Oncogenic chromosomal translocations and human cancer (Review)

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Abstract. Chromosomal translocations are very common in human cancer. The molecular mechanisms of chromosomal translocations are complex and are not fully understood. Recent studies showed organization of genomes is higher-order in the nucleus and every chromosome or chromatin has its preferential position and territory. These findings suggest the spatial arrangements of chromosomes and gene loci in the interphase nucleus are responsible for non-random chromosomal translocations in human cancer. Chromosomal translocations are favored in neighboring chromosomes or genes in spatial proximity within the nucleus. Chromosomal translocations leading to cancer are generally via two ways, formation of oncogenic fusion protein or oncogene activation by a new promoter or enhancer. This review focuses mainly on the recent advances in oncogenic chromosomal translocations in human cancer.

Contents

1. Introduction

Chromosomal translocations are very common in human cancer, particularly in hematopoietic and lymphoid tumors (1). They are involved in the initiation of some types of cancer although the exact mechanism is not fully understood. These translocations may provide a selective growth advantage or chance of subsequent mutations in some stem or progenitor cells, which may subsequently initiate the development of some malignant tumors. For oncogenic chromosomal translocations, gene rearrangements may change the original locations of proto-oncogenes to generate the obvious effects on phenotype via the two major ways (2,3). One is to generate oncogenic fusion proteins. The best example is translocation between chromosomes 9 and 22 [t(9;22)], i.e. Philadelphia (Ph) chromosome, in chronic myeloid leukemia (CML), resulting in the translocation of proto-oncogene *ABL* at 9q34 to *BCR* on chromosome 22. The formation of BCR-ABL oncoprotein has an abnormal activity of tyrosine kinase (TK) which is associated with the tumorigenesis of CML and acute lymphoblastic leukemia (ALL) (4). Another way is that proto-oncogenes are brought into proximity with the new cis-regulatory elements. The classic example is the overexpression of proto-oncogene c-*MYC* in Burkitt lymphoma due to t(8;14) to result c-*MYC* juxtaposed to immunoglobulin heavy chain (IGH) regulatory elements.

Chromosomal translocations *in vivo* are a complex biological process and there are two essential steps for the formation of chromosomal translocations. First, DNA double-strand breaks (DSBs) occur simultaneously at the two loci. Second, the ends of DSBs need to approach each other and are illegitimately joined together. Aside from these essential steps, increasing evidence shows that there are still several factors that influence the formation of chromosomal translocations, such as nuclear architecture, activation induced deaminase (AID)-mediated V(D)J recombination, gene expression, and other unknown mechanisms (5-7). In the present study, I focus on the effects of chromosome or gene positioning on chromosomal translocations, on the functional impacts owing to oncogenic chromosomal translocations in human cancer.

2. Chromosomal translocations are related to chromosome or gene positioning

Chromosomal translocations in cancer are generally considered to be no-random. The factors that could influence chromosomal translocation are complex and several factors, such as the spatial positions of broken loci, recombination, DNA repair elements, are involved. The two spatial proximal broken loci have more probability to illegitimately join than two distant broken loci (8). For example, investigations have shown that chromosomes 9 and 22 neighbor in lymphoid

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cells (9,10). This may partly explain why t(9;22) easily occurs in lymphocytes. Similar to t(9;22), t(15;17), resulting in the formation of promyelocytic leukemia-retinoic acid receptor α (PML-RARα) fusion oncoprotein, can be detected in most cells in acute promyelocytic leukemia (APL) (11). The study also showed that chromosomes 15 and 17 were close to each other in lymphoid cells (10); this may also partly explain why t(15;17) easily occurs in hematopoietic cells. Furthermore, intergenic distance between the *PML* and *RARα* or *BCR* and *ABL* is shorter in hematopoietic precursors than in B-lymphoid cells (10), consistent with the theory that cancer originates from stem cells.

The reason why 70% of Burkitt lymphomas, a B-cell tumor, often contains t(8;14), i.e. the c-*MYC* gene (8q24) juxtaposes to *IGH* gene (14q32) (Fig. 1B), is because chromosome 8 closes spatially chromosome 14 in B lymphocytes (12,13). Research has shown that when B lymphocytes are stimulated, the *MYC* gene is preferentially recruited to the same transcription factory as the highly transcribed *IGH* gene. While the c-*MYC* and *IGH* are close to each other, it increases the incidence of specific chromosomal translocations (14). With the exception of t(8;14), c-*MYC* less often rearranges with the immunoglobulin light chain κ (*IGK*) or λ (*IGL*) genes of chromosome 2 or 22 in Burkitt lymphoma, t(2;8)(p11.2;q24.1) or t(8;22)(q24.1;q11.2) places c-*MYC* under the control of *IGK* or *IGL* locus, respectively, resulting in the overexpression of c-*MYC*. In fact, the mechanism of t(2;8) or t(8;22) translocation is similar to that of t(8;14) in Burkitt lymphoma, relating to spatial organization of the B cell genome (12).

