KIT (CD117): A Review on Expression in Normal and Neoplastic Tissues, and Mutations and Their Clinicopathologic Correlation

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Abstract: CD117 (KIT) is a type III receptor tyrosine kinase operating in cell signal transduction in several cell types. Normally KIT is activated (phosphorylated) by binding of its ligand, the stem cell factor. This leads to a phosphorylation cascade ultimately activating various transcription factors in different cell types. Such activation regulates apoptosis, cell differentiation, proliferation, chemotaxis, and cell adhesion. KIT-dependent cell types include mast cells, some hematopoietic stem cells, germ cells, melanocytes, and Cajal cells of the gastrointestinal tract, and neoplasms of these cells are examples of KIT-positive tumors. Other KIT-positive normal cells include epithelial cells in skin adnexa, breast, and subsets of cerebellar neurons. KIT positivity has been variably reported in sarcomas such as angiosarcoma, Ewing sarcoma, synovial sarcoma, leiomyosarcoma, and MFH; results of the last three are controversial. The variations in published data may result from incomplete specificity of some polyclonal antibodies, possibly contributed by too high dilutions. Also, KIT is expressed in pulmonary and other small cell carcinomas, adenoid cystic carcinoma, renal chromophobe carcinoma, thymic, and some ovarian and few breast carcinomas. A good KIT antibody reacts with known KIT positive cells, and smooth muscle cells and fibroblasts are negative. KIT deficiency due to hereditary nonsense/missense mutations leads to disruption of KIT-dependent functions such as erythropoiesis, skin pigmentation, fertility, and gastrointestinal motility. Conversely, pathologic activation of KIT through gain-of-function mutations leads to neoplasia of KIT-dependent and KIT-positive cell types at least in three different systems: mast cells/myeloid cells—mastocytosis/acute myeloid leukemia, germ cells—seminoma, and Cajal cells—gastrointestinal stromal tumors (GISTs). KIT tyrosine kinase inhibitors such as imatinib mesylate are the generally accepted treatment of metastatic GISTs, and their availability has prompted an active search for other treatment targets among KIT-positive tumors such as myeloid leukemias and small cell carcinoma of the lung, with variable and often nonconvincing results.

Key Words: KIT, CD117, gastrointestinal stromal tumor, lymphoma, melanoma, seminoma, carcinoma, mutation

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KIT receptor tyrosine kinase was assigned cluster number CD117 during the fifth international conference of leukocyte typing in Boston in November 1993. KIT is a tyrosine kinase growth factor receptor expressed in diverse cell types, including Cajal cells of the gastrointestinal tract, mast cells and subsets of hematopoietic stem cells, germ cells, and melanocytes. The significance of KIT is illustrated by the consequences of its inactivating mutations that lead to impairment of dependent cell types with macrocytic anemia, sterility, and loss of skin pigmentation. Conversely, gain-of-function KIT mutations lead to tumors of KIT-dependent cell types, such as Cajal cells (gastrointestinal stromal tumors [GISTs]), mast cells, and germ cells.[1] The new KIT tyrosine kinase inhibitor imatinib mesylate (Gleevec, Novartis Pharma, Basel, Switzerland, formerly known as STI571) as an effective treatment of metastatic and unresectable GISTs has sparked a wide interest in the search for other KIT-driven tumors.[2] To date, nearly all types of tumors have been tested for KIT positivity as potential targets for KIT inhibitor treatment, but mutational KIT activation has only rarely been found and therapeutic success has been less clear, perhaps with the exception of some myeloid leukemias. Variability and poor reproducibility of KIT staining have been prevalent problems, especially with polyclonal antisera, and this has led to significant data heterogeneity, which is currently difficult to reconcile for some tumors.

In this article we provide a short, practically oriented review on the structure and function of KIT and its expression and known mutations. Expression without mutational activation will also be discussed, with brief comments on KIT tyrosine kinase inhibitor treatment.

HISTORY

KIT was originally isolated as a retroviral oncogene (v-kit) from the acute transforming Hardy-Zuckerman 4 feline retrovirus. Also, its cellular homolog (c-kit) was identified in normal cat DNA and was found to have homologies with other tyrosine kinase oncogenes by Besmer et al in 1986.[3] KIT was named by its isolation from a pet cat from a peripheral soft

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tissue tumor diagnosed as a fibrosarcoma. The name KIT (instead of c-kit) is often and is here used for simplicity for both the protein and gene name. Usually the context tells which one is meant; the gene name can be italicized for clarity.

KIT was soon after its discovery defined as a receptor tyrosine kinase[4] and identified as the gene product of the previously known white-spotting (W) locus of mouse and rat;[5,6] its partial loss of function conveys a phenotype with defective skin pigmentation, macrocytic anemia, lack of mast cells and infertility, but the most severe loss of function mutations are lethal to embryos.[7,8]

Subsequently, stem cell factor (mast cell growth factor) was identified as the KIT ligand and was found to correspond with the mouse Steel (Sl) locus, whose functional defect conveys similar phenotypic traits as defects in the W locus, indicating the functional relationship between KIT and its ligand.[9,10]

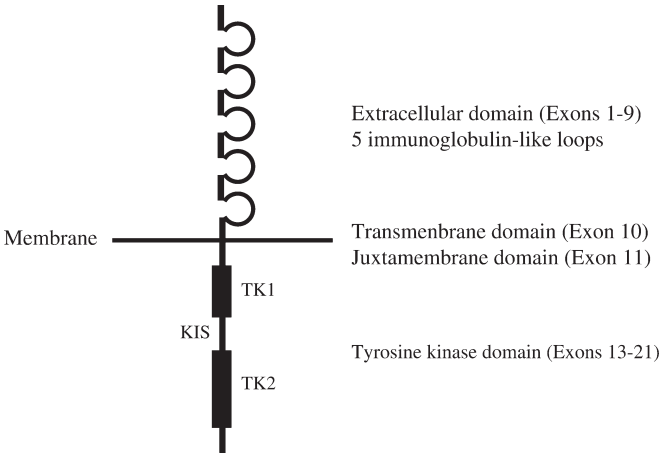

FIGURE 1. KIT protein and its different domains. Amino-terminus is at the top and carboxy-terminus at the bottom.

KIT GENE AND PROTEIN

In human, KIT gene has been mapped at chromosome 4q12 in the pericentromeric location of the long arm of chromosome 4, adjacent to the highly homologous PDGFRA gene.[4,11] In mouse, KIT maps to chromosome 5 and was identified as the gene corresponding the white-spotting (W) locus.[4,5]

The genomic DNA of human KIT gene spans approximately 89 kB and contains 21 exons.[12,13] There is high homology in the coding sequences between human and mouse KIT, indicating high evolutional conservation.[14] The typical KIT cDNA is approximately 3.5 kB. Splice variants such as GNNK+/− that alternatively splices 12 bp immediately following exon 9 sequences were found in a variety of normal and neoplastic tissues and were shown to have different signaling capabilities.[15]

KIT protein (relative molecular mass 145 kD) is a transmembrane protein that belongs to the type III subfamily of the receptor tyrosine kinases, including PDGFRA/B, FLT3, and GM-CSF. All of these have similarly composed extracellular and two-part (split) intracellular tyrosine kinase domains.[16]

The extracellular domain of KIT contains five immunoglobulin-like loops (encoded by exons 1–9), a transmembrane domain (encoded by exon 10), a juxtamembrane domain (encoded by exon 11), and a split tyrosine kinase domain encoded by exons 13–21. The kinase domain is composed of TK1, kinase insert (KIS), and TK2 (Fig. 1). The second immunoglobulin-like loop is the high-affinity ligand binding site.[17] The KIT juxtamembrane domain (JM) contains alpha-helical elements whose proper configuration is essential to inhibitory regulation of tyrosine phosporylation.[18]

