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Inactivation of X-linked tumor suppressor genes in human cancer

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Abstract

Cancer cells silence autosomal tumor suppressor genes by Knudson's two-hit mechanism in which loss-of-function mutations and then loss of heterozygosity occur at the tumor suppressor gene loci. However, the identification of X-linked tumor suppressor genes has challenged the traditional theory of "two-hit inactivation" in tumor suppressor genes, introducing the novel concept that a single genetic hit can cause loss of tumor suppressor function. The mechanism through which these genes are silenced in human cancer is unclear, but elucidating the details will greatly enhance our understanding of the pathogenesis of human cancer. Here, we review the identification of X-linked tumor suppressor genes and discuss the potential mechanisms of their inactivation. In addition, we also discuss how the identification of X-linked tumor suppressor genes can potentially lead to new approaches to cancer therapy.

Keywords

X-linked genes; tumor suppressors; single-hit inactivation; X chromosome inactivation; cancer

Introduction

Cancer cells silence tumor suppressor genes by Knudson's two-hit mechanism, [1] in which a loss-of-function mutation at the tumor suppressor locus is followed by a loss of heterozygosity (LOH), and therefore a loss of the wild-type tumor suppressor gene. Deletions, insertions, nonsense mutations, frame-shift mutations, missense mutations, or epigenetic alterations that inactivate functional activity of a protein are all observed in tumor suppressor genes. In most tumor suppressor genes, such as *retinoblastoma* (*RB*), both alleles of the gene must be inactivated for tumorigenesis [1]. In other tumor suppressor genes like *TP53* and *PTEN*, a mutation at one allele may be sufficient to give rise to an altered cell phenotype, resulting in a lower level of tumor suppressor function during tumor development and progression [2, 3]. Males carry only one allele of the X-linked genes, and one allele in each female cell is inactivated as a method of dosage compensation between the

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sexes. These genes are therefore more susceptible to genetic damages promoting tumor development and progression [4–6] and a single genetic hit is sufficient to inactivate an X-linked tumor suppressor gene [7] as X chromosome inactivation acts as a functional LOH for X-linked tumor suppressor genes [8, 9].

Potential implication of X-linked tumor suppressor genes in human cancers

The possibility of tumor suppressor genes on the X chromosome was raised over two decades ago [7, 10]. The first piece of strong evidence for one such gene was provided by Klein *et al*. in 1991, using X-chromosome-transfer analysis [11]. Transfection of a normal Chinese hamster X chromosome to a nickel-transformed Chinese hamster cell line with an Xq deletion resulted in senescence of these previously immortal cells [11, 12]. Since then, numerous chromosomal regions including Xp11–22, Xq25–26, and Xq27–28 have been proposed as potential loci for tumor suppressor genes [13–24]. LOH and skewed X chromosome inactivation at these putative X-linked tumor suppressor loci have been frequently identified in breast, ovarian, and prostate cancers. Several studies have shown as high as 40% of ovarian cancer samples have LOH of X-linked genes [15, 16, 18, 19, 25–29]. In particular, LOH at Xp22.2–3 of the active X chromosome is frequently found in ovarian cancers with germline *BRCA1* mutations [18]. LOH at Xp25–26 is significantly associated with *TP53* LOH in ovarian cancer [28]. These results suggest that these loci may harbor tumor suppressor genes that functionally interact with other tumor suppressor genes [7, 9]. LOH at the active X chromosome may cause complete loss of tumor suppressor function of these X-linked genes, leaving individuals susceptible to cancer formation [7, 9]. In breast cancer, extensive LOH at the X chromosome has been identified [13, 14, 30, 31] and linked to higher tumor grade and lymph node metastasis [32, 36]. Interestingly, *BRCA1* mutations have also been implicated in skewed X chromosome inactivation in breast cancer [33–35]. One report found a loss of X-linked gene expression in 22% of various cancers, including breast and ovarian cancers [36]. LOH at the X chromosome is also associated with sporadic colorectal carcinoma [37], renal-cell carcinoma [38, 39], melanoma [40] and neuroendocrine tumor [41–46].

Recent epidemiological studies have suggested a role for X-linked genes in susceptibility to human prostate cancer. Hereditary prostate cancer, X-linked (HPCX) region at Xq27–28 is a putative prostate cancer susceptibility locus [24, 47–50]. Xu *et al*. firstly identified the X-linked inheritance of familial prostate cancers at this locus, which may account for as much as 16% of hereditary prostate cancer cases [24]. Recent data clearly show that deletions within the HPCX locus are associated with sporadic prostate cancers, which raises the possibility that this locus may play a functional role as a tumor suppressor in prostate cancer [51]. Recently, a haplotype at Xq27.2 [24, 48] and common sequence variant at Xp11.22 [52] were shown to confer susceptibility to prostate cancer. While these two loci have been implicated in prostate cancer, the genes in these regions, including at the HPCX locus, have not been fully identified.

Identification of X-linked tumor suppressor genes

Although LOH analysis following Klein *et al.*'s paper [11] suggested the presence of X-linked tumor suppressor genes in human cancer, no specific genes were identified by such analysis. However, two studies published since 2007 have identified the first X-linked tumor suppressor genes [6, 53]. One study describes involvement of the X-linked gene, *FAM123B* (also call *WTX*) at Xq11.2 in Wilms tumor [53] and we have reported that *FOXP3* at Xp11.23 is an X-linked tumor suppressor gene involved in both breast cancer and prostate cancer [5, 6], suggesting a single-hit inactivation of X-linked tumor suppressor genes in human cancer.

Recent whole genome-wide scan analyses provided substantial information regarding X-linked cancer-related genes and have identified a large number of somatic driver mutations in potential cancer-related genes [54–57]. These driver mutations have been proposed to contribute to the neoplastic process and are positively selected for during tumorigenesis. Interestingly, driver mutations are frequently found in numerous X-linked genes, which may be additional potential X-linked tumor suppressor genes. In breast cancer, a group of X-linked, cancer-related genes have been found, including *FLNA*, *PFC*, *PRPS1*, *TARD8*, *MAGEE1*, *TAF* and *KLH4* [54–56]. In colorectal cancer, X-linked *FLNA*, *TBX22*, *KIAA2022*, *IRS4*, *PCDH11X*, *GPR112* and *F8* are proposed cancer-related genes. In melanoma, the suggested X-linked cancer-related genes include *ZNF280C*, *IL3RA*, *PNMA3*, *NHS* and *FGD1*. The role of these genes in tissue-specific carcinogenesis needs to be clarified and will be important in our understanding of the mechanism of single-hit inactivation of X-linked tumor suppressor genes during cancer initiation and progression. We describe below several confirmed and putative X-linked tumor suppressor genes (Table 1).