Except for t(8;14) in Burkitt lymphoma, a reciprocal translocation between chromosomes 14 and 18 is also extremely common in follicular lymphoma (70-95%), a B cell lymphoma with follicular architecture. This translocation leads to the juxtaposition of the *BCL-2* gene at 18q21 and the *IGH* locus, resulting in anti-apoptotic protein BCL-2 overexpression (Fig. 1D). Measuring BCL-2 expression can be used to distinguish follicular lymphoma from benign follicular hyperplasia, in which BCL-2 expression is low (15). In mantle cell lymphoma, an aggressive subtype of B cell lymphoma, most tumor cells have a t(11;14), i.e. the cyclin D1 (*CCND1*) gene at 11q13 moves to *IHG* locus, resulting in the overexpression of cyclin D1 (Fig. 1C) (16). Cyclin D1, a cell cycle regulator, is not expressed in normal B cells. In diffuse large B-cell lymphoma (DLBCL), approximately one third of patients have a t(3;14), i.e. the oncogene *BCL-6* on chromosome 3 moves to *IHG* locus, resulting in the overexpression of *BCL-6* (Fig. 1A), a specific transcriptional repressor that inhibits the differentiation of B cells. The mechanism of chromosomal translocations in follicular lymphoma, mantle cell lymphoma and DLBCL are similar to that in Burkitt lymphoma, relating to spatial proximity of translocation-prone gene loci in the interphase nucleus (12).

Approximately 60% of patients with anaplastic large-cell lymphoma (ALCL) have t(2;5), that leads to the formation of a characteristic fusion gene between anaplastic lymphoma kinase (*ALK*) at 2p23 and nucleophosmin (*NPM*) at 5q35. ALK, a receptor tyrosine kinase (RTK) belonging to the insulin receptor superfamily, has been reported to be active due to chromosomal translocations in several types of human cancer, such as ALCL, non-small cell lung carcinoma (NSCLC) and DLBCL (17,18). ALK expression is generally restricted to neural tissue (19), t(2;5) leading to the expression of truncated *ALK* driven by *NPM* promoter in lymphocytes. Accumulating evidence suggests that DSBs and the formation of translocation are preceded by the two gene loci being in close proximity. For example, Mathas *et al* (20) found that the formation of *ALK-NPM* fusion gene was related to spatial proximity of two gene loci which was prior to the generation of translocation. This spatial proximity of two gene loci leads to upregulation of ALK which facilitates to induce DSBs.

Aside from interchromosomal translocations, intrachromosomal translocations are also associated with spatial distance of two gene loci. For example, 60-70% of papillary thyroid carcinomas have a characteristic inv(10)(q11.2q21), i.e. breakpoint *RET* (10q11.2) is relegated to opposite breakpoint the *H4 (D10S170)* or *NCOA4 (ELE1)* gene (10q21) in the same chromosome (21). RET, an RTK, is often found in translocation in papillary thyroid carcinoma (PTC), particularly in patients who had radiation exposure. The H4 protein is widely expressed in the nucleus and cytoplasm and its function is unknown (22). According to the different rearrangement loci, to date, PTC has 11 rearranged forms, referred to as PTC1-11 (23). PTC1(H4, CCDC6)-RET and PTC3(NCOA4)-RET are the most common intrachromosomal rearrangements in PTC. By contrast, PTC2-RET and other less common types of PTC-RET are interchromosomal translocations (24). These rearrangements can lead to constitutively ligand-independent RET activity, involved in thyroid carcinogenesis. Although the distances between *RET* and *H4* loci are 18 Mb, chromosome folding can offer two loci close to each other in thyroid cells, thus increasing the probability of recombination between them in the interphase nuclei. This chromosomal folding is specific for thyroid cells, and this may explain why inv(10)(q11.2q21) is frequently seen in PTC (25). The translocation of *H4* and *RET* occurs less in other types of cells. If it happens in non-thyroid cells, this type of translocation may not cause tumor.