The KIT ligand stem cell factor, also known as mast cell growth factor and formerly as Steel factor, is a growth factor produced, among others, by fibroblasts and mast cells. It appears both in soluble and membrane-bound form. Under normal circumstances, the ligand binding links two KIT molecules to a dimer, leading to cross-phosphorylation of specific tyrosine residues in the catalytic domain and elsewhere. These then phosphorylate and activate downstream protein targets such as mitogen-activated protein kinase (MAPK) in a cascade manner. The ultimate phosphorylation targets include transcription factors, some of which are cell type specific. They include the family of signal transducers and activators of transcription (STAT) proteins, microphthalmia transcription factor in melanocytes, and Slug in hematopoietic cells and germ cells.[15] The end results of KIT activation include regulation of apoptosis, cell proliferation, differentiation, adhesion, and motility.[1,19]

KIT ACTIVATING MUTATIONS

KIT activating mutations have been documented in a variety of human and animal tumors. Activating mutations typically confer constitutional KIT phosphorylation and downstream activation independent of ligand binding. These mutations represent a spectrum of changes such as point mutations, in frame deletions, and internal tandem duplications and combinations thereof. Some of KIT mutations have specific clinicopathologic connotations and differ in inhibitor sensitivity. A great majority of KIT mutations cluster in relatively small regions (KIT JM exon 11, KIT TK2, exon 17). Less frequently, mutations are seen in KIT extracellular domain (exons 2, 8, and 9) or KIT TK1 (exons 13 and 14). In general, involvement of different regions is mutually exclusive. However, a few studies reported tumors with more than one KIT mutation.[1,20]

KIT ANTIBODIES AND KIT DETECTION IN DIFFERENT ORGAN SYSTEMS

Numerous polyclonal and monoclonal anti-KIT antibodies have been produced and made commercially available. Unfortunately, the quality of many of them has fluctuated, probably because the high interest in KIT detection created a demand exceeding the resources used for quality assurance. Therefore, the reagent user must rigorously test each new batch with positive and negative controls to ensure high specificity and sensitivity. Often it has been difficult to interpret the significance of weakly positive staining. In some

earlier surveys, weak positive staining in many tumors has not been reproducible with other antibodies.

Whether epitope retrieval techniques such as heat should or should not be used may depend on the antibody and dilution used. Most investigators, including us, have used heat retrieval with acid (citrate, ph 6.0) or alkaline buffer (EDTA, 372 mg/L, pH 8.0). Others have advocated the use of no epitope retrieval, but in our experience this leads to loss of detection sensitivity; such a technique has yielded lower percentages of positivity in tumor categories others have found to be more commonly KIT positive.

The normal cell types immunohistochemically positive for KIT include mast cells, certain hematopoietic stem cells, germ cells, melanocytes, gastrointestinal Cajal cells, epithelial cells such as ductal epithelia of breast, sweat gland epithelia, some basal cells of skin adnexa, and subsets of neurons, especially in the cerebellum (Fig. 2).[21–26] Each of these can serve as a positive control for IHC. Good negative controls include normal smooth muscle and lymphoid tissue.

Below we review different cell type and organ systems for KIT expression. These systems include Cajal cells and gastrointestinal stromal tumors (GISTs), other sarcomas,

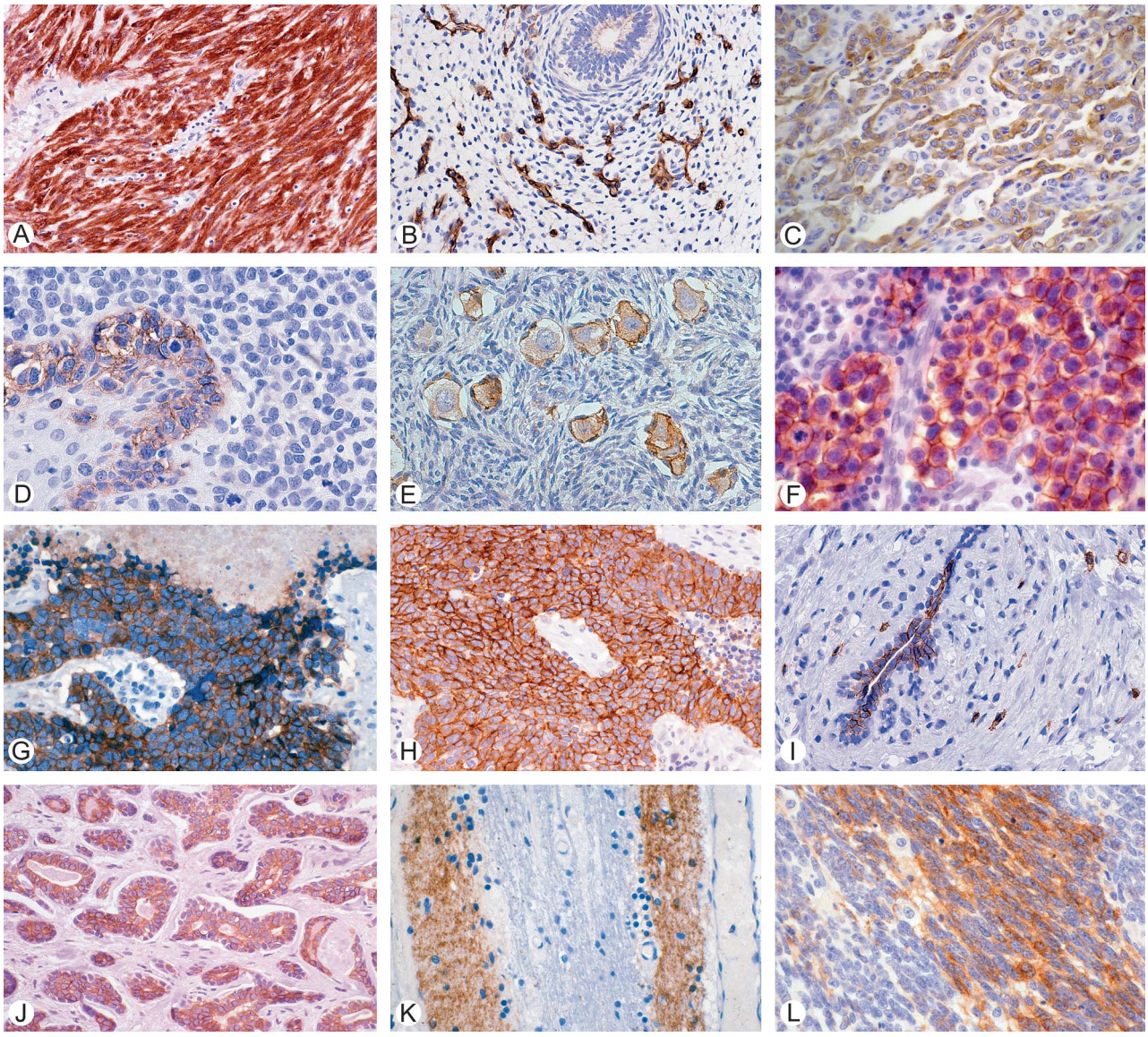

FIGURE 2. Examples of KIT expression in normal and neoplastic tissues. A, Strong positivity in spindle cell GIST. B, Fetal pulmonary capillaries are KIT positive, in contrast to adult endothelia. C, Angiosarcoma shows patchy KIT positivity. D, Junctional component of cutaneous melanoma is KIT positive, but the invasive component is negative. E, Ovarian primordial follicular germ cells are KIT positive. F, Seminoma shows membrane positivity for KIT. G, Small cell carcinoma is KIT positive. H, This pulmonary large cell neuroendocrine carcinoma shows membrane positivity for KIT. I, Normal breast epithelium is KIT positive, but invasive lobular carcinoma is negative. Note positive mast cells between tumor cells. J, Adenoid cystic carcinoma of salivary gland is KIT positive. K, The molecular layer of adult cerebellum is KIT positive. L, This poorly differentiated neuroblastoma is KIT positive.

melanocytes and melanoma, germ cells and their tumors, hematopoietic cells and tumors, and some carcinomas (see Fig. 2). Some carcinomas, such as small cell carcinoma of lung, are KIT-positive without known KIT-positive ancestral cells. In some organ systems, the normal cells, for example ductal epithelia of breast, are generally KIT-positive, whereas KIT expression is lost in corresponding tumors.

