

Review

Cancer Genes: Origins and Directions

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Abstract

Avian viruses formed the foundation of early retrovirology. The historical line extends from the discovery of the first sarcoma virus by Peyton Rous to the quantitative determination of oncogenic activity in cell culture by the focus assay. As a viral group, avian retroviruses offered exclusive advantages that allowed the assembly of a unique and powerful tool chest for the analysis of viral activity. Among the fundamental discoveries facilitated by these tools were viral and cellular oncogenes, cell surface receptors, virus-specific detection of inapparent infection, high-frequency genetic recombination between retroviruses, and the genetic maps of simple retroviruses. The work with avian viruses was soon complemented by research on mammalian retroviruses, and several oncogenes that became the basis of successful targeted therapies were defined. The field of cancer genes is at a point of transition. Future developments will be driven by new technologies and interpretations. They will also require a more comprehensive approach.

Keywords: oncogenes; SRC; MYC; transduction; transcription

1. Introduction

The purpose of this communication is to describe, analyze and assess the origins and consequences of cancer genes. The commentary consists of two parts, “Origins” and “Considerations”. The section “Origins” is not a comprehensive historical review or a coherent outline of discoveries, but a targeted and intentionally narrow selection of highlights that illuminate sources and growth in the field of cancer genes. The emphasis is on avian retroviruses, because this viral group provided unique technical advantages that made it the driving force of the field. The subject is restricted to genes that induce oncogenesis by gain of function; it does not include the broad category of tumor suppressor genes, which act by loss of function. The section “Considerations” is an attempt to point out developments that open new perspectives, but also to focus on deficiencies in our present understanding of cancer.



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2. Origins

Research on avian tumor viruses defined the leading edge of early retrovirology. Two elements contributed to the prevalence of avian viruses at the onset of retrovirology: history and serendipity.

2.1. The Historical Origin

Tumor virology started with the discovery of a virus that could cause solid tumors in vertebrate animals. This discovery, made by Peyton Rous in 1910, marked the beginning of a scientific development that led to the recognition of cancer as a genetic disease [1].

In the first five decades after 1910, work with Rous sarcoma virus (RSV) was conducted exclusively in animals. It included studies on expanding the viral host range from chickens to other animal species and observations on the immune response to the virus [2–5]. By the middle of the last century, work with RSV had created a formidable body of knowledge, and innovative research was being pursued in several areas [6–8]. Then, *in vitro* cell culture, notably that of chicken embryo fibroblasts, became a widely adopted laboratory tool [9–11]. This technical innovation moved the attention in animal virology from animals to cultured cells. The critical impulse for that change came from phage research. The main representatives of that movement are the groups around Delbrück, Lwoff and Luria [12–15]. They followed strictly reductionist approaches and emphasized quantitation over description, ushering in the concept of quantitative biology. The principal technique of that scientific approach was the phage plaque assay [16]. Plaques are discrete areas of bacterial lysis induced by a single replicating viral particle. The phage plaque assay had been adapted to cytotoxic animal viruses, with poliovirus and monkey kidney cells as first examples [17]. The approach was extended to Rous sarcoma virus, but instead of cell lysis, discrete foci of morphologically transformed cells in monolayers of avian fibroblasts became the indicator of viral infection and oncogenic activity [18]. This focus assay induced a fundamental change in the thinking of tumor virologists and became the backbone technique for early retrovirology. It is rapid, reliable and simple (Figure 1) [19]. In today's cancer research, the focus assay is a fringe technique, but it has found new and valuable applications, thanks to novel vectors based on the RSV genome. It can now be used with a large number of cancer-inducing DNA sequences [20,21].

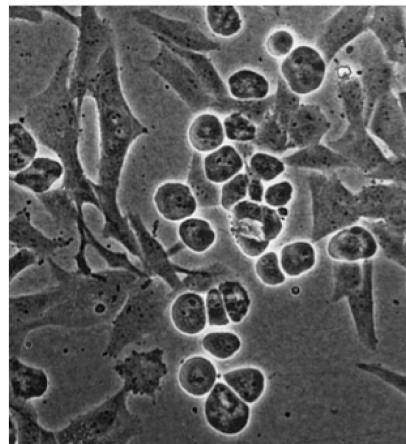


Figure 1. Chicken embryo fibroblasts infected by Rous sarcoma virus (RSV) form a focus of morphologically altered cells (adapted from [19]).

2.2. Serendipity

The serendipitous aspects contributing to the early prevalence of the avian field emerged from the unique structural and biological properties of avian retroviruses. These properties provided the components for building an exclusive, powerful, and novel set of tools and, thus, contributed decisively to our understanding of retroviruses.

The most important of these unusual properties of the avian retroviruses is the non-defectiveness of the RSV genome, combining the information needed for viral replication with the ability to transform cells [22]. RSV is unique in this respect. All other retroviruses carrying cellular oncogenes have exchanged viral genetic information for cellular sequences and, consequently, are defective in replication. But genomic non-defectiveness is a prerequisite for genetic analysis; and the groundbreaking studies of retroviral gene function and gene mapping depended on it. The singularity of non-defective RSV could reflect a

unique feature of the viral capsid that allows the accommodation of a genome carrying an additional, nonviral gene.

Notations for RSV in the scientific literature always include a “strain” designation. The common strains are the Prague, Carr–Zilber, and Schmidt–Ruppin strains and the presumably independent viral isolate of B77. All of these are non-defective. The Bryan Hi-titer strain is an exception to this rule, carrying a defective genome that lacks the information for the viral glycoprotein. This defectiveness probably resulted from a method of virus production that selected for rapid growth and high yield. It is a strategy bound to generate short, defective viral genomes that depend on a ubiquitous helper virus that lacks an oncogene.

The second and less obvious of these serendipitous features consists of the multiplicity of viral surface glycoproteins. Avian retroviruses occur in nine distinct surface glycoproteins (Table 1) [23–27]. Each of these glycoproteins defines a viral subgroup and targets a specific cell surface receptor. Several of the most common cell surface receptors have been molecularly cloned. If they encode a dispensable gene, that gene can be deleted or inactivated, generating cells and animals that are genetically resistant to the corresponding subgroup of avian retroviruses (Table 2). More importantly, the viral glycoproteins give rise to the phenomenon of viral interference [28–30]. A cell infected with an avian retrovirus produces an excess of viral surface glycoprotein, which presumably saturates the cell surface receptor. Consequently, these cells become resistant to superinfection with a virus of the same subgroup but remain susceptible to infection with viruses of other subgroups (Table 3). Before DNA sequencing and nucleic acid hybridization became routine experimental techniques, viral interference was a specific and powerful tool to discover inapparent infection. Such inapparent infections are common with retroviruses, which can replicate in cultured cells without inducing any change in cell morphology or growth rate. However, their presence and subgroup affiliation can be readily detected by viral interference. Detection of inapparent infections is essential for genetic investigations. Viral glycoproteins and mutated cell surface receptors were also instrumental in the discoveries of high-frequency genetic recombination and of phenotypic mixing between retroviruses [31–33].

Table 1. Viral surface glycoproteins define avian retroviral subgroups.

Subgroup	Viral Glycoprotein
A	gp85-A
B	gp85-B
C	gp85-C
[...]	
J	gp85-J

Table 2. Viral surface glycoproteins interact with cell surface receptors.

Subgroup	Cell Surface Receptors
A	tv-a (dispensable gene)
B	tv-b (dispensable gene)
C	tv-c (dispensable gene)
[...]	
J	tv-j (dispensable gene)

Table 3. Viral interference.

Pre-Infecting Virus		Excluded Super-Infecting Virus					
Subgroup	A	B	C	D	E	J	
A	★						
B		★					
C			★				
D				★			
E					★		
J						★	

The findings of multiple glycoproteins, cell surface receptors, viral interference, and genetic non-defectiveness could be dismissed as merely archival information (Table 4), yet these tools played critical parts in experiments that led to fundamental discoveries. Here are two further examples:

Table 4. Important features of avian retroviruses.

• A non-defective sarcoma virus genome • The multiplicity of distinct surface glycoproteins • Specific interference by glycoprotein-receptor occupancy • Cellular resistance caused by receptor mutation.
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A fast and reliable identification of viral surface proteins was essential in the experiments that showed early DNA synthesis in retroviral infection is virus-specific, which suggested the possible presence of a DNA polymerase in the viral particle [34]. It triggered the race that led to the discovery of reverse transcriptase [35,36].

The ability to detect inapparent infections led to the identification of the first oncogene, *src*. Serial passage of non-defective RSV commonly generates two types of progeny: one identical to the parental virus, capable of active replication and of inducing oncogenic cellular transformation, and a second one that produces infectious progeny without the ability to transform [30,37]. At the time, the transformation-defective virus was detectable only by viral interference, and this method revealed that, eventually, the transformation-defective virus prevails and constitutes most of the progeny virus. A possible reason for this enhanced fitness of the transformation-defective variant is a smaller genome that grows faster and, thus, replaces the parent. It has lost the genetic information that is essential for oncogenic transformation.

2.3. The *src* Paradigm

A comparison of genome length between transforming and transformation-defective viruses showed that this hypothesis is correct and that the RNA of the transforming virus is larger than that of the transformation-defective virus (Figure 2) [38]. This observation signaled the discovery of the viral oncogene *src*, the first principal proof of a molecular underpinning of the cancer gene hypothesis [38,39].