Hormones also influence chromosomal translocations via their receptors. Previous studies showed that ~50% of prostate cancer cases have del(21)(q22) and t(7;21) (1,26-28), resulting in the translocation of an ETS (E26 transformation-specific)-regulated gene *(ERG)* (21q22.3) or ETS variant 1 (*ETV1*) gene (7p21.2) to the transmembrane protease serine 2 (*TMPRSS2*) gene (21q22.2) promoter region, which contains androgen receptor (AR) binding sites (29). ETS is a transcription factor family in which every family member contains ETS domain, a winged helix-loop-helix DNA binding domain. To date, 28 members of ETS have been identified, such as *FLI* (11q24), *ERG*, *ETV1*, *ETV4* (17q21), *ETV5* (3q) and *ETV6* (12p13) (30). The translocations of ETS are often found in human cancer, such as Ewing sarcoma (31,32), leukemia (33,34), prostate cancer (1,27-28) and breast cancer (35). *TMPRSS2* is a specific expression gene in the prostate and its expression is increased in prostate cancer (28,36). Although it is 2.7 Mb genomic distances between *ERG* and *TMPRSS2* on the same chromosome and *TMPRSS2* and *ETV1* are on the different chromosomes, *ERG* and *ETV1* regulatory regions also have AR binding sites and androgen can induce *TMPRSS2* and *ERG* or *ETV1* spatial proximity via AR (27,28,37,38). These studies explain why the *TMPRSS2-ERG* and *TMPRSS2-ETV1* translocations are easily seen in prostate cancer as the prostate is an androgen-sensitive organ. That hormones induce inter-

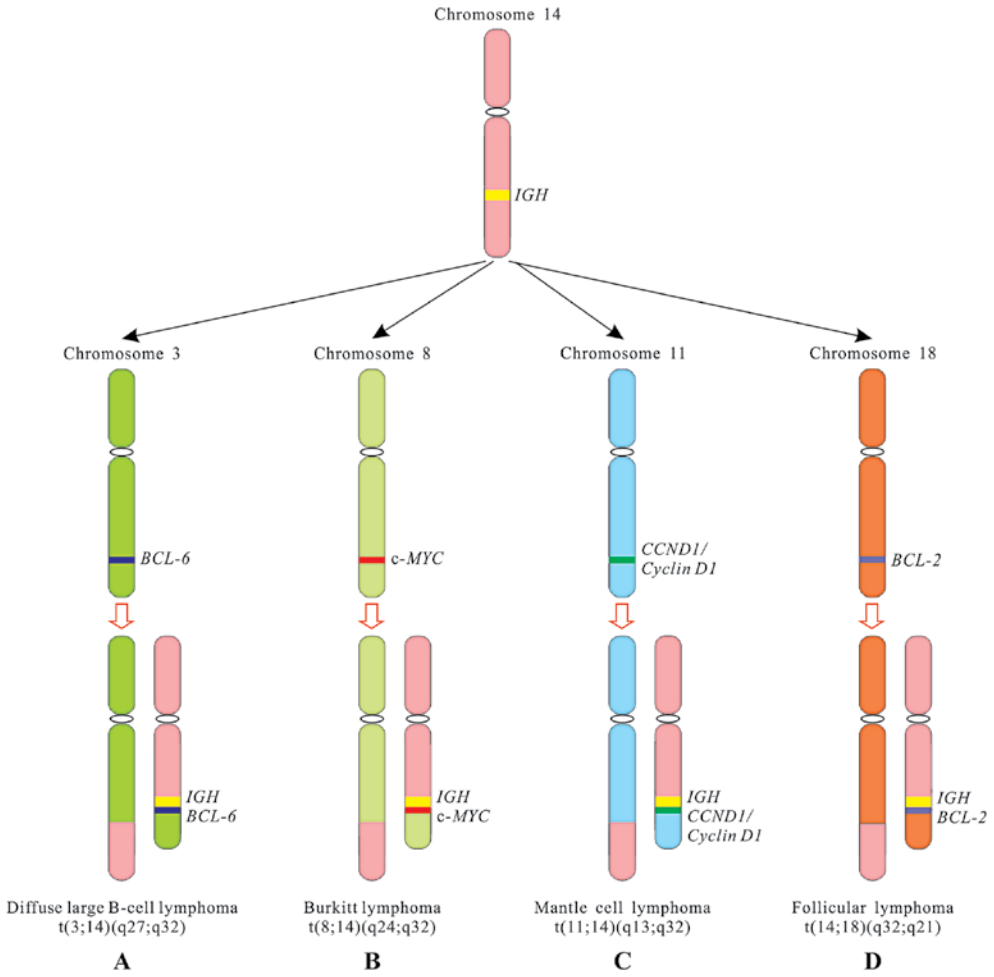

Figure 1. Proto-oncogenes are under the control of the *cis-IGH*-regulatory elements in B cell malignancies. *IGH* is on chromosome 14. Chromosomal translocations make c-*MYC* and other proto-oncogenes under the control of *cis-IGH* locus in Burkitt lymphoma and other B cell lymphomas (as indicated).

actions between gene loci on different chromosomes is also found in estrogen. Hu *et al* (39) reported that estrogen induced rapid chromosome interactions to coordinate specific gene expression via estrogen receptor α (ERα).