KIT IN CAJAL CELLS AND GIST

Cajal Cells

Interstitial cells of Cajal (ICCs) are dendritic-shaped, delicate mesenchymal spindle cells located around the myenteric plexus from the esophagus to the anus and at least in some parts of the GI tract also inside the muscular layers. ICCs were discovered by the Spanish histochemist Santiago Ramon y Cajal by silver stains; these cells are almost impossible to detect with conventional histologic stains. Now they can be easily identified as unique, immunohistochemically KIT-positive GI tract cells (with the exception of mast cells).

ICCs are functional intermediaries between the autonomic innervation and smooth muscle cells and regulate intestinal peristalsis and autonomic nervous system function. ICCs were found to be KIT dependent, because KIT-deficient mice lacked their development and suffered from intestinal dysmotility.[25,26] Cajal cells include a subset of multipotential stem cell-like components that can differentiate into smooth muscle cells after disruption of KIT signal.[27]

KIT Expression in GISTs

Based on cumulative knowledge, GISTs are defined as KIT or PDGFRA driven, almost uniformly KIT-positive spindle cell, epithelioid, or rarely pleomorphic mesenchymal tumors that phenotypically resemble Cajal cells and probably originate from their stem cell pool.[20,28–30] GISTs occur throughout the GI tract and are most common in the stomach and small intestine, where they are the most common mesenchymal tumors, encompassing a spectrum from benign to malignant.[20,31] In most cases, these tumors are strongly KIT positive regardless of the site of origin (see Fig. 2A). Tumors with spindle cell morphology typically have diffuse cytoplasmic and membrane positivity, whereas tumors with epithelioid morphology may show a distinct membrane staining. In addition, there is often Golgi zone-like perinuclear dot-like staining.[32] Some epithelioid tumors have only focal KIT positivity, and up to 5% to 7% of gastric GISTs, especially those that carry PDGFRA instead of KIT mutations, can be immunohistochemically KIT negative.[33,34]

KIT Mutations in GISTs

Sixty to 70% of GISTs have KIT activating mutations. Examples of these are shown in Figure 3. Most common are KIT exon 11 mutations, which occur in tumors anywhere in the GI tract.[35–39] These include in frame deletions of one to several codons, most often involving codons 557–560, point mutations, and internal tandem duplications, typically in the 3′-part of exon 11. Deletions may be associated with a more aggressive course than point mutations.[38]

Insertion/duplication of two codons 502-503AY in exon 9 is relatively rare and seen almost exclusively in intestinal versus gastric GISTs; it tends to occur in clinically malignant tumors.[37,39,40] Also, another exon 9 insertion/duplication of three codons, 506–508 FAF, has been reported.[31] Exon 13 mutation K642E and exon 17 mutations (variable point mutations in codon 822) are very rare and have been reported in only a handful of cases.[20,31,40] Several families with constitutional KIT mutations and familial GIST syndrome have been reported. Some of the patients have other signs of pathologic KIT activation, such as cutaneous hyperpigmentation.[41–43] The key role of KIT mutations in GIST pathogenesis is also illustrated by transgenic mice: those with KIT exon 11 deletion similar to those seen in human GISTs develop multiple GISTs.[44]

KIT Tyrosine Kinase Inhibitor Imatinib Mesylate

Imatinib mesylate is an ATP analog that inhibits KIT, PDGFRA/B, and ABL tyrosine kinases. Originally used against chronic myeloid leukemia, in clinical trials it was found to be highly effective against metastatic and unresectable GISTs.[2] The response is best in tumors with exon 11 mutations; response is moderate with exon 9 mutations, poor with wild-type sequences, and expectedly poor with exon 17 mutations because of primary resistance.[31] Secondary resistance often develops within a few years in GISTs treated with imatinib. Its mechanisms include development of secondary KIT mutations (V654A, T670I, D716N, D816G, D820I, D820Y, and N822K), and KIT gene amplification.[45]

KIT IN OTHER MESENCHYMAL CELLS AND TUMORS

Based on several earlier series, sarcomas and mesenchymal tumors other than GISTs are relatively rarely KIT positive. Sarcomas reported at least to some degree as KIT positive by all major series include angiosarcoma and Ewing sarcoma. There is much more variation in reporting on KIT in synovial sarcoma, rhabdomyosarcoma, leiomyosarcoma, and MFH. Sarcomas other than GISTs have not yet been major targets for imatinib, and so far no KIT mutations have been reported in them. Results on the KIT positivity of sarcomas based on several surveys are shown in Table 1.

Endothelial and Vascular Tumors

Although normal adult endothelia are KIT negative by IHC, fetal endothelia, such as pulmonary alveolar capillaries, are KIT positive (see Fig. 2B). Angiosarcomas are often KIT positive (by our study, 56%), showing an oncofetal type of neoexpression (see Fig. 2C), but they do not have KIT exon 11 or exon 17 mutations.[46] Others have shown lower (around 20%[47]) and 0 of 4[48] and higher, nearly consistent (2 of 3) KIT positivity in angiosarcoma.[49] In a series of canine angiosarcomas, KIT expression was found in 7 of 10 tumors, and KIT was not detected in normal endothelia.[50] Hemangioendotheliomas and hemangiomas seem to be KIT negative, although some juvenile hemangiomas of immature phenotype have been positive.[46]