Reverse transcriptase was discovered at the same time, and it opened the door to the molecular genetics of retroviruses [35,36]. Single-stranded DNA generated by reverse transcriptase from the genome of transformation-competent RSV was subjected to subtractive hybridization with the RNA of the transformation-defective variant. This allowed the purification of a single-stranded DNA probe specific for the *src* gene. The probe showed the presence of *src* sequences in the cellular genome, fundamentally changing the concept of

oncogene from viral to cellular [40]. The corresponding SRC protein, discovered a few years later and shown to be a tyrosine kinase, provided a basic understanding of the regulatory role that oncoproteins play in cancer [41,42]. In the following years, a basic map of the RSV genome emerged that defined four protein-coding regions starting from the 5' end: the viral *gag*, *pol*, and *env*, and the cell-derived *src* (Figure 3). Oligonucleotide mapping and conventional genetics, including temperature-sensitive mutants, genome deletions and truncations, were essential for achieving this result [43–50].

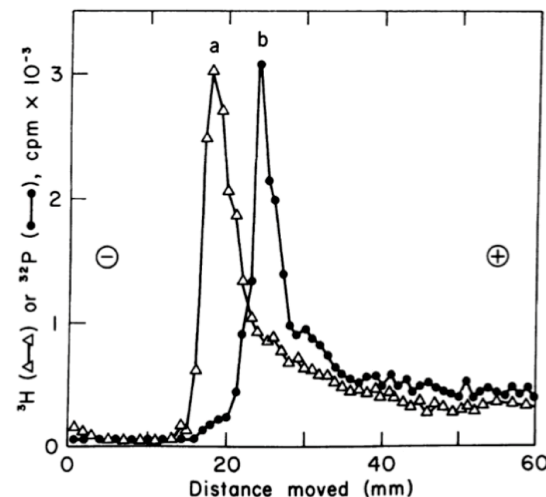


Figure 2. Viral genome size is correlated with oncogenic activity: The discovery of the *src* oncogene. Gel electrophoresis of RNA from an avian sarcoma virus capable of replication and oncogenic transformation (a). RNA from a transformation-defective but replication-competent derivative of the sarcoma virus (b) (adapted from [38]).

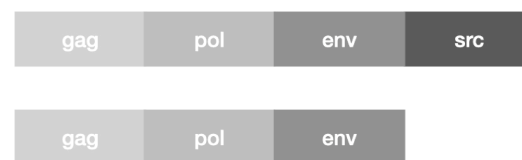


Figure 3. The *src* paradigm. Schematic representation of the genomes of an avian sarcoma virus capable of replication and of oncogenic transformation (**top**) and a deletion mutant of that virus that still replicates but cannot induce transformation (**bottom**). *Gag*, *pol*, and *env* are viral gene regions necessary for replication; *src* mediates oncogenicity.

2.4. The Discovery of *myc*

After *src* and RSV, there were other avian retroviruses that attracted attention. Among them was avian myelocytomatosis virus 29 (MC29), isolated in Bulgaria in 1967. Unlike common avian leukemia viruses, which induce inapparent infections, MC29 can form foci of transformed cells in avian embryo fibroblast cultures [51–53]. MC29 is replication-defective, and its genome is smaller than that of a replication-competent retrovirus. This size difference facilitated the separation of the MC29 RNA from that of its associated helper virus. Oligonucleotide fingerprints of MC29 RNA, and of the RNA of its helper virus, revealed non-viral sequences in the MC29 genome [54]. Complementary information came from the analysis of viral proteins produced by MC29-transformed cells. These cells synthesize a large protein, in which parts of the viral *gag* sequences are fused to non-viral sequences presumed to represent the oncogene (Figure 4) [54,55]. Together, oligonucleotide maps and protein analysis marked the discovery of a new oncogene, which was later termed *myc*. The non-viral sequences of MC29 were soon shown to be derived from the cellular genome, suggesting that the host cell is the universal source of viral oncogenes [56].

Following the genetic and structural analysis of the MC29 genome, the *myc* oncogene was also discovered in other avian retroviruses, including CMII, OK10, and MH2 [57]. The mechanism leading to multiple viral transductions of the same cellular oncogene is not understood. A possible explanation is provided by the retroviral life cycle. It includes recombination with the cellular genome that can lead to the acquisition of host sequences. With the exception of RSV, such acquisitions generate shorter, defective viral genomes that show enhanced fitness in replication.

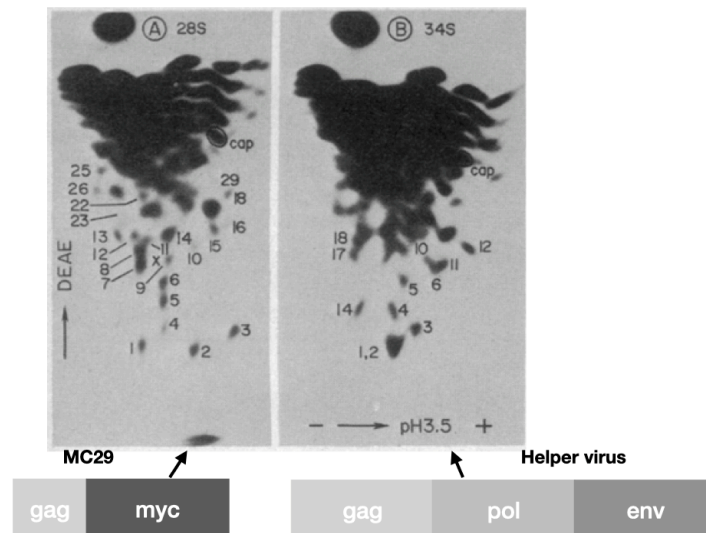


Figure 4. The discovery of *myc*. Oligonucleotide maps reveal unique sequences in MC29 (left, A) compared to the helper virus (right, B). The oncogenic virus MC29 is replication-defective, with a short genome that encodes a single gag-myc fusion protein (left, A). The helper virus genome (right, B) provides the missing replicating functions (adapted from [54,55]).

The retroviral transduction of cellular genes with oncogenic potential provided the foundation for the genetic interpretation of cancer.

The MYC protein contains a dimerization and a DNA-binding domain, referred to as basic helix–loop–helix leucine zipper (bHLH-LZ) structure. The unliganded MYC is intrinsically disordered, but when it is bound to its partner protein MAX, forms a sequence-specific DNA-binding complex [58–60]. MYC was the first retroviral oncogene whose cellular counterpart was shown to be involved in human cancer [61]. It acts as a driving force in most human cancers [62–65], but has not been successfully targeted by a small, clinically approved inhibitor. However, the field of MYC inhibition is increasingly active [66,67], with interesting attempts to circumvent existing hurdles [68].

MYC was also the first cellular oncogene found to be activated by retroviral insertional mutagenesis [69]. It was shortly followed by the discovery of the WNT oncogene, activated by insertion of the mouse mammary tumor retrovirus genome into the host genome [70,71]. Activation of cellular oncogenes by retroviral insertion represents a distinct mechanism of tumorigenesis. It has been used to identify and characterize new genes and signaling pathways important in cancer [72,73].

Detailed biochemical analysis of the MC29-related retrovirus MH2 revealed that its genome contains, in addition to *myc*, a second, independently expressed, cell-derived insert termed *mil* [74,75]. At the same time, a cell-derived insert termed *raf* was found in the genome of a murine sarcoma virus [76]. *mil* and *raf* turned out to be derived from orthologous genes in the chicken and the mouse [60,77]. They represent a unique example of retroviral infection in two different classes of animals, leading to the transduction of the same gene. The Human Gene Nomenclature Committee has chosen the term *RAF* for the

human ortholog. In the human genome, *RAF* represents a family of genes; one of these is referred to as *BRAF*. Mutated *BRAF* acts as an important driver in several human tumors, notably cancers of the colon and lung, and melanoma [78].

2.5. From Avian Erythroblastosis to HER2

Avian erythroblastosis is caused by a group of closely related retroviruses that are commonly designated as AEV “strains” [79–84]. Early molecular investigations used the AEV strain ES4 and identified two independently transcribed putative viral oncogenes, referred to as *erbA* and *erbB* [85–87], with *erbB* emerging as the likely driver of the disease. This possibility was confirmed by work on avian erythroblastosis virus strain H. Strain H carries only the *erbB* oncogene, yet it is fully capable of causing the disease [88,89]. *erbA*, a homolog of the thyroid hormone receptor, is connected to oncogenesis in a different context [90,91]. For *erbB*, the analysis of nucleotide and of amino acid sequences showed that it is a homolog of the epidermal growth factor receptor (EGFR) [92,93]. The EGFR family of proteins gained additional importance for cancer by the discovery of a related oncogene in a chemically induced tumor [94]. The gene, originally termed *neu* or *erbB-2*, but now referred to as *HER2*, also encodes an EGFR-related protein. *HER2* is frequently amplified in breast cancer [95] and, like other EGFRs, it is expressed at the cell surface. That made it accessible to monoclonal antibodies leading to the development of the drug Herceptin [96]. Herceptin represents a prime example of successful targeted cancer therapy [97]. It is connected to avian erythroblastosis through a series of pivotal discoveries.

2.6. Finding New Viral Oncogenes

The incidence of cancer increases with age. Screening populations of old animals enhances the chances of making new discoveries. Chickens constitute the largest populations of animals that are professionally screened for tumors. Older birds, referred to as “retired layers”, used to be processed for human consumption and, hence, were inspected by a veterinarian of the Department of Agriculture. A single such processing plant would typically handle a minimum of 30,000 birds per day. Several spontaneous tumors detected in the course of two days in a plant in Los Angeles led to the discovery of multiple novel oncogenes. Three representative examples are *jun*, recovered from avian sarcoma virus 17 (ASV 17) [98]; *qin*, from ASV 31 [99]; and phosphoinositide 3-kinase (*pi3k*), from ASV 16 [100].

Jun was the first oncogene found to encode a transcriptional regulator. It is a leucine zipper protein and dimerizes with the related leucine zipper oncoprotein *Fos* to form the transcriptional activator complex AP1 [101–103].