In general, when DSBs occur, the ends of DSBs are relatively stable and mobile <250 nm (40), supporting the observation that chromosomal translocations occur in close genes. We can image if the broken ends are relatively stable, they may be rejoined by themselves, thereby preventing chromosomal translocation. If the broken ends roam, it increases the chances of illegitimate recombination. Thus, the relative stability of the broken ends decreases the probability of gene rearrangement and favor genomic integrity (40,41).

3. Effects of oncogenic chromosomal translocations

Effects of oncogenic chromosomal translocations on cellular phenotypes are complex and diverse. Following translocations, oncogenes may influence cellular phenotypes via the formation of oncogenic fusion proteins or under the control of the new regulatory elements (1-3).

Oncogenic fusion proteins. Although the products of oncogenic fusion genes are diverse, they can primarily be classified into two groups, transcription factors and TKs. Several oncogenic fusion proteins are transcription factors and TKs. In fact, the products of fusion genes are diverse; some may be neutral, some may play less important roles in cellular phenotypes and some may cause cell death in which we can not see this type of the translocation. The translocations found in cancer, however, clearly have critical functions in tumorigenesis. Generally, transcription factors and TKs play more important roles in cellular phenotypes, and this may partly explain why many fusion proteins detected in human cancer are transcription factors and TKs. It should be noted, that these so-called oncogenic fusion proteins as transcription factors and TKs are already different from their functions of parental proteins in several aspects and they often acquire some new functions.

It is clear that the sites of DSBs are related to the functional consequences of fusion genes. DSBs are not random (42) and occur preferentially in large and evolutionarily conserved genes (43,44), fragile sites (45), transcription start sites (14,46,47) and euchromatin (48,49). The breakpoints do not usually occur in their functional domains if these genes are encoded for transcription factors or TKs, thus fusion proteins can still retain the activities of transcription factors or TKs (42). Several studies have shown that DSBs preferentially occur in euchromatin, consistent with a greater chance for translocation to occur in the sites with transcription activity (14,46,47). Following exposure to ionizing radiation, DSBs occur more

often in euchromatin than heterochromatin, suggesting the highly compacted chromatin can prevent from radiation damage. From another point, euchromatin is relatively loose and has a lack of protective mechanism, so it is easily attacked by radiation (48,49). In addition, the mechanisms of DSB repair in euchromatin are also different from heterochromatin. Since the time for DSB repair in heterochromatin is longer than euchromatin (50,51), by extrapolation, the higher frequency of chromosomal translocations in euchromatin than in heterochromatin is reasonable.

Oncogenic fusion protein as transcription factor. The products of several oncogenic fusion genes function as transcription factors. In this group, each fusion protein consists of N-terminal partner fused to the DNA binding domain at the C-terminus (Fig. 2). For example, EWS-FLI fusion protein, a characterized protein in Ewing sarcoma, consists of N-terminal part of EWS, a member of the TET family at the N-terminus, and C-terminal part of FLI, a member of the ETS family, at the C-terminus (31). As a chimeric transcription factor, EWS-FLI fusion protein has different transcription functions compared to its parental transcription factor FLI (32), despite identical DNA-binding domain. This mistargeting is associated with 85% of Ewing sarcoma development (52).