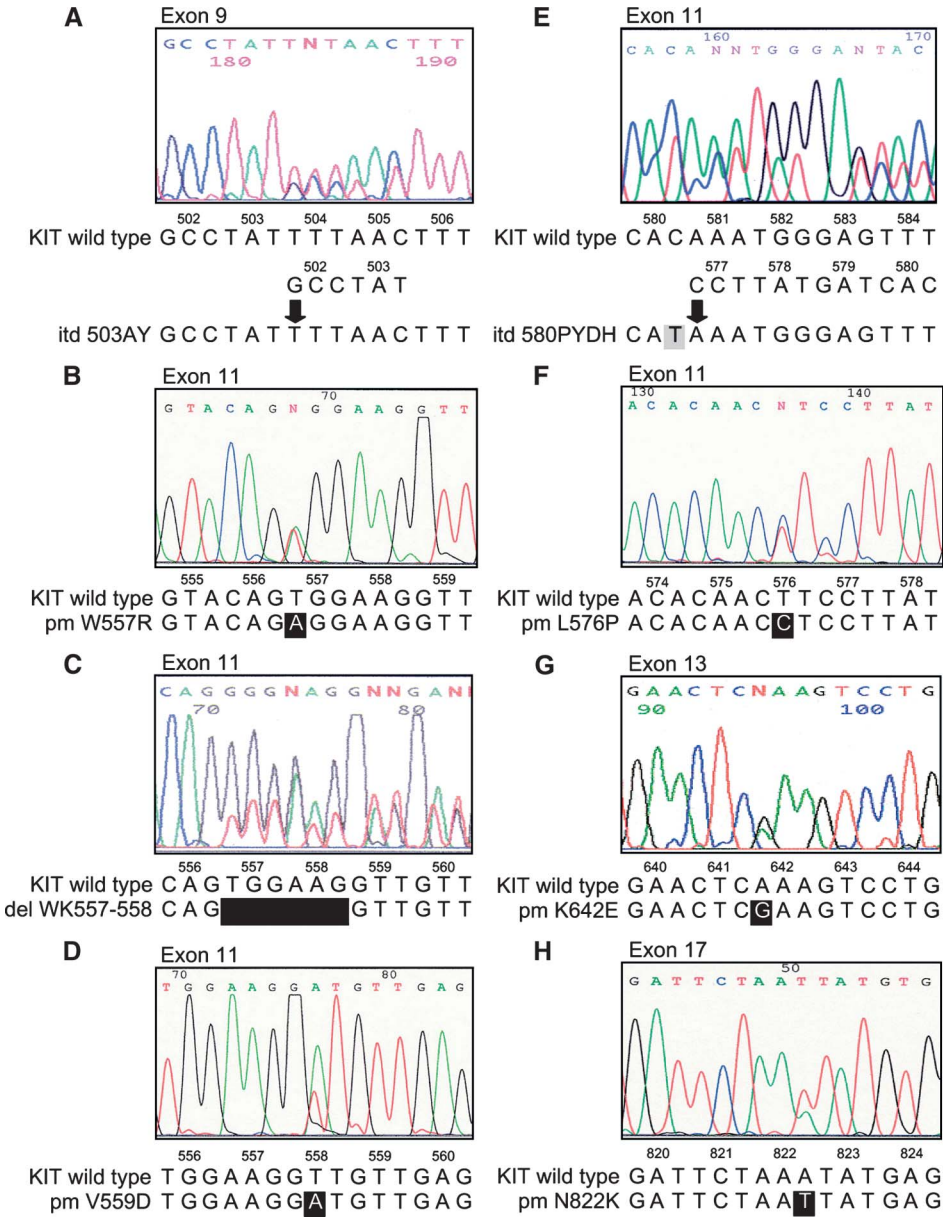

FIGURE 3. Examples of KIT mutations in GISTs, as seen in printouts of automatic direct sequencing. Missense mutations and deletions are indicated by black boxes, silent mutations as gray boxes. A, Internal tandem duplication (itd) in exon 9 involving codons 502 and 503. B, Point mutation (pm) in exon 11, codon 557 W557R. C, In frame deletion (del) encompassing two codonsWK557-558. D, Point mutation in codon 559, V559D. E, Internal tandem duplication in 3′ part of exon 11; codons 577–580 are duplicated. F, Point mutation in 3′ part of exon 11, L576P. G, Point mutation in exon 13, K642I. H, Point mutation in exon 17, N822K.

Kaposi sarcoma is less commonly KIT positive than angiosarcoma (2 of 13) in our experience.[46] In AIDS-associated Kaposi sarcoma, human herpesvirus 8 has been shown to induce KIT expression, and autocrine or paracrine KIT activation occurs.[51] A small clinical trial of imatinib in AIDS-associated Kaposi sarcoma showed partial response or stable disease in most patients.[52]

Ewing Sarcoma

Ewing sarcoma family tumors (ES), including PNETs, are commonly KIT positive by IHC, and KIT expression has been confirmed by Western blotting. In three studies, tissue sections were positive in 31%, 45%, and 65% of cases; the latter series showed higher expression with epitope retrieval.[53–55] In the first study, positivity was not found to be a significant prognostic factor, but based on the second series it was more commonly associated with EWS-Fli1 non-type1 fusions. ES cell lines have been shown positive for KIT and also for stem cell factor, with ligand-dependent KIT phosphorylation indicating a functional receptor with autocrine or paracrine type of activation.[56,57] KIT mutations were not found in complete analysis of KIT coding sequences in four cell lines and four tumor samples.[54]

Imatinib has shown some effectiveness against ES cell lines, but only with concentrations above 10 μm, higher than those obtained with usual clinical doses[58,59]; others have shown resistance to imatinib in vitro.[60] However, this drug may potentiate conventional chemotherapeutic agents, such as doxorubicin.[54] No results are yet available from clinical trials.

TABLE 1. KIT Expression in Some Types of Sarcomas According to Eight Published Series

Angiosarcoma	Synovial Sarcoma, NOS	MFH	Leiomyo Sarcoma	MPNST	RMS, Embryonal and NOS	Endo-Metrial Stromal Sarcoma	Reference
	0/10	1/20	0/10	0/12	0/8		30
5/20	0/20	0/20*	0/40	0/20	0/10	0/10	47
	0/4	3/7	0/4†	0/4			61
	14/14				10/13		63
6/7		20/27	18/22	13/16			64
28/50							46
2/3		2/6			0/6		49
			0/4†			1/10	69
0/4	0/3	0/29	0/37	0/8	0/14	0/3	48

*Designated as myxofibrosarcomas, equaling myxoid MFH.
†Uterine tumors.

Synovial Sarcoma

Synovial sarcomas have been generally KIT negative in our experience, except for weak positivity in the epithelial component of occasional biphasic tumors. Three series without specified subtypes found no positive cases among 34 synovial sarcomas.[29,47,61] However, one series found that 5 of 47 monophasic (11%) and 1 of 13 poorly differentiated tumors (8%) were positive, although only one case showed strong positivity.[62] In contrast, two more recent studies reported all 24 synovial sarcomas as KIT positive, the former examining childhood examples.[63,64]

Co-expression of KIT and stem cell factor has been detected in synovial sarcoma both by mRNA demonstration by RT-PCR and IHC, and KIT was shown by Western blotting.[65] In that study, KIT positivity occurred especially in the epithelial component of biphasic synovial sarcoma. Interestingly, a subsequent study by the same authors[66] did not detect any KIT expression with one of the polyclonal antibodies used (Dako), whereas one third of the cases were positive with another one (Santa Cruz). These and other differences reported in KIT expression in different studies await scientific explanation.

Other Sarcomas and Mesenchymal Tumors

There are significant differences of reported rates of KIT positivity in other sarcomas. Although some studies found no KIT expression, others reported rather widespread KIT positivity in sarcomas other than GISTs (Table 2). In many but not all cases, KIT positivity in these tumors has been reported as weak, which introduces the possibility of background staining. It is difficult to reconcile these differences on a scientific basis, although we believe that reported widespread KIT positivity in non-GIST sarcomas in many instances represents an artifact, possibly related to poor specificity or too high dilutions of certain lots of polyclonal KIT antibodies.

Both embryonal and alveolar rhabdomyosarcomas have been reported as KIT negative in two earlier series,[29,47] but one series showed 10 of 13 (77%) embryonal but 0 of 16 alveolar rhabdomyosarcomas to be KIT positive.[63] Studies on rhabdomyosarcoma cell lines have noted a low level of KIT mRNA, but stem cell factor was expressed in cell lines of alveolar and embryonal rhabdomyosarcomas.[67]

Leiomyosarcomas of soft tissues have been KIT negative based on 50 cases in two earlier series, one of which includes our experience,[29,47] but subsequently have been reported as KIT positive in 20 of 27 (82%) cases.[64] There is similar data heterogeneity on uterine leiomyosarcomas, which were first reported as nearly uniformly KIT negative in four series comprising 35 cases[61,68–70] but subsequently found to be KIT positive in a 35 of 55 cases (64%) in three separate series.[71–73] A large recent survey analyzed 37 leiomyosarcomas and found all to be KIT negative; the occurrence of cytoplasmic-only KIT in 142 not further specified tumors was mentioned, and such positivity occurred despite absorption with KIT peptide, suggesting an antibody reaction due to a cellular component other than KIT.[48] This could well be part of the explanation for divergent results on some tumor entities, such as leiomyosarcoma.