Family with sequence similarity 123B (FAM123B) / Wilms Tumor on the X (WTX)

Wilms tumor is cancer of the kidneys that typically occurs in children, rarely in adults [58–60]. *Wilms tumor 1* (*WT1*) at chromosome 11p13 is a zinc finger transcription factor gene and is the most completely characterized gene in the field of Wilms tumor genetics, but just 5~10% of cases are caused by inactivation of the *WT1* tumor-suppressor gene [60]. Recently, a genome-wide scan for DNA copy-number changes in 51 primary tumor specimens found small overlapping deletions at Xq11.1 in approximately 30% (15/51) of tumors [53]. The deletions were associated with an uncharacterized gene (*FAM123B*) that the researchers named *WTX* [53]. Of interest, the *FAM123B* deletions were all heterozygous in female Wilms tumors and targeted to the active X chromosome, leading to gene inactivation by a single-hit mechanism [53]. Similarly, heterozygous intragenic truncating mutations were found in 7.3% (6/82) of Wilms tumors examined. Only the mutant copy was expressed, indicating placement on the active X chromosome. In addition, the tumors with *FAM123B* deletions or mutation did not carry mutations of *WT1*, suggesting *FAM123B* genomic alterations may occur independently of *WT1* mutations in Wilms tumor.

FAM123B at Xq11.1 is close to the centromere and encodes an 1135 amino acid protein with no conserved functional domains except for a predicted nuclear localization signal. Functional analyses in cultured *Xenophus* and zebra fish cells have provided a possible

mechanism for the tumor suppressor activity of *FAM123B* in Wilms tumor by demonstrating that *FAM123B* promotes β-catenin ubiquitination and degradation, antagonizing Wnt/β -catenin signaling [61]. A recent study determined that FAM123B shuttles between the cytoplasm and the nucleus, where it is present in a distinct subnuclear compartment implicated in transcription and RNA processing [62]. Moreover, the C-terminus of FAM123B binds to the transcription factor *WT1* and modulates its transcriptional activity [62]. Thus, *FAM123B* may play a role in the transcriptional regulation of genes determining cellular differentiation [61, 62].

Rivera *et al*. have determined that approximately 20% of Wilms tumor cases are caused by inactivation of *FAM123B*, independent of mutations in *WT1* [53]. This observation has been confirmed by other recent studies. Ruteshouser *et al*. identified 18.4% (23/125) of Wilms tumors carrying 16 deletions and 8 mutations of *FAM123B*; of these, 20% had accompanying mutations in *WT1* and/or *CTNNB1* (coding for β –catenin) vs. 17.5% with mutations in *FAM123B* alone [63]. Perotti *et al*. identified Wilms tumors with *FAM123B* deletions in 11% (5/45) of male samples and LOH in 18% (9/50) of female samples. In the latter group, only two cases had a deletion in the active X chromosome, and sequence analyses detected an inactivating somatic mutation in just one tumor [64]. However, just 7% of Wilms tumor cases had functionally null genes, suggesting that previously reported estimates on the proportion of Wilms tumors due to *FAM123B* alterations should be reconsidered [64]. Wegert *et al*. examined mutations of *FAM123B* in a large set of 429 Wilms tumors [65]. They found that 11.5% of tumor samples lacked expression of *FAM123B* mRNA. Gene deletion was identified in 17% of Wilms tumor cases, equally distributed between males (deletion) and females (LOH), but point mutations were found in just 2% of tumors. These genetic alterations appear to be independent of *WT1* mutations. However, they did not find a significant correlation between *FAM123B* deletion status or expression level and clinical parameters, suggesting that *FAM123B* alteration is not an essential and early mutation necessary to drive tumorigenesis, but rather a later event that may affect only a fraction of cells with unclear clinical relevance [65]. Overall, these data show that *FAM123B* has been somatically inactivated in 11~29% of cases of Wilms tumor [53, 63–65]. Recently, Fukuzawa *et al*. indicated that the expression levels of the *FAM123B* were not reduced in females bearing this gene deletion, suggesting mosaic deletion or deletions occurring on the inactive X chromosome [66] Although they found somatic missense mutations with one allele in 2 patients, the wild-type allele is still expressed. Perotti *et al*. also suggested that gene deletions can occur randomly on both the active and inactive X chromosome [64, 67]. More recently, Jenkins *et al*. identified germline mutations of *FAM123B* that caused an X-linked sclerosing bone dysplasia, osteopathia striata congenita with cranial sclerosis [68]. This condition is lethal in males and causes increased bone density and craniofacial malformations in females [68]. However, patients do not have any predisposition to Wilms tumor [68, 69]. These data suggest that Wilms tumor may require the acquisition of a specific order of mutations for tumorigenesis, in which somatic mutation of *FAM123B* occurs later in tumor development [65, 69], while germline mutation of this gene does not predispose individuals to Wilms tumor [69].

Forkhead box P3 (FOXP3)

FOXP3 at Xp11.23 is a member of the forkhead-box/winged-helix transcription factor family. It was identified during positional cloning of *Scurfin*, a gene causing X-linked autoimmune diseases in mice and humans [70–73]. *Scurfin* was later renamed *FOXP3* and found to be the master regulator of development and function of regulatory T cells [74]. However, *FOXP3* is expressed not only in lymphocytes but also in epithelial tissues of the breast, lung, and prostate [75]. The human *FOXP3* gene has alterative splicing variants, including Δ2, Δ3, Δ7, Δ3–4, Δ3/8 and Δ8. Normal cells express the splice variants Δ2 and Δ7 [76–80], while cancer cells predominantly express splice variants Δ3, Δ3–4, Δ3/8 and Δ8 [6, 81–83].

Our lab previously observed that mice with a spontaneous mutation of *FoxP3* developed mammary tumors at a high rate. Nuclear FOXP3 protein is expressed in normal human breast epithelial cells but is lost in 80% of human breast cancers [6]. The significance of *FOXP3* as an X-linked tumor suppressor gene in humans is supported by the prevalence of somatic mutations (36%), gene deletions (13%) and lack of nuclear FOXP3 in the majority of breast cancer samples examined [6]. Interestingly, an overwhelming majority of the mutations are heterozygous and the deletion of the gene is heterozygous in all cases. These data reaffirm the notion that a single-hit is sufficient to inactivate X-linked genes. Furthermore, mammary carcinomas exhibited *FOXP3* inactivation while over-expressing two critical oncogenes, *HER2/ErbB2* [6] and *SKP2* [84], and have low expression of the tumor suppressor genes *p21* [85] and *LATS1/2* [86] in both mice and humans. Functional analysis demonstrated that *FOXP3* inhibits breast tumor growth by directly repressing the transcriptional activity of oncogenes *HER2* and *SKP2* while inducing transcription of tumor suppressor genes *p21* and *LATS1/2* [6, 84–86]. These data identified *FOXP3* as an X-linked tumor suppressor in breast cancer in both mice and humans.