The functions of the fusion proteins as oncogenic transcription factors are various. Some stimulate gene expression, such as TMPRSS2-ERG and TMPRSS2-ETV1. Whether the TMPRSS2-ETS are really fusion proteins is under debate. Some people consider that the *TMPRSS2-ETS* translocations are the expression of *ETS* under the influence of the *TMPRSS2* promoter as the expression of *MYC* under the *IGH* regulatory elements in Burkitt lymphoma (2). In fact, the *TMPRSS2-ETS* translocations are very heterogeneous, both *TMPRSS2* at the 5'-end and *ETS* at the 3'-end have different fusion forms which generate different fusion transcripts, including splice variants (26,29,53,54). In most cases, the *TMPRSS2* promoter and first exon or first 2 exons are juxtaposed to the *ETS* exons, with deletion of the *ETS* promoter and first exon or first 2 exons (55). Therefore, the fusion genes are under the control of the androgen-regulated *TMPRSS2* promoter, resulting in the high level expression of oncogenic *ETS* fusion genes. For example, *TMPRSS2-ERG* gene fusion is the most common among these translocations and some are composed of the *TMPRSS2* promoter and the first exon at the 5'-end and the transcription factor domain of *ERG* at the 3'-end, resulting in a truncated ERG protein lacking TMPRSS2 as the *TMPRSS2* exon 1 is noncoding and does not contain an ATG (53), some are composed of the *TMPRSS2* promoter and the first 2 exons (exon 2 containing an *ATG* at 142) at the 5'-end and the transcription factor domain of *ERG* at the 3'-end (designed type VI), resulting in a true fusion protein containing the first 5 amino acids of the TMPRSS2 at the N-terminus and a slightly truncated ERG protein at the C-terminus (Fig. 2) (53). Androgen can stimulate the transcription of the *TMPRSS2-ETS* fusion since all *TMPRSS2-ETS* fusions retain the *TMPRSS2* promoter which contains AR binding sites. In most cases, ETS retains DNA-binding domain, which can stimulate the transcription of target genes for cell growth, invasion and metastasis and promote prostate cancer progression (26,28).

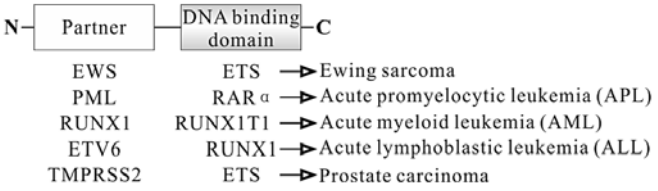

Figure 2. The functions of fusion proteins as transcription factors and associated malignant tumors. Fusion proteins consist of two parts (from different genes). The functions of these fusion proteins are different from their parental proteins. The N-terminal partners provide transactivation domains or dimerization/oligomerization domains. In the C-terminus, these oncogenic fusion proteins retain the DNA binding domains.

Some inhibit gene expression, such as t(12;21)/ETV6-(TEL1)-RUNX1(runt-related transcription factor 1, previously known as AML1), t(8;21)/RUNX1-RUNXIT1(ETO), t(15;17)/PML-RARα and inv(16)/CBFB-MYH11, which inhibit the transcriptional activity of genes required for normal differentiation of hematopoietic cells. Although these fusion proteins may not be sufficient to induce leukemia alone (56), they increase the developmental risk of acute leukemia in patients with these fusion proteins (4,34,57). These fusion proteins repress the functions of transcription via the different molecular mechanisms. For example, RUNX1-RUNXIT1 protein is found in ~13% of acute myeloid leukemia (AML) (58). In RUNX1-RUNXIT1 protein, the translocation deletes the transactivation domain but retains the runt homology domain (RHD) responsible for binding to DNA at N-terminus of RUNX1 (Fig. 2) (59). RUNX1-RUNXIT1 protein interferes with wild-type RUNX1-dependent transcription via RUNXIT1 recruiting the nuclear corepressor (N-CoR)-histone deacetylase (HDAC) complex (60). ETV6-RUNX1 protein is the most common abnormality in childhood ALL, occurring in ~25% (4). In ETV6-RUNX1 protein, the translocation deletes the ETS domain of ETV6, a member of the ETS family, but retains the runt domain of RUNX1 (Fig. 2). Similar to the RUNX1-RUNXIT1 protein as a dominant negative inhibitor of RUNX1, the ETV6-RUNX1 protein represses RUNX1-dependent transcription via ETV6 recruiting N-CoR-HDAC complex (61). RUNX1 targeting genes are required for normal hematopoietic cell development. PML-RARα protein is linked to the development of APL, a genetic distinct subtype of AML. This fusion protein is composed of most of the functional domains of RARα (including the RAR binding domain and the DNA binding domain) and the majority of PML, including dimerization domain (Fig. 2). As a transcription factor, wild-type RARα releases SMRT/N-CoR corepressor after binding retinoic acid (RA) and induces the transcription of target genes that promote cell differentiation. However, this fusion protein alters the sensitivity to physiological levels of RA and impairs the release of SMRT/N-CoR corepressor from RARα, therefore blocking the differentiation of promyelocytes (62). One of the mechanisms of pharmacologic levels of all-trans retinoic acid (ATRA) treatment APL promotes the release of the corepressor from RARα and recovers RA response (11). Arsenic trioxide (As_2O_3) is also used to treat APL by promoting degradation of PML-RARα protein (63).

