies enhanced self-renewal may be shaped also by epigenetic modifications, such as those conferred by the Polycomb component Bmi1 [113].

The evolutionarily related Wnt and Hedgehog signaling pathways control stem cell renewal in multiple tissues and share similar components and a common logic of signal transduction. Lipidation and incorporation in lipoprotein particles as well as reversible binding to cell surface proteoglycans enable both Wnt and Hh ligands to form extracellular gradients and thereby shape tissue morphogenesis [114]. Moreover, in both cases the receptors recruit multicomponent complexes that retain key transcriptional effectors in the cytoplasm and tag them for proteolysis. Finally, both pathways are characterized by metastable “on” and “off” states (Fig. 7).

Like many other signaling pathways, Wnt signaling exerts distinct function depending on the cell type and developmental stage in which it is activated. Intriguingly, Wnt signals are necessary to drive the self-renewal of adult stem cells located at the bottom of intestinal crypts, in the bulge region of hair follicles, in the mammary gland, and in the bone marrow. When deregulated in these cells, Wnt signaling promotes tumorigenesis, linking enhanced self-renewal to tumor initiation. Deletions and other mutations eliminating the scaffolding function of APC underlie the formation of pre-malignant intestinal polyps and are prevalent in colorectal carcinomas. Point mutations that prevent β -catenin from being phosphorylated are found in multiple tumor types, and axin mutations are found in colorectal and hepatocellular carcinomas, providing additional evidence for the role of enhanced self-renewal in tumorigenesis [35].

Although the Hh pathway is evolutionarily related to the Wnt pathway, it is distinctively regulated by the inclusion or exclusion of some of its components in cilia. Although many molecular details are not yet understood, it is clear that selective incorporation of pathway components in the cilium dictates the dual response of the mammalian Hedgehog pathway (“on” and “off” state) (Fig. 7) [108,111]. The Hh pathway has been implicated in the maintenance of stem or progenitor cells in many adult tissues, including the epithelia of many internal organs and brain [108]. Consistent with this, Hh signaling is critical for regeneration of the pulmonary epithelium, prostate epithelium, and exocrine pancreas. Importantly, abnormal Hh pathway activation in some of these tissues is also associated with tumorigenesis. Mutations in Hh pathway components, including Ptc1 and Smo, leading to pathway activation, have been linked to basal cell carcinoma and medulloblastoma [115]. One hallmark of these tumors is constitutive pathway activation in the absence of Hh ligand. In contrast, ligand-dependent pathway activation is important for growth, survival, or both of a wide variety of cancers, including gastrointestinal tumors, prostate cancer, hematological malignancies, and gliomas [108].

Notch signaling is initiated by the binding of Notch receptor to Delta or another transmembrane ligand (Serrate or Lag2) on an adjacent cell. The ensuing conformational change in the extracellular domain of Notch initiates a series of proteolytic events that release the intracellular domain, allowing it to localize in the nucleus to function as a transcription factor [109,110] (Fig. 7). In addition to regulating cell fate during development, Notch signaling is required for the maintenance of the stem cell compartment in various normal tissues, including the hemopoietic system [109]. Notably, more than half of T-cell Acute Lymphoblastic Leukemias carry missense mutations that expose the ADAM-metalloprotease cleavage site of Notch or non sense mutation that delete the C-terminal PEST degron of the ICN, providing strong evidence that deregulated Notch signaling contributes to leukemogenesis. Furthermore, it has been suggested that Notch signaling maintains the self-renewal capacity of a stem cell-like subpopulation of tumor cells in colorectal cancer and medulloblastoma and that it functions downstream of Wnt signaling in breast cancer and melanoma [110].

Hitting Drivers and their Underlings

Cell biological studies have played a crucial role in placing the proteins encoded by proto-oncogenes and tumor suppressor genes within signaling networks governing cell fate. The successive elucidation of the mechanisms by which mutant versions of these genes produce the cardinal traits of the malignant phenotype has led to the identification of rational targets for cancer drugs. The extraordinary efficacy of the first of such drugs, Imatinib (Gleevec), which blocks the kinase activity of Bcr-Abl in CML and c-Kit or PDGFR- α in gastrointestinal stromal tumors (GIST), has provided the first tangible evidence of the validity of a rational approach to cancer therapy [116]. At the same time, experiments employing temporally regulated alleles have revealed that oncogene-deactivation causes tumor regression in several mouse models of cancer, suggesting that tumors may remain dependent on the initiating, so called “driver”, oncogenic lesion for their maintenance [117]. These advances have led to the now widely held view that tumor cells depend primarily on oncogenic signaling for their survival and expansion, a property called oncogene dependence or addiction [118,119]. Although the mechanisms that lead tumor cells to this dependency are not fully understood, systems biology simulations based on signaling data may help to decipher the rewiring of signaling networks that appears to produce this effect. Needless to say, the success of oncogene-targeted therapies is entirely predicated on the existence of oncogene dependency.

