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Retroviral Oncogenes: A Historical Primer

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Abstract

Retroviruses are the original source of oncogenes. The discovery and characterization of these genes were made possible by the introduction of quantitative cell biological and molecular techniques for the study of tumor viruses. Key features of all retroviral oncogenes were first identified in *src*, the oncogene of Rous sarcoma virus. These include non-involvement in viral replication, coding for a single protein, and cellular origin. The *myc*, *ras* and *erbB* oncogenes quickly followed *src*, and these together with *pi3k* are now recognized as critical driving forces in human cancer.

Introduction

Most oncogenes that play predominant roles in human cancer were first recognized in retroviruses. This includes the receptor tyrosine kinase epidermal growth factor receptor (EGFR), the small GTPase Ras, the lipid kinase PI3K and the transcriptional regulator Myc. The discovery of retroviral oncogenes during the last four decades has set in motion an era of progress that culminated in our current view of cancer as a genetic disease (Timeline). This view guides and inspires efforts of therapeutic innovation. At this time it appears attractive to look back to the origins of the oncogene field, because they illustrate first principles that are still valid and applicable to the legions of oncogenes encountered today.

There are slightly over 30 retroviral oncogenes, identified almost exclusively in avian and rodent viruses. Their products can be grouped into eight functional classes (Table 1). The unifying functional assignment of these genes and proteins is signaling in the control of cellular replication. From this list, I will discuss a few oncogenes that best illustrate the history of experimental and theoretical breakthroughs but also play critical roles in human disease.

The *src* paradigm

Src was the first retroviral oncogene discovered. This was no accident. Preparations of Rous sarcoma virus (RSV), the avian sarcoma virus carrying the *src* gene, induce readily visible oncogenic transformation within a few days in primary fibroblasts. RSV can be accurately titrated in cell culture with a focus assay developed in 1958[1]. In this assay, the focus number is directly proportional to the amount of virus, hence a single RSV particle can fully transform a host cell, and no cooperation between complementing viruses is required. Soon methods for the biological cloning of RSV particles were developed, the fruit of extensive studies devoted to a replication-defective variant of RSV[2, 3]. A procedure for assaying non-oncogenic but actively replicating avian retroviruses by interference with RSV focus formation had also been devised[4]. In the 1960ies, these were powerful quantitative cell biological tools, and the avian sarcoma viruses were the only retroviruses for which such tools were available. This technological advantage was decisive in the discovery of the first oncogene.

Our knowledge of *src* and of its protein product is the culmination of a long and complex evolution with stepwise, successive contributions from genetics, biochemistry, immunology, and structural biology[5]. Each of these steps built on and complemented the preceding one. Three early genetic observations helped define the problem: First, there are mutants of RSV that instead of transforming the fibroblast host into a rounded cell, induce an elongated, fusiform cell shape[6,7]. Therefore, the phenotype of the transformed cell is under the control of the viral genome. Second, a replication-defective variant of RSV transforms cells without producing infectious progeny, which indicated that the generation of progeny virus is not a prerequisite for oncogenicity[8, 9]. Third, most strains of RSV are non-defective[10, 11] (meaning that they carry all viral replicative genes and the oncogene in the same RNA molecule) (Fig. 1) but spontaneously segregate deletion mutants that still replicate but can no longer transform cells[12, 13]. Reproduction and oncogenicity are separate and distinct functions.

The critical proof for the existence of a viral gene that initiates and maintains the transformed cellular phenotype came from temperature-sensitive mutants. In 1970, a groundbreaking paper in Nature described a mutant of the replication-competent Schmidt-Ruppin strain of RSV that transforms cells at a low, permissive temperature but fails to transform at an elevated, non-permissive temperature[14]. However, production of progeny virus is unaffected by temperature. The mutant pointed to the existence of a viral gene that directs oncogenicity but is dispensable for virus replication. An earlier report of temperature-sensitive mutants of RSV had also shown this temperature-dependence of transformation, but the temperature effect extended to virus replication as well, probably due to multiple mutations[15].

Biochemistry then provided the physical underpinning for the existence of a specific oncogene in RSV. This work depended on a unique property of the RSV genome, its non-defectiveness, as discussed above. All other oncogene-carrying retroviruses are replication-defective, the oncogene having displaced one or several of the viral replicative genes. Mutant RSVs that are transformation-defective, but replication-competent, contain a smaller RNA than the parental virus, suggesting that the lost sequences represent the oncogene[16] (Fig. 1). This hypothesis was supported by genetic mapping experiments. Temperature-sensitive mutations that affect the ability to transform cells were located to the region of the RSV genome that is deleted in the transformation-defective viruses[17]. Biochemical mapping with RNA fingerprinting showed that the deleted RNA was a contiguous fragment, located at the 3’ terminus of the viral RNA genome[18]. Here then was a piece of the retroviral genome, not required for virus survival but essential for oncogenic transformation. The fact that this gene was readily lost from the viral genome showed that it did not convey an evolutionary advantage to the virus.

Where did this accessory piece of information come from? The biochemical experiments had defined a distinct nucleic acid segment of the retroviral RNA genome as the oncogene. This definition then paved the way to a physical isolation of *src*. The discovery of reverse transcriptase in 1970 had shifted the biochemistry of retroviruses from RNA to DNA for which there existed better and more versatile tools of experimentation[19, 20]. One of these tools, subtractive hybridization, was applied to DNA transcripts of non-defective RSV and its replication-defective deletion mutant and resulted in the isolation of *src*-specific DNA sequences. With these sequences it was possible to explore the origin of *src*, using hybridization as a measure of relatedness. These experiments showed that *src* originated from the cellular genome and that it was a cellular, not a viral gene[21]. This fundamental insight, at first ridiculed, was soon extended to other retroviral oncogenes that had been discovered in the meantime, and it changed the landscape of tumor virology[22]. Retroviruses were no longer originators of oncogenic information; they were demoted to mere carriers of

oncogenes that are part of the host genome. This discovery resulted in a huge expansion of the oncogene concept. Any cellular gene with an oncogenic potential that could be activated by a gain of function qualified as an oncogene. Most of these activating genetic events do not involve viruses, but retroviruses that lack an oncogene in their genome can still activate cellular oncogenes by insertional mutagenesis (Box 1).