There are some mistarget gene expressions, such as mixed lineage leukemia (MLL) fusions (64). *MLL* gene on 11q23 is often rearranged with other partner genes in ALL and AML, accounting for 8% of pediatric and 10% of adult ALL (4), 15-20% of pediatric AML and <3% of adult AML (65), or biphenotypic (mixed lineage) leukemias. The *MLL* gene encodes a complex DNA binding protein with histone H3 lysine 4 (H3K4)-specific methyltransferase activity, which positively regulates gene expression including HOX genes. MLL protein consists of multiple functional domains, including the AT-hooks, DNA methyltransferase homology domain that contains a CXXC zinc finger motif and trithorax PHD domains at the N-terminus, the transactivation domain (TAD) and SET domain that possesses H3K4 methyltransferase activity at the C-terminus. Post-translationally, taspase I cleaves MLL to generate two fragments (MLLN p300 and MLLC p180) that form a stable complex by direct interaction of the FYRN and FYRC domains (66). Unlike classical sequence-specific DNA-binding transcription factor, MLL regulates the expression of target genes via epigenetic mechanisms, such as DNA and histone methylation modification (66).

Chromosomal translocations lead to the fusion of 5'-end portion of MLL to one of >60 different partner genes, resulting in the formation of different fusion genes, such as *MLL-AF4* (4q21), *MLL-AF9* (9p22), *MLL-ENL* (19p13.3), *MLL-AF10* (10p12), *MLL-AF6* (6q27), *MLL-ELL* (19p13.1) (Fig. 3) (66,67). All MLL fusion proteins retain N-terminal AT-hooks, DNA methyltransferase homology domain, thus preserving DNA binding activity whereas the trithorax PHD domains, TAD and SET domains are always replaced by the partners. In these fusions, the original MLL H3K4 methyltransferase activity is replaced by the partners which play a critical role in MLL oncoproteins (68). Although MLL fusion proteins lose the activity of H3K4 methylation, these fusion proteins gain the activity of H3K79 methylation via recruiting the H3K79 methyltransferase hDOT1L which can cause dysregulation of whole genomic expression and is associated with MLL leukemogenesis (67,69). Since hDOT1L plays a key role in the development of MLL leukemia, hDOT1L is an ideal target for MLL leukemia. Several hDOT1L inhibitors are underdeveloped. In particular, EPZ004777, a specific hDOT1L inhibitor, seems to be a promising drug for leukemia with MLL gene translocation (70).

Since >60 MLL fusion proteins have been found (71), the functions of MLL fusion proteins are very different, and the functions of some MLL fusion proteins remain unclear or not fully understood. To date, we know that MLL oncoproteins induce leukemia through several pathways. First, MLL oncoproteins act as transcriptional regulators that can bind DNA and induce aberrant expression of leukemic stem cell target genes, such as *HOX*, *MEIS1*, *WNT* and *RNA polymerase II*. Among MLL target genes, transcription factor *HOX* genes are particular and essential for MLL leukemogenesis (72). MLL-ENL, MLL-ELL, MLL-AF4, MLL-AF9 and MLL-AF10 have been demonstrated to induce acute leukemia using this pathway (Fig. 3) (67,73-75). Second, MLL fusion partners provide a dimerization motif, such as AF1p/Eps15 and GAS7. The MLL dimerization/oligomerization proteins can recruit co-activators or basal transcriptional machinery to result in the aberrant expression of target genes for inducing

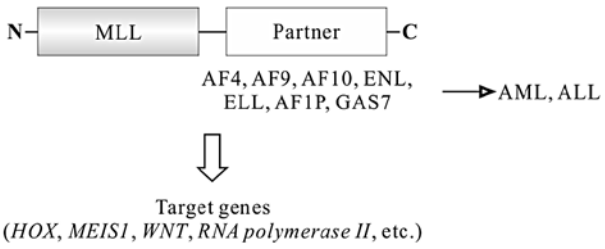

Figure 3. MLL fusions. At least >60 MLL chimeric proteins have been found in which the N-terminal portion of MLL is fused to the C-terminal portion of the partner. Unlike classical sequence-specific DNA-binding transcription factor, MLL fusions mainly regulate the expression of target genes via epigenetic mechanisms.