The *qin* protein belongs to the family of Fox proteins and is now officially referred to as *FoxG1* [99]. It is expressed exclusively in the telencephalon and is essential for the development of the brain in vertebrates. *FoxG1* represents the only homeotic gene that has been recruited as an oncogene by a retrovirus.

Phosphoinositide 3-kinase (*pi3k*), a lipid kinase, became a promising drug target when overexpression and somatic mutation of the α isoform were discovered in human cancer [104]. The mutations are clustered in three sites of the gene and cause gain of function of the enzyme [104,105]. Expression of the mutated gene in cultured cells induces oncogenic transformation [106].

In the genomes of ASV17, ASV31, and ASV16, the 5′-ends of the respective oncogenes are fused to partial viral *gag* sequences, and in the virus-induced animal tumors, these oncogenes are expressed as *gag* fusion proteins. The *gag* sequence can contribute to the oncogenicity of the cellular sequences by determining cellular location or by enhancing the efficiency of translation.

In the following section of this commentary, we will briefly cite a few examples of oncogenes derived from mammalian retroviruses.

2.7. *Ras*

Two murine sarcoma viruses, the Harvey [107] and the Kirsten viruses [108], yielded oncogenic members of the Ras gene family, referred to as *HRas* and *KRas*. Early work was devoted to the genome structure of these viruses and the presence of host-derived sequences in their genomes [109–111]. The identification of the human *HRAS* as the determinant of the oncogenic phenotype of a human cancer cell line led to a burst of discoveries that showed the pervasive involvement of *RAS*, especially *KRAS*, in human cancer [112–118]. *RAS* is the most mutated oncogene in human cancer. The activating mutations map to a few hot spots of the gene and are single amino acid substitutions that lock the protein in its activated, GTP-bound form. Mutated *RAS* proteins are critical therapeutic targets. However, conventional paths to the design of small molecule inhibitors were ruled out by the apparent lack of suitable binding pockets and by the extremely high affinity of the protein for its target. These obstacles were overcome by fundamentally novel approaches that resulted in the identification of covalently binding, mutant-specific inhibitors [119].

2.8. *Fos*

Fos is the oncogene of the Finkel–Biskis–Jenkins (FBJ) mouse osteosarcoma virus [120,121]. In the virus-infected cell, it is expressed as a *gag-fos* fusion protein. The oncogenic activity of this protein is not dependent on its *gag* component, but on structural changes in the *fos* sequence [122,123], probably a result of the DNA-damaging agents that caused the original FBJ tumor. As already mentioned, *fos* binds to the *jun* protein using its leucine repeat sequence, forming the transcriptional enhancer factor AP1 [102,103,124].

2.9. *Abl*

The source of the retroviral oncogene *abl* is the Abelson leukemia virus [125]. A molecular investigation of its genome structure and expression detected a transformation-specific *gag-abl* fusion protein that functions as a tyrosine-specific protein kinase [126–128]. The significance of the *abl* oncogene for human cancer rests in the chromosomal translocation that fuses the human *ABL* gene on chromosome 9 to the *BCR* gene on chromosome 22, generating the fusion protein BCR-ABL [129–131]. BCR-ABL is a critical factor in the development of chronic myeloblastic leukemia [132,133]. The BCR-ABL fusion protein retains the kinase activity of ABL and was recognized as an attractive and promising drug target. Development of a small molecule inhibitor generated the compound STI571, marketed as Gleevec [134]. Therapeutic inhibition of BCR-ABL with Gleevec induces long-lasting remissions of chronic myelogenous leukemia [135,136]. Treatment with Gleevec or similar kinase inhibitors is now an important part in the standard of care of chronic myelogenous leukemia [136]. It is one of the most successful examples of targeted therapy.

3. Considerations

In this essay, we have followed an intentionally tight and confined path from the discovery of retroviral oncogenes to human cancer. It is a small segment of the abundant data that show that mutated genes play a critical role in the causation of cancer. Cancer genome landscapes reveal multiple somatic mutations that, in concert, contribute to uncontrolled cell growth [62,137]. Some of the most prevalent driver genes and their products were first identified in retroviruses. The functional significance of these oncoproteins is strongly supported by multiple dependency maps [138,139] (see also the cancer dependency project carried out at the Broad Institute, <https://depmap.org/portal/> (accessed on 17 June 2026)). Cancer genetics is now fully integrated in clinical practice [140,141]. It is the origin and

basis of targeted therapy. Cancer genetics is also the elementary tool for non-invasive early diagnosis [142].

However, advances in technologies, interpretations, and concepts are reshaping the field. Among the technologies that have undergone transformative developments are DNA and RNA sequencing and proteomics. Nucleic acid sequencing has made large gains in rapidity and can be scaled to single cell and single gene. New RNA sequencing methods have been introduced, and DNA sequencing has been expanded to long reads [143–146]. The results include novel insights into cancer genes and gene signatures, and the roles of genes in the origin and development of cancers [147–149]. New sequencing technologies have also led to a better understanding of the workings and failures of targeted therapy [150,151]. Additionally, they were instrumental in recognizing cellular plasticity as an important hallmark of cancer [152,153]. Plasticity, or mesenchymal drift, further plays a critical role in a recent proposal on the origin and nature of cancer, which integrates our knowledge of embryonal development and evolution in the process of oncogenesis [154]. Proteomics has undergone similar changes, with great improvements in speed and scale at single-cell level [155–161]. A technical fusion of proteomics and nucleic acid sequencing has also become an option [162].

Sequencing has further opened the door to an exploration of noncoding RNAs. The importance of the noncoding transcriptome as the genetic regulator of cell fate is experimentally supported and widely acknowledged [163]. One class of noncoding RNAs, the micro RNAs (miRNAs), has become an important part of cancer genetics, guiding diagnosis and treatment [164]. This discovery was facilitated by the fact that all miRNAs share basic molecular mechanisms of biogenesis and action [165]. But the large remainder of the noncoding genome is poorly understood. Most of these transcripts are long noncoding RNAs (lncRNAs, transcripts of more than 200 nucleotides). First discovered in a study of X-chromosome inactivation [166], they share several characteristic properties [167]. Although numerous publications have linked one or several lncRNAs to a specific cancer, there has not been a paradigmatic breakthrough that could integrate the entire class of lncRNAs into cancer development [167–171].

Ultimately, all questions that are raised by current cancer research merge into one unifying problem: the control of gene expression, specifically gene expression in higher vertebrates. The prevailing opinion of the control of transcription and gene regulation sees it primarily, if not exclusively, based on protein (transcription factor)–DNA interactions. The exclusivity of this view is almost certainly incorrect.

Early voices have pointed out the fundamental deficiencies and the inadequacy of these views, especially when applied to higher forms of life. One of them was Barbara McClintock, who focused on transposable elements as mediators of gene regulation [172–175].

A comprehensive hypothesis of the control of gene expression in the development and evolution of higher organisms was offered by Eric Davidson and collaborators [176,177]. They were the first to propose an essential role of regulatory RNA in the control of transcription. Their revolutionary concepts on hierarchical gene regulatory networks did not fit into the dominant views and, therefore, were initially ignored [178]. Today, the basic elements of the Davidson hypothesis are widely discussed [179–183], but have still not become part of the molecular biology canon.

A more recent voice emphasizing the centrality of regulatory RNA comes from John Mattick [184]. It is based on transcriptomic deep sequencing [185]. Mattick presents a compelling argument for the need of a “Kuhnian Revolution”, a paradigm shift, in molecular biology [186] and supports this with a comprehensive account of ideas and data from the past and the present in his book “RNA, the epicenter of genetic information” [163].

Contemporary reviews of transcriptional mechanisms and of RNA–protein interactions point in the same direction [187,188].

Much current work in biochemistry and chemistry is ultimately aimed at drug discovery. Proteins are the standard targets; RNAs are much less approachable. This situation creates a hidden bias that should not be extended to our understanding of the molecular mechanisms governing life. We need to remain open to ideas that contradict established dogma and that may have no immediate utilitarian value.

A final thought: Sequencing and proteomic technologies have introduced a fundamental change in the conduct of cancer research and of research in general. The reductionist fervor that started quantitative biology has yielded to a detached, statistics-guided analysis of large data sets. The philosophical consequences of this shift in approaching the unknown and in conducting science are frequently mentioned, but have not been fully explored [189].