Low-grade endometrial stromal sarcoma has been reported only occasionally as KIT positive (8/51, 16%),[47,68–71,74]

TABLE 2. Examples of KIT Mutations Reported in Acute Myeloid Leukemia

KIT			Mutation	Reference
EC	Exon 2	pm	D52N	141
	Exon 8	del	D419	139, 140
		itd	420DR	139
		del+ins	TYD417-419F	139
		del+ins	TYD417-419Y	139
	Exon 9	itd	502AYFNF	140
JM	Exon 11	ins+itd	575EFCELPYDHKWEFPRNR	140
		ins+itd	571ESVDPTQLPYDHKW	140
		itd	575QLPYDHKWEFPPRNRL	139
KIS	Exon 16	pm	I748T	140
TK2	Exon 17	pm	L773S	140
		pm	D816Y, D816V, D816H	140
		pm	N822K	140
		pm	V825I	140

del, deletion; ins, insertion; itd, internal tandem duplication; pm, point mutation.

but some have suggested that high-grade examples may be more commonly KIT positive (7/12, 58%, in three series).[72–74]

Fibroblastic tumors were generally KIT negative in two larger series, with occasional focally positive cases among cases of benign and malignant entities (desmoid, fibrosarcoma variants).[29,47] However, some have reported common KIT positivity (75%) in fibroblastic tumors such as desmoid[75] and fibrosarcoma and malignant fibrous histiocytoma, which have been found as KIT positive in up to 70% of cases.[61,64] Similarly divergent observations have been made on malignant peripheral nerve sheath tumors,[61,64] which are KIT negative in our experience. When properly titrated and purified polyclonal antibodies are used, desmoid tumors do not seem to be KIT positive,[76,77] and we suspect that the same applies to other fibroblastic tumors such as MFH. There is some evidence that imatinib could be useful against dermatofibrosarcoma protuberans, a tumor with autocrine/paracrine activation of the PDGFB-PDGFRB axis activated by COL1A1/PDGFB pathologic gene fusion protein; in this case, imatinib sensitivity is probably mediated through inhibition of PDGFRB instead of KIT.[78,79]

Soft tissue tumors with infrequent KIT positivity include epithelioid sarcoma,[80] perineurioma, and extraskeletal myxoid chondrosarcoma.[47] There is a report on consistent KIT positivity in hepatic and renal angiomyolipoma,[81] but in another study only 17% of 29 angiomyolipomas were positive.[82]

KIT IN MELANOCYTES AND MALIGNANT MELANOMA

Normal Melanocytes

KIT is constitutionally expressed in epidermal melanocytes and is important in their proper development, as can be seen in W mutant mice that have areas with loss of cutaneous melanocytes pigmentation.[7] In humans, loss-of-function KIT mutations cause similar spots lacking hair and skin pigmentation, referred to as piebaldism.[83]

Melanocytic Tumors

Like normal melanocytes, junctional nevus cells regularly show KIT positivity, whereas the dermal components of nevi are more variably positive, with a tendency to a lesser expression in the deeper components.[84–87] Ordinary blue nevi have been reported as KIT negative,[84–86] cellular blue nevi as positive.[84] In a study of congenital nevi, KIT was only exceptionally (1/30) detected in the dermal nevus cells, whereas proliferative nevus cell nodules in these lesions were usually positive (29/30).[88]

Primary malignant melanomas are variably KIT positive. The positivity seems to be more consistent in the superficially spreading components and variable in the vertical components (see Fig. 2D).[84–87] Desmoplastic melanomas are generally KIT negative (only 1/7 positive).[89] Uveal melanomas have been reported as KIT positive in 64% to 88% of cases in three large series,[90–92] and their metastases may more commonly retain KIT expression,[93] which is variably lost in melanoma metastases[85–87,93,94]; approximately one third of melanoma metastases seem to be KIT positive in our experience. Like melanoma, in our experience clear cell sarcoma is variably KIT positive,[30] although others have found these tumors consistently negative.[47]

KIT in Experimental Melanomas and Cell Lines

The role of KIT in melanomas by in vitro studies is complex, and both KIT and its ligand SCF may be expressed. Spontaneous KIT R816W mutation in cultured Wf/Wf mouse melanocytes was tumorigenic and was suggested to be a primary transforming force.[95] Also, in melanomas that regularly occur in RET activated mutant transgenic mice, melanomagenesis was suppressed if activated RET was introduced in relatively KIT-deficient W mutants,[55] and also after postnatal administration of anti-KIT antibody, indicating that the KIT pathway promotes melanoma growth.[96] However, apparently contradictory observations have been reported: in one study SCF inhibited the growth of KIT-expressing melanoma cells, probably because it induced tumor cell apoptosis.[97]

Evidence of KIT mutations in melanoma is tenuous. In one study, one out of two strongly KIT-positive examples had a L576P exon 11 mutation.[48] This mutation has been previously reported in GIST.[20,31] Another study found no KIT exon 2, 8, 9, 11, 13, and 17 mutations in 10 uveal melanomas,[90] and a third study found no KIT exon 9, 11, 13, and 17 mutations in four melanoma cell lines.[98]

Melanoma, especially the uveal type, has been suggested as a potential target for KIT inhibitor, based on some success against melanoma cell lines in vitro.[98] However, another in vitro study did not show good growth inhibition by imatinib, although such an effect could be derived from interference of both KIT and PDGFRA/B, two receptors potentially expressed in these tumors.[99]

KIT IN GERM CELLS AND GERM CELL TUMORS

Normal Tissues

KIT is important in germ cell migration and development, and sterility is a typical feature in mice with loss-of-function KIT mutations.[7] In female gonads, KIT is expressed in ovocytes in the primary follicles (see Fig. 2E), but practically nowhere else by IHC. In normal testicular tissue, KIT is expressed in several germ cell developmental stages (spermatogonia) but not in Sertoli cells; the latter produce stem cell factor.[100] Expression of truncated KIT with only the kinase domain present has been detected in the acrosomal portion of the spermatozoa and is probably important for fertilization. In mice, truncated KIT alone can activate ovocytes in parthenogenetic manner.[100] KIT expression in Leydig cells is controversial; possibly older positive findings were due to avidin-biotin background.

Seminoma and Related Tumors

In testicular neoplasia, KIT has been expressed in intratubular germ cell neoplasia and seminoma, but generally not in non-seminomatous germ cell tumors. KIT expression in developing germ cells (different types of spermatogonia) must be considered when using it as a marker for intratubular germ cell neoplasia.[100–103]

Over 90% of classic testicular seminomas express KIT protein, typically with a membrane pattern (see Fig. 2F).[22,101–105]

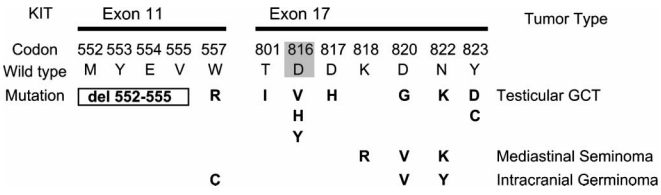

FIGURE 4. Reported KIT mutations in germ cell tumors.[106–108,110–113] The gray box indicates the most commonly mutated codon.