Recent epidemiological studies have indicated two loci at Xp11.22 [52] and Xq27–28 [24, 48] associated with susceptibility to prostate cancer, but the genes in these regions have not been identified. *FOXP3* resides near the Xp11.22 region and has significant linkage disequilibrium (LD) between these two loci, raising the possibility that the *FOXP3* locus may contribute to X-linked prostate cancer susceptibility and may, in fact, act as a tumor suppressor in prostate cancer. Consequently, we analyzed *FOXP3* expression in a large panel of human prostate cancer samples. As expected, nuclear FOXP3 is present in normal human prostate epithelial cells but is lost in approximately 70% of human prostate cancers. *FOXP3* is frequently inactivated in prostate cancer samples by deletion (14%) and somatic mutation (25%). An inverse correlation was observed between *FOXP3* and *c-MYC* expression in human primary prostate cancers [5]. Functional analysis showed that *FOXP3*-mediated transcriptional repression of c-*MYC* is necessary to control c-MYC levels in normal prostate epithelial cells, contributing to the widespread overexpression of *c-MYC* in prostate cancer [5]. Wild-type (WT) *FOXP3* exhibits strong growth inhibition of prostate cancer cell lines [5]. Importantly, prostate-specific ablation of *FoxP3* in the mouse caused early onset of prostate hyperplasia and prostatic intraepithelial neoplasia (PIN) [5]. These data indicate that *FOXP3* is also an X-linked tumor suppressor gene in prostate cancer.

However, *FOXP3* expression in human cancers, as reported in recent studies, is subject to debate. While Merlo *et al*. reported a 2-fold higher rate of *FOXP3* expression in breast cancer samples [87] than that in our report [6], the former did not discriminate cytoplasmic from nuclear forms and the latter only considered nuclear FOXP3 protein. The majority of mutant FOXP3 is located in the cytoplasm, whereas WT FOXP3 is a nuclear protein [5, 6, 84, 85]. Reported mutants of *FOXP3* in prostate cancer cells abrogate normal FOXP3 function by disrupting its translocation into nuclei [5]. Ladoire *et al*. recently revealed that while *FOXP3* is expressed in 57% of breast cancer samples, expression is limited to the cytoplasm in *HER2* mutant-positive breast cancer samples [88, 89]. Karanikas *et al*. broadly identified *FOXP3* expression in 25 tumor cell lines of different tissue origins including lung cancer, colon cancer, breast cancer, melanoma, erythroid leukemia, and acute T cell leukemia, with both FOXP3 mRNA and protein detected in all tumor cell lines [90]. Immunohistochemical staining of these cell lines showed predominantly cytoplasmic expression of FOXP3 in melanoma (GERL), colon (HCA 2.6) and breast cancer (MCF7) cell lines, and both cytoplasmic and nuclear expression in lung cancer (GILI) and T lymphoblastic leukemia (JURKAT) cell lines. Similarly, cytoplasmic staining of *FOXP3* was detected in pancreatic cancers [91]. Currently, there is debate regarding the clinical significance of FOXP3 expression in human cancers. FOXP3 expression was correlated with better disease outcome and survival in patients with HER2+-breast cancer [92] and colorectal cancer [93], but the converse was true in patients with breast cancer [87], non-small cell lung cancer, urinary bladder cancer [94], hepatocellular carcinoma, [95] and tongue squamous cell carcinoma [96]. However, most of them did not divide FOXP3 expression by cellular localization, which is essential for FOXP3 tumor suppressor function. The cytoplasmic localization is associated with the loss of tumor inhibition [97], thus nuclear FOXP3 may be a useful marker for predicting disease outcome in human cancers.

Ebert *et al*. identified the *FOXP3* mRNA variant lacking Δ3–4 as widely expressed in human melanoma cell lines but absent in T regulatory cells. This alternative splicing event introduces a translation frame-shift that is predicted to encode a novel protein in tumor cells and therefore may contribute to the malignant progression of cells [81]. Likewise, recent studies revealed that specific splice variants of *FOXP3*, such as deletion of Δ3, Δ3–4, Δ3/8 and Δ8, are preferably expressed in breast and ovarian cancers, and malignant melanomas and malignant T cells of Sezary syndrome [6, 81–83, 92]. Inactivation of *FOXP3* function by disruption of intracellular localization or alternative splicing events might help to reconcile reported differences in *FOXP3* expression in human cancer samples [4, 5].

FOXP3 has been demonstrated to be a master regulator controlling transcriptional activity of *SKP2*, *HER-2/ErbB2* and *p21* in breast cancer and *c-MYC* in prostate cancer [5, 6, 84, 85]. The context of *FOXP3* regulation during tumor development remains largely unexplored. A recent study demonstrated that *FOXP3* up-regulation in human breast and colon carcinoma cells requires p53 function. DNA-damaging agents can induce *FOXP3* expression in p53-positive carcinoma cells, but not in cells lacking p53 function. However, knockdown of *FOXP3* can blunt this p53-mediated growth inhibition [93]. These results indicate that *FOXP3* expression is directly regulated by p53 during DNA damage responses. *FOXP3* may therefore be a key determinant of cell fate in p53-dependent DNA damage responses. In

addition, Zhang *et al*. found that *FOXP3* is expressed weakly or not at all in ovarian cancer cells. Up-regulation of *FOXP3* led to decreased expression of Ki-67 and cyclin-dependent kinases, resulting in inhibition of cell proliferation. Up-regulation of *FOXP3* also caused reduced cell migration and invasion, possibly due to reduced expression of matrix metalloproteinase-2 and urokinase-type plasminogen activator [83]. The authors further proposed that *FOXP3* inhibits the activation of mammalian target of rapamycin (mTOR) and nuclear factor (NF)-κB signaling. Therefore, *FOXP3* might play divergent functional roles in different tissues and tumor stages.

Ribosomal protein L10 (RPL10)

This gene is located at Xq28 and encodes a ribosomal protein that is a component of the 60S subunit and most likely involved in the later steps of the 60S ribosomal subunit assembly [94, 95]. *RPL10* was initially identified as a candidate tumor suppressor gene in Wilms tumor [96], but later studies refuted this claim [97]. RPL10 can repress transcriptional activity of the proto-oncogene *c-Jun in vitro*, but these activities have not been verified *in vivo* [97–103]. c-Jun works with c-Fos to form the transcription factor AP-1, which facilitates signaling through the estrogen and androgen receptors [104–108]. Inhibition of AP-1 activity presumably suppresses development and growth of sex hormone-regulated tumor cells. *RPL10* may therefore function as a tumor suppressor in hormonally-dependent cancers through its inhibition of c-Jun and AP-1 activity. Furthermore, it may play a role in multiple endocrine neoplasia type 1 (MEN1), which is caused by inactivation of the tumor suppressor *MEN1*. RPL10 was 8-fold down-regulated in a neuroendocrine tumor cell line, BON1, transfected with *MEN1* [109]. RPL10 is expressed in islets, tumors, and exocrine cells of the pancreas in human MEN1 carriers and Men1 heterozygous mice [110], suggesting that RPL10 may play a role in MEN1-related pancreatic tumorigenesis. It has been reported that LOH (18~30%) and microsatellite instability (12~50%) at Xq28 frequently occur in ovarian cancer and are significantly associated with susceptibility to ovarian cancer [111]. In prostate cancer, decreased *RPL10* expression may be associated with early development of prostate cancer, but high levels of *RPL10* at later stages of tumor development may facilitate progression into a more aggressive phenotype [112]. It is therefore premature to draw any conclusions regarding the functional role of *RPL10* in human cancer.