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References

1. Rous, P. A Transmissible Avian Neoplasm. (Sarcoma of the Common Fowl.). *J. Exp. Med.* **1910**, *12*, 696–705. [[CrossRef](#)] [[PubMed](#)]
2. Rous, P.; Lange, L.B. The Characters of a Third Transplantable Chicken Tumor Due to a Filterable Cause. A Sarcoma of Intracanalicular Pattern. *J. Exp. Med.* **1913**, *18*, 651–664. [[CrossRef](#)] [[PubMed](#)]
3. Rous, P.; Murphy, J.B. On the Causation by Filterable Agents of Three Distinct Chicken Tumors. *J. Exp. Med.* **1914**, *19*, 52–68. [[CrossRef](#)] [[PubMed](#)]
4. Rous, P.; Murphy, J.B. On Immunity to Transplantable Chicken Tumors. *J. Exp. Med.* **1914**, *20*, 419–432. [[CrossRef](#)] [[PubMed](#)]
5. Furth, J. The Relation of Leukosis to Sarcoma of Chickens: Iii. Sarcomata of Strains 11 and 15 and Their Relation to Leukosis. *J. Exp. Med.* **1936**, *63*, 145–155. [[CrossRef](#)] [[PubMed](#)]
6. Groupe, V.; Manaker, R.A. Discrete foci of altered chicken embryo cells associated with Rous sarcoma virus in tissue culture. *Virology* **1956**, *2*, 838–840. [[CrossRef](#)] [[PubMed](#)]
7. Groupe, V.; Dunkel, V.C.; Manaker, R.A. Improved pock counting method for the titration of Rous sarcoma virus in embryonated eggs. *J. Bacteriol.* **1957**, *74*, 409–410. [[CrossRef](#)] [[PubMed](#)]
8. Dougherty, R.M.; Stewart, J.A.; Morgan, H.R. Quantitative studies of the relationships between infecting dose of Rous sarcoma virus, antiviral immune response, and tumor growth in chickens. *Virology* **1960**, *11*, 349–370. [[CrossRef](#)] [[PubMed](#)]
9. Shannon, J.E., Jr.; Earle, W.R. Qualitative comparison of the growth of chick heart and strain L fibroblasts planted as suspensions on pyrex glass and perforated cellophane substrates. *J. Natl. Cancer Inst.* **1951**, *12*, 155–177. [[CrossRef](#)] [[PubMed](#)]
10. Abercrombie, M.; Heaysman, J.E. Observations on the social behaviour of cells in tissue culture. I. Speed of movement of chick heart fibroblasts in relation to their mutual contacts. *Exp. Cell Res.* **1953**, *5*, 111–131. [[CrossRef](#)] [[PubMed](#)]
11. Littlefield, J.W. Control mechanisms in animal cell cultures. *Arch. Biochem. Biophys.* **1968**, *125*, 410–415. [[CrossRef](#)] [[PubMed](#)]
12. Ellis, E.L.; Delbruck, M. The Growth of Bacteriophage. *J. Gen. Physiol.* **1939**, *22*, 365–384. [[CrossRef](#)] [[PubMed](#)]
13. Luria, S.E. Reactivation of Irradiated Bacteriophage by Transfer of Self-Reproducing Units. *Proc. Natl. Acad. Sci. USA* **1947**, *33*, 253–264. [[CrossRef](#)] [[PubMed](#)]
14. Lwoff, A. Lysogeny. *Bacteriol. Rev.* **1953**, *17*, 269–337. [[CrossRef](#)] [[PubMed](#)]
15. Cairns, J.; Stent, G.S.; Watson, J.D. (Eds.) *Phage and the Origins of Molecular Biology—The Centennial Edition*; Cold Spring Harbor Laboratory Press: Long Island, NY, USA, 2017; p. 394.
16. Jones, D.; Krueger, A.P. A rapid slide plaque technic for bacteriophage assay. *J. Gen. Physiol.* **1951**, *34*, 347–357. [[CrossRef](#)] [[PubMed](#)]
17. Dulbecco, R.; Vogt, M. Plaque formation and isolation of pure lines with poliomyelitis viruses. *J. Exp. Med.* **1954**, *99*, 167–182. [[CrossRef](#)] [[PubMed](#)]

18. Temin, H.M.; Rubin, H. Characteristics of an assay for Rous sarcoma virus and Rous sarcoma cells in tissue culture. *Virology* **1958**, *6*, 669–688. [[CrossRef](#)] [[PubMed](#)]
19. Himly, M.; Foster, D.N.; Bottoli, I.; Iacovoni, J.S.; Vogt, P.K. The DF-1 chicken fibroblast cell line: Transformation induced by diverse oncogenes and cell death resulting from infection by avian leukosis viruses. *Virology* **1998**, *248*, 295–304. [[CrossRef](#)] [[PubMed](#)]
20. Aoki, M.; Batista, O.; Bellacosa, A.; Tschlis, P.; Vogt, P.K. The akt kinase: Molecular determinants of oncogenicity. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 14950–14955. [[CrossRef](#)] [[PubMed](#)]
21. Hughes, S. The RCAS System. Available online: <https://ccr.cancer.gov/hiv-dynamics-and-replication-program/resources/rcas-system> (accessed on 2 April 2026).
22. Vogt, P.K. The Importance of Being Non-Defective: A Mini Review Dedicated to the Memory of Jan Svoboda. *Viruses* **2019**, *11*, 80. [[CrossRef](#)] [[PubMed](#)]
23. Duff, R.G.; Vogt, P.K. Characteristics of two new avian tumor virus subgroups. *Virology* **1969**, *39*, 18–30. [[CrossRef](#)] [[PubMed](#)]
24. Vogt, P.K. Envelope classification of avian RNA tumor viruses. In *Comparative Leukemia Research 1969*; Karger Publishers: Basel, Switzerland, 1971; pp. 153–167. [[CrossRef](#)] [[PubMed](#)]
25. Fujita, D.J.; Chen, Y.C.; Friis, R.R.; Vogt, P.K. RNA tumor viruses of pheasants: Characterization of avian leukosis subgroups F and G. *Virology* **1974**, *60*, 558–571. [[CrossRef](#)] [[PubMed](#)]
26. Troesch, C.D.; Vogt, P.K. An endogenous virus from Lophortyx quail is the prototype for envelope subgroup 1 of avian retroviruses. *Virology* **1985**, *143*, 595–602. [[CrossRef](#)] [[PubMed](#)]
27. Payne, L.N.; Howes, K.; Gillespie, A.M.; Smith, L.M. Host range of Rous sarcoma virus pseudotype RSV(HPRS-103) in 12 avian species: Support for a new avian retrovirus envelope subgroup, designated J. *J. Gen. Virol.* **1992**, *73*, 2995–2997. [[CrossRef](#)] [[PubMed](#)]
28. Vogt, P.K.; Ishizaki, R. Patterns of viral interference in the avian leukosis and sarcoma complex. *Virology* **1966**, *30*, 368–374. [[CrossRef](#)] [[PubMed](#)]
29. Vogt, P.K. Cooperative and antagonistic interactions among RNA tumor viruses. *Natl. Cancer Inst. Monogr.* **1968**, *29*, 421–426. [[PubMed](#)]
30. Vogt, P.K. Spontaneous segregation of nontransforming viruses from cloned sarcoma viruses. *Virology* **1971**, *46*, 939–946. [[CrossRef](#)] [[PubMed](#)]
31. Vogt, P.K. Phenotypic mixing in the avian tumor virus group. *Virology* **1967**, *32*, 708–717. [[CrossRef](#)] [[PubMed](#)]
32. Vogt, P.K. Genetically stable reassortment of markers during mixed infection with avian tumor viruses. *Virology* **1971**, *46*, 947–952. [[CrossRef](#)] [[PubMed](#)]
33. Kawai, S.; Hanafusa, H. Genetic recombination with avian tumor virus. *Virology* **1972**, *49*, 37–44. [[CrossRef](#)] [[PubMed](#)]
34. Duesberg, P.H.; Vogt, P.K. On the role of DNA synthesis in avian tumor virus infection. *Proc. Natl. Acad. Sci. USA* **1969**, *64*, 939–946. [[CrossRef](#)] [[PubMed](#)]
35. Baltimore, D. RNA-dependent DNA polymerase in virions of RNA tumour viruses. *Nature* **1970**, *226*, 1209–1211. [[CrossRef](#)] [[PubMed](#)]
36. Temin, H.M.; Mizutani, S. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature* **1970**, *226*, 1211–1213. [[CrossRef](#)] [[PubMed](#)]
37. Estis, L.F.; Temin, H.M. Suppression of multiplication of avian sarcoma virus by rapid spread of transformation-defective virus of the same subgroup. *J. Virol.* **1979**, *31*, 389–397. [[CrossRef](#)] [[PubMed](#)]
38. Duesberg, P.H.; Vogt, P.K. Differences between the ribonucleic acids of transforming and nontransforming avian tumor viruses. *Proc. Natl. Acad. Sci. USA* **1970**, *67*, 1673–1680. [[CrossRef](#)] [[PubMed](#)]
39. Bister, K. Discovery of oncogenes: The advent of molecular cancer research. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 15259–15260. [[CrossRef](#)] [[PubMed](#)]
40. Stehelin, D.; Varmus, H.E.; Bishop, J.M.; Vogt, P.K. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature* **1976**, *260*, 170–173. [[CrossRef](#)] [[PubMed](#)]
41. Brugge, J.S.; Erikson, R.L. Identification of a transformation-specific antigen induced by an avian sarcoma virus. *Nature* **1977**, *269*, 346–348. [[CrossRef](#)] [[PubMed](#)]
42. Hunter, T.; Sefton, B.M. Transforming gene product of Rous sarcoma virus phosphorylates tyrosine. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 1311–1315. [[CrossRef](#)] [[PubMed](#)]
43. Mason, W.S.; Friis, R.R.; Linial, M.; Vogt, P.K. Determination of the defective function in two mutants of Rous sarcoma virus. *Virology* **1974**, *61*, 559–574. [[CrossRef](#)] [[PubMed](#)]
44. Wang, L.H.; Duesberg, P.; Beemon, K.; Vogt, P.K. Mapping RNase T1-resistant oligonucleotides of avian tumor virus RNAs: Sarcoma-specific oligonucleotides are near the poly(A) end and oligonucleotides common to sarcoma and transformation-defective viruses are at the poly(A) end. *J. Virol.* **1975**, *16*, 1051–1070. [[CrossRef](#)] [[PubMed](#)]