Similar KIT expression has been detected in seminoma analogs of mediastinum,[106] ovaries (dysgerminoma),[107] and the pineal region (germinoma/pinealoma).[108] KIT expression seems to be reduced in atypical seminomas, of which only 8 of 14 (57%) were positive in one study.[104] Spermatocytic seminomas show variable KIT expression, with only 11 of 17 cases positive overall in one study,[104] but another study found them to be generally negative.[109]

KIT mutations have been reported in up to 30% of seminomas and their extratesticular analogs (Fig. 4). These represent point mutations clustering between codons 816 and 823 in exon 17. The great majority of these mutations affect codon 816, leading to substitution D816V/H/Y.[106–108,110–114] However, a few point mutations and a deletion in exon 11 have also been reported.[108,112,113] KIT exon 17 mutations involving codon 816 have been suggested to predict the occurrence of bilateral testicular germ cell tumors.[111] The apparent lack of KIT mutations in seminomas in some series[48] might be a result of incomplete tumor cell purification, because studies employing rigorous tumor cell purification by laser capture microdissection reported mutations in 30% or more of analyzed cases.[110,111]

Non-seminomatous Germ Cell Tumors

KIT positivity is less common than in seminoma, and mutations have not been detected.[107,110] Among 25 yolk sac tumors, only 1 showed occasional KIT-positive tumor cells.[114] Another study found some KIT positivity in 9 of 29 (32%) non-seminomatous testicular germ cell tumors. Typically, such positivity was cytoplasmic and non-membranous, differing from the membrane positivity typically seen in seminoma.[103] KIT positivity may more commonly occur in prepubertal non-seminomatous germ cell tumors (9/15 vs. 2/10 in one study).[115]

KIT IN HEMATOPOIETIC AND LYMPHOID SYSTEMS AND THEIR TUMORS

Mast Cells and Their Neoplasms

KIT is constitutively expressed in mast cells, along with its ligand stem cell factor, both of which are needed for the development of tissue mast cells.[7,21–24,116,117] Mice without functional KIT or stem cell factor lack mast cells restorable by transfection with normal KIT or supplementation of stem cell factor, respectively.[7,116]

Normal mast cells serve as good, nearly ubiquitous internal control for KIT immunostaining. In mast cell disease urticaria pigmentosa and mastocytosis, KIT positivity in a distinct membrane pattern, in contrast to absence of KIT in lymphoid cells, is a consistent and diagnostically helpful feature, as noted in studies on mast cell infiltrates of skin, bone marrow, and elsewehere.[118,119]

Human mast cell neoplasms have KIT activating mutations, the most common of which is D816V in exon 17 in the tyrosine kinase 2 domain; this mutation conveys primary imatinib resistance.[120] KIT mutations involving codon 560 of exon 11 have also been reported in adult mastocytosis.[121,122] However, E839K dominant inactivating mutation has been detected in three cases of pediatric mastocytosis.[120]

Other Hematopoietic Cells and Leukemias

KIT is expressed in a subset of hematopoietic stem cells and is especially important for erythropoiesis because KIT-deficient mice typically have macrocytic anemia. In humans, KIT-positive hematopoietic stem cells has been estimated as half of the $CD34^+$ population and up to 4% of the mononuclear cell population.[123,124] KIT is also detected in up to one third of the primitive $CD3^-CD4^-CD8^-$ (triple-negative) thymic lymphoid precursor cells, prothymocytes,[124] and a small subset of $CD56^+$ natural killer cells.[123]

KIT is commonly expressed in acute myeloid leukemias (AML), as detected by flow cytometry, and has been considered a more myeloid specific marker than CD13 and CD33.[125] The percentage of KIT-positive AMLs has been estimated as 70%, varying between 60% and 90% in different series essentially independent of the FAB class.[126–129] Some studies have noted less frequent KIT positivity among myelomonocytic and monocytic AMLs (FAB4, FAB5)[130] and among $CD34^-$ AMLs compared with $CD34^+$ ones. Most myelodysplasias and blast transformations of CML have been significantly KIT positive. Although KIT expression was initially believed to be an adverse prognostic factor in adult AML, most studies have not detected a prognostic significance.[131–133] Similarly, KIT positivity identifies extramedullary myeloid tumors regardless of the level of differentiation and differentiated them from lymphoid, especially B-cell infiltrations, which are rarely if ever KIT positive. In an immunohistochemical study on paraffin sections, 26 of 30 cases were positive, whereas 2 of 13 lymphoblastic lymphomas and 1 of 28 large B-cell lymphomas were positive.[134]

Low levels of soluble KIT are detectable in normal serum,[135,136] and the levels can be elevated in AML; this is suggested as a potential marker of tumor load.[137] Conversely, lower than normal values of serum soluble KIT after bone marrow transplantation have been suggested as a marker for delayed engraftment.[138]

A spectrum of KIT activating mutations have been detected in AML, especially in the core binding factor (CBF) variants characterized by t(8;21) or inv16(p13q22) and rearranging CBF genes (see Table 2). These mutations were often deletions/insertions affecting exon 8, exon 11, and point mutations in different parts of the kinase domains. Some of these mutations were similar to KIT mutations in mastocytoma, GIST, and seminoma. Mutational activation of KIT in AML has been suggested to represent a second crucial oncogenic force after CBF rearrangement.[139,140] A few examples of KIT mutations were also reported in chronic myeloproliferative disorders, such as primary myelofibrosis and CML.[141,142]

The ability of an introduced KIT mutation to transform normal hematopoietic cells indicates a critical pathogenetic role of such KIT mutations.[143] One phase 2 pilot study with imatinib on 21 AML patients showed a 20% response rate.[144]

KIT in Lymphomas, Myeloma, and Lymphoid Leukemias

In B-cell lymphomas, KIT positivity is rare. In a large tissue array study, only 1 example of 70 grade I/grade II follicular lymphomas was the only KIT-positive B-cell lymphoma among over 800 cases.[145] In a separate report, one t(14;18)-positive follicular lymphoma was also reported as KIT positive,[146] and in one series 2 of 19 mantle cell lymphomas were positive.[147] Similar to B-cell lymphomas, B-lymphoid leukemias do not express KIT.[148]

Plasma cell myelomas are usually KIT negative, and a large IHC study showed 2 of 78 (3%) of these tumors to have membrane positivity for KIT; mutations were not found.[149] An earlier study reported more common KIT positivity in myelomas by flow cytometry, in 18 of 56 cases (32%).[150] In one study, all 13 cutaneous infiltrates were KIT positive.[151] Imatinib has been found to inhibit the growth of myeloma cell lines in vitro, in some cases independent of KIT positivity, suggesting that targets other than KIT may be involved.[152]

T-cell lymphomas may be more commonly KIT positive than B-cell ones. In one series, 1 of 14 peripheral T-cell lymphomas was positive,[145] and in another series on cutaneous peripheral T-cell lymphomas, focal positivity was found in 2 of 8 cutaneous pleomorphic T-cell lymphomas, 6 of 18 mycosis fungoides, and 3 of 5 Sézary syndrome tumors.[153] Whereas B-lymphoid leukemias have been consistently KIT negative, a minority (<5%) of childhood T-lymphoid leukemias have been KIT positive.[148]

Hodgkin and large cell anaplastic lymphomas have been reported as almost uniformly KIT negative in two recent large studies,[145,154] but one earlier series showed common positivity in both,[155] and in another recent series 7 of 18 cutaneous examples of LCAL showed KIT positivity.[153]

Unique among lymphomas, sinonasal type NK/T-cell lymphomas from patients in different regions of China, Korea, and Japan have been reported to have KIT exon 11 and 17 mutations. These include exon 11 mutation affecting the same region mutated in GIST.[156–158] KIT expression of these tumors, however, has not been clarified (Fig. 5).