The observation that EGF-R kinase inhibitors, such as Gefitinib (Iressa) and Erlotinib (Tarceva), display efficacy only in the subset of patients with non small cell lung cancer (NSCLC) carrying activating mutations in the EGF-R gene has vividly illustrated the power but also the limits of targeted therapies: success depends in large part on the correct identification of the underlying “driver” mutation [120]. The therapeutic efficacy of monoclonal antibodies or small molecules targeting ErbB2 when used in combination with chemotherapy for the treatment of HER2+ breast cancer and a few other successes have provided further evidence for this model [121]. Only recently, however, it has become evident that specific inhibition of a mutated oncoprotein can lead to remarkable regression of an aggressive and prevalent solid tumor: the small molecule PLX4032 (Vemurafenib),

which targets V600E mutant B-Raf, has been shown to induce significant shrinkage of metastases in about half of melanoma patients carrying such mutation [122,123].

However, although Imatinib is able to induce a complete hematological response and durable remissions in the large majority of CML patients, in fact these patients have the same life expectancy of unaffected individuals of the same age, some patients, who have initially responded to the drug, later develop a drug-resistant form of the disease (therapy-induced or de novo resistance) [116,124]. This problem is even more vexing in NSCLC and melanoma, where the large majority – virtually all – patients, who initially respond to EGFR or B-Raf inhibitors, respectively, undergo relapse at a later time [120,123]. Improved understanding of cell signaling is helping to elucidate the mechanisms of therapy-induced resistance, so that strategies can be designed to circumvent it. For example, most of the relapse of CML and EGFR mutant lung cancers treated with kinase inhibitors are caused by secondary mutations, which prevent drug binding to the catalytic site without affecting kinase activity [116,120]. Structural and functional information on tyrosine kinases has been instrumental not only in identifying these mechanisms of resistance but also in identifying second line inhibitors that are able to target the kinases carrying secondary mutations [116]. Similarly, increased understanding of cell signaling has helped to explain the seemingly paradoxical ability of PLX4032 to activate wild type Raf signaling and to identify several potential mechanisms of drug bypass [125]. Moreover, knowledge of the signaling networks activated by tyrosine kinases is helping to design therapies that target the pathways activated by a specific oncogenic lesion rather than the oncoprotein itself – the only possible approach when the driver mutation is in a tumor suppressor gene, such as *PTEN*, or when pharmacological features make it difficult to target the mutated oncoprotein, as in the case of Ras [126,127]. Finally, combination therapies are being designed to prevent the aberrant signaling that ensues upon release of the negative feedback loops so commonly embedded within signaling networks as well as to “prevent” prevalent drug bypass mechanisms.

Challenges

In spite of these significant advances and the possibility to overcome the practical challenges outlined above, there are a number of important theoretical issues that would need to be overcome to extend the “Gleevec paradigm” to other malignancies, especially to the most prevalent types of solid tumors.

First, in contrast to CML and certain other hematological malignancies, which remain essentially monoclonal throughout their clinical course, most solid tumors undergo clonal evolution as they acquire additional oncogenic mutations [128]. It is likely that malignant subclones that have acquired additional oncogenic lesions remain only partly dependent on the signaling pathways activated by the initiating oncogenic mutation [116]. At present, this model seems to provide the most plausible explanation for the intrinsic resistance of a fraction of solid tumors to molecularly targeted therapies. As genomic investigations of ever increasing sophistication and power lead to the identification of the predominant oncogenic alterations present in many cancers, cell biological and genetic studies in organotypic 3D cultures and mouse models should help to model these tumors and characterize their profiles of dependency.

Second, the cancer stem cells that are necessary for tumor maintenance as well as the outgrowth of metastases seems to be less sensitive to conventional as well as targeted therapy than their immediate derivatives [129,130]. Although cancer stem cells may be relatively drug-resistant because they cycle very slowly and express elevated levels of antiapoptotic proteins and drug efflux ABC transporters, more work seems to be required to fully understand the molecular basis of their relative resistance to targeted therapies. In addition, further elucidation of the signaling networks that sustain cancer stem cells may be needed in order to devise strategies to effectively inhibit these cells.