The essential foundation for the genetics of *src* and of other retroviral oncogenes is the unique life cycle of retroviruses that involves reverse transcription of the virion RNA into DNA and integration of this DNA into the host genome[23-25]. The genetic stability of the oncogenic phenotype induced by RSV had prompted Temin to propose the main elements of such a life cycle as the provirus hypothesis[26, 27]. At the time, this seemed a preposterous idea, because RNA-dependent synthesis of DNA overturned the central dogma and its unidirectional flow of genetic information from DNA to RNA to protein. The sensitivity of retrovirus replication to inhibitors of DNA synthesis supported Temin's claim, but the evidence was far from compelling until the discovery of reverse transcriptase provided firm proof for the provirus hypothesis[19, 20]. Today reverse transcriptase is a routine tool for copying genetic information, so it is important to remember that the generation of a double-stranded DNA copy from virion RNA and the integration of the provirus into the cellular genome are at the root of our understanding of retroviral oncogenes. Proviral integrations are genetic recombination events that can result in the incorporation of a cellular oncogene into the viral genome (Fig. 2.) Such acquisitions are rare. They can occur during viral passage in an animal but are almost never seen in cell culture. There is no experimental system that predictably reproduces spontaneous oncogene acquisition, therefore the molecular details remain hypothetical[28, 29].

The data on the *src* gene had left an important question unanswered: what is the product of this oncogene? Considering the technical arsenal available at the time, it was not an easy question to answer. The phenomenal breakthrough was achieved in 1977 with a Src-specific antibody raised by a technique that was as ingenious as it was non-obvious: injecting a mammalian-adapted RSV into young rabbits[30]. This antibody identified the *src* product as a 60 kD protein which soon was found to have protein kinase activity[31, 32]. The critical insight that differentiated the Src kinase from other protein kinases known at the time came with the discovery of its target amino acid: it is not serine or threonine but tyrosine[33]. The Src protein was the first representative of this new class of tyrosine protein kinases, rapidly followed by EGFR[34]. Today the members of this class are actively studied; they perform key regulatory functions in the cell[35].

In the early 1980ies, the cellular and viral *src* genes were sequenced[36-39]. The viral Src protein differs from its cellular progenitor by a C-terminal deletion that includes a critical regulatory phosphorylation site and by several point mutations. A comparison of the two proteins showed that the cellular Src had a lower kinase and negligible oncogenic activity compared to viral Src[40-42]. The explanation of this difference evolved from the discovery that Src carries two modular protein-protein interaction domains, a phosphotyrosine binding SH2 and a poly-proline binding SH3 domain[43, 44]. Both are crucial for the regulation of Src kinase activity. The molecular details of this regulation were revealed by the crystal structure of Src and of the Src family kinase Hck[45, 46]. Cellular Src requires activation that opens the catalytic domain by disrupting intramolecular interactions involving both the SH2 and SH3 domains. In viral Src, these inhibitory interactions are absent because of the C-terminal deletion and point mutations in the SH3 domain, making viral Src constitutively active.

The kinase activity of Src invited a search for target proteins that would shed light on the normal and oncogenic functions of the enzyme. Multiple direct and indirect Src targets have

been identified, but the search for cancer-relevant functions is far from complete and remains an active area of cancer research[47].

Discovering diversity

For the discovery and characterization of other retroviral oncogenes, some lessons from *src* could be transferred, but there were also new and unique challenges. Other retroviruses that carry an oncogene are replication-defective, in contrast with non-defective RSV. Replication-defective viruses require a helper virus that supplies the missing viral functions in trans. These viruses always occur as mixtures of transforming and of non-transforming helper virus. Because of this dependence on a helper, the genetic experiments are less straightforward than with RSV. However, the structure of the genomes of replication-defective viruses can also offer an advantage: the displacement of viral replicative genes by an oncogene can generate a fusion gene, combining cell-derived and viral sequences and resulting in the production of an oncogenic fusion protein. Such viral-cellular fusion products are readily identifiable with available viral antibodies.

A standard succession of events characterizes the history of most retroviral oncogenes. It starts with the identification of the gene in the virus. Here two criteria first established for *src* have become signature traits of virtually all retroviral oncogenes: cellular origin and non-identity with viral replicative genes. Identification of the protein, cloning and sequencing are the next steps and are extended to the cellular counterpart of the gene. Questions of oncogenic and normal functions are then addressed; such studies build on pre-existing knowledge of the cellular protein. In the early days of oncogene discovery, temperature sensitive mutants played an important role. With the advances in cloning and sequencing, identifying such mutants became less critical. The discovery of oncogenes in DNA viruses also started with temperature-sensitive mutants[31]. However the genetic origins and molecular mechanisms of these oncogenes and oncoproteins stand in contrast to those of retroviruses. The critical differences are summarized in Box 2.

The potent trio in human cancer

Myc

Myc was one of the first oncogenes that emerged after *src*. An RNA fingerprint analysis of the genome of the avian myelocytomatosis virus MC29 had revealed oligonucleotides unrelated to viral replicative genes or to *src*[48]. The same sequences were also identified in the avian retroviruses CMII, OK10 and MH2[49-51]. The sequences were shown not to be scattered over the genome but to form a contiguous stretch of RNA, indicating that they were derived from a distinct gene. A fusion protein combining viral Gag sequences of MC29 with the presumptive new oncoprotein was rapidly identified with viral antibodies[52]. DNA sequencing had just been invented[53, 54] and within a few years was applied to the viral and the human *myc* genes[55, 56].