Retinoblastoma binding protein 7 (RBBP7, also known as BRAP46)

This gene is located at Xp22.2 and codes for a ubiquitously-expressed nuclear protein that binds to Rb protein, which regulates cell proliferation [113]. *WT1* also signals through RBBP7 to inhibit growth [116]. Ectopic expression of *RBBP7* in several tumor cell lines suppresses cell growth and proliferation *in vitro* and *in vivo* [117], suggesting that *RBBP7* may be a tumor suppressor in some cancers [115]. In human breast cancer, *RBBP7* can activate c-Jun NH2-terminal kinase-dependent apoptosis and suppress tumorigenicity and estrogen-stimulated progression of breast cancer *in vitro* and *in vivo* [118–121]. The suppressive activity of *RBBP7* may be mediated by up-regulation of GSK-3β, which attenuates β-catenin/TCF signaling [122]. However, other studies have suggested that *RBBP7* induces epithelial-mesenchymal transition in mammary epithelial cells [123]. High expression of *RBBP7* may be associated with development/progression of human breast

cancer [124], and RBBP7 protein can inhibit *BRCA1* transactivation activity and may therefore attenuate DNA damage response [114, 115]. The levels of RBBP7 serum, mRNA and protein were significantly increased in non-small cell lung cancer and elevated serum level was highly correlated with distant metastasis, suggesting RBBP7 is involved in cancer metastasis through regulation of E-cadherin [125, 126]. Recent studies indicate that RBBP7 is specifically expressed in brain tumors [127] and can directly convert mitotic germ cells into specific neuronal cells by several histone remodeling and modifying [128]. However, the functional role of *RBBP7* during tumor development requires further experiments to be explained.

Ectodysplasin A2 receptor (EDA2R)

EDA2R is located at Xq12 and is highly expressed during embryonic development, with a particular role in epidermal morphogenesis [129]. Mutations in this gene manifest clinically as loss of hair, sweat glands, and teeth [129, 130]. Mice lacking *EDA2R* are indistinguishable from their WT littermates, but myodegeneration induced by EDA-A2 (the ligand of EDA2R) can be prevented by *EDA2R* deficiency [131]. *EDA2R* activates the NF-κB and JNK pathways [132, 133] while inducing apoptosis through a caspase 8-dependent mechanism [134]. Studies suggest that *EDA2R* is a potential downstream effector of p53-induced apoptosis in cancer cells [136, 137] and may therefore be a potential tumor suppressor to carcinogenesis., It is down-regulated in breast and colorectal cancers [135], and mutations and promoter hypermethylation of *EDA2R* have been identified in colorectal cancer cells [136, 137].

PHD finger protein 6 (PHF6)

PHF6 at Xq26.3 is a member of the plant homeodomain (PHD)-like finger family. It encodes a protein with two PHD-type zinc finger domains, indicating a potential role in transcriptional regulation localizing proteins to the nucleolus [138]. Mutations affecting the coding region of this gene, splicing of the gene transcript, or gene deletions have been associated with Borjeson-Forssman-Lehmann syndrome (BFLS), characterized by mental retardation, epilepsy, hypogonadism, hypometabolism, obesity, swelling of facial subcutaneous tissue, narrow palpebral fissures, and large ears [138, 139]. Van Vlierberghe *et al*. identified inactivating mutations and deletions in the X-linked *PHF6* in 16% of pediatric and 38% of adult primary T cell acute lymphoblastic leukemia (T-ALL) samples [140]. Notably, *PHF6* mutations are almost exclusively found in T-ALL samples from male subjects. Mutational loss of *PHF6* function is associated with leukemias driven by aberrant expression of the homeobox transcription factor oncogenes *TLX1* and *TLX3* [140]. Additionally, recent studies support the involvement of this gene in adult acute myeloid leukemia [141, 142], T-cell lymphoblastic leukemia [142–144] and hepatocellular carcinoma [142]. Consistent with these data, *Phf6* alterations have been identified in murine models of lymphoma [145]. These results suggested that *PHF6* may be a new X-linked tumor suppressor in leukemias.

E74-like factor 4 (ELF4, also known as MEF)

ELF4 is located on chromosome Xq26.1 and its protein is a transcriptional activator that binds and activates *CSF2*, *IL3*, *IL8*, and *PRF1* [146, 147]. The encoded protein is involved in natural killer (NK) cell development and function, innate immunity, and induction of cell cycle arrest in naive CD8+ cells [146, 147]. Early studies identified LOH at the *ELF4* locus in both ovarian and breast cancers [14, 28]. A later study reported that *ELF4* suppress the transcription of *MMP-9* and *IL-8* in non-small-cell lung cancer cells, suggesting that *ELF4* may be a candidate tumor suppressor gene [148]. Although *ELF4* inhibits tumor growth *in vitro*, *Elf4*-deficient mice do not spontaneously develop tumors [148, 149].

Chromosomal rearrangements resulting in the fusion transcript *BCORL1-ELF4* have been identified in hepatocellular carcinomas [150]. *ELF4* is also targeted by the t(X;21)(q26;q22) in acute myelogenous leukemia. Lacorazza *et al*. suggested that *ELF4* regulates the proliferation of primitive hematopoietic progenitor cells at steady state by controlling their entry into the cell cycle, thus affecting the decision of stem/primitive progenitor cells to divide or remain quiescent [151]. However, recent studies have also indicated that *ELF4* may be a candidate oncogene [152, 153]. *ELF4* functions as a tumor promoting factor in ovarian cancer [152], activating *MDM2* expression and blocking oncogene-induced p16 activation [153]. However, recent functional analysis showed that ELF4 contributes to the persistence of γH2AX DNA damage foci and promotes the DNA damage response, leading to the induction of apoptosis [154]. These contrary roles of *ELF4* need to be clarified by further studies.

Leucine zipper, down-regulated in cancer 1 (LDOC1)

LDOC1 is located at Xq27 and encodes a nuclear protein down-regulated in some cancer cell lines [155]. It is thought to play a role in inhibiting the NF-κB pathway and promoting apoptosis of cancer cells [156, 157]. Interestingly, *LDOC1* is located in the HPCX region, which is a major locus for hereditary prostate cancer, and deletions here are also associated with sporadic prostate cancers [24, 48, 51, 158];, no prostate susceptibility genes have been identified thus far. *LDOC1* inhibits the degradation of p53 [159] and has therefore may be a potential X-linked tumor suppressor gene. However, high levels of LDOC1 correlate with poor prognosis in untreated chronic lymphocytic leukemia patients, suggesting that *LDOC1* functions as an oncogene [160]. Further study is therefore needed.

Dyskeratosis congenita 1 (DKC1)

This gene is located at Xq28 and encodes the protein dyskerin, which is involved in rRNA processing and modification [161, 162]. Mutations in this gene lead to X-linked dyskeratosis congenita, characterized by reticulate skin pigmentation, mucosal leukoplakia, nail dystrophy, and progressive bone marrow failure [161, 162]. *DKC1* has been proposed to function in telomerase activity, ageing and cancer [163]. However, recent functional analyses indicate that *DKC1* may be a putative tumor suppressor by promoting p53- and p27-dependent translational control of ribosome biogenesis, suggesting a role of dyskerin in the inactivation of p53 in human tumors [164–166]. Therefore, *DKC1* is a promising candidate X-linked tumor suppressor gene.