45. Blair, D.G.; Mason, W.S.; Hunter, E.; Vogt, P.K. Temperature-sensitive mutants of avian sarcoma viruses: Genetic recombination between multiple or coordinate mutants and avian leukosis viruses. *Virology* **1976**, *75*, 48–59. [[CrossRef](#)] [[PubMed](#)]
46. Wang, L.; Galehouse, D.; Mellon, P.; Duesberg, P.; Mason, W.S.; Vogt, P.K. Mapping oligonucleotides of Rous sarcoma virus RNA that segregate with polymerase and group-specific antigen markers in recombinants. *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 3952–3956. [[CrossRef](#)] [[PubMed](#)]
47. Alevy, M.C.; Vogt, P.K. Ts pol mutants of avian sarcoma viruses: Mapping and demonstration of single cycle recombinants. *Virology* **1978**, *87*, 21–33. [[CrossRef](#)] [[PubMed](#)]
48. Hu, S.F.; Lai, M.M.; Vogt, P.K. Characterization of the env gene in avian oncoviruses by heteroduplex mapping. *J. Virol.* **1978**, *27*, 667–676. [[CrossRef](#)] [[PubMed](#)]
49. Duesberg, P.H.; Wang, L.H.; Beemon, K.; Kawai, S.; Hanafusa, H. Sequences and functions of Rous sarcoma virus RNA. *Hamatol. Bluttransfus.* **1976**, *19*, 327–340. [[CrossRef](#)] [[PubMed](#)]
50. Wang, L.H.; Duesberg, P.H.; Kawai, S.; Hanafusa, H. Location of envelope-specific and sarcoma-specific oligonucleotides on RNA of Schmidt-Ruppin Rous sarcoma virus. *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 447–451. [[CrossRef](#)] [[PubMed](#)]
51. Mladenov, Z.; Heine, U.; Beard, D.; Beard, J.W. Strain MC29 avian leukosis virus. Myelocytoma, endothelioma, and renal growths: Pathomorphological and ultrastructural aspects. *J. Natl. Cancer Inst.* **1967**, *38*, 251–285. [[CrossRef](#)] [[PubMed](#)]
52. Bolognesi, D.P.; Langlois, A.J.; Sverak, L.; Bonar, R.A.; Beard, J.W. In vitro chick embryo cell response to strain MC29 avian leukosis virus. *J. Virol.* **1968**, *2*, 576–586. [[CrossRef](#)] [[PubMed](#)]
53. Ishizaki, R.; Langlois, A.J.; Chabot, J.; Beard, J.W. Component of strain MC29 avian leukosis virus with the property of defectiveness. *J. Virol.* **1971**, *8*, 821–827. [[CrossRef](#)] [[PubMed](#)]
54. Duesberg, P.H.; Bister, K.; Vogt, P.K. The RNA of avian acute leukemia virus MC29. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 4320–4324. [[CrossRef](#)] [[PubMed](#)]
55. Bister, K.; Hayman, M.J.; Vogt, P.K. Defectiveness of avian myelocytomatosis virus MC29: Isolation of long-term nonproducer cultures and analysis of virus-specific polypeptide synthesis. *Virology* **1977**, *82*, 431–448. [[CrossRef](#)] [[PubMed](#)]
56. Sheiness, D.; Bishop, J.M. DNA and RNA from uninfected vertebrate cells contain nucleotide sequences related to the putative transforming gene of avian myelocytomatosis virus. *J. Virol.* **1979**, *31*, 514–521. [[CrossRef](#)] [[PubMed](#)]
57. Bister, K.; Jansen, H.W. Oncogenes in retroviruses and cells: Biochemistry and molecular genetics. *Adv. Cancer Res.* **1986**, *47*, 99–188. [[CrossRef](#)] [[PubMed](#)]
58. Blackwood, E.M.; Eisenman, R.N. Max: A helix-loop-helix zipper protein that forms a sequence-specific DNA-binding complex with Myc. *Science* **1991**, *251*, 1211–1217. [[CrossRef](#)] [[PubMed](#)]
59. Fieber, W.; Schneider, M.L.; Matt, T.; Krautler, B.; Konrat, R.; Bister, K. Structure, function, and dynamics of the dimerization and DNA-binding domain of oncogenic transcription factor v-Myc. *J. Mol. Biol.* **2001**, *307*, 1395–1410. [[CrossRef](#)] [[PubMed](#)]
60. Stefan, E.; Bister, K. MYC and RAF: Key Effectors in Cellular Signaling and Major Drivers in Human Cancer. *Curr. Top. Microbiol. Immunol.* **2017**, *407*, 117–151. [[CrossRef](#)] [[PubMed](#)]
61. Dalla-Favera, R.; Bregni, M.; Erikson, J.; Patterson, D.; Gallo, R.C.; Croce, C.M. Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 7824–7827. [[CrossRef](#)] [[PubMed](#)]
62. Vogelstein, B.; Papadopoulos, N.; Velculescu, V.E.; Zhou, S.; Diaz, L.A., Jr.; Kinzler, K.W. Cancer genome landscapes. *Science* **2013**, *339*, 1546–1558. [[CrossRef](#)] [[PubMed](#)]
63. Gabay, M.; Li, Y.; Felsher, D.W. MYC activation is a hallmark of cancer initiation and maintenance. *Cold Spring Harb. Perspect. Med.* **2014**, *4*, a014241. [[CrossRef](#)] [[PubMed](#)]
64. Dhanasekaran, R.; Deutzmann, A.; Mahauad-Fernandez, W.D.; Hansen, A.S.; Gouw, A.M.; Felsher, D.W. The MYC oncogene—The grand orchestrator of cancer growth and immune evasion. *Nat. Rev. Clin. Oncol.* **2022**, *19*, 23–36. [[CrossRef](#)] [[PubMed](#)]
65. Das, S.K.; Lewis, B.A.; Levens, D. MYC: A complex problem. *Trends Cell Biol.* **2023**, *33*, 235–246. [[CrossRef](#)] [[PubMed](#)]
66. Hart, J.R.; Garner, A.L.; Yu, J.; Ito, Y.; Sun, M.; Ueno, L.; Rhee, J.K.; Baksh, M.M.; Stefan, E.; Hartl, M.; et al. Inhibitor of MYC identified in a Krohnke pyridine library. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 12556–12561. [[CrossRef](#)] [[PubMed](#)]
67. Llombart, V.; Mansour, M.R. Therapeutic targeting of “undruggable” MYC. *eBioMedicine* **2022**, *75*, 103756. [[CrossRef](#)] [[PubMed](#)]
68. Diamond, P.D.; Sauer, P.V.; Holm, M.; Swanson-Swett, C.J.; Ferguson, L.; Bratset, N.M.; Wienker, G.W.; Sim, J.S.; Adams, H.K.; Kenner, L.; et al. Context-dependent translation inhibition as a novel oncology therapeutic modality. *bioRxiv* **2025**. [[CrossRef](#)]
69. Hayward, W.S.; Neel, B.G.; Astrin, S.M. Activation of a cellular onc gene by promoter insertion in ALV-induced lymphoid leukosis. *Nature* **1981**, *290*, 475–480. [[CrossRef](#)] [[PubMed](#)]
70. Nusse, R.; Varmus, H.E. Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. *Cell* **1982**, *31*, 99–109. [[CrossRef](#)] [[PubMed](#)]
71. Rijsewijk, F.; Schuermann, M.; Wagenaar, E.; Parren, P.; Weigel, D.; Nusse, R. The Drosophila homolog of the mouse mammary oncogene int-1 is identical to the segment polarity gene wingless. *Cell* **1987**, *50*, 649–657. [[CrossRef](#)] [[PubMed](#)]
72. Mikkers, H.; Berns, A. Retroviral insertional mutagenesis: Tagging cancer pathways. *Adv. Cancer Res.* **2003**, *88*, 53–99. [[CrossRef](#)] [[PubMed](#)]