A first important insight into the functions of the Myc protein came with the discovery that it is localized in the cell nucleus[57]. One of the possible roles for this protein was to act as a transcriptional regulator. However, the failure of Myc to bind DNA under physiological conditions could not be easily reconciled with this idea. The impasse was broken with the discovery of the Max protein as an obligatory dimerization partner of Myc. Only the Myc-Max heterodimer can bind DNA with high affinity and affect transcription[58]. Max is the required partner of several Myc-related proteins, forming the central component of a regulatory network that can stimulate as well as repress transcription[59]. The workings of this network are based on selective dimerization. Max forms DNA-binding homodimers, but

none of its partners have that ability, so they depend on dimerization with Max to bind DNA and to regulate transcription.

The identification of Myc target genes has been challenging, because thousands of copies of its short DNA target sequence, the E-box CACGTG, are present in vertebrate genomes. A recent study using a combination of chromatin immunoprecipitation and deep sequencing identified over 7000 genomic binding sites in a cell that overexpresses Myc[60]. Cellular levels of Myc are tightly regulated, and overexpression leads to uncontrolled cell replication or to apoptosis, depending on contextual factors that are not completely understood.

There are three *MYC* genes in the human genome, *c-MYC L-MYC* and *N-MYC*[55,61, 62], The cellular homolog of the retroviral *myc* gene is *c-MYC*. *N-MYC* and *L-MYC* were discovered later in human cells; they play important roles in diverse human cancers[63]. The two representative mechanisms for the involvement of *MYC* in human disease came to light from studies of Burkitt lymphoma and neuroblastoma. Burkitt lymphoma cells always carry a chromosomal translocation that places *c-MYC* under the control of an immunoglobulin enhancer[64]. The result is increased transcription of *c-MYC* driven by the immunoglobulin-regulatory sequences. The discovery of c-*MYC* rearrangements in a human lymphoma was the first indication that cellular counterparts of retroviral oncogenes are involved in the pathogenesis of human disease. In neuroblastoma, the *N-MYC* gene is frequently amplified, and the expression of *N-MYC* is correspondingly elevated[65]. Upregulated transcription and amplification are the two mechanisms for the oncogenic gain of function in the *MYC* genes. Mutations in the coding region of *MYC* do not play a significant role in human cancer.

Recent studies indicate that the role of *MYC* in cancer goes beyond the situations where it appears to be the primary driver. c-*MYC* has emerged as the mediator of resistance to inhibitors of PI3-kinase, and dominant negative Myc causes regression of Ras-induced tumors in mice[66, 67].

Ras

The discovery of *ras* faced a different set of challenges. The two principal viruses carrying this oncogene, Harvey sarcoma virus and Kirsten sarcoma virus, arose by recombination with the host genome during passage of murine leukemia virus in rats[68, 69]. The rat-derived oncogene in these replication-defective viruses is not fused to viral genes, and in the absence of such viral markers, the Ras protein could not be identified with viral antibodies. However, animals bearing Kirsten or Harvey sarcomas generated antibodies that interacted with the 21 kD product of the *ras* gene[70]. The Ras protein was also obtained by in vitro translation of the viral genome[71]. Cloning and sequencing of the Harvey and Kirsten sarcoma viruses defined the viral and rat-derived contributions to these recombinant genomes and completed the molecular information on the viral *ras* gene[72-74]. The two *ras* genes, *Kras* and *Hras,* do not differ in the properties we consider here.

A first clue about biochemical functions came from the observation that Ras has guanine nucleotide binding activity, a finding that quickly culminated in the discovery that Ras is a GTPase[75-78]. In its active form, Ras is bound to GTP, and binding could be enhanced by activated EGFR[79]. How could Ras be integrated into cellular signaling and what was responsible for the oncogenic activity of that protein? Half of the answer came from linking an adaptor protein and a guanine nucleotide exchange factor to the activity of Ras[80, 81]. The SH2 domain of the adaptor, GRB2, binds to phosphorylated tyrosine, typically in a receptor tyrosine kinase (such as EGFR) and with its SH3 domain GRB2 can recruit the guanine nucleotide exchange factor (GEF). This GEF stimulates the release of GDP from Ras and thus enhances loading with GTP. This sequence of interactions established the upstream signaling path that leads to Ras activation[82].

The other half of the answer, outlining the downstream activities of Ras, was initiated by the discovery of the *raf* oncogene in a murine sarcoma virus [83, 84] and of its avian homolog *mil* in the chicken tumor virus MH2[85, 86]. The Raf protein binds to GTP-loaded Ras and connects it to the MAP kinase pathway[87-89]. Activated Ras also binds to the catalytic subunit of PI3K, and this interaction is important for PI3K signaling[90]. Although numerous somatic mutations occur within the catalytic subunit of human PI3K, no mutations have been found in the Ras binding domain, suggesting that interaction with Ras is essential for the function of PI3K. The oncogenic activities of PI3K are discussed in greater detail below.

The GTPase activity of Ras is stimulated by association with a GTPase-activating protein (GAP)[91]. Ras acquires oncogenic potency by point mutations affecting residues 12 and 61. These mutations disturb the interaction with GAPs. They reduce the rate of GTP hydrolysis and result in elevated levels of the active, GTP-bound Ras[78, 91-96]. An important aspect of all Ras activity is cellular localization. Ras is positioned at the inner side of the plasma membrane, and this location is essential for activity[97]. The interaction with membrane lipids is mediated by an obligatory posttranslational isoprenylation of the protein[98, 99].

A series of exciting and dramatic experiments linked Ras directly to human cancer. Initially, transfer of DNA from human cancer cells was found to transform recipient mouse cells. Integration of the source DNA into the genome of the recipient cells was verified by the presence of readily identifiable repetitive human sequences[100, 101]. The breakthrough came with the discovery that the transforming DNA derived from human cancer cells is homologous to *ras*[102-105]. This discovery also linked a retroviral oncogene that in experimental systems induces sarcomas to epithelial cancers in humans. The activity of retroviral oncogenes is clearly not restricted to fibroblasts or hematopoietic cells but includes epithelial cells. Oncogenic activity in DNA transfection experiments also revealed the existence of a third *ras* gene, *Nras,* in the human genome[106].