KIT IN EPITHELIAL CELLS AND TUMORS

Pulmonary Small Cell Carcinoma

Co-expression of KIT and its ligand stem cell factor was originally shown by mRNA expression studies,[159] and an autocrine mechanism of KIT activation was confirmed in further studies.[160] IHC studies have documented KIT expression in pulmonary small cell carcinoma (see Fig. 2G).[21–23] The percentage of positive cases in nine larger series has ranged between 28% and 88% (median value of series 51%).[161–169] There does not seem to be KIT positivity in normal pulmonary epithelia, indicating that KIT expression in small cell carcinoma is "aberrant." The prognostic significance of KIT expression is controversial, as KIT positivity has been variably found as an unfavorable,[161,165] a favorable,[168,169] or an indifferent factor.[162,166,167]

Evidence for KIT mutations in small cell carcinoma is scant. KIT point mutations N495I in exon 9 and N567K in exon 11 were recently reported in 5 of 60 cases (8%) of small cell carcinoma.[166] However, other studies failed to find KIT exon 11 mutations in series of 91 tumors and 15 cell lines.[163,169–171] In a series of 13 small cell carcinomas, no mutations were found in screening of the entire KIT coding sequence,[169] and no mutations were found in 28 small cell carcinomas sequenced from exon 9 to carboxyterminus.[170] However, two polymorphisms, M541L and D745I, were found in some cases.[169,171] The latter has been reported in only one study.[169]

Because imatinib and other tyrosine kinase inhibitors can block KIT activation and growth of small cell carcinoma cells in vitro,[172–174] and blocking of KIT by antisense RNA in vitro can limit the growth of small cell carcinoma cells in vitro,[175] there have been expectations of the clinical use of inhibitors in vivo. However, a clinical trial has shown minimal if any effectiveness of imatinib, although KIT positivity was not used as a selection criterion in the trial where only 21% of tumors were KIT positive.[176] Also, imatinib was not effective in mice with xenografted small cell carcinomas in vivo.[177]

Other Pulmonary Tumors and Mesothelioma

Large cell neuroendocrine carcinomas expressed KIT in 55% and 77% of cases in two series (see Fig. 2H).[178,179] In one study, over half of pulmonary adenocarcinomas (61/95, 64%) were KIT positive, but no correlation was found between KIT positivity and tumor stage. However, patients whose tumor was KIT positive had a 1.7-fold increased risk of dying of tumor.[179] One study that found 19 of 88 (32%) adenocarcinomas to be positive for KIT suggested that KIT positivity has a positive correlation with tumor size and aggressive behavior; also, 7% of squamous carcinomas were positive.[180]

Malignant mesothelioma has been found to be KIT negative on IHC and RT-PCR studies for KIT mRNA. However, nuclear staining of unknown significance has been observed.[181,182] One study showed KIT positivity in 5% of mesotheliomas.[183] KIT has been detected in cultured mesothelioma cells, and KIT signaling has been suspected to contribute to their multidrug resistance.[184]

Breast Epithelia and Mammary Tumors

Normal ductal epithelia of breast are generally KIT positive, but breast carcinomas only rarely express KIT, indicating loss of this marker upon transformation (see Fig. 2I).[20–22,185] However, an early study based on mRNA analysis found common KIT and stem cell factor co-expression in

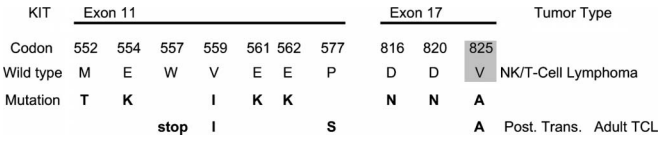

FIGURE 5. Reported KIT mutations in NK/T cell lymphomas. The gray box indicates the most commonly mutated codon.

a majority of breast tumors, and autocrine growth loop was suggested as a mechanism of possible KIT-mediated growth.[186] The finding of common KIT mRNA expression in breast tumors might have been a result of inclusion of benign lesions, such as cystic fibrosis, which may retain KIT expression by the high differentiation status of epithelia, and also detection of KIT mRNA originating from other cell sources.

In normal breast, the ductal and acinar cells are positive, whereas at least based on one report, the myoepithelial cells seem to be negative. Male breast gynecomastia epithelium is also KIT positive. Fibroadenomas and at least benign phyllodes tumors generally retain KIT expression similar to normal epithelia, but in fibrocystic disease and intraductal papillomas KIT expression varies. Atypical neoplastic epithelia and in situ carcinomas of breast may already lack KIT expression, suggesting that loss of KIT is an early event in breast tumorigenesis, and typical ductal and lobular carcinomas are usually negative (see Fig. 2I).[187] In a comprehensive TMA study on nearly 800 breast cancers, very few (2.1%) conventional ductal carcinomas and only 0.5% of lobular carcinomas were KIT positive, with the numbers also including weak positivity. Mucinous, tubular, and cribriform carcinomas had only weakly KIT-positive cases, representing no more than 2% to 3% of tumors of those types. However, 19% of medullary carcinomas were positive, half of them strongly. No KIT mutations were found in 10 cases of strongly KIT-positive breast cancers.[188]

KIT positivity may be more common in ductal carcinomas with basal/myoepithelial cell differentiation, a subset of largely basal cell keratin-positive, $HER2^+$, ER/PR^-, high-grade, and prognostically unfavorable tumors. In two studies, KIT positivity was commonly found in such tumors (>30%).[189,190] The relatively high percentage of overall KIT positivity (10–14%) in those studies was probably attributable to the inclusion of all weakly positive cases. Even higher percentages of KIT expression in high-grade ductal carcinomas (33/40, 82%) have been presented, with no correlation to HER positivity.[191] Adenoid cystic carcinomas of the breast, another subset of tumors with myoepithelial-like components, have been found as KIT positive,[192] similar to analogous tumors in salivary glands. According to one study, male breast cancers differ from female ones by being more commonly KIT positive.[193]

The significance of KIT expression in breast carcinoma cells has been investigated in the MCF7 cell line in vitro with apparently conflicting results. These cells naturally express stem cell factor but not KIT. Transfection of MCF7 cells with KIT was found to establish an autocrine loop and increase sensitivity to epidermal growth factors in one study,[194] whereas an earlier study found that a similar transfection led to growth suppression.[195]

Phyllodes tumors of the breast usually retain the epithelial KIT expression comparable to normal breast epithelia;[193] however, one study found the epithelia to be positive in two thirds of benign and malignant phyllodes tumors.[196] Stromal expression of KIT has been preferentially reported in malignant versus benign phyllodes tumors (50–100% of cases), often specifically in the subepithelial zone.[196–199]

Several investigators have reported KIT sequences in phyllodes tumor. One study of 13 cases revealed only silent mutations in exon 17: 2415C>T (I798I) in two benign tumors.[196] In another study, no KIT mutations were found in a survey of exons 8 to 15 and 17 in malignant and borderline tumors, and only a single nucleotide polymorphism M541L in exon 10 was detected.[197] However, in a third study, two KIT exon 11 alterations were detected, one missense mutation (N564S) and another non-sense mutation (Q556stop).[198] These types of mutations differ from the activating mutations seen in GIST and may reflect genetic instability in malignant tumors.

