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Review

Fusion genes in solid tumors: an emerging target for cancer diagnosis and treatment

Brittany C. Parker[1,2] and Wei Zhang[1,2]

Abstract

Studies over the past decades have uncovered fusion genes, a class of oncogenes that provide immense diagnostic and therapeutic advantages because of their tumor-specific expression. Originally associated with hemotologic cancers, fusion genes have recently been discovered in a wide array of solid tumors, including sarcomas, carcinomas, and tumors of the central nervous system. Fusion genes are attractive as both therapeutic targets and diagnostic tools due to their inherent expression in tumor tissue alone. Therefore, the discovery and elucidation of fusion genes in various cancer types may provide more effective therapies in the future for cancer patients.

Key words Cancer genomics, fusion genes, tumorigenesis, therapy, chromosomal instability

Genomic instability, or the rearrangement of the genome inside of a cell, can result in cancer as well as other diseases. Genomic instability can describe gene mutations, translocations, copy number alterations, deletions, and inversions of pieces of DNA or even single nucleotides. There are many causes of genomic instability, including external factors such as radiation, tobacco, or ultraviolet light—all of which can damage DNA—or internal factors such as faulty DNA repair processes.

Many genes in the body, called proto-oncogenes, are mutated in cancer, thereby becoming oncogenes. Conversely, tumor suppressor genes also exist, and mutation or deletion of these genes can cause cancer. For example, the gene *TP53* is coined "guardian of the genome" because it is a powerful tumor suppressor gene. However, in many cancers, *TP53* is mutated and rendered nonfunctional, allowing cancer to form. Some other genes are amplified in cancer, such as epidermal growth factor receptor (*EGFR*). *EGFR* amplification is observed in several different cancers, such as high-grade brain tumor and lung cancer. When mutated in a high-grade brain tumor, *EGFR* becomes constitutively activated. Other genetic events, including gene translocations and deletions, can also occur and lead to cancer. These genetic events can cause the formation of fusion genes, whereby two previously separate genes are rearranged to form a hybrid gene.

Authors' Affiliations: [1]Department of Pathology, Unit 85, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [2]The University of Texas Graduate School of Biomedical Sciences, Houston, TX 77030, USA.

Corresponding Author: Wei Zhang, Department of Pathology, Unit 85, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Tel: +1-713-745-1103; Fax: +1-713-792-5549; Email: wzhang@mdanderson.org.

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History of DNA Sequencing and the Discovery of Fusion Genes

Fusion genes were originally discovered in hematologic malignancies but have been recently found in several solid tumors through the use of modern, advanced sequencing technologies (**Figure 1**; **Table 1**). The first stretch of sequence published was the *lac* operon, in 1972[1]. A few years later, Sanger sequencing technology was developed and is still highly used in laboratories across the world today[2]. In 1983, the American biochemist Kary Mullis developed polymerase chain reaction (PCR), which revolutionized biochemistry and molecular biology[3]. More advances followed shortly, with the development of the first automated DNA sequencer by Applied Biosystems in 1987, and the development of next-generation sequencing in 2005.

Next-generation sequencing was created out of the demand for high-throughput, low-cost sequencing. This technology was able to revolutionize sequencing by producing thousands to millions of read sequences concurrently[4]. Detection of fusion genes became much easier compared with original methods, which utilized cytogenetic analysis (i.e. Giemsa staining of chromosomes during metaphase to observe abnormal gains or losses in chromosome structures) (**Table 1**). The ability to target these fusion genes has led to the development of many successful anti-cancer drugs and will translate to more targeted therapy opportunities in the future.

The beginning: fusion genes in hematologic malignancies

The first fusion gene, known as the Philadelphia chromosome, was discovered in 1973 in chronic myelogenous leukemia and