Within the span of two years, 1982 to 1984, the findings of *c-MYC* in Burkitt lymphoma, *N-MYC* in neuroblastoma and oncogenic *RAS* in diverse human cancers, linked the two retroviral oncogenes unequivocally to human disease as probable causative agents. These connections between retroviral model systems and human cancer could have been predicted from the cellular origin of retroviral oncogenes, but they came as a surprise nonetheless. The discoveries with *MYC* and *RAS* have special historical significance, because they consolidated the view of cancer as a genetic disease.

ErbB

The story of *ErbB* takes us back to the early days of retrovirology. *ErbB* is the oncogene of avian retroviruses that induce an acute form of erythroid leukemia called erythroblastosis. One of these viruses, referred to as strain R, dates from 1935[107]. It contains two cell-derived oncogenes, *erbA,* a hormone receptor, and *erbB*[22, 108-110]. For the induction of oncogenic growth, *erbA* is auxiliary but dispensable, whereas *erbB* is both necessary and sufficient, because a separate isolate of erythroblastosis virus, strain H, carries only the *erbB* oncogene yet does not differ significantly from strain R in tumor spectrum or pathogenic potency[111]. Studies on additional independent isolates of avian erythroblastosis virus have supported this dominant role of *erbB* in oncogenesis[112]. Analyses of the cloned genomes and of in vitro translated proteins from strain R and H viruses suggested that the viral ErbB protein is produced by a fused mRNA consisting of a very short N-terminal viral sequence and part of the cellular erbB[113-116]. In addition, specific antibodies detected a 74 kD transformation-specific protein in cells infected by avian erythroblastosis virus[117, 118].

At the time, this information on chicken viruses seemed almost esoteric, but it has acquired great relevance for human disease. Within a period of a few months in 1984, the viral ErbB

protein was found to be glycosylated and phosphorylated and structurally related to tyrosine kinases. It showed sequence features of tyrosine kinases and was localized as an integral membrane protein at the cell surface[115, 119-125]. Finally and most importantly, sequence analysis revealed both close homology to EGFR and a large deletion in the extracellular domain of viral ErbB[126, 127]. In addition to the N-terminal truncation, viral ErbB proteins also show mutations in the kinase domain located in the C-terminal cytoplasmic portion of the protein. Viral ErbB functions as a constitutively active receptor tyrosine kinase; the activity is ligand-independent and also requires the kinase domain mutations. The mutations in viral ErbB do not cause a mere quantitative enhancement of the same signaling pathways that are controlled by cellular EGFR but induce qualitative changes in the spectrum of signaling targets. These changes are critical to the oncogenic potency of the protein[112].

EGFR can function as an oncogenic “driver” in diverse human cancers. Mutations that mechanistically resemble those seen in viral ErbB occur in the EGFR of glioblastoma multiforme and non-small cell lung cancer. About 50% of glioblastomas carry the EGFRvIII mutant which has lost a large portion of the extracellular domain and no longer binds ligand but signals constitutively, addressing targets that are different from those of wild-type EGFR[128]. Such a cancer-specific mutation in a kinase would appear to be an ideal therapeutic target. However, the clinical experience with inhibitors of EGFR in glioblastoma has been uneven, with tumor shrinkage linked to the co-expression of EGFRvIII and of the tumor suppressor PTEN[129]. In non-small cell lung cancer, EGFR mutations are located in the kinase domain and lead to constitutive autophosphorylation and activation. Such cancers, seen mostly in non-smokers, are uniquely sensitive to EGFR inhibitors but regularly develop resistance to these drugs[130-133].

The human genome contains three additional genes that are closely related to *EGFR*, *HER2, HER3* and *HER4*[134-136]. The oncogenic potential of *HER2* was discovered in transfection experiments with DNA from human neuroblastoma cells. The cell-transforming gene in these experiments was identified as *EGFR*-related with an activating mutation in the transmembrane domain[137]. *HER2* is frequently amplified in breast cancer[138]. A humanized monoclonal antibody that inhibits *HER2* signaling (trastuzumab) shows substantial clinical benefit and is now part of standard therapy for *HER2+* breast cancers[139]. *HER3* is unusual in that it has extremely low kinase activity and functions predominantly as a dimerization partner of other EGFR family members[140]. *HER4* differs from the other EGFR-related genes in that it mediates cellular differentiation and inhibits replication[141].

Oncogenes from slaughterhouse viruses

In the 1980ies, it became clear that avian retroviruses are a particularly rich source of oncogenes. In chickens, retrovirus infection is common and widespread. Most of these viruses are replication-competent, do not carry an oncogene, and induce tumors (mostly lymphoid leukosis) by insertional activation of a cellular oncogene[142]. But occasionally the genetic recombination between virus and host results in the incorporation of an oncogene into the viral genome. Such an acquisition converts the virus from slowly oncogenic to rapidly oncogenic, resulting in solid tumors that are distinct from the endemic leukosis (Fig. 2). Chicken slaughterhouses process up to 30,000 birds a day; each of these is inspected for signs of disease. At these numbers, even rare viral-cellular recombination events that result in aggressive cancers can be found.

Slaughterhouse veterinarians have been the source of several new, rapidly oncogenic retroviruses, and from these viruses, three new oncogenes were isolated: *jun, qin* and *pi3k*[143-145]. The discovery of the retroviral Jun, the finding of its cellular counterpart in the transcription factor complex AP1, and the identification of the tight partnership with the

oncoprotein Fos (discovered separately in the Finkel-Biskis-Jinkins murine sarcoma virus[146]), marked an exciting period in the history of oncogenes. The story of these events has been told elsewhere[147, 148]. Qin (also referred to as FOXG1) is a representative of the winged helix or FOX family of DNA-binding proteins which function as developmental and metabolic transcriptional regulators[144]. Although Qin has not been implicated in human cancer, the FOX protein family is linked to human disease by the involvement of *FOXO1* in a chromosomal translocation that contributes to the development of alveolar rhabdomyosarcoma, an aggressive childhood tumor. Another member of the family, FOXA1 controls the sexual dimorphism seen with hepatocellular carcinoma[149]. A broader survey of the association of FOX proteins with cancer has been presented in a recent review[150].