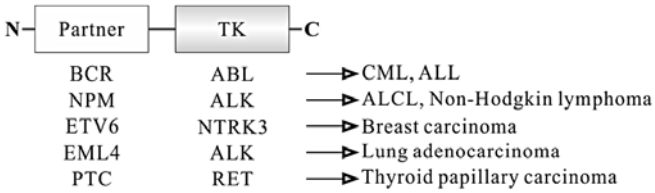

Figure 4. The functions of fusion proteins as TKs and associated malignant tumors. The functions of these fusion proteins are different from their parental proteins.

acute leukemia (76,77). Third, MLL fusion partners increase the stabilization of MLL oncoproteins. For example, all MLL-AF4, MLL-AF9, MLL-ENL and MLL-ELL exhibit resistance to degradation mediated by the cell cycle ubiquitin-proteasome system (71).

Oncogenic fusion protein as tyrosine kinase. Another group of oncogenic fusion proteins harbor activities of TKs. In this group, each translocation generates a different fusion protein consisting of N-terminal partner fused to the TK domain at the C-terminus (Fig. 4). TK domain in these fusion proteins is intact although they are the truncated proteins (2,78,79). For example, in ALCL, ALK breakpoints are located in the intron flanked by exons 16 and 17, and exons 17-26 encoding the intracytoplasmic kinase domain of ALK are intact (80). It is similar to that of RET in PTC (81). As the regulatory parts of kinase are often lost and replaced by unrelated sequences, the kinase activity of these fusion proteins is determined by the N-terminal partners. In most cases, the N-terminal partners supply domains that promote dimerization/oligomerization, allowing fusion kinase to be activated in the absence of physiological stimulating signals (79,81-85).

BCR-ABL fusion protein is linked to the development of CML and ALL (4). ABL protein has two isoforms, 1a and b. ABL1b contains a C14 myristoyl saturated fatty acid moiety covalently linked to the Cap region at the N-terminus and is expressed at higher levels than ABL1a, which is not myristoylated. The Cap region of ABL contains endogenous autoregulatory domain which can inhibit kinase activity via stabilizing SH3 and SH2 domains of ABL (86,87). This fusion protein is composed of the majority of BCR at the N-terminus and most of the functional domains of ABL

except Cap domain at the C-terminus (Fig. 4), resulting in the disregulatory activation of BCR-ABL TK (88). In addition, oligomerization domain and GRB2-binding site at tyrosine 177 (Y177) in BCR partner are also essential for BCR-ABL-mediated CML (82,89). Imatinib/Gleevec®, a specific BCR-ABL inhibitor, was the first molecular target drug approved by the US Food and Drug Administration (FDA) to treat patients with CML in 1996. Dasatinib and nilotinib, second generation inhibitors of ABL, have also been approved to treat patients with imatinib-resistant CML (90).

H4-RET fusion protein is the most common chromosomal translocation in PTC, and accounts for 60-70% of PTC. This protein consists of the N-terminal promoter and leucine zipper domain of H4 at the N-terminus and the TK domains of RET at the C-terminus (Fig. 4). RET lacks the signal peptide and transmembrane domain in this chimeric oncoprotein, thus the aberrant TK activity of RET fusion is controlled by H4 partner which provides an active promoter and dimerization domain for ligand-independent activation of the fusion protein (91).

Approximately 5% of NSCLCs have inv(2)(p21;p23), resulting in the formation of echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion gene (85). EML4-ALK protein consists of various length EML4 containing the coiled-coil domain at the N-terminus and the intracellular catalytic domain of ALK at the C-terminus (Fig. 4). As ALK lacks the extracellular and transmembrane domain in this oncoprotein, so EML4 partner constitutively activates the TK of ALK via the dimerization of EML4-ALK, involved in the carcinogenesis of NSCLC (85). EML4-ALK is most commonly detected in non-smokers with NSCLC. NSCLC with EML4-ALK has unique pathological and clinical features, such as Asian patients, younger, adenocarcinoma and lack of EGFR and KRAS mutations (92). Crizotinib, an ALK inhibitor, was recently approved by the FDA to treat patients with ALK-positive NSCLC (93).

Oncogenes under the control of a stronger promoter. Proto-oncogenes are brought into proximity with the new *cis*-regulatory elements, leading to their overexpression which is seen in several types of lymphoma and leukemia, particularly in B and T cell malignancies. This is because V(D)J recombination exists during B and T cell development, which generates antibody and T cell receptor (TCR) diversity. However, V(D)J recombination may also increase the risk of chromosomal translocation in the same regions, which may partly explain why chromosomal translocation frequently occurs in several types of lymphoma and leukemia. For example, the overexpression of oncogenes *c-MYC*, *BCL-2*, *CCND1* and *BCL-6* in B cell lymphomas may be associated with errors in V(D)J recombination (Fig. 1) (16,94-96), suggesting the mechanism of chromosomal translocations in these B cell lymphomas is similar.