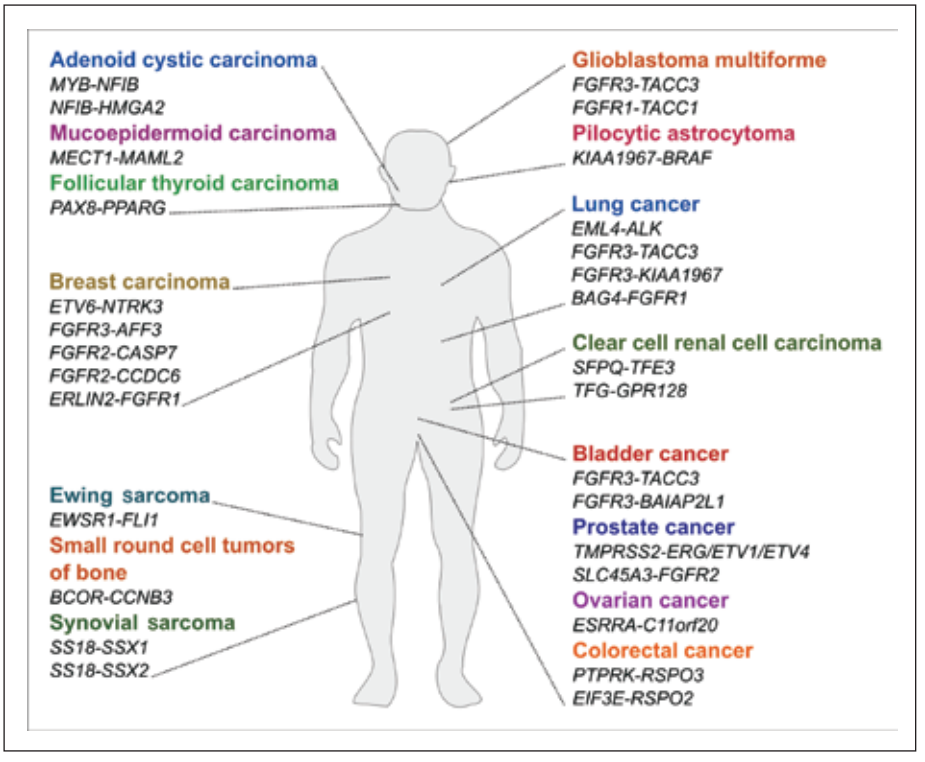

Figure 1. **Fusion location in the human body.**

consisted of the central portion of the breakpoint cluster region (*BCR*) gene fused to the second exon of the Abelson murine leukemia viral oncogene homolog 1 (*ABL1*) gene[5-7]. *BCR-ABL1* has been found to occur in more than 95% of chronic myeloid leukemia patients[8] and to exert its oncogenic phenotype by encoding a constitutively active ABL1 kinase[9]. Around the same time, another fusion was discovered in Burkitt lymphoma. This fusion, which was present at comparable frequencies to *BCR-ABL1*, consisted of immunoglobulin genes fused to *MYC*, a product of reciprocal translocation of chromosomes 8 and 14[10-12].

Since then, dozens of fusions have been identified in hematologic cancers, some of which have exhibited vast therapeutic benefit when targeted. The first fusion-targeted drug was imatinib, a tyrosine kinase inhibitor approved by the Food and Drug Administration in 2001 for the treatment of Philadelphia-chromosome–positive chronic myeloid leukemia. This drug's vast therapeutic benefit led to it being featured on the cover of *Time* magazine and coined as the "magic bullet" to cure cancer[13]. Similarly, other drugs have been proven beneficial in targeting fusions. For example, the promyelocytic leukemia (*PML*)−retinoic acid receptor alpha (*RARA*) fusion found in nearly 95% of acute promyelocytic leukemias occurs via reciprocal translocation of chromosomes 15 and 17[14,15], producing fusions that contain the oncogenic retinoic acid receptor α. Clinical trials involving the treatment of *PML-RARA*–positive patients with tretinoin (all-trans–retinoic acid), the drug commonly known in the cosmetic world in its topical form as Retin-A and used to treat photoaging[16], showed vast therapeutic benefit across independent studies[17-19].

Fusion Genes in Solid Tumors

With the development of more sophisticated sequencing technologies came the discovery of fusion genes in solid tumors, including sarcoma, carcinoma, and tumors of the central nervous system (**Figure 2**). Each tumor type has both fusions that are tumor-specific and others that are common to several cancers, such as the fibroblast growth factor receptor 3 (*FGFR3*)–transforming acidic coiled-coil containing protein 3 (*TACC3*) fusion, which is found in brain, lung, and bladder cancers[20-23].

Fusion genes in sarcoma

Sarcomas account for approximately 2% of human cancers and are a heterogeneous group of cancers that arise from cells of mesenchymal origin, such as the bone, cartilage, muscle, and fat. Compared with carcinomas, which arise from epithelial cells (as in breast, colon, and lung cancers), sarcomas are quite rare, with only 15,000 new cases per year in the United States[24]. Sarcomas are classified by the tissue from which they arise. For example, sarcomas arising from the bone, cartilage, and fat are called osteosarcoma, chondrosarcoma, and liposarcoma, respectively. The current standard of care to treat most sarcomas is surgery followed by radiation and chemotherapy.