Ribosomal protein S6 kinase, 90kDa, polypeptide 6 (RPS6KA6, also known as RSK4)

This gene is located at Xq21 and encodes a member of the ribosomal S6 kinase family, a group of serine-threonine protein kinases regulated by growth factors [167]. Exogenous expression of *RPS6KA6* resulted in decreased cell proliferation, increased accumulation of cells in G(0)-G(1) phase, and increased expression of tumor suppressor genes such as *Rb*, *RbAp46*, and *p21* [168, 169]. *In vitro* over-expression of *RPS6KA6* also induced cell arrest and senescence in normal fibroblasts and malignant colon cancer cell lines. Interestingly, *RPS6KA6* mRNA levels in these cell lines were increased both in replicative- and stress-induced senescence. Cells expressing E1A or *RB* short interfering RNA were resistant to *RPS6KA6*-mediated senescence [170]. Overexpression of *RPS6KA6* also led to reduced colony formation in soft agar and suppressed invasive and migratory activities of MDA-MB-231 cells both *in vitro* and *in vivo*. These effects may have been due to up-regulation of claudin-2 and down-regulation of *CXCR4*, both of which play roles in invasion and chemotaxis [168]. One study determined that *RPS6KA6* was down-regulated in 90% of colon carcinomas, 86% of colon adenomas, and 80% of renal cell carcinomas examined [170]. These results suggest that *RPS6KA6* may act as an important tumor suppressor gene in breast cancer by inhibiting invasion and migration of cancer cells and in colon and renal cell carcinomas by modulating induction of senescence and controlling cell proliferation. Although no functional mutation has been identified in human cancers, a recent study showed that RSK4 is expressed in normal uterine tissue but is absent or reduced by hypermethylation in both endometrial cancer cell lines and primary tumors [171].

CD99 molecule (CD99)

This gene is found in the pseudoautosomal regions of the X and Y chromosomes (Xp22.32 and Yp11.3, respectively) and escapes X chromosome inactivation [172]. CD99 is a cell surface glycoprotein involved in leukocyte migration, T cell adhesion, ganglioside and protein transport, and apoptosis of T cells [174]. This gene encodes two different proteins produced by alternative splicing, with the short form harboring a deletion in the cytoplasmic domain [173].. While the longer isoform inhibited migration and metastasis in tumors, the shorter form actually increased motility and *MMP-9* expression of human breast cancer cells through the AP-1 activated AKT, ERK, and JNK signaling pathways [175, 176]. *CD99* appears to induce tumors and bone metastases in human Ewing sarcoma cell lines *in vitro* and *in vivo* [177], suggesting that *CD99* may actually be an oncogene in human Ewing sarcoma cells. In two studies, 78–100% of pancreatic neuroendocrine tumors stained positive for CD99 [178, 179]. However, a recent study indicated that down-regulation of CD99 protein (62/100 in tumors but 34/35 in normal tissues) by gene promoter hypermethylation is a critical event in the transitional cell carcinomas of urinary bladder, especially in advanced stages [180], implicating a tumor suppressor function.

Alpha thalassemia/mental retardation syndrome X-linked (ATRX)

ATRX is located at Xq21.1 and its protein contains an ATPase/helicase domain, belonging to the SWI/SNF family of chromatin remodeling proteins. This gene is a major epigenetic regulator of transcription, nuclear architecture, and chromosome stability in mammalian cells [181, 182]. Mutations of this gene affect chromatin remodeling, DNA methylation, and

transcriptional regulation. Such mutations are associated with an X-linked mental retardation syndrome, often complicated by alpha-thalassaemia and myelodysplastic syndrome [183–187]. Interestingly, skewed X chromosome inactivation was found in patients with alpha-thalassaemia syndrome and abnormal imprinted X chromosome inactivation was also identified in *ATRX*-deficient mice [182].

Recent evidence indicates that *ATRX* is abnormally regulated in several types of cancers, including acute myeloid leukemia, prostate cancer, breast cancer, esophageal squamous cell carcinoma, and pancreatic neuroendocrine tumors [46, 188–192]. In 132 patients with *de novo* acute myeloid leukemia, low expression levels of this gene correlated with an adverse karyotype and poor prognosis [192]. The low miRNA levels of this gene in gene expression profiling experiments were also observed in primary prostate cancers [189], irradiated breast cancers, [191] and esophageal squamous cell carcinomas [188]. Importantly, recent studies revealed that frameshift and nonsense somatic mutations of *ATRX* are frequently observed in pancreatic neuroendocrine tumors and loss of *DAXX* or *ATRX* function in 43–45% of tumors with high levels of chromosome instability [46, 190, 193, 194]. More recently, somatic mutations in the H3.3-ATRX-DAXX chromatin remodelling pathway were also identified in 44% of pediatric glioblastoma [195]. Therefore, *ATRX* is a novel candidate X-linked tumor suppressor gene.

Mechanism of inactivation of X-linked tumor suppressor genes

Identification of X-linked tumor suppressor genes has furthered our understanding of the pathogenesis of human cancer. However, the silencing mechanism of these genes in human cancer is still unclear. Since females have two X chromosomes while males have only one, the inactivation mechanism of these genes in human cancer should be different between male and females (Fig. 1). This mechanism provides a novel genetic paradigm in the pathogenesis of human cancer.

Inactivation of X-linked tumor suppressor genes in females

X chromosome inactivation is a mechanism of gene dosage compensation that has evolved in mammals. One X chromosome in each female cell is randomly inactivated and remains inactive throughout the lifetime of the cell and its descendants. Females are thus a mosaic of two cell populations, expressing either paternal or maternal X-linked alleles. In females, an X-linked tumor suppressor gene is more susceptible to additional genetic damage since one of the alleles is already silenced by X-chromosome inactivation. Here we propose that X-linked tumor suppressor genes in female cancer may be inactivated by multiple events such as LOH, mutation, bi-allelic methylation and skewed X-inactivation, etc (Fig. 1).

Gene deletion and mutation—The role of heterozygous tumor suppressors in cancer pathogenesis has been demonstrated recently with the identification of two X-linked tumor suppressor genes, *FOXP3* [6] and *WTX* [53], which are inactivated by a single genetic hit [4]. Female mice with a *FoxP3*-heterozygous mutation develop spontaneous breast cancer at a higher rate than WT mice [6]. The majority of the mutations and all deletions of *FOXP3* are heterozygous in human breast cancer [6]. Likewise, all mutations and deletions of *WTX* identified are heterozygous in Wilms tumor [53]. Rivera *et al*. used DNA sequencing to

identify inactivating mutations in the *WTX* allele on the active X chromosome in female Wilms tumors. FISH analysis confirmed the deletion of *WTX* on the active X chromosome in several of these tumors. WT *WTX* allele was only found on the inactive X chromosome. [53]. These data suggest that X-linked tumor suppressor genes may be inactivated by a single gene deletion or mutation targeting the active allele.