Third, since genetic instability appears to drive the emergence of drug-resistant clones, we need a better understanding of this process so that we can design therapies that selectively inhibit genetically unstable tumor cells. The efficacy of PARP inhibitors in *BRCA1* and 2-mutant breast cancer illustrates the potential power of this approach [131]. Combining drugs targeting genetic instability with drugs targeting oncogenic signaling may be a rational approach to prevent the emergence of resistance.

Finally, most metastatic relapses from solid tumors occur years – often several years – after initial surgery. Early dissemination of tumor cells followed by a protracted period of dormancy at premetastatic sites is likely to explain this prevalent clinical behavior [132]. The genetic or epigenetic changes that allow extravasated tumor cells to adapt and survive in a quiescent state in the target organ remain poorly understood, and so are the mechanisms that enable a fraction of these cells to eventually outgrow to give rise to macroscopic metastases [89,133]. Identification of the signaling networks that enable the survival of dormant tumor cells and their final outgrowth at ectopic sites may reveal additional Achilles's heels that could be exploited to treat metastatic cancer.

Outlook

Cancer cell biology has been instrumental in elucidating the signaling pathways and the molecular machineries that drive the ability of cancer cells to proliferate, to invade, and to resist attrition (driver functions; Fig. 1) and, in so doing, in identifying rational targets for cancer therapy. The early clinical success of several targeted therapies represents, in my view, the most vivid illustration of the power of cell biology in cancer research.

Embedded in the history of this progress is the evolution of cancer cell biology as a discipline. Current trends suggest that the practitioners of this discipline will use genetic and pharmacological methods of increasing sophistication to conduct mechanistic investigations in an expanding range of experimental models: from standard cell culture through 3-D organotypic cultures to animal models. By integrating methods horizontally and models vertically, cancer cell biology will provide an increasingly detailed, 4-dimensional view of the physiology of normal and neoplastic cells in proper context.

As genomic studies on human cancer specimens and high-throughput screens in cells and mice unveil novel and potentially oncogenic mutations in various types of cancer [18,134,135], mechanistic studies on the biology of cancer cells will play an important role in assessing whether these mutations are pathogenic and in elucidating their mechanism of action. Conversely, studies on cell signaling will reveal novel pathways or signaling

connections implicated in the controls of the basic cellular functions that sustain tumorigenesis. Whereas cancer cell biology approaches will play a key role in identifying novel potential oncogenes and tumor suppressor genes within these pathways, genomic studies will be required to determine if they are mutated and at what frequency in human cancer.

Finally, a complete understanding of tumorigenesis will require also the elucidation of the complex signaling circuits that regulate the tumor microenvironment, thus fostering tumor progression and metastatic dissemination [5,136]. Although the composition and function of the tumor microenvironment may ultimately be dictated by the spectrum of genetic and epigenetic changes acquired by tumor cells as well as their histological origin, future studies may be able to distill core pathways that play a role in multiple tumor types. The ability of HIF1 and its transcriptional target VEGF to mediate neoangiogenesis [137], NF- κ B to support tumor inflammation [138], and TGF- β to mediate wound healing and fibrosis and suppress immune recognition [72] may explain their ubiquitous roles in the tumor microenvironment. Agents that target these or other core signaling pathways that sustain the tumor microenvironment may display efficacy when used in combination with oncogene-targeted therapies.

Considering the extraordinary intellectual progress made since the discovery of oncogenes and the initial success of targeted therapies, one cannot avoid but being cautiously optimistic about the future of cancer research [139]. Unless myopic concerns over government spending restrict investment in basic science in the U.S. and Western Europe, reversing a long standing trend of global expansion of the scientific enterprise, one can anticipate that research on the biology of cancer will ultimately lead to dramatically improved treatments for many prevalent cancers.

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Figure 1.

Hallmarks and oncogenic functions. Deregulated signaling endows tumor cells with several attributes (hallmarks or traits), which in turn sustain oncogenic functions. Increased cell proliferation, decreased cell attrition, and invasion are necessary for oncogenesis and are thus categorized as driver functions; genetic instability and a permissive tumor microenvironment are provisionally classified as fostering functions.

Figure 2.