Ewing sarcoma

Ewing sarcoma is a highly metastatic class of sarcoma and is the second most frequent bone tumor in children. Ewing sarcoma is

Table 1. Fusion genes and their methods of discovery

Fusion gene	Discovery year	Discovery method	Reference
BCR-ABL1 (CML)	1960	Cytogenetic analysis	[5]
EWSR1-FLI1	1983	Cytogenetic analysis	[26]
SS18-SSX1	1987	Cytogenetic analysis	[40]
PML-RARA	1990	Cytogenetic analysis	[14]
EWSR1-ATF1	1990	Cytogenetic analysis	[50]
ETV6-NTRK3	1998	Cytogenetic analysis	[61]
PAX8-PPARG	1999	Cytogenetic analysis	[94]
MECT1-MAML2	2003	Cytogenetic analysis	[90]
TMPRSS2-ERG	2005	Microarray technology	[55]
TMPRSS2-ETV1	2005	Microarray technology	[55]
EML4-ALK	2007	PCR technology followed by Sanger sequencing	[80]
KIAA1549-BRAF	2008	PCR technology followed by Sanger sequencing	[101]
MYB-NFIB	2009	Cytogenetic analysis	[89]
ESRRA-C11orf20	2011	Next-generation sequencing	[76]
FGFR3-TACC3 (GBM)	2012	Next-generation sequencing	[21]
FGFR3-TACC3 (BC)	2012	RT-PCR following by Sanger sequencing	[22]
PTPRK-RSPO3	2012	Next-generation sequencing	[69]
EIF3E3-RSPO2	2012	Next-generation sequencing	[69]
SFPQ-TFE3	2013	Next-generation sequencing	[99]

BCR, breakpoint cluster region; ABL1, Abelson murine leukemia viral oncogene homolog 1; CML, chronic myelogenous leukemia; EWSR1, Ewing sarcoma breakpoint region 1; ETS, E–twenty six; FLI1, friend leukemia virus integration 1; IGH, immunoglobulin heavy chain; SSX, synovial sarcoma X chromosome breakpoint; PML, promyelocytic leukemia; RARA, retinoic acid receptor alpha; ATF1, activating transcription factor 1; ETV, ETS variant gene; NTRK3, neurotrophic tyrosine receptor kinase, type 3; PAX8, paired box gene 8; PPARG, peroxisome proliferator-activated receptor gamma; MECT1, mucoepidermoid carcinoma translocated 1; MAML2, mastermind-like protein 2; TMPRSS2, transmembrane protease, serine 2; ERG, ETS-related gene; EML4, echinoderm microtubule-associated protein-like 4; ALK, anaplastic lymphoma receptor tyrosine kinase; NFIB, nuclear factor 1 B-type; ESRRA, estrogen receptor related alpha; FGFR3, fibroblast growth factor receptor 3; GBM, glioblastoma multiforme; BC, bladder cancer TACC3, transforming acidic coiled-coil containing protein 3; PTPRK, protein tyrosine phosphatase receptor type K; RSPO3, R-spondin family protein 3; EIF3E3, eukaryotic translation initiation factor 3, subunit E gene; RT-PCR, reverse transcription polymerase chain reaction.

characterized by undifferentiated, small, round cell tumors occurring in soft tissues and bone; 25% of patients with Ewing sarcoma have metastatic disease at the time of diagnosis[25]. The first detected fusion genes in sarcoma were found in a patient with Ewing sarcoma in 1983. This fusion, which is prevalent in 90% of these patients, forms via translocation between chromosomes 11 and 22, resulting in fusion of the Ewing sarcoma breakpoint region 1 (*EWSR1*) gene to members of the E–twenty six (*ETS*) gene family of transcription factor genes[26-28]. Specifically, the translocation juxtaposes 5' sequences from the *EWSR1* gene with the 3' sequences of friend leukemia virus integration 1 (*FLI1*), which encodes an ETS family transcription factor. This transcription factor contains a DNA-binding motif, which allows for the activation of specific downstream genes when overexpressed. Accumulating evidence suggests that this fusion exhibits specific gene signatures consisting of genes that are up-regulated, such as insulin-like growth factor 1 receptor (*IGF1R*)[29], and genes that are down-regulated, such as insulin-like growth factor binding protein 3 (*IGFBP3*)[30,31]. IGF-1R is a transmembrane receptor that promotes cellular transformation as well as cell survival[32], and is highly overexpressed in malignant tissues[33]. Epidemiologic studies have illustrated that several cancers show a survival correlation with high IGF-1 (the ligand for IGF-1R) and low IGFBP-3 (a binding protein of IGF-1R)[34,35]. Efforts to produce a targeted therapy for *EWSR1-FLI1*–positive patients led to the development of molecules that suppress IGF-1R levels. IGF-1R blockade with these molecules showed promising results *in vitro* and *in vivo*, decreasing cell proliferation, tumorigenesis, and metastasis, and sensitizing cancer cells to radiation and chemotherapy[36]. Although preclinical studies showed promising results, a less dramatic result was observed in phase II clinical trials, where it appeared that only some patients with this fusion benefitted from IGF-1R inhibition[37]. Therefore, current efforts are focused on identifying a measure to predict response to IGF-1R inhibition and on developing more potent therapeutics for *EWSR1-FLI1*–positive patients.