It should be noted that while X-linked tumor suppressor genes are subjected to X inactivation, some X-linked genes can escape X chromosome inactivation such as *RBBP7, CD99, PHF6* and *LDOC1* [209]. It has been suggested that escape from X inactivation may be regulated by long non-coding RNA (lncRNA) within the escaping chromosomal domains [210]. Many of the genes which escape inactivation are present in particular regions of the X chromosome and silenced and escape regions have been shown to have distinct chromatin marks [211], but the precise mechanism of inactivation of such X-linked tumor suppressor genes in cancer is unknown.

Bi-allelic epigenetic inactivation—In a two-hit mechanism for inactivation of autosomal tumor suppressor genes, methylation of one allele may serve as the second hit in cases with a functional mutation or LOH of the other allele. In females, one of the alleles in X-linked genes is silenced by X chromosome inactivation under a complex mechanism involving a long noncoding RNA, *XIST* (X inactivation specific transcript) [10, 212, 213], as well as *XIST* is expressed at high levels on the inactive X chromosome and is not expressed on the active X-chromosome [212–214]. DNA/histone methylation and histone hypoacetylation [196, 197] also contribute to X chromosome inactivation. Methylation of most X-linked genes occurs on the inactive X chromosome. Our analysis using pyrosequencing technology revealed that the CpG island motif of *FOXP3* was approximately 50% methylated in normal breast epithelial cells (unpublished data), which is consistent with X-inactivation. Although somatic genetic defects at the *FOXP3* locus have been identified in 36% of human breast cancers, it is still unexplained why there is a lack of *FOXP3* in the majority of breast cancers [6]. It is therefore of interest whether the transcriptional activity of *FOXP3* is down-regulated by the epigenetic changes in breast cancers such as bi-allelic methylation. Moreover, evidence suggests that *BRCA1* is associated with *XIST* regulation on the active X chromosome, and *XIST* can be abnormally expressed on an active X-linked allele in breast cancer cells, silencing the gene [30, 198]. In addition, recent studies indicate that X-linked *EDA2R* is also down-regulated in breast cancer by promoter hypermethylation [135, 137]. Thus, bi-allelic epigenetic inactivation may be more frequent in X-linked genes than autosomal genes and is a potential mechanism for inactivation of X-linked tumor suppressor genes during cancer development. This mechanism needs to be validated by further study.

Skewed X-inactivation—X-inactivation is random and therefore expression of the paternal and maternal alleles of a gene should be roughly 50% for each. Skewed X-inactivation can occur naturally, such as in the peripheral blood cells of older females [202] and in a very small percentage (2.7~4.5%) of the general female population [35, 202, 203]. In females carrying mutations in critical X-linked genes, selective X-inactivation is observed due to negative selection of cells expressing the mutant allele [204]. This selection allows

for phenotypic suppression of X-linked dominant disorders in females by selecting for expression of the WT allele in relevant tissues [204]. However, in female carriers of a mutant allele, if skewed X-inactivation selects against the WT allele, the cells will undergo a positive selection for the mutant allele (Fig. 1) [6, 204]. Consequently, it is hypothesized that skewed X-inactivation in combination with a single genetic hit can inactivate an X-linked tumor suppressor gene [4, 204]. Previous studies [8, 35, 205, 206] have reported an increased frequency of skewed X-inactivation in DNA from peripheral blood cells of patients with ovarian and breast cancer and *BRCA1* mutation carriers; *BRCA1* is involved the regulation of many X-linked genes [34, 207] and may contribute to the maintenance of the inactive X chromosome [33, 208]. Skewed X-inactivation, through either chance or selection, in females who are heterozygous carriers of an X-linked disorder can lead to the clinical manifestation of a nominally recessive disease. In cancer, a gain-of-function or loss-of-function mutation in an X-linked oncogene or tumor suppressor, respectively, may give a proliferative advantage to cells carrying this mutation on the active X chromosome, causing not only skewed X-inactivation but also an increased risk of cancer [35, 205]. Additionally, if X-linked gene inactivation affects a cluster of neighboring genes, as has been suggested, the active allele of an X-linked tumor suppressor gene can be silenced during the inactivation of a nearby mutated gene [9]. However, these hypotheses have not been tested experimentally and the prevalence of skewed X-inactivation in human cancer cells is still unknown.

Inactivation of X-linked tumor suppressor genes in males

FOXP3 deletion has been identified in 23 (14%) of 165 prostate cancer samples [5]. Among them, 5 of the 23 cases showed an increase in X chromosome number. Interestingly, the deletion was complete in all X chromosomes [5], suggesting that X chromosome duplications in cancer tissues likely occurred after deletion of *FOXP3*. Our sequencing analyses identified single base-pair changes in 5 (25%) of 20 samples (4 missense and one intronic) leading to the functional inactivation of *FOXP3* [5]. Although *FOXP3* is frequently inactivated in prostate cancer by deletion and somatic mutation, approximately 70% of prostate cancer samples exhibited a loss of nuclear FOXP3 expression that was not fully explained by the two somatic alterations [5]. Thus, inactivation of *FOXP3* in prostate cancer may also be caused by additional mechanisms such as DNA methylation, histone hypoacetylation and gene regulation, etc (Fig. 1). To date, there is no more information regarding inactivation of X-linked tumor suppressors in male-specific cancers.

Conclusion

The identification of X-linked tumor suppressor genes has challenged the traditional theory of “two-hit inactivation” of tumor suppressors, suggesting a tumorigenic mechanism involving a single genetic hit. In contrast to bi-allelic inactivation of autosomal tumor-suppressor genes, single-hit damage is sufficient to functionally inactivate X-linked tumor suppressor genes in human cancers [4]. In males, the single-hit events can be caused by genetic or epigenetic alterations of somatic or germline origin (Fig. 1). In females, the potential single-hit events include those affecting males as well as skewed X-inactivation and positive selection (Fig. 1). A functional single-hit event in a X-linked tumor suppressor

gene on the active X chromosome will result in gene silencing in female cells, unless these cells are subjected to negative selection, inhibiting tumor formation. Otherwise, cells lacking tumor suppressor function are likely to undergo positive selection, with skewed X-inactivation and an increased risk of developing cancer [35, 205]. However, the mechanism of skewed X inactivation in X-linked tumor suppressor genes is still unknown. Between 25–35% of human X-linked genes either are not inactivated or subject to varying inactivation [215]. If an X-linked tumor suppressor gene is located in either of these clusters, the inactivation of this gene in females should behave like autosomal tumor suppressor genes and follow Knudson's two-hit mechanism. While there are numerous putative X-linked tumor suppressor genes currently being researched, only two have been verified by repeated study, *FOXP3* and *WTX*. Neither is located in the regions of the X chromosome that partially or completely escape inactivation and, therefore, are susceptible to a novel single-hit genetic activation.