Among the oncogenes derived from these recently isolated avian retroviruses, *pi3k* stands out, because its cellular counterpart controls signaling pathways that show aberrant activation in most human tumors and contain promising drug targets. The retroviral *pi3k* has served as an important model for the oncogenic activities of human PI3K. There has long been a suspicion that the lipid kinase PI3K may have oncogenic potential. In early work, the oncoproteins of DNA viruses as well as Src were shown to be associated with a cellular lipid kinase activity[151-155]. The interaction was essential for the oncogenicity of these viral proteins. The transformation-associated lipid kinase activity was then found to catalyze the phosphorylation of the D3 position of the inositol ring, defining a novel enzymatic activity that generates phosphatidylinositol 3 phosphates[156]. The fundamental importance of this finding was not realized until much later when it became clear that this PI3K was at the center of an extensive and versatile cellular signaling network that becomes corrupted in most cancers[157, 158]. Direct evidence for the oncogenicity of PI3K came with the discovery of an avian hemangiosarcoma virus, ASV16, in a tumor obtained from a chicken processing plant. ASV16 is a replication-defective virus with a genome that encodes a single protein encompassing the p110α isoform of the catalytic subunit of chicken PI3K fused N-terminally to viral *gag* sequences [145].

The viral *pi3k* harbors several mutations in the p110α coding sequence, but these do not induce a gain of function and are irrelevant for oncogenic activity. Oncogenicity depends on the N-terminal Gag sequences[159]. The function of the *gag* sequences was first thought to facilitate membrane localization and to bring the enzyme in direct contact with its substrate. Support for this idea comes from the observation that a myristylation signal added to the N-terminus of cellular p110α also has a strongly activating effect and makes the protein oncogenic. However, recent data cast doubt on this interpretation. Even random amino acid sequences, added to the N-terminus of p110α, are activating, there is no requirement for a membrane localizing function in these sequences. Rather, these N-terminal additions appear to induce a conformational change that mimics activation of p110α by upstream signals[160]. A similar mechanism for constitutive activity is seen with cancer-specific mutations that carry an amino acid substitution in the helical domain of p110α [161-164]. In such mutants, the inhibitory interaction with the regulatory subunit p85 is disrupted.

PI3K has moved into the limelight as a cancer target because of frequent cancer-specific genetic and epigenetic changes that result in enhanced activity. These include loss of function in the PI3K antagonist and tumor suppressor PTEN, elevated activity and amplification of PI3K and gain-of-function mutations in the catalytic subunit p110α[165-170]. Enhanced PI3K signaling is a driving force in cancer development. Academic laboratories and the pharmaceutical industry have responded to this situation by generating small molecule inhibitors of PI3K, and several of these are currently in advanced clinical trial[171].

From simplicity to complexity

As we look at the history of oncogenes and their significance for human disease, two developmental trends unfold (see Timeline). One is a steady increase in relevance, the other a broadening of the concept of cancer as genetic disease. Rapidly tumorigenic retroviruses that carry oncogenes have been found mostly in chickens and in mice. Early work with these viruses focused on cancer as an infectious condition. But the concepts and mechanisms uncovered with readily transmissible animal tumors appeared not applicable to the human situation. Therefore the significance of identifying specific oncogenes in viruses was at first exclusively experimental and theoretical. These discoveries showed that normal vertebrate cells could be transformed into cancer cells by the action of a single gene. This was a revolutionary insight, offering simplicity and the prospect of complete molecular understanding.

Retroviral oncogenes remained mainly experimental tools with uncertain ties to human cancer until 1976, when oncogene sequences were found in cellular genomes[21]. This discovery transformed the field. Retroviruses with their ability to acquire and transduce host genes became just one out of several possible ways by which a cellular oncogene can be activated. In principle, any genetic change in the cellular oncogene is potentially activating. The next transformative step on the way to relevance established the direct connection between the cellular versions of retroviral oncogenes and human cancer. The key discoveries were finding transcriptional activation of *c-MYC* by chromosomal translocation in Burkitt lymphoma, amplification of *N-Myc* in neuroblastoma and identification of activated *RAS* in DNA from human cancer cells (see also Table 2)[64, 65, 102-104]. These findings were fundamental in revealing cancer as a genetic disease. They also appeared like a reductionist triumph, explaining cancer with changes in one or at most a few genes that would generate novel and highly specific therapeutic targets.

This development took retroviral oncogenes from obscurity to prominence. But in subsequent years, genetic changes that affect the oncogenic cellular phenotype have steadily increased in type and in number. If we define an oncogene as a replication-promoting gene that encodes a protein and shows gain of function in cancer, then the number of such genes is probably in excess of a thousand and growing. A comprehensive view of cell-autonomous genetic alterations in cancer further includes tumor suppressors which contribute to the oncogenic phenotype by a loss of function, often as a result of epigenetic changes[172]. Micro RNAs have added another layer of complexity with both pro- and anti-oncogenic effects[173]. The vast extend of the non-coding transcriptome including large antisense transcripts and pseudogenes is beginning to be functionally explored and likely holds even more surprises[174]. The cancer genome project has uncovered an unexpected multitude of genetic changes in all cancers, revealing mutational landscapes that are characteristic of tumor origin and histology. A similar trend toward complexity can be seen in our understanding of oncoprotein functions. All these proteins show multiple activities, generating diverse signals. A complete molecular understanding of how these activities initiate and maintain cancer remains a challenge.