Recent studies have identified another small subset of Ewing sarcoma patients who have fusions between the nuclear factor of activated T-cell transcription factor family with *EWSR1*[38]. The nuclear factor of activated T-cell family, like the *ETS* gene family, encodes transcription factors; these proteins are implicated in immune response and are present in cells of the immune system.

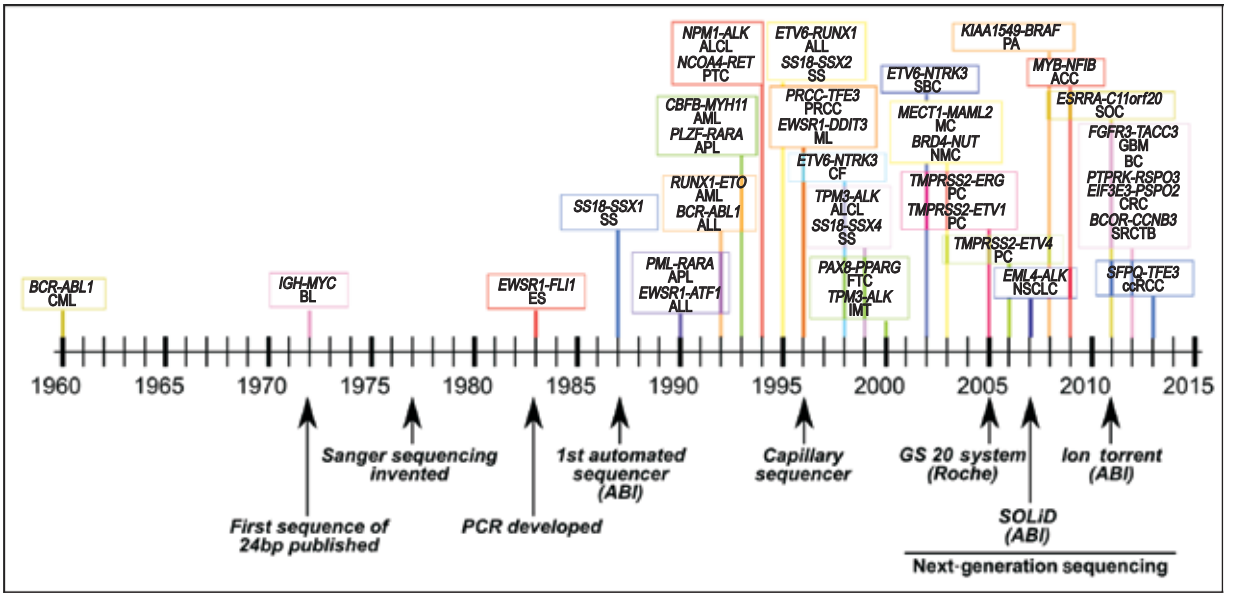

Figure 2. **Discovery of fusions coincides with improved DNA sequencing technologies. The top of the timeline denotes the year in which the particular fusion was discovered. The bottom denotes the year in which DNA sequencing technologies became available. CML, chronic myelogenous leukemia; BL, Burkitt lymphoma; ES, Ewing sarcoma; SS, synovial sarcoma; APL, acute promyelocytic leukemia; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ALCL, anaplastic large cell lymphoma; PRCC, pediatric renal cell carcinoma; ML, myxoid liposarcoma; CF, congenital fibrosarcoma; FTC, follicular thyroid carcinoma; IMT, inflammatory myofibroblastic tumor; SBC, secretory breast carcinoma; MC, mucoepidermoid carcinoma; NMC, nut midline carcinoma; PC, prostate cancer; NSCLC, non–small cell lung cancer; PA, pilocytic astrocytoma; ACC, adenoid cystic carcinoma; SOC, serous ovarian cancer; GBM, glioblastoma multiforme; BC, bladder cancer; CRC, colorectal cancer.**

Small round cell tumors of the bone (EWSR1-ETS–negative)

Ewing sarcoma and osteosarcoma are the most predominant bone sarcomas. As mentioned previously, Ewing sarcoma is characterized by exhibiting fusions between *EWSR1* and the ETS family of transcription factors[28]. Recently, other fusions have been observed in patient samples that histologically resemble Ewing sarcoma but lack the canonical fusion. Specifically, fusions between the BCL-6 corepressor (*BCOR*) gene and cyclin B3 (*CCNB3*) gene were identified in 4% (24/594) of *EWSR1-ETS*–negative patients[38]. The authors concluded that they discovered a new subset of "Ewing-like" tumors that are characterized by this *BCOR-CCNB3* fusion but lack other known Ewing sarcoma fusions[38].