Future perspectives

The identification of X-linked tumor suppressor genes has significant clinical potential in the treatment of human cancer. One of the biggest challenges in cancer therapy is restoration of tumor suppressor function following inactivation, since it is difficult to repair what is genetically broken [4]. Deletions and/or mutations identified in known X-linked tumor suppressor genes *FOXP3* and *WTX* are often heterozygous in female cancer cells [6, 53]. While the inactive X chromosome is sometimes lost during cancer development [30, 34], in cancers retaining the inactive chromosome there is the possibility of reactivating the silenced WT allele of these genes for cancer therapy. For example, *FOXP3* expression is lost in the majority of breast cancers and up-regulation of WT *FOXP3* inhibits cell growth and proliferation in breast cancer cells [6]. If *FOXP3* is indeed mutated exclusively on the active X chromosome, then the inactive X chromosome contains a WT allele that may serve as an important target for treatment of breast cancer. Development of such a therapy requires further study into the mechanisms inactivating X-linked tumor suppressor genes in cancer as well as strategies to selectively activate the inactive WT allele cancer cells. A recent study observed that anisomycin treatment induced *FOXP3* expression in both mouse and human breast cancer cell lines [216]. Such induction resulted in increased apoptosis of cancer cells and reduced growth of established mouse mammary tumors [216]. This observation raises the intriguing possibility of restoring *FOXP3* function through drug treatment.

DNA methylation, *XIST*, and histone hypoacetylation work in concert to maintain inactivation of X-linked genes [10, 212–214], and epigenetic changes and *XIST* deregulation observed during cancer development may reduce the steps needed to reactivate X-linked tumor suppressor genes [44]. However, restoration of gene expression in the inactive X chromosome may bring about unexpected or undesired results due to loss of dosage compensation of various important X-linked genes. We therefore need to develop a specific therapeutic strategy for the targeted reactivation of only the X-linked tumor suppressor gene of interest. Furthermore, some X-linked tumor suppressor genes have multiple functions at different stages of development or in different tissues and cell types. For instance, *FOXP3* is both an X-linked tumor suppressor in breast and prostate tissue [5, 6] and a master regulator of regulatory T cell development and function [74]. Reactivation of *FOXP3* expression from

the inactive X chromosomes may therefore affect immune responses. Thus, the specific therapeutic strategy should be localized to tumor tissues and the toxicity and side effects of any drug must be also considered.

A recent study has evaluated the clinical efficacy of a monoclonal antibody Fv-FOXP3 protein in therapies for breast, ovarian, and colon cancer [217]. The Fv-FOXP3 is a fusion protein produced by *Pichia pastoris*. Treatment with Fv-FOXP3 resulted in dose-dependent cell death of cancer cells *in vitro*, with increased production of the p17-activated fragment of caspase-3 leading to apoptosis of cancer cells. *In vivo*, Fv-FOXP3 treatment led to a significant reduction in tumor burden in a syngeneic mouse model of metastatic colon cancer. Therefore, the identification of *FOXP3* as an X-linked tumor suppressor gene has already been used in clinical research to develop a novel potential treatment of human cancers.

Numerous studies have cited other X-linked genes with putative tumor suppressor functions. However, many of these genes have conflicting functions that give them a dual characterization of tumor suppressor gene and oncogene in different cell types and tumor stages. Their exact, context-specific functional roles in cancer development remain to be fully clarified. Future studies will need to explore how to best identify true X-linked tumor suppressor genes and specifically reactivate their expression, as well as further elucidate the differences between X-linked and autosomal tumor suppressor genes.

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Executive summary

- **Introduction:** The existence of X-linked tumor suppressors has long been suspected, particularly in breast, ovarian, and prostate cancers.
- **Potential implication of X-linked tumor suppressor genes in human cancers**: These genes represent a novel mechanism of tumorigenesis, since X-inactivation in females and the presence of only one X chromosome in males allows for inactivation of an X-linked gene by a single-hit mechanism.
- **Identification of X-linked tumor suppressor genes:** Two X-linked tumor suppressor genes have been verified by repeated study: *FOXP3* in breast and prostate cancer and *FAM123B/WTX* in Wilms tumor. Over half a dozen putative X-linked tumor suppressor genes have been identified, but further study is needed to determine their true function in tumorigenesis.
- **Mechanism of inactivation of X-linked tumor suppressor genes:** A single genetic hit, in the form of a mutation, deletion, or aberrant methylation, can lead to loss of tumor suppressor function in males; in females, this may occur if combined with skewed X-inactivation.
- **Future perspectives:** A female cell that has undergone a loss-of-function genetic alteration of an X-linked tumor suppressor gene may still possess a wild-type allele of the gene on the inactive X chromosome. Activation of this gene and restoration of tumor suppressor function represents a novel potential therapy for female cancers.