The complexity of genetic alterations becomes irrelevant in certain cancers that show a striking and apparently irreversible dependency on a single, dominant genetic change. Such oncogene addiction can be the basis for stunning clinical successes with targeted therapy[175]. However, it is questionable whether the model of cellular addiction to a single oncoprotein is applicable to a broad spectrum of cancers. In the more common scenario, complexity rules and dictates a therapeutic strategy that relies on targeting a few critical drivers of the oncogenic cellular phenotype. Success depends on the identification and validation of these drivers as cancer targets[176, 177]. These efforts are guided by the general principle that it is

easier to correct a gain of function than to restore a loss of function. Oncogenes remain very much in the line of fire.

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This review is dedicated to Harry Rubin. His pioneering work started the field.

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Text Box 1

Activation of cellular oncogenes by insertional mutagenesis. Retroviruses of the subfamily oncovirus that lack an oncogene in their genome are able to induce cancer by insertional mutagenesis[178]. In this process, a provirus integrating in the vicinity of a cellular oncogene functions as positive transcriptional regulator and thus activates the latent tumorigenic potential of the cellular gene. Insertional, retrovirus-mediated mutagenesis is a slow process that occurs only in the vertebrate host and typically requires prolonged and extensive viral replication and integration. It has been widely used to reveal the oncogenic potential of cellular genes that are never transduced by viruses[179].

Text Box 2

Contrasting mechanisms in viral oncogenicity: RNA versus DNA viruses. The oncogenes of retroviruses are cell-derived; they deregulate cellular signaling and transcriptional controls. In contrast, oncogenic DNA viruses, including the papilloma viruses, polyoma virus, simian virus 40 (SV40) and some tumor-inducing adeno- and herpesviruses carry their own oncogenes. Some of the best understood among these disrupt the retinoblastoma (Rb) protein-mediated control of the cell cycle[180-184]. During the G_1 phase of the cell cycle, the Rb protein is hypophosphorylated and bound to E2F transcription factors, forming transcriptional repressor complexes. These are essential components of the restriction point that prevents entry into the S phase of the cell cycle. Upon mitogenic stimulation, cyclin-dependent kinases phosphorylate Rb, thus releasing the E2F proteins which then initiate a transcriptional program that marks the entry into the S phase. Several DNA viral proteins bind to hypophosphorylated Rb: the E1A protein of adenoviruses, the large T antigen of SV40 virus and the E7 proteins of oncogenic human papilloma viruses. These interactions free the E2F proteins without a requirement for mitogenic signals and start the S phase of the cell cycle. Proteins of oncogenic DNA viruses can also operate as constitutive signaling receptors or can interfere with the functions of inhibitors of cyclin-dependent kinases[185].

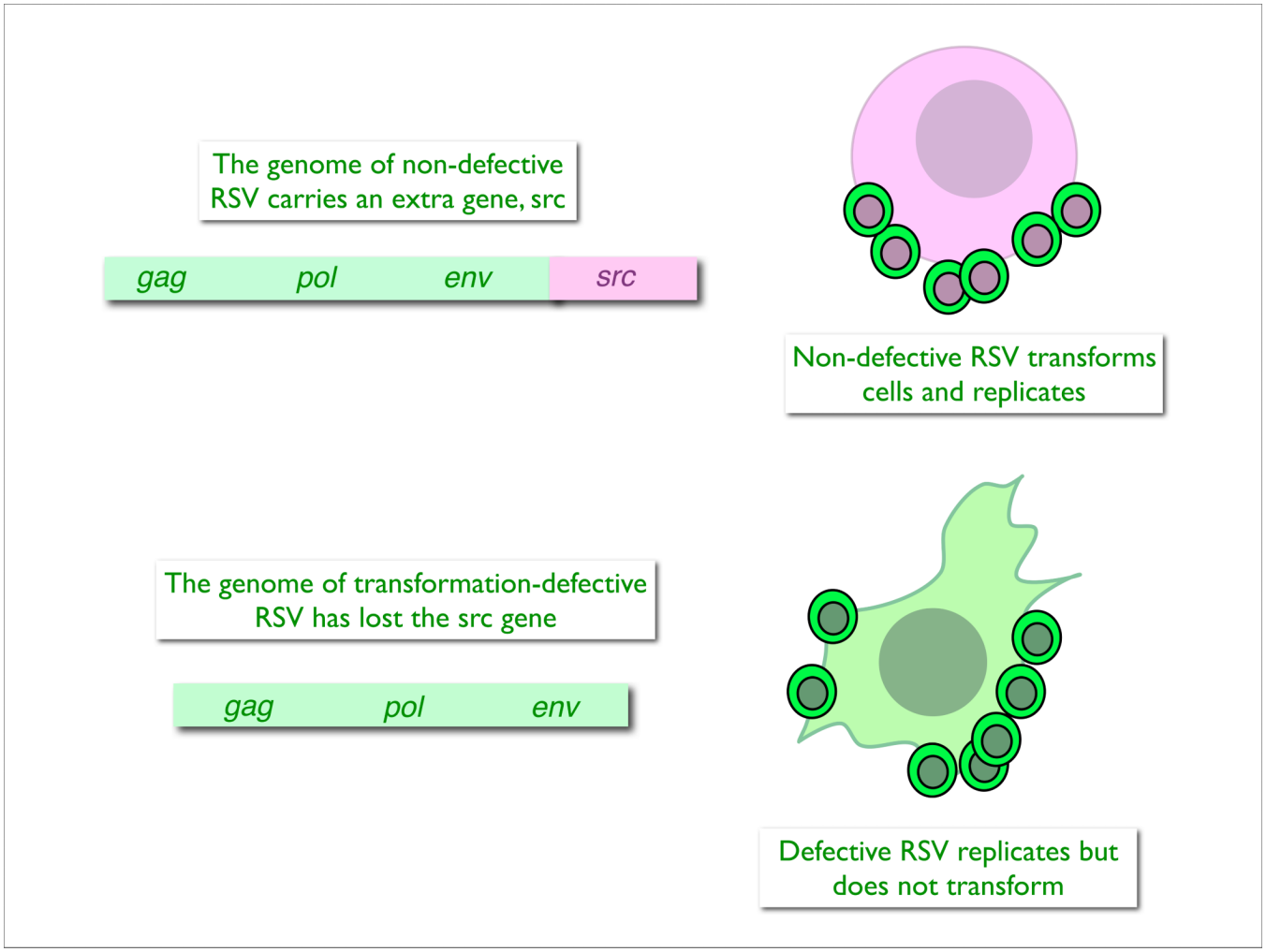


Fig. 1. The biochemical definition of src

The protein-coding regions of non-defective RSV encompass the complete information required for virus reproduction (*gag, pol, env*) and the information needed for oncogenic transformation (*src*). The RSV-infected cell produces progeny virus and is transformed. During the replication of RSV, mutant viruses are generated that are no longer oncogenic but contain all the essential viral genes and are fully capable of producing progeny virus that fails to transform cells in culture.