Synovial sarcoma

Synovial sarcoma is a type of soft tissue sarcoma that most commonly forms near the joints of the arm or leg but has been documented in various places in the body, including the heart, prostate, and brain. It is extremely aggressive and occurs equally in children and adults[39]. The term "synovial sarcoma" was coined from the appearance of the cancer as having a microscopic similarity to tumors of the synovium in the joints. A fusion that resulted from a reciprocal translocation was discovered in 1995 between the X chromosome and chromosome 18, fusing one of the three synovial sarcoma X (*SSX*) genes (*SSX1*, *SSX2*, and *SSX4*), which are cancer-testis antigens, with the transcriptional coactivator *SS18* on chromosome 18[40-43]. This fusion occurs in almost all patients diagnosed with synovial sarcoma and joins the transcriptional activation domain of *SS18* to the transcriptional repression domains of the *SSX* genes. *In vitro* and *in vivo* studies have shown that the presence of this fusion is required to support tumorigenesis[44]. The primary function of the *SS18-SSX1* and *SS18-SSX2* fusions is purportedly to regulate transcription, although no canonical DNA-binding domain exists in the fusion[45]. However, current results have illustrated that SS18-SSX can serve as a bridge between activating transcription factor 2 (ATF-2) and the transducing-like enhancer of split 1 to repress ATF-2 target genes, leading to tumorigenesis. Treatment with histone deacetylase inhibitors abolished this effect[46], in agreement with preclinical models illustrating the sensitivity of synovial sarcomas to these inhibitors[47,48].

Other sarcomas

Clear-cell sarcoma is a highly aggressive but rare sarcoma that is most commonly diagnosed in elder adults and often occurs in tendons within the extremities[49]. These sarcomas commonly harbor a translocation fusing *EWSR1* on chromosome 22 to *ATF1* on chromosome 12. This translocation was discovered in 1990 and occurs in approximately 90% of patients with this type of tumor[50,51].

Mixoid liposarcoma is a cancer that arises from the fat. A fusion between chromosomes 12 and 16 occurs in nearly 90% of these tumors and fuses the fused in sarcoma (*FUS*) gene to DNA damage-inducible transcript 3 (*DDIT3*), which has been found to exert oncogenicity by altering transcription activity and thereby manipulating the oncogenic NF-κB pathway[52].

Fusion genes in carcinoma

A carcinoma is a tumor arising from cells of epithelial origin, specifically those from the endodermal or ectodermal germ layer during embryogenesis. A carcinoma, then, retains properties of epithelial cells[53] and most commonly occurs in the prostate, breast, lung, bladder, colon, and pancreas.

Prostate cancer

Prostate cancer arises from cells in the prostate and most commonly occurs in males over the age of 50. It is the sixth leading cause of cancer-related death in men worldwide[54]. Three fusion genes have been characterized in prostate cancer, occurring in 50% to 70% of patients. These fusions join the androgen-regulated promoter for transmembrane protease, serine 2 (*TMPRSS2*) gene with genes encoding the ETS transcription factors v-ets avian erythroblastosis virus E26 oncogene homolog (*ERG*), ETS variant gene (*ETV1*), and *ETV4*[55,56], which leads to the overexpression of these oncogenic transcription factors in an androgen-regulated manner[57]. Fusions containing another androgen-regulated promoter for the solute carrier family 45, member 3 (*SLC45A3*) gene have also been reported to be fused to the same three ETS family members and behave in a similar fashion to *TMPRSS2*, although this fusion occurs less commonly[58]. A more recent finding in prostate cancer is a fusion of *SLC45A3* to the fibroblast growth factor receptor 2 (*FGFR2*) gene[23], which encodes a receptor tyrosine kinase implicated in various cancers, including breast, gastric, ovarian, lung, and endometrial cancers[59].

The current standard of care for prostate cancer patients can include anti-androgen therapy, which aims to limit the amount of androgens in the body that are capable of reaching the prostate. Research on prostate cancer should include studies of the effect of anti-androgen drugs on *TMPRSS2* fusion–positive or *SLC45A3* fusion–postive patients and/or cell lines.

Breast carcinomas

Secretory breast carcinoma is a rare (less than 1% of cases) type of breast carcinoma that occurs most commonly in young women (median age of 25 years). Patients diagnosed with secretory breast carcinoma usually have a favorable prognosis. This type of cancer is called “secretory” because an abundant secretion of mucin occurs within the tumor. In 2002, the *ETV6*−neurotrophic tyrosine receptor kinase, type 3 (*NTRK3*) fusion was discovered, which fused *ETV6*, an ETS family transcription factor located on chromosome 12, with *NTRK3*, which is located on chromosome 15[60]. This fusion, originally characterized in congenital fibrosarcoma[61], was found to promote oncogenesis via activation of the Ras-MAPK and PI3K-AKT pathways[62,63].