Receptor tyrosine kinase signaling. **(a)** The membrane-proximal events and major effector pathways activated by RTKs are depicted. Ras and AKT activate multiple targets. Signaling strength and duration are controlled by negative as well as positive feed-back loops. **(b)** Major signaling pathways activated by Ras proteins and multiple mechanisms of negative feed-back regulation. **(c)** Major target-effectors and pathways regulated by AKT.

Figure 3.

Adhesion receptor signaling. The major signaling mechanisms underlying the ability of integrins to buttress mitogenic signaling and that of cadherin to exert the opposite effect are depicted.

Figure 4.

TOR signaling. Multiple inputs regulate the AKT-mTORC1 signaling axis. mTORC1 in turn regulates anabolic processes by phosphorylating multiple target-effectors. The inset illustrates two major mechanisms of negative feedback regulation.

Figure 5. Metabolic reprogramming in cancer. The major mechanisms by which oncogenic alterations alter flux through multiple metabolic pathways are illustrated.

Figure 6.

Intrinsic tumor suppression. Mutant Ras and overproduced Myc induce senescence or apoptosis through common as well as distinct mechanisms.

Figure 7.

Signaling pathways involved stem cell function. **(a)** Wnt signaling. In cells that are removed from Wnt, the cytosolic fraction of β -catenin, which is not associated with E-cadherin at adherens junctions, is targeted for ubiquitin-mediated degradation by a series of phosphorylation events governed by the destruction complex, consisting of the scaffolding protein Axin, the tumor suppressor APC, casein kinase 1 (CK1), and GSK3. As participants in the destruction complex, CK1 and GSK3 sequentially phosphorylate the N-terminus of β -catenin, enabling its recognition by the E3 ubiquitin ligase β -Trcp. Continuous degradation prevents β -catenin from accumulating in the nucleus. Unhindered by β -catenin, TCF/LEF transcription factors repress their target genes (OFF state). In cells that produce or are close to cells that produce Wnt proteins, binding of Wnt to Frizzled (Fz) receptors and LRP6/5 co-receptors induces recruitment of Dishevelled (Dvl) and thereby of Axin and its partner kinases. Sequential phosphorylation of the cytoplasmic domain of LRP6/5 by GSK3 and CK1 stabilizes its binding to Axin. Incorporation of Axin and its partner kinases in the activated receptor complex prevent them from functioning in the destruction complex. Upon stabilization and entry into the nucleus, β -catenin binds to TCF/LEF, displacing the Groucho repressor and recruiting coactivators. The once repressed genes are now activated (ON state). **(b)** In the absence of Sonic (Shh), Indian (Ihh), or Desert hedgehog (Dhh), the Patched 12-transmembrane receptor (Ptch 1 and 2) localizes to the cilium and maintains a second transmembrane protein, Smoothened (Smo), in an inactive state by preventing its trafficking from an intracellular vesicular compartment to the cilium. The kinesin-like protein Kif7 (Costal 2 in flies), which appears to be involved in the removal of the transcription factor Gli (Gli1, 2, and 3; Cubitus interruptus in flies) from the tip of the cilium, accumulates at the base of the cilium in a complex with kinases, which promote phosphorylation and proteolytic inactivation of Gli, and with Suppressor of Fused (Sufu), which inactivates the remaining fraction of Gli (OFF state). Binding of Shh, Ihh, or Dhh to Ptch alleviates the inhibition exerted by the latter on Smo's trafficking to the cilium. This allows Smo to accumulate on the membrane of the cilium. No longer retained at the base of the cilium, Gli translocates to the tip of this extension and is activated by Smo. Finally, activated Gli is transported out of the cilium by the dynein motor and intracellular transport (IFT) particles and moves into the nucleus to activate target genes (ON state). **(c)** Notch signaling. Notch binding exposes a proteolytic cleavage site in the juxta-membrane segment of the extracellular domain of Notch. Mechanical forces, presumably generated by the endocytic machinery that normally operates to removes the receptor from the membrane, help to unravel 3 Lin12/Notch repeats wrapped around the heterodimerization domain in the juxta-membrane segment of the receptor. This process exposes a cleavage site that is attacked by ADAM-metalloproteases. The resulting transient intermediate is finally cleaved by γ -secretase, liberating the intracellular domain of Notch (ICN), which translocates into the nucleus to form a transcriptional activation complex with the DNA-binding factor CSL (Suppressor of Hairless) and Mastermind-like (MAML) co-activators.