73. Uren, A.G.; Kool, J.; Berns, A.; van Lohuizen, M. Retroviral insertional mutagenesis: Past, present and future. *Oncogene* **2005**, *24*, 7656–7672. [[CrossRef](#)] [[PubMed](#)]
74. Jansen, H.W.; Ruckert, B.; Lurz, R.; Bister, K. Two unrelated cell-derived sequences in the genome of avian leukemia and carcinoma inducing retrovirus MH2. *EMBO J.* **1983**, *2*, 1969–1975. [[CrossRef](#)] [[PubMed](#)]
75. Coll, J.; Righi, M.; Taisne, C.; Dissous, C.; Gegonne, A.; Stehelin, D. Molecular cloning of the avian acute transforming retrovirus MH2 reveals a novel cell-derived sequence (v-mil) in addition to the myc oncogene. *EMBO J.* **1983**, *2*, 2189–2194. [[CrossRef](#)] [[PubMed](#)]
76. Rapp, U.R.; Goldsborough, M.D.; Mark, G.E.; Bonner, T.I.; Groffen, J.; Reynolds, F.H., Jr.; Stephenson, J.R. Structure and biological activity of v-raf, a unique oncogene transduced by a retrovirus. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 4218–4222. [[CrossRef](#)] [[PubMed](#)]
77. Jansen, H.W.; Lurz, R.; Bister, K.; Bonner, T.I.; Mark, G.E.; Rapp, U.R. Homologous cell-derived oncogenes in avian carcinoma virus MH2 and murine sarcoma virus 3611. *Nature* **1984**, *307*, 281–284. [[CrossRef](#)] [[PubMed](#)]
78. Smiech, M.; Leszczynski, P.; Kono, H.; Wardell, C.; Taniguchi, H. Emerging BRAF Mutations in Cancer Progression and Their Possible Effects on Transcriptional Networks. *Genes* **2020**, *11*, 1342. [[CrossRef](#)] [[PubMed](#)]
79. Engelbreth-Holm, J.; Meyer, A.R. On the connection between erythroblastosis (haemocytoblastosis), myelosis and sarcoma in chicken. *Acta Pathol. Microbiol. Scand.* **1935**, *12*, 352–365. [[CrossRef](#)]
80. Wallbank, A.M.; Sperling, F.G.; Stubbs, E.L.; Hubben, K. Studies of avian sarcoma and erythroblastosis (strain 13). II. Virus susceptibility to ether and chloroform. *Proc. Soc. Exp. Biol. Med.* **1962**, *110*, 809–811. [[CrossRef](#)] [[PubMed](#)]
81. Bonar, R.A.; Purcell, R.H.; Beard, D.; Beard, J.W. Virus of Avian Myeloblastosis (Bai Strain a). Xxiv. Nucleotide Composition of the Pentose nucleic Acid and Comparison with Strain R (Erythroblastosis). *J. Natl. Cancer Inst.* **1963**, *31*, 705–716. [[CrossRef](#)] [[PubMed](#)]
82. Graf, T. In vitro transformation of chicken bone marrow cells with avian erythroblastosis virus. *Z. Naturforsch C Biosci.* **1975**, *30*, 847–849. [[CrossRef](#)] [[PubMed](#)]
83. Nedialkov, S.; Todorov, G. Sensitivity of avian leukosis (erythroblastosis) strain E-26 to ether, chloroform and different pH values. *Acta Microbiol. Virol. Immunol.* **1975**, *2*, 64–68. [[PubMed](#)]
84. Karakoz, I.; Geryk, J.; Svoboda, J. In vivo effect of three transformation-defective mutants of subgroup C avian sarcoma viruses. *Folia Biol.* **1980**, *26*, 62–69. [[CrossRef](#)]
85. Sheiness, D.; Vennstrom, B.; Bishop, J.M. Virus-specific RNAs in cells infected by avian myelocytomatosis virus and avian erythroblastosis virus: Modes of oncogene expression. *Cell* **1981**, *23*, 291–300. [[CrossRef](#)] [[PubMed](#)]
86. Privalsky, M.L.; Bishop, J.M. Proteins specified by avian erythroblastosis virus: Coding region localization and identification of a previously undetected erb-B polypeptide. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 3958–3962. [[CrossRef](#)] [[PubMed](#)]
87. Vennstrom, B.; Bishop, J.M. Isolation and characterization of chicken DNA homologous to the two putative oncogenes of avian erythroblastosis virus. *Cell* **1982**, *28*, 135–143. [[CrossRef](#)] [[PubMed](#)]
88. Yamamoto, T.; Hihara, H.; Nishida, T.; Kawai, S.; Toyoshima, K. A new avian erythroblastosis virus, AEV-H, carries erbB gene responsible for the induction of both erythroblastosis and sarcomas. *Cell* **1983**, *34*, 225–232. [[CrossRef](#)] [[PubMed](#)]
89. Yamamoto, T.; Kawai, S.; Koyama, T.; Hihara, H.; Shimizu, T.; Toyoshima, K. Newly generated avian erythroblastosis virus produces noninfectious particles lacking env-gene products. *Virology* **1983**, *129*, 31–39. [[CrossRef](#)] [[PubMed](#)]
90. Privalsky, M.L. v-erb A, nuclear hormone receptors, and oncogenesis. *Biochim. Biophys. Acta* **1992**, *1114*, 51–62. [[CrossRef](#)] [[PubMed](#)]
91. Sap, J.; Munoz, A.; Damm, K.; Goldberg, Y.; Ghysdael, J.; Leutz, A.; Beug, H.; Vennstrom, B. The c-erb-A protein is a high-affinity receptor for thyroid hormone. *Nature* **1986**, *324*, 635–640. [[CrossRef](#)] [[PubMed](#)]
92. Downward, J.; Yarden, Y.; Mayes, E.; Scrace, G.; Totty, N.; Stockwell, P.; Ullrich, A.; Schlessinger, J.; Waterfield, M.D. Close similarity of epidermal growth factor receptor and v-erb-B oncogene protein sequences. *Nature* **1984**, *307*, 521–527. [[CrossRef](#)] [[PubMed](#)]
93. Merlino, G.T.; Xu, Y.H.; Ishii, S.; Clark, A.J.; Semba, K.; Toyoshima, K.; Yamamoto, T.; Pastan, I. Amplification and enhanced expression of the epidermal growth factor receptor gene in A431 human carcinoma cells. *Science* **1984**, *224*, 417–419. [[CrossRef](#)] [[PubMed](#)]
94. Bargmann, C.I.; Hung, M.C.; Weinberg, R.A. The neu oncogene encodes an epidermal growth factor receptor-related protein. *Nature* **1986**, *319*, 226–230. [[CrossRef](#)] [[PubMed](#)]
95. Slamon, D.J.; Clark, G.M.; Wong, S.G.; Levin, W.J.; Ullrich, A.; McGuire, W.L. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* **1987**, *235*, 177–182. [[CrossRef](#)] [[PubMed](#)]
96. Shepard, H.M.; Jin, P.; Slamon, D.J.; Piro, Z.; Maneval, D.C. Herceptin. In *Therapeutic Antibodies*; Handbook of Experimental Pharmacology, vol 181; Springer: Berlin/Heidelberg, Germany, 2008; pp. 183–219. [[CrossRef](#)] [[PubMed](#)]
97. Finn, R.S.; Slamon, D.J. Monoclonal antibody therapy for breast cancer: Herceptin. *Cancer Chemother. Biol. Response Modif.* **2003**, *21*, 223–233. [[CrossRef](#)] [[PubMed](#)]

98. Maki, Y.; Bos, T.J.; Davis, C.; Starbuck, M.; Vogt, P.K. Avian sarcoma virus 17 carries the jun oncogene. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2848–2852. [[CrossRef](#)] [[PubMed](#)]
99. Li, J.; Vogt, P.K. The retroviral oncogene qin belongs to the transcription factor family that includes the homeotic gene fork head. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 4490–4494. [[CrossRef](#)] [[PubMed](#)]
100. Chang, H.W.; Aoki, M.; Fruman, D.; Auger, K.R.; Bellacosa, A.; Tsichlis, P.N.; Cantley, L.C.; Roberts, T.M.; Vogt, P.K. Transformation of chicken cells by the gene encoding the catalytic subunit of PI 3-kinase. *Science* **1997**, *276*, 1848–1850. [[CrossRef](#)] [[PubMed](#)]
101. Bohmann, D.; Bos, T.J.; Admon, A.; Nishimura, T.; Vogt, P.K.; Tjian, R. Human proto-oncogene c-jun encodes a DNA binding protein with structural and functional properties of transcription factor AP-1. *Science* **1987**, *238*, 1386–1392. [[CrossRef](#)] [[PubMed](#)]
102. Curran, T.; Franza, B.R., Jr. Fos and Jun: The AP-1 connection. *Cell* **1988**, *55*, 395–397. [[CrossRef](#)] [[PubMed](#)]
103. Rauscher, F.J., 3rd; Cohen, D.R.; Curran, T.; Bos, T.J.; Vogt, P.K.; Bohmann, D.; Tjian, R.; Franza, B.R., Jr. Fos-associated protein p39 is the product of the jun proto-oncogene. *Science* **1988**, *240*, 1010–1016. [[CrossRef](#)] [[PubMed](#)]
104. Samuels, Y.; Wang, Z.; Bardelli, A.; Silliman, N.; Ptak, J.; Szabo, S.; Yan, H.; Gazdar, A.; Powell, S.M.; Riggins, G.J.; et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science* **2004**, *304*, 554. [[CrossRef](#)] [[PubMed](#)]
105. Samuels, Y.; Ericson, K. Oncogenic PI3K and its role in cancer. *Curr. Opin. Oncol.* **2006**, *18*, 77–82. [[CrossRef](#)] [[PubMed](#)]
106. Kang, S.; Bader, A.G.; Vogt, P.K. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 802–807. [[CrossRef](#)] [[PubMed](#)]
107. Harvey, J.J. An unidentified virus which causes the rapid production of tumours in mice. *Nature* **1964**, *204*, 1104–1105. [[CrossRef](#)] [[PubMed](#)]
108. Scolnick, E.M.; Rands, E.; Williams, D.; Parks, W.P. Studies on the nucleic acid sequences of Kirsten sarcoma virus: A model for formation of a mammalian RNA-containing sarcoma virus. *J. Virol.* **1973**, *12*, 458–463. [[CrossRef](#)] [[PubMed](#)]
109. Scolnick, E.M.; Parks, W.P. Harvey sarcoma virus: A second murine type C sarcoma virus with rat genetic information. *J. Virol.* **1974**, *13*, 1211–1219. [[CrossRef](#)] [[PubMed](#)]
110. Scolnick, E.M.; Goldberg, R.J.; Williams, D. Characterization of rat genetic sequences of Kirsten sarcoma virus: Distinct class of endogenous rat type C viral sequences. *J. Virol.* **1976**, *18*, 559–566. [[CrossRef](#)] [[PubMed](#)]
111. Shih, T.Y.; Williams, D.R.; Weeks, M.O.; Maryak, J.M.; Vass, W.C.; Scolnick, E.M. Comparison of the genomic organization of Kirsten and Harvey sarcoma viruses. *J. Virol.* **1978**, *27*, 45–55. [[CrossRef](#)] [[PubMed](#)]
112. Parada, L.F.; Tabin, C.J.; Shih, C.; Weinberg, R.A. Human EJ bladder carcinoma oncogene is homologue of Harvey sarcoma virus ras gene. *Nature* **1982**, *297*, 474–478. [[CrossRef](#)] [[PubMed](#)]
113. Vachtenheim, J. Occurrence of ras mutations in human lung cancer. *Minireview. Neoplasma* **1997**, *44*, 145–149. [[PubMed](#)]
114. Piva, S.; Ganzinelli, M.; Garassino, M.C.; Caiola, E.; Farina, G.; Broggin, M.; Marabese, M. Across the universe of K-RAS mutations in non-small-cell-lung cancer. *Curr. Pharm. Des.* **2014**, *20*, 3933–3943. [[CrossRef](#)] [[PubMed](#)]
115. Luo, J. KRAS mutation in pancreatic cancer. *Semin. Oncol.* **2021**, *48*, 10–18. [[CrossRef](#)] [[PubMed](#)]
116. Singhal, A.; Li, B.T.; O'Reilly, E.M. Targeting KRAS in cancer. *Nat. Med.* **2024**, *30*, 969–983. [[CrossRef](#)] [[PubMed](#)]
117. Drizyte-Miller, K.; Talabi, T.; Somasundaram, A.; Cox, A.D.; Der, C.J. KRAS: The Achilles' heel of pancreas cancer biology. *J. Clin. Investig.* **2025**, *135*, e191939. [[CrossRef](#)] [[PubMed](#)]
118. Zhang, M.; Wu, D.; Tang, Y.; Zhang, L.; Zhang, S.; Li, W.; Li, N.; Yan, X. Targeting KRAS in colorectal cancer (Review). *Mol. Clin. Oncol.* **2025**, *23*, 78. [[CrossRef](#)] [[PubMed](#)]
119. Ostrem, J.M.L.; Peters, U.; Shokat, K.M. Direct RAS inhibitors turn 10. *Nat. Chem. Biol.* **2024**, *20*, 1238–1241. [[CrossRef](#)] [[PubMed](#)]
120. Finkel, M.P.; Biskis, B.O.; Jenkins, P.B. Virus induction of osteosarcomas in mice. *Science* **1966**, *151*, 698–701. [[CrossRef](#)] [[PubMed](#)]
121. Curran, T.; Teich, N.M. Identification of a 39,000-dalton protein in cells transformed by the FBJ murine osteosarcoma virus. *Virology* **1982**, *116*, 221–235. [[CrossRef](#)] [[PubMed](#)]
122. Miller, A.D.; Verma, I.M.; Curran, T. Deletion of the gag region from FBR murine osteosarcoma virus does not affect its enhanced transforming activity. *J. Virol.* **1985**, *55*, 521–526. [[CrossRef](#)] [[PubMed](#)]
123. Cohen, D.R.; Curran, T. The structure and function of the fos proto-oncogene. *Crit. Rev. Oncog.* **1989**, *1*, 65–88. [[PubMed](#)]
124. Abate, C.; Curran, T. Encounters with Fos and Jun on the road to AP-1. *Semin. Cancer Biol.* **1990**, *1*, 19–26. [[PubMed](#)]
125. Abelson, H.T.; Rabstein, L.S. Lymphosarcoma: Virus-induced thymic-independent disease in mice. *Cancer Res.* **1970**, *30*, 2213–2222. [[PubMed](#)]
126. Sefton, B.M.; Hunter, T.; Raschke, W.C. Evidence that the Abelson virus protein functions in vivo as a protein kinase that phosphorylates tyrosine. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 1552–1556. [[CrossRef](#)] [[PubMed](#)]
127. Wang, J.Y.; Prywes, R.; Baltimore, D. Structure and function of the Abelson murine leukemia virus transforming gene. *Prog. Clin. Biol. Res.* **1983**, *119*, 57–63. [[PubMed](#)]
128. Yi, C.R.; Rosenberg, N. Gag influences transformation by Abelson murine leukemia virus and suppresses nuclear localization of the v-Abl protein. *J. Virol.* **2007**, *81*, 9461–9468. [[CrossRef](#)] [[PubMed](#)]
129. Nowell, P.C.; Hungerford, D.A. Chromosome studies on normal and leukemic human leukocytes. *J. Natl. Cancer Inst.* **1960**, *25*, 85–109. [[CrossRef](#)] [[PubMed](#)]