Other fusions have been reported in metastatic breast cancers that fuse FGFR family members to various proteins, including *FGFR3*-AF4/FMR2 Family, member 3 (*AFF3*), *FGFR2*-caspase 7 (*CASP7*), *FGFR2*−coiled-coil domain containing 6 (*CCDC6*), and *FGFR1*−endoplasmic reticulum lipid raft-associated 2 (*ERLIN2*). However, these fusions are not recurrent[23].

Bladder cancer

Bladder cancer arises from the epithelial lining within the urinary bladder. More than half of the cases in men and one-third of the cases in women are associated with smoking[64]. Bladder cancer is the fourth most common type of cancer in men and ninth most common in women in the United States. Bladder cancer is historically associated with activating mutations in the *FGFR3* gene but has recently been shown to also harbor *FGFR3-TACC3* fusion in about 10% of patients[22]. This fusion contains part of the *TACC3* gene, which encodes a microtubule-associated protein known to be involved in mitosis. This fusion was found to promote MAPK signaling in bladder cancer cell lines, as well as increased cell proliferation and transformation[22]. Around the same time, the *FGFR3*-BAI1–associated protein 2-like 1 (*BAIAP2L1*) gene fusion was discovered in 4 patients, and contained the *FGFR3* gene fused to the *BAIAP2L1* gene. This fusion links signals at the plasma membrane to actin reorganization within the cell and is expressed in the bladder, liver, testes, heart, and lung. This fusion protein is phosphorylated by Src, an event that promotes cell migration[65].

Colorectal cancer

Colorectal cancer is characterized by uncontrolled cell growth in either the large intestine or the appendix, and is the fourth most prevalent cancer[66]. Colorectal cancer is the third most diagnosed cancer in the world and kills over 608,000 people annually, although 75% to 95% of colon cancer patients have no genetic predisposition for the disease[67,68]. The first fusion discovered in colorectal cancer contains R-spondin family members, and is found in approximately 10% of colon tumors[69]. R-spondin family proteins (RSPO) are involved in cellular proliferation, differentiation, and maintenance of stem cells by modulating the Wnt/β-catenin pathway[70]. The protein tyrosine phosphatase receptor type K (*PTPRK*)–*RSPO3* fusion joins *RSPO3* to *PTPRK*, a putative tumor suppressor gene in melanoma[71], lymphoma[72], lung cancer[73], and prostate cancer[74]. The other *RSPO* fusion connects the eukaryotic translation initiation factor 3, subunit E gene (*EIF3E*) to *RSPO2*, which is the largest translation initiation factor in mammals[75]. Studies found that both RSPO family fusions, *PTPRK-RSPO3* and *EIF3E-RSPO2*, activated the Wnt signaling pathway *in vitro*, and found that fusion-positive tumors carried alterations in the Wnt pathway. Thus, therapeutic strategies targeting Wnt pathway signaling may be proven to be an effective treatment for fusion-positive colorectal cancer[37].

Ovarian cancer

Ovarian cancer accounts for 3% of all cancers among women and is estimated to result in 140,000 deaths in women every year. Women are at the highest risk for developing ovarian cancer if they have a family history of breast, ovarian, endometrial, prostate, or colon cancers, and more so if their mother or sister had ovarian cancer. Ovarian cancers can further be classified into subtypes based on molecular features of the tumor.

Serous ovarian cancer is the most common subtype of ovarian cancer, and is especially lethal because it normally goes undetected until it has already progressed and spread to other tissues. The

estrogen receptor–related alpha (*ESRRA*)–*C11orf20* fusion gene was discovered in 2011 and was found to occur in 15% of samples tested[76]. The fusion connects the *ESRRA* gene to the *C11orf20* gene, an uncharacterized but conserved gene in the mammalian genome. ESRRA is a nuclear receptor that resembles the estrogen receptor and regulates transcription. Interestingly, ESRRA expression correlates with poor prognosis in both breast and ovarian cancers[77,78]. However, the functional role of this fusion has yet to be established.