Ovarian Carcinoma

Both KIT and stem cell factor may be expressed in some ovarian epithelial cancers, suggesting autocrine stimulation.[200] There is significant variation between different studies. One found KIT expression in 25 of 34 malignant epithelial tumors, including a positivity rate of 68% in serous carcinomas. KIT positivity was found to be prognostically favorable and often associated with SCF expression.[201] Another study found KIT exclusively in high-grade serous carcinomas (8/31, 26%); no prognostic correlation was attempted.[202] A recent large study on 522 serous carcinomas found low KIT expression in 10% and high expression in only 2% of cases. KIT positivity was associated with high grade, high proliferative rate, aberrant p53 status, and lower 5-year survival. No KIT mutations were found in exons 9, 11, 13, and 17.[203] It has also been suggested that KIT positivity in ovarian carcinoma (52% in mixed types) is associated with a poorer response to chemotherapy.[204]

Colon Cancer

The GI tract and derivative endodermal epithelia (pancreas, liver) are negative for KIT. IHC studies have not detected KIT in conventional colon carcinomas.[205–207] However, strong KIT positivity was detected in 15 of 66 (23%) colorectal neuroendocrine carcinomas, including both small cell and large cell variants; no exon 11 mutations were detected.[207] KIT transcripts have been detected in normal and neoplastic colon more often, but this has been rightfully ascribed to non-tumor cells.[206]

A truncated form of KIT lacking the extracellular and transmembrane and part of tyrosine kinase domains has been detected in Colo201 and BM314 colon carcinoma cell lines by Northern analysis, analogous to similar truncated other receptor tyrosine kinases, such as HER2.[208] This aberrant activation of KIT was suggested to protect tumor cells from apoptosis and increase invasive potential.[209]

Renal Carcinoma

KIT expression has been reported in renal tubules using the streptavidin-based detection system.[210] However, avidin-biotin blocking was not used, and this type of background therefore cannot be excluded. Typical clear cell carcinomas are practically uniformly negative for KIT, but nearly consistent KIT positivity has been found in chromophobe carcinoma and oncocytoma, with some investigators also reporting positivity in papillary renal carcinoma.

KIT was originally identified as an overexpressed gene specifically in chromophobe renal carcinoma in cDNA microarray studies, and expression was confirmed by IHC; stem cell

factor was also detected.[211] Subsequently, five series found 111 of 124 cases (90%) to be positive for KIT, whereas these series reported only 3 of 368 (<1%) of conventional clear cell carcinomas as KIT positive.[81,210,212–214] Significant KIT positivity has also been detected in renal oncocytoma: 52 of 58 cases (90%) were KIT positive in four series.[81,210,213,214] Demonstration of KIT mRNA in oncocytoma indicates that IHC positivity is not an artifact.[81] The data on papillary renal carcinoma are contradictory, with most investigators finding these KIT negative; however, uniform positivity has also been reported.[81,210,213,214] Whenever any types of renal carcinomas undergo sarcomatous transformation, these sarcomatous components seem to become KIT positive, based on one study.[215] Unusual KIT intron 17 point mutations have been reported in renal papillary carcinoma with a high frequency,[212] but these observations have not yet been confirmed.

Prostate Carcinoma

IHC studies have shown no KIT expression in normal prostate, except in mast cells. However, low mRNA expression was detected in basal epithelial cells. In prostate carcinomas, KIT expression was detected in only 1 of 46 cases (2%) by IHC, although low mRNA expression by ISH was common.[216]

Expression of truncated KIT mRNA, similar to that seen in germ cells of some species and in colon carcinoma cell lines, has been reported in prostate carcinomas, more commonly (66%) in those with higher Gleason scores than in those in lower scores (28%). In prostate carcinoma, truncated KIT was found to activate other signaling pathways, such as that of the Src kinase.[217]

Adenoid Cystic Carcinoma

Initial observation of KIT positivity in one adnexal (not further specified) adenoid cystic carcinoma[118] prompted others to study expression and mutation in these tumors. Adenoid cystic carcinomas of salivary gland are nearly always KIT positive (see Fig. 2J). In a large study, 27 of 30 cases (90%) were KIT positive. The search for KIT exon 11 and 17 yielded no mutations.[218] Comparative studies have shown that whereas nearly all (94% of 62 cases) adenoid cystic carcinomas were KIT positive, only 8% of other tumors such as pleomorphic adenoma, polymorphous low-grade adenocarcinoma (PLGA), and basal cell carcinoma were positive.[22] In addition to adenoid cystic carcinomas (26/30), one study found that lymphoepithelial (6/6) and myoepithelial carcinomas (2/2) were also consistently KIT positive, but all other salivary gland carcinomas were negative.[23] Others found more common KIT expression in PLGA, although the staining patterns were still thought to be discriminatory between adenoid cystic carcinoma and PLGA.[219–221] However, others have reported common KIT expression in other salivary gland tumors, such as pleomorphic adenoma and PLGA.[222,223] Imatinib was not found effective in a clinical trial of 16 patients with adenoid cystic carcinoma.[224]

Merkel Cell Carcinoma and Other Nonpulmonary Small Cell Carcinomas

Merkel cell carcinoma has been reported as KIT positive in most cases, with the percentage of positive cases varying from 59% to 95% (total number of 69 cases). However, many tumors, up to half in one series, were only weakly positive. No prognostic correlation has been found related to KIT expression.[225–227] In one series, small cell carcinomas of urinary bladder were KIT positive in 14 of 52 cases (27%).[228] In contrast, uterine cervical small cell carcinomas were found to be KIT negative.[229]

Thymic Carcinoma and Thymoma

A great majority of thymic carcinomas have been reported as KIT positive (19/22 in one series), but KIT mutations were not found in exons 9, 11, 13, and 17. In contrast, no thymomas were positive.[230] Another study also found a majority of thymic carcinomas to be KIT positive (11/15), whereas only 1 of 20 thymomas were positive.[231] In one patient, a KIT-positive thymic carcinoma had a KIT exon 11 V560del mutation, and the patient responded to imatinib.[232] This mutation is activating and has been previously reported in GIST.[30]

KIT IN NEURAL TISSUES AND TUMORS

KIT expression can be detected in the neurons of certain regions of the brain, especially the molecular layer of the cerebellum (see Fig. 2K).[24] KIT is variably expressed in neuroblastoma and medulloblastoma. KIT has also been reported in glioma cell lines and gliomas.

Neuroblastoma

In an early study, all 14 neuroblastoma cell lines and 8 of 18 (45%) tumor samples expressed KIT mRNA. Detection of simultaneous stem cell factor expression suggested autocrine or paracrine stimulation.[233] In one IHC study, KIT was expressed in 27% of neuroblastomas, more often in differentiated forms; in approximately half of differentiated neuroblastomas and ganglioneuroblastoma, but only 13% to 19% in undifferentiated and poorly differentiated examples (see Fig. 2L). Expression was prognostically favorable.[234] In another IHC series, KIT was expressed in 13% of all neuroblastomas, preferentially in MYCN (nMyc)-amplified ones known to be clinically more aggressive.[235] Because neuroblastoma cells have been found to be imatinib sensitive in vitro (at concentrations around 10 μM), neuroblastoma patients may be candidates for this treatment.[235,236]

Neural, Glial, and Other Brain Tumors

Only a few studies are available. KIT seems to be consistently expressed in medulloblastoma; in one study all 10 examples were positive by RT-PCR, and 9 of 10 by IHC. Mutations were not detected in KIT exons 9, 11, or 13.[237]

KIT has been found to be minimally if at all expressed in low-grade astrocytomas and only rarely in high-grade gliomas, such as glioblastoma multiforme.[48,238] However, KIT expression has also been detected in some glioma cell lines.[239] Meningiomas have been uniformly negative.[48]

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