130. Rowley, J.D. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* **1973**, *243*, 290–293. [[CrossRef](#)] [[PubMed](#)]
131. Heisterkamp, N.; Groffen, J. Molecular insights into the Philadelphia translocation. *Hematol. Pathol.* **1991**, *5*, 1–10. [[PubMed](#)]
132. Sawyers, C.L. The bcr-abl gene in chronic myelogenous leukaemia. *Cancer Surv.* **1992**, *15*, 37–51. [[PubMed](#)]
133. Sawyers, C.L. Molecular consequences of the BCR-ABL translocation in chronic myelogenous leukemia. *Leuk. Lymphoma* **1993**, *11*, 101–103. [[CrossRef](#)] [[PubMed](#)]
134. Druker, B.J.; Talpaz, M.; Resta, D.J.; Peng, B.; Buchdunger, E.; Ford, J.M.; Lydon, N.B.; Kantarjian, H.; Capdeville, R.; Ohno-Jones, S.; et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N. Engl. J. Med.* **2001**, *344*, 1031–1037. [[CrossRef](#)] [[PubMed](#)]
135. Druker, B.J. Imatinib as a paradigm of targeted therapies. *Adv. Cancer Res.* **2004**, *91*, 1–30. [[CrossRef](#)] [[PubMed](#)]
136. Druker, B.J. Translation of the Philadelphia chromosome into therapy for CML. *Blood* **2008**, *112*, 4808–4817. [[CrossRef](#)] [[PubMed](#)]
137. Vogelstein, B.; Kinzler, K.W. Cancer genes and the pathways they control. *Nat. Med.* **2004**, *10*, 789–799. [[CrossRef](#)] [[PubMed](#)]
138. Tsherniak, A.; Vazquez, F.; Montgomery, P.G.; Weir, B.A.; Kryukov, G.; Cowley, G.S.; Gill, S.; Harrington, W.F.; Pantel, S.; Krill-Burger, J.M.; et al. Defining a Cancer Dependency Map. *Cell* **2017**, *170*, 564–576.e516. [[CrossRef](#)] [[PubMed](#)]
139. Pacini, C.; Duncan, E.; Goncalves, E.; Gilbert, J.; Bhosle, S.; Horswell, S.; Karakoc, E.; Lightfoot, H.; Curry, E.; Muyas, F.; et al. A comprehensive clinically informed map of dependencies in cancer cells and framework for target prioritization. *Cancer Cell* **2024**, *42*, 301–316.e9. [[CrossRef](#)] [[PubMed](#)]
140. Varmus, H.E. Viruses, genes, and cancer. I. The discovery of cellular oncogenes and their role in neoplasia. *Cancer* **1985**, *55*, 2324–2328. [[CrossRef](#)]
141. Varmus, H.; Pao, W.; Politi, K.; Podsypanina, K.; Du, Y.C. Oncogenes come of age. *Cold Spring Harb. Symp. Quant. Biol.* **2005**, *70*, 1–9. [[CrossRef](#)] [[PubMed](#)]
142. Wang, Y.; Joshu, C.E.; Curtis, S.D.; Douville, C.; Burk, V.A.; Ru, M.; Popoli, M.; Ptak, J.; Dobbyn, L.; Silliman, N.; et al. Detection of Cancers Three Years prior to Diagnosis Using Plasma Cell-Free DNA. *Cancer Discov.* **2025**, *15*, 1794–1802. [[CrossRef](#)] [[PubMed](#)]
143. Satija, R.; Farrell, J.A.; Gennert, D.; Schier, A.F.; Regev, A. Spatial reconstruction of single-cell gene expression data. *Nat. Biotechnol.* **2015**, *33*, 495–502. [[CrossRef](#)] [[PubMed](#)]
144. Logsdon, G.A.; Vollger, M.R.; Eichler, E.E. Long-read human genome sequencing and its applications. *Nat. Rev. Genet.* **2020**, *21*, 597–614. [[CrossRef](#)] [[PubMed](#)]
145. Lobato-Moreno, S.; Yildiz, U.; Claringbould, A.; Servaas, N.H.; Vlachou, E.P.; Arnold, C.; Bauersachs, H.G.; Campos-Fornes, V.; Kim, M.; Berest, I.; et al. Single-cell ultra-high-throughput multiplexed chromatin and RNA profiling reveals gene regulatory dynamics. *Nat. Methods* **2025**, *22*, 1213–1225. [[CrossRef](#)] [[PubMed](#)]
146. Yildiz, U.; Lobato-Moreno, S.; Claringbould, A.; Bauersachs, H.G.; Servaas, N.H.; Vlachou, E.P.; Arnold, C.; Campos-Fornes, V.; Prummel, K.D.; Zaugg, J.B.; et al. Single-cell ultra-high-throughput multiplexed chromatin accessibility and gene expression sequencing (SUM-seq). *Nat. Protoc.* **2026**, *Online ahead of print*. [[CrossRef](#)] [[PubMed](#)]
147. Martincorena, I.; Raine, K.M.; Gerstung, M.; Dawson, K.J.; Haase, K.; Van Loo, P.; Davies, H.; Stratton, M.R.; Campbell, P.J. Universal Patterns of Selection in Cancer and Somatic Tissues. *Cell* **2018**, *173*, 1823. [[CrossRef](#)] [[PubMed](#)]
148. Tate, J.G.; Bamford, S.; Jubb, H.C.; Sondka, Z.; Beare, D.M.; Bindal, N.; Boutselakis, H.; Cole, C.G.; Creatore, C.; Dawson, E.; et al. COSMIC: The Catalogue of Somatic Mutations in Cancer. *Nucleic Acids Res.* **2019**, *47*, D941–D947. [[CrossRef](#)] [[PubMed](#)]
149. Alexandrov, L.B.; Kim, J.; Haradhvala, N.J.; Huang, M.N.; Tian Ng, A.W.; Wu, Y.; Boot, A.; Covington, K.R.; Gordenin, D.A.; Bergstrom, E.N.; et al. The repertoire of mutational signatures in human cancer. *Nature* **2020**, *578*, 94–101. [[CrossRef](#)] [[PubMed](#)]
150. Krishnan, V.; Schmidt, F.; Nawaz, Z.; Venkatesh, P.N.; Lee, K.L.; Ren, X.; Chan, Z.E.; Yu, M.; Makheja, M.; Rayan, N.A.; et al. A single-cell atlas identifies pretreatment features of primary imatinib resistance in chronic myeloid leukemia. *Blood* **2023**, *141*, 2738–2755. [[CrossRef](#)] [[PubMed](#)]
151. Warfvinge, R.; Geirsonson Ulfsson, L.; Dhapola, P.; Safi, F.; Sommarin, M.; Soneji, S.; Hjorth-Hansen, H.; Mustjoki, S.; Richter, J.; Thakur, R.K.; et al. Single-cell multiomics analysis of chronic myeloid leukemia links cellular heterogeneity to therapy response. *eLife* **2024**, *12*, RP92074. [[CrossRef](#)] [[PubMed](#)]
152. Derynck, R.; Weinberg, R.A. EMT and Cancer: More Than Meets the Eye. *Dev. Cell* **2019**, *49*, 313–316. [[CrossRef](#)] [[PubMed](#)]
153. Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* **2022**, *12*, 31–46. [[CrossRef](#)] [[PubMed](#)]
154. Frank, S.A. How cancer arises: Genetics releases, plasticity creates, genetics stabilizes. *Proc. Natl. Acad. Sci. USA* **2025**, *122*, e2505377122. [[CrossRef](#)] [[PubMed](#)]
155. Mesri, M. Advances in Proteomic Technologies and Its Contribution to the Field of Cancer. *Adv. Med.* **2014**, *2014*, 238045. [[CrossRef](#)] [[PubMed](#)]
156. Gomes, F.P.; Yates, J.R., 3rd. Recent trends of capillary electrophoresis-mass spectrometry in proteomics research. *Mass Spectrom. Rev.* **2019**, *38*, 445–460. [[CrossRef](#)] [[PubMed](#)]
157. Yates, J.R., 3rd. Recent technical advances in proteomics. *F1000Research* **2019**, *8*, 351. [[CrossRef](#)] [[PubMed](#)]