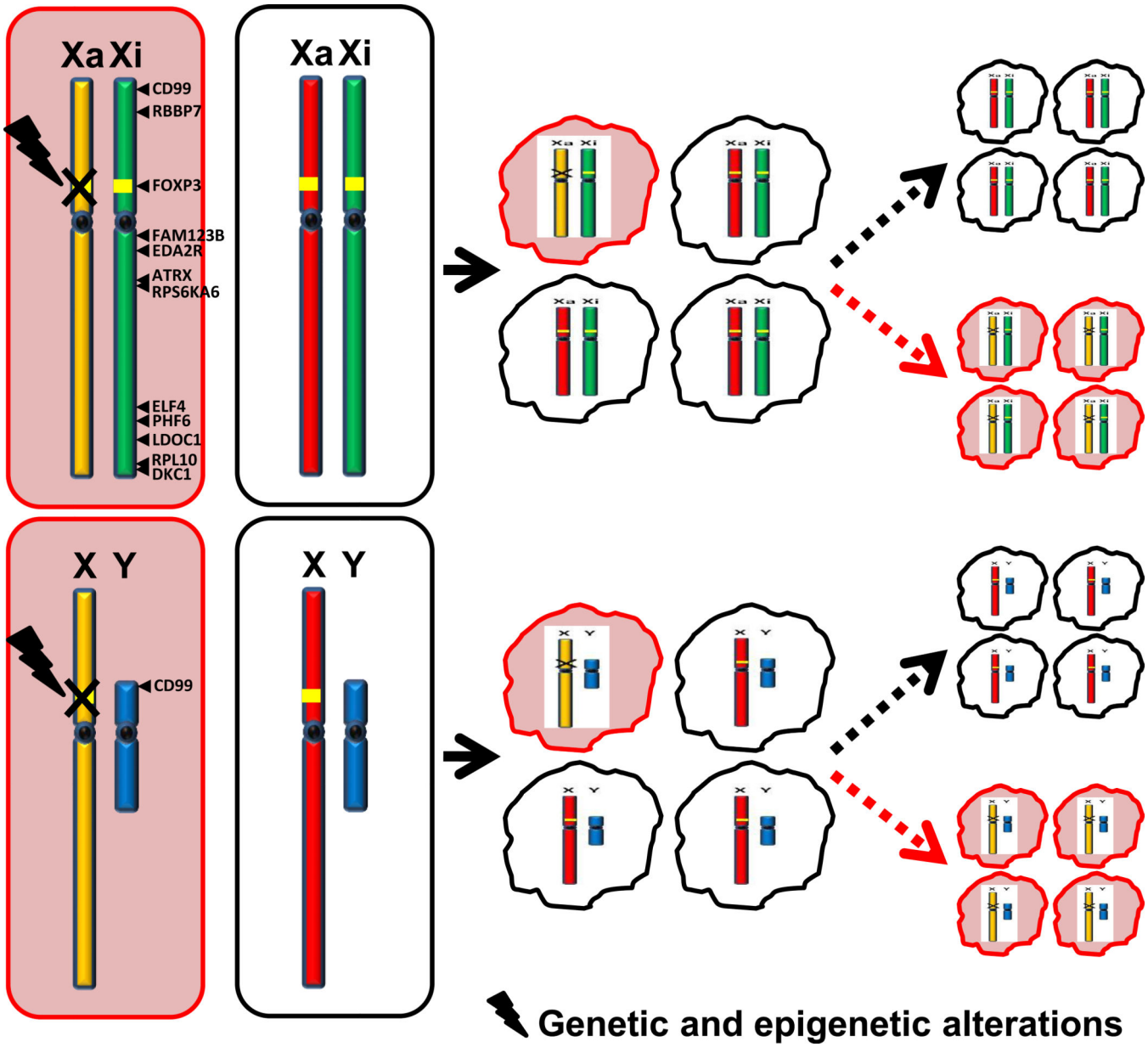

Fig. 1.

Mechanism of inactivation of X-linked tumor suppressor gene. X-linked tumor suppressor genes in male cancer may be inactivated by multiple genetic or epigenetic events such as gene deletion, mutation, DNA methylation and post-transcriptional modification, etc., and in female cancer may also be implicated in LOH, bi-allelic methylation and skewed X-inactivation, etc. Cells with those genetic or epigenetic alterations will undergo a negative or positive selection during tumorigenesis. The pink elliptic boxes or irregular circles indicate cells with genetic or epigenetic damage in an active allele. The black dotted arrows indicate a negative selection while the red dotted arrows indicate a positive selection. The black solid arrows indicate a location of the putative tumor suppressor genes. Xa: active X-chromosome; Xi: inactive X-chromosome.

Table 1

Putative X-linked tumor suppressor genes in human cancers

Gene	Locus	X-linked in other mammals	Function	Signaling pathway	Involvement in cancer
FOXP3	Xp11.23	Mouse, Rat, Dog	Transcriptional factor; Master regulator in the development and function of regulatory T cells; Tumor suppressor	Nuclear transcritional regulation of the *HER2, SKP2, c-Myc* and *p21*	Down-regulated in breast cancer, prostate cancer and ovarain cancer tissues, but overexpression in pancreatic cancer tissues; Gene deletions and somatic mutations identified in breast cancer and prostate cancer
RBBP7	Xp22.2	Mouse, Rat, Dog	Putative tumor suppressor involved in cell proliferation, differentiation and apoptosis	Regulation of the Rb, BRCA1, WT1 and beta-catenin/TCF signalings	Unknown
CD99	Xp22.32 and Yp11.3	Dog, but not in Mouse, Rat	cell-cell adhesion; Leukocyte migration, T-cell adhesion, ganglioside GM1 and transmembrane protein transport, and T-cell death and involved in in tumor malignancy and metastases	Caspase-independent pathway and AKT-, ERK-, and JNK-dependent AP-1 activation signaling pathways	Down-regulation in osteosarcoma, gallbladder carcinomas, nasopharyngeal carcinoma, gastric adenocarcinoma, and transitional cell carcinomas of urinary bladder, but up-regulated in desmoplastic small-cell tumours, synovial sarcomas, primitive neuroectodermal tumours and hepatocarcinomas; LOH at this locus and promoter methylation identified in gastric adenocarcinoma
FAM123B	Xq11.1	Mouse, Rat, Dog	Tumor suppressor for Wilms tumor	Inhibition of the beta-catenin signaling and modulation of WT1 activity	Gene deletion and somatic mutation identified in Wilms tumors

Gene	Locus	X-linked in other mammals	Function	Signaling pathway	Involvement in cancer
EDA2R	Xq12	Mouse, Rat, but unknow in Dog	Promoting apoptosis in tumor cells and epidermal morphogenesis during embryonic development	Activation of the NF-kappaB and JNK pathways; downstream target of p53	Down-regulated in breast cancer and colorectal cancer; mutation and hypermethylation identified in colorectal cancer
RPS6KA6	Xq21	Mouse, Rat, Dog	Inducing cell arrest and senescence and involved in invasion and chemotaxis	Up-regulation of Rb, retinobl astoma-associated 46 kDa protein, p21, and claudin-2, but down-regulation of CXCR4	Down-regulated in colon carcinomas, colon adenomas, renal cell carcinomas, and endometrial cancers
ATRX	Xq21.1	Mouse, Rat, Dog	Nevol tumor suppressor involved in transcriptional regulation, nuclear architecture, and chromosome stability	Regulation of chromatin remodeling, DNA methylation and gene transcription	Down-regulation in acute myeloid leukemia, prostate cancer, breast cancer, esophageal squamous cell carcinoma; loss-of-function somatic mutations in pancreatic neuroendocrine tumor and paediatric glioblastoma
ELF4	Xq26.1	Mouse, Rat, Dog	Transcriptional regulation, DNA damage response, and involved in natural killer (NK) cell development and function	Transcriptional activation of the *CSF2*, *IL3*, IL8, and *PRF1* and repression of *MMP-9* and *IL-8*	LOH at this locus identified in ovarian and breast cancers; translocation in acute myelogenous leukemia; rearrangements of BCORL1-ELF4 in hepatocellular carcinomas
PHF6	Xq26.3	Mouse, Dog, but unknow in Rat	Transcriptional regulation	Regulation of homeobox transcription factor oncogenes TLX1 and TLX3	Mutation and deletion frequently found in T-cell acute lymphoblastic leukemia, adult acute myeloid leukemia, and hepatocellular carcinoma
LDOC1	Xq27	Mouse, Rat, Dog	Inducing apoptosis in tumor cells	Inhibition of the NF-kappaB signaling and	Down-regulated in pancreatic and gastric cancer cell lines; deletions identified in

Gene	Locus	X-linked in other mammals	Function	Signaling pathway	Involvement in cancer
				the degradation of p53	prostate cancers, but high levels of LDOC1 correlate with poor prognosis in chronic lymphocytic leukemia
RPL10	Xq28	Mouse, Rat, Dog	Putative tumor suppressor for hormonally dependent cancers	Repression of the c-Jun and AP-1-mediated transcriptional activation	LOH and microsatellite instability at this locus frequently occurred in ovarian cancer; down-regulated in prostate cancer and multiple endocrine neoplasia type 1
DKC1	Xq28	*Mouse, Rat, Dog*	Multiple functions in telomerase, ageing and cancerr	RNA processing and modification; p53- and p27-dependent translational control in ribosome biogenesis	Unknown