A comparison of the genome sizes of parental RSV and transformation-defective mutant shows that loss of oncogenicity is correlated with loss of about 20% of the genome. The lost sequences represent the *src* gene which is not essential for virus replication. Using DNA transcripts of these two viral genomes, *src* sequences can be purified by subtractive hybridization.

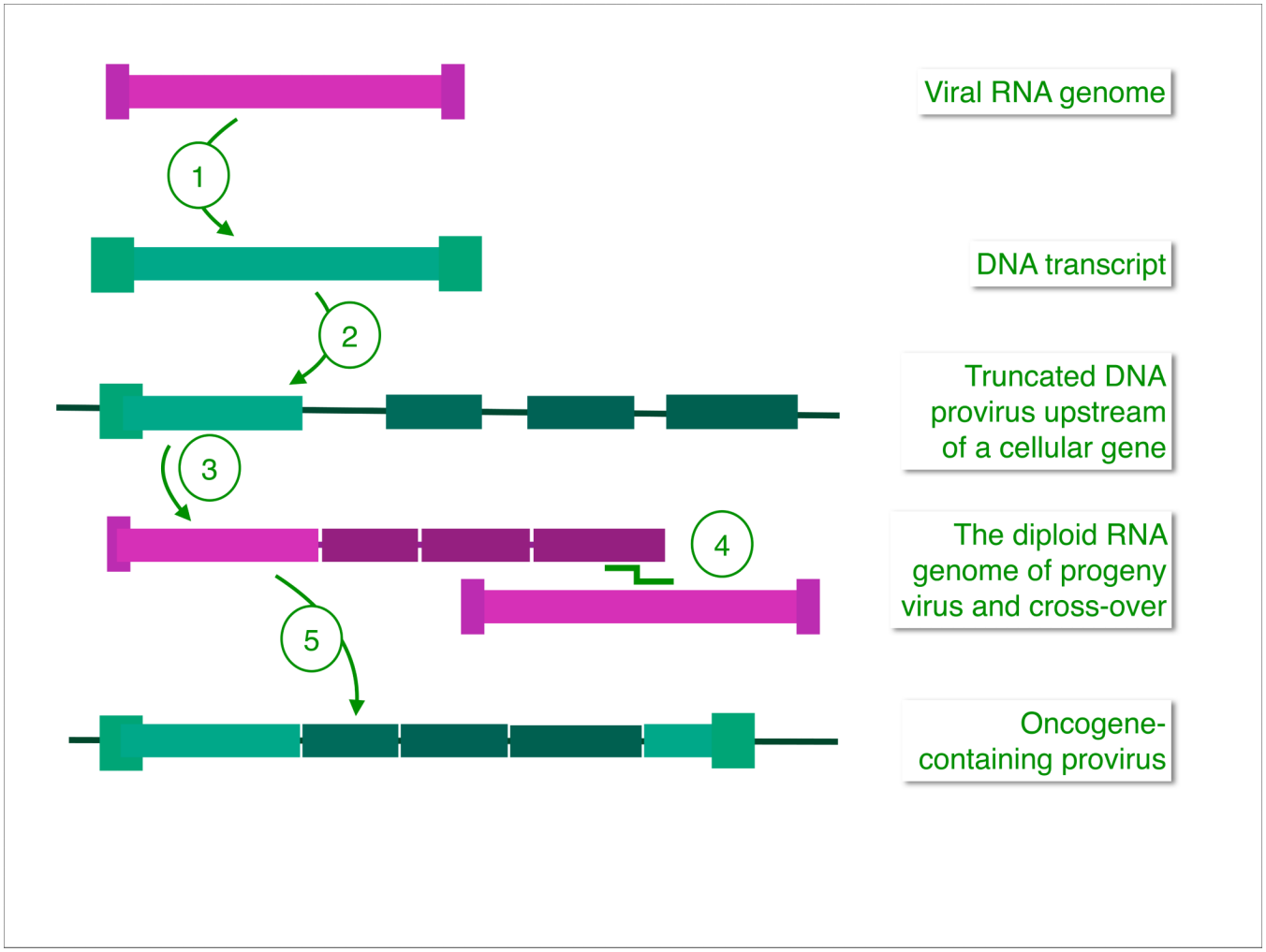
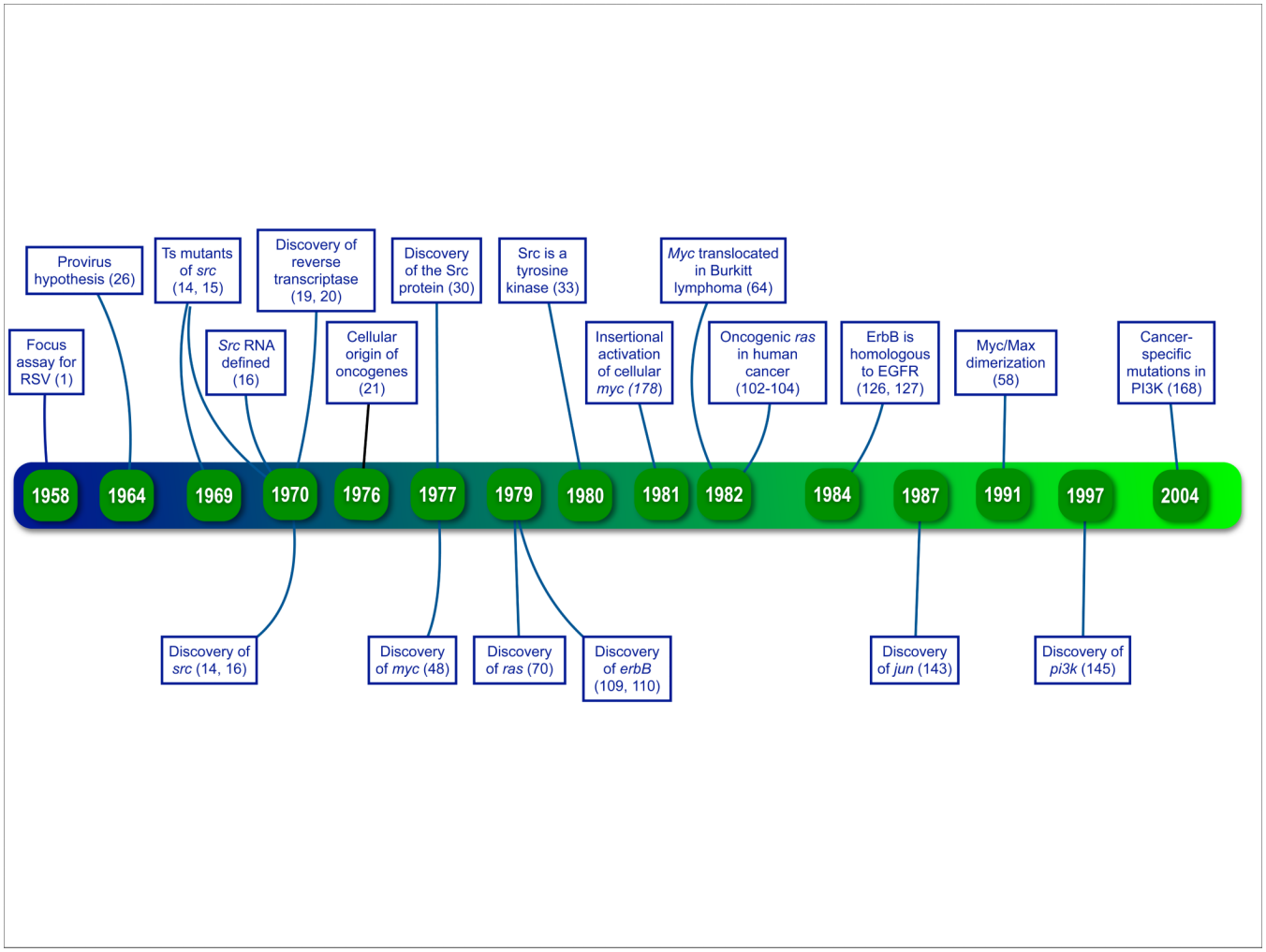