158. Santos, M.D.M.; Lima, D.B.; Fischer, J.S.G.; Clasen, M.A.; Kurt, L.U.; Camillo-Andrade, A.C.; Monteiro, L.C.; de Aquino, P.F.; Neves-Ferreira, A.G.C.; Valente, R.H.; et al. Simple, efficient and thorough shotgun proteomic analysis with PatternLab V. *Nat. Protoc.* **2022**, *17*, 1553–1578. [[CrossRef](#)] [[PubMed](#)]
159. Movassaghi, C.S.; Sun, J.; Jiang, Y.; Turner, N.; Chang, V.; Chung, N.; Chen, R.J.; Browne, E.N.; Lin, C.; Schweppe, D.K.; et al. Recent Advances in Mass Spectrometry-Based Bottom-Up Proteomics. *Anal. Chem.* **2025**, *97*, 4728–4749. [[CrossRef](#)] [[PubMed](#)]
160. Melby, J.A.; Su, P.; Gomes, F.P. Recent Advances in Top-Down Proteomics for Single-Cell Research. *Mass Spectrom. Rev.* **2026**; *Online ahead of print*. [[CrossRef](#)] [[PubMed](#)]
161. Zhu, G.; Alvarez Rodriguez, D.A.; Gould, N.; Ivanov, A.R.; Jooss, K.; Sun, L. Recent Advances (2023–2025) of Capillary Electrophoresis-Mass Spectrometry (CE-MS) for Top-Down Proteomics. *Mass Spectrom. Rev.* **2026**, *in press*. [[CrossRef](#)] [[PubMed](#)]
162. Karlsson, F.; Kallas, T.; Thiagarajan, D.; Karlsson, M.; Schweitzer, M.; Navarro, J.F.; Leijonacker, L.; Geny, S.; Pettersson, E.; Rhomberg-Kauert, J.; et al. Molecular pixelation: Spatial proteomics of single cells by sequencing. *Nat. Methods* **2024**, *21*, 1044–1052. [[CrossRef](#)] [[PubMed](#)]
163. Mattick, J.; Amaral, P. *RNA, the Epicenter of Genetic Information: A New Understanding of Molecular Biology*; CRC Press: Abingdon, UK, 2022.
164. Kim, T.; Croce, C.M. MicroRNA: Trends in clinical trials of cancer diagnosis and therapy strategies. *Exp. Mol. Med.* **2023**, *55*, 1314–1321. [[CrossRef](#)] [[PubMed](#)]
165. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front Endocrinol.* **2018**, *9*, 402. [[CrossRef](#)] [[PubMed](#)]
166. Lee, J.T.; Jaenisch, R. The (epi)genetic control of mammalian X-chromosome inactivation. *Curr. Opin. Genet. Dev.* **1997**, *7*, 274–280. [[CrossRef](#)] [[PubMed](#)]
167. Mattick, J.S.; Amaral, P.P.; Carninci, P.; Carpenter, S.; Chang, H.Y.; Chen, L.L.; Chen, R.; Dean, C.; Dinger, M.E.; Fitzgerald, K.A.; et al. Long non-coding RNAs: Definitions, functions, challenges and recommendations. *Nat. Rev. Mol. Cell Biol.* **2023**, *24*, 430–447. [[CrossRef](#)] [[PubMed](#)]
168. Cheetham, S.W.; Gruhl, F.; Mattick, J.S.; Dinger, M.E. Long noncoding RNAs and the genetics of cancer. *Br. J. Cancer* **2013**, *108*, 2419–2425. [[CrossRef](#)] [[PubMed](#)]
169. Kopp, F.; Mendell, J.T. Functional Classification and Experimental Dissection of Long Noncoding RNAs. *Cell* **2018**, *172*, 393–407. [[CrossRef](#)] [[PubMed](#)]
170. Mattick, J.S. The State of Long Non-Coding RNA Biology. *Noncoding RNA* **2018**, *4*, 17. [[CrossRef](#)] [[PubMed](#)]
171. Chen, L.L.; Kim, V.N. Small and long non-coding RNAs: Past, present, and future. *Cell* **2024**, *187*, 6451–6485. [[CrossRef](#)] [[PubMed](#)]
172. McClintock, B. Controlling elements and the gene. *Cold Spring Harb. Symp. Quant. Biol.* **1956**, *21*, 197–216. [[CrossRef](#)] [[PubMed](#)]
173. McClintock, B. The significance of responses of the genome to challenge. *Science* **1984**, *226*, 792–801. [[CrossRef](#)] [[PubMed](#)]
174. Jones, R.N. McClintock's controlling elements: The full story. *Cytogenet. Genome Res.* **2005**, *109*, 90–103. [[CrossRef](#)] [[PubMed](#)]
175. Fedoroff, N.V. McClintock's challenge in the 21st century. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 20200–20203. [[CrossRef](#)] [[PubMed](#)]
176. Britten, R.J.; Davidson, E.H. Gene regulation for higher cells: A theory. *Science* **1969**, *165*, 349–357. [[CrossRef](#)] [[PubMed](#)]
177. Erwin, D.H.; Davidson, E.H. The evolution of hierarchical gene regulatory networks. *Nat. Rev. Genet* **2009**, *10*, 141–148. [[CrossRef](#)] [[PubMed](#)]
178. Rothenberg, E.V. Eric Davidson: Steps to a gene regulatory network for development. *Dev. Biol.* **2016**, *412*, S7–S19. [[CrossRef](#)] [[PubMed](#)]
179. Deichmann, U. From Gregor Mendel to Eric Davidson: Mathematical Models and Basic Principles in Biology. *J. Comput Biol.* **2019**, *26*, 637–652. [[CrossRef](#)] [[PubMed](#)]
180. Rothenberg, E.V. Causal Gene Regulatory Network Modeling and Genomics: Second-Generation Challenges. *J. Comput Biol.* **2019**, *26*, 703–718. [[CrossRef](#)] [[PubMed](#)]
181. Nguyen, P.; Pease, N.A.; Kueh, H.Y. Scalable control of developmental timetables by epigenetic switching networks. *J. R. Soc. Interface* **2021**, *18*, 20210109. [[CrossRef](#)] [[PubMed](#)]
182. Deichmann, U. Self-Organization and Genomic Causality in Models of Morphogenesis. *Entropy* **2023**, *25*, 873. [[CrossRef](#)] [[PubMed](#)]
183. Andrews, S.S.; Wiley, H.S.; Sauro, H.M. Design patterns of biological cells. *Bioessays* **2024**, *46*, e2300188. [[CrossRef](#)] [[PubMed](#)]
184. Morris, K.V.; Mattick, J.S. The rise of regulatory RNA. *Nat. Rev. Genet.* **2014**, *15*, 423–437. [[CrossRef](#)] [[PubMed](#)]
185. Clark, M.B.; Amaral, P.P.; Schlesinger, F.J.; Dinger, M.E.; Taft, R.J.; Rinn, J.L.; Ponting, C.P.; Stadler, P.F.; Morris, K.V.; Morillon, A.; et al. The reality of pervasive transcription. *PLoS Biol.* **2011**, *9*, e1000625. [[CrossRef](#)] [[PubMed](#)]
186. Mattick, J.S. A Kuhnian revolution in molecular biology: Most genes in complex organisms express regulatory RNAs. *Bioessays* **2023**, *45*, e2300080. [[CrossRef](#)] [[PubMed](#)]
187. Henninger, J.E.; Young, R.A. An RNA-centric view of transcription and genome organization. *Mol. Cell* **2024**, *84*, 3627–3643. [[CrossRef](#)] [[PubMed](#)]

188. Hentze, M.W.; Sommerkamp, P.; Ravi, V.; Gebauer, F. Rethinking RNA-binding proteins: Riboregulation challenges prevailing views. *Cell* **2025**, *188*, 4811–4827. [[CrossRef](#)] [[PubMed](#)]
189. Saetra, H.S. Science as a Vocation in the Era of Big Data: The Philosophy of Science behind Big Data and humanity's Continued Part in Science. *Integr. Psychol. Behav. Sci.* **2018**, *52*, 508–522. [[CrossRef](#)] [[PubMed](#)]

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