Lung cancers

Non–small cell lung cancer (NSCLC) accounts for nearly 80% of lung cancer cases and exhibits a median survival of less than one year following diagnosis[79]. NSCLC can be divided into 3 main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Adenocarcinoma accounts for approximately 40% of all lung cancers and starts in mucus-secreting cells. Although commonly found in smokers, this type of lung cancer is also the most prevalent lung cancer observed in non-smokers. The first fusion to be discovered in adenocarcinoma joined the echinoderm microtubule-associated protein-like 4 (*EML4*) gene on chromosome 2 to the anaplastic lymphoma receptor tyrosine kinase (*ALK*) on chromosome 2 via inversion. This highly transforming oncogene, *EML4-ALK*, is found in approximately 4% of NSCLC patients[80]. The oncogenic function of the fusion is believed to be caused by overexpression of the ALK tyrosine kinase, which leads to constitutive activation of downstream signaling cascades, including Akt, MAPK, and signal transducer and activator of transcription 3 (STAT3)[81]. The ALK inhibitor PF02341066, known as crizontinib, is currently undergoing clinical trials and has demonstrated significant clinical efficacy thus far in patients with *EML4-ALK*–positive NSCLC[82]. Other fusions have also been reported in lung adenocarcinomas, including the kinesin family member 5B-rat proto-oncogene (*KIF5B-RET*)[83,84], *CCDC6*-c-ros oncogene 1 (*ROS1*), and *FGFR2*-citron (*CIT*) [85].

Lung squamous cell carcinoma accounts for 30% of NSCLCs. It arises from the tissue that lines the air passages in the lungs and is strongly linked to smoking. Three different fusions have been reported in lung squamous cell carcinoma, all of which contain members of the FGFR family. The *FGFR3-TACC3* fusion, initially reported in glioblastoma multiforme (GBM)[21,80] and bladder cancers[22], has also been found in patients with lung squamous cell carcinoma (n = 4), whereas two other fusions, *FGFR3-KIAA1967* (n = 1) and *FGFR1*-BCL2−associated athanogene (*BAG4*) (n = 1), were not recurrent[23].

Adenoid cystic carcinoma

The adenoid cystic carcinoma subtype is a rare form of adenocarcinoma. Occuring most often in the salivary glands of the head and neck but sometimes in the uterus, this subtype spreads along the nerves or throughout the bloodstream. Adenoid cystic carcinoma is the most common malignant salivary gland tumor, and although tumors are typically slowly growing, they are still aggressive, yielding poor patient prognosis[86].

In 2009, a group discovered the *MYB*−nuclear factor 1 B-type (*NFIB*) fusion, which formed as a result of translocation between chromosomes 6 and 9, with on occurrence rate of 90%. The *MYB* gene encodes the MYB proto-oncogene, which is a member of the myeloblastosis family of activating transcription factors. NFIB is a transcription factor that contains a DNA-binding and dimerization domain[87]. In fact, pleomorphic salivary gland adenomas have also been shown to harbor fusions of *NFIB* with high mobility group AT-Hook 2 (*HMGA2*)[88]. The formation of the *MYB-NFIB* fusion resulted in the deletion of the 3' untranslated region of *MYB*. This allowed the fusion mRNA to go undetected by specific microRNA that usually would target, and therefore degrade, any mRNA transcribed from the *MYB* gene. A similar mechanism facilitating oncogene overexpression has recently been described in GBM (please see "GBM" section)[20]. Overexpression of MYB then changed the expression landscape in these tumors and as a result increased the expression of *MYB*-activating genes, including survival genes B-cell lymphoma 2 (*BCL2*) and set nuclear oncogene (*SET*), as well as genes associated with cell proliferation and angiogenesis such as vascular endothelial growth factor a (*VEGFA*), and fibroblast growth factor 2 (*FGF2*). The authors of this study concluded that this fusion may serve as a highly beneficial therapeutic target for adenoid cystic carcinoma[89].

Mucoepidermoid carcinoma

Mucoepidermoid carcinomas are common salivary gland neoplasms, account for 35% of all salivary cancers, and are most common in adults between the ages of 20 to 40 years. The mucoepidermoid carcinoma translocated 1 (*MECT1*)–Notch coactivator mastermind-like protein 2 (*MAML2*) fusion occurs in approximately 60% of patients with mucoepidermoid carcinoma[90] and contains the *MECT1* gene, also known as CREB-regulated transcription coactivator 1, fused to *MAML2*[91]. The fusion was found to induce Notch signaling and cause cellular transformation of RK3E epithelial cells[90]. Recent studies have shown that the presence of *MAML2* rearrangements as measured by fluorescence *in situ* hybridization can be used as a mean to distinguish mucoepidermoid carcinoma from other oncocytic lesions[92].

Follicular thyroid carcinoma

Thyroid cancer is the most common type of endocrine cancer and is classified according to histopathologic characteristics. The main type of thyroid cancer is papillary thyroid carcinoma (75% to 85% of cases), which often occurs in young females and most commonly metastasizes to cervical lymph nodes[93]. The next most common type is follicular thyroid cancer (10% to 20% of cases) and is most common in women over the age of 50 years[93]. Unlike papillary thyroid carcinoma, follicular thyroid carcinoma normally metastasizes via the bloodstream to the lung and bone.