Fig 2. Acquisition of a cellular oncogene by a retroviral genome

(1) Virion RNA is transcribed into double-stranded DNA. (2) An accidentally truncated provirus is located upstream of a cellular gene. (Cellular exons indicated in dark green.) (3) A spliced fusion transcript of viral and cellular sequences is packaged into a progeny virion together with a wild type viral genome. (Retroviruses are diploid.) (4) During next-generation reverse transcription, recombination between the two genomes generates a DNA provirus that encodes the cellular oncogene fused to viral sequences (5). As a result of acquiring cellular sequences, viral information essential for the production of progeny has been lost, and such highly oncogenic viruses are replication-defective, with the exception of most strains of RSV which can reproduce and are oncogenic. This mechanism for the acquisition of cellular sequences is hypothetical but in agreement with available experimental data.



Timeline. Retroviral oncogenes: 50 years of discovery

The top banners refer to transforming discoveries that have shaped the development of the field. The bottom banners mark the years in which the important oncogenes highlighted in this article were identified.

Table 1

Functional classes of retroviral oncoproteins

Functional class	Representative example	Source virus
Growth factor	Sis, platelet-derived growth factor	Simian sarcoma virus
Receptor tyrosine kinase	ErbB, epidermal growth factor receptor	Avian erythroblastosis virus
Hormone receptor	ErbA, thyroid hormone receptor	Avian erythroblastosis virus
G-protein	H-Ras, GTPase K-Ras, GTPase	Harvey sarcoma virus Kirsten sarcoma virus
Adaptor protein	Crk, modular signaling link	CT10 avian sarcoma virus
Non-receptor tyrosine kinase	Src, signaling protein kinase Abl, signaling protein kinase	Rous sarcoma virus Abelson murine leukemia virus
Serine-threonine kinase	Akt, signaling protein kinase Mos, signaling protein kinase	Akt8 murine thymoma virus Moloney murine sarcoma virus
Transcriptional regulator	Jun, component of the AP-1 (activator protein 1) complex Fos, component of the AP-1 (activator protein 1) complex Myc, transcription factor	Avian sarcoma virus 17 Finkel-Biskis-Jinkins murine sarcoma virus Avian myelocytomatosis virus MC29
Lipid kinase	Pi3k, phosphatidylinositol 3-kinase	Avian sarcoma virus 16

Table 2

Oncogenes first identified in retroviruses can function as drivers in human cancer

Oncogene	Mechanism of activation	Cancer type	References
MYC	Increased transcription	Burkitt lymphoma	64, 186
	Increased transcription	B-cell lymphoma	187, 188
	Amplification	Neuroblastoma	65, 189
	Amplification	Medulloblastoma	190 - 192
EGFR	Mutation	Glioblastoma	128, 193
	Mutation	Non-small cell lung cancer	130 - 133
RAS	Mutation	Pancreatic cancer	194 - 196
RAF	Mutation	Melanoma	197