In 2000, the paired box gene 8 (*PAX8*)−peroxisome proliferator-activated receptor gamma (*PPARG*) fusion was identified in 60% of follicular thyroid cancer cases[94]. The fusion contains the transcription factor *PAX8*, a gene that encodes a nuclear protein involved in follicular cell development in the thyroid. *PPARG* is a regulator of fatty acid storage and glucose metabolism, where mice that do not have *Pparg* fail to generate adipose tissues[95]. The fusion contains the

promoter and 5' coding sequence for *PAX8* and most of the coding sequence for *PPARG*. The *PAX8* promoter being active in thyroid cells causes high expression of the fusion[94] and therefore induces tumorigenesis by increasing cell cycle progression, cell survival, and loss of anchorage-dependent cell growth[96].

Clear cell renal cell carcinoma (RCC)

RCC is cancer of the kidney that originates in the epithelial cells that line the proximal convoluted tubule. RCC makes up 80% of kidney cancer cases[97]. Clear cell RCCs are histologically characterized by cells with a clear cytoplasm surrounded by distinct cell membranes. Clear cell RCC cases make up 60% to 70% of RCC cases. The recurrent fusion *SFPQ-TFE3*, a fusion that was previously linked to non-clear cell translocation–associated RCC[98], was recently identified in small series of clear cell RCC patient samples (5 of 416 samples, 1.2%)[99]. Another fusion was also identified, connecting the trk-fused gene (*TFG*) gene to G protein-coupled receptor 128 (*GPR128*), in about 1% of patients analyzed[99].

Fusion genes in tumors of the central nervous system

Central nervous system tumors can be classified based on the cell type from which they arose in the brain or spinal cord. Tumors arising from glial cells, the meninges, pituitary glands, and nerve sheaths are termed glioma, meningioma, pituitary adenomas, and nerve sheath tumors, respectively. Glioma comprise 50.4% of all primary brain tumors[100]. Gliomas are further classified according to the type of glial cells from which they originate. More specifically, tumors arising from astrocytes are called astrocytoma, ependymal cells are ependymomas, and tumors arising in oligodendrocytes are called oligodendroglioma. According to the World Health Organization, each type of glioma is then further classified according to grade, or severity, of the tumor. Astrocytomas are graded on a scale from I to IV. Grade IV tumors, GBM, yield the worst prognosis for patients and are also the most common and aggressive type of primary brain tumor in humans.

GBM

The *FGFR3-TACC3* fusion gene, which has been reported in bladder[22] and lung cancers[23], has recently been identified in a subset of glioblastoma patients, yielding a recurrence rate between 0% and 5%[20,21]. This fusion has been found to induce ERK and STAT3 signaling and also to promote tumorigenesis both *in vitro* and *in vivo*[20,21]. Similar to the *MYB-NFIB* fusion found in adenoid cystic carcinoma, the *FGFR3-TACC3* fusion was found to be overexpressed via lack of microRNA regulation. Specifically, the 3'-untranslated region of *FGFR3* is lost in the fusion, allowing it to go undetected by miR-99a, a microRNA that is highly prevalent in both GBM and normal brain[20]. Because of high miR-99a levels in the brain, expression of endogenous wild-type *FGFR3* is exceedingly low. Therefore, treatment of *FGFR3-TACC3*–positive patients with an FGFR3 inhibitor may be proven to be a valuable therapy, as it would target tumor-positive (i.e., *FGFR3-TACC3*–positive) tissues while sparing normal, healthy tissues that do not express *FGFR3*[20]. Another fusion (*FGFR1-TACC1*) was also discovered in GBM but was only found in one patient[21].

Pilocytic astrocytoma

Pilocytic astrocytoma is a type of benign brain tumor that commonly arises in the cerebellum in the base of the brain and most frequently occurs in young adults. The most common fusion observed in pilocytic astrocytoma links the *KIAA1549* gene to *BRAF* and occurs in 70% of pilocytic astrocytoma cases[101]. The *BRAF* gene encodes the proto-oncogene *B-Raf*, which is frequently mutated in a wide variety of cancer types[102].

Conclusions

Genomic instability is a hallmark of cancer and can be described as gene mutation, amplification, translocation, deletion, and inversion events. The discovery of fusion genes in hematologic malignancies in the 1970s led to the development of potent therapeutics. Fusion genes also showed their value by serving as a diagnostic tool to monitor treatment progress by measuring the disappearance of the fusion and, thus, the disappearance of the tumor tissue. The development of more sophisticated sequencing technologies in the early 21st century led to the discovery of more fusion genes in solid tumors. There are currently several clinical trials aimed at treating fusion-positive patients with a range of targeted therapies, which will hopefully lead to better treatment options for patients in the future.

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