In a subset of T cell ALL (T-ALL), chromosomal translocation can make proto-oncogenes under the control of TCR regulatory elements, resulting in the deregulated transcription of these proto-oncogenes, such as *TLX1 (HOX11)*, *TLX3 (HOX11L2)*, *LMO1*, *LMO2*, c-*MYC*, *LYL1*, T-cell acute lymphocytic leukemia-1/stem cell leukemia (*TAL1*/*SCL*), *TAL2* and *NOTCH1* (Fig. 5). TLX1 and TLX3 belong to

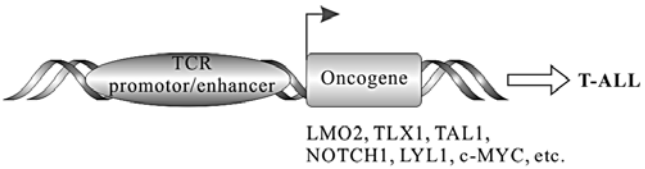

Figure 5. Oncogenes are under the control of the *TCR* promoter/enhancer in a subset of T-ALL. The promoter is usually located upstream of the gene, while the enhancer can be located upstream, downstream, or even within the gene it control. In T-ALL, the chromosomal translocations are mainly involved in the *TCR* enhancer.

homeobox transcription factors. LIM domain only (LMO) 1 and LMO2 belong to LIM transcription factors containing LIM zinc-finger motifs. c-MYC, LYL1, TAL1/SCL and TAL2 belong to basic helix-loop-helix (bHLH) transcription factors. NOTCH1, one of NOTCH family, is a transmembrane protein.

The TCR is composed of two different protein chains. In 95% of T cells, TCR consists of αβ chains, whereas in 5% of T cells, TCR consists of γδ chains. TCRα (*TCRA*) and δ (*TCRD*) chain genes are localized on 14q11.2, TCRβ (*TCRB*) and TCRγ (*TCRG*) loci are localized on 7q34 and 7p15, respectively. The breakpoints often occur in *TCRA/D* or *TCRB*. The t(11;14)(p13;q11) and t(7;11)(q34;p13) have been found in 3% T-ALL (97). Both translocations lead to *LMO2* (11p13) under the control of the *TCRD* or *TCRB* locus, resulting in LMO2 overexpression which may be involved in the T-ALL development (98). Proto-oncogene *TLX1* (T-cell leukemia homeobox 1, previously known as *HOX11* or *TCL3*) on 10q24 is normally not expressed in T cells and its expression is often deregulated in T-ALL (99). This deregulated expression of *TLX1* is related to t(7;10)(q34;q24) and t(10;14)(q24;q11) which account for 7% of childhood and 31% of adult T-ALL (97). These translocations make *TLX1* under the control of the *TCRB* or *TCRA* locus, resulting in the overexpression of *TLX1* which may contribute to T-ALL via blocking apoptosis of developing T cell in the thymus (100). TLX1 overexpression has also been demonstrated in the absence of a 10q24 rearrangement, suggesting that other mechanisms, such as epigenetic alterations, can lead to this aberrant expression of *TLX1* (101,102). The situation is similar to *TAL1* (1p32). Approximately 7% of childhood T-ALL and 12% of adult T-ALL have t(1;14)(p32;q11), leading to deregulated expression of *TAL1* under control of the *TCRA/D* loci (4). However, the overexpression of *TAL1* in T-ALL also occurs in the absence of *TAL1* rearrangement, suggesting that other mechanisms may influence the overexpression of *TAL1* (103).

NOTCH1 plays crucial roles in cell development, hematopoietic stem cell maintenance and T cell fate specification in the mature organism (104). NOTCH1 is regarded as an oncoprotein. In a low number of human T-ALL patients, they had t(7;9)(q34;q34.3) which results to fuse the 3' end of *NOTCH1* (9q34.3) to *TCRB* locus, leading to overexpression of a truncated NOTCH1 protein that lack the negative regulatory region (NRR) (105). NRR is NOTCH1 extracellular domain and responsible for preventing ligand-independent receptor activation.

4. Conclusion

Chromosomal translocations in human cancer are not random and tend to occur in some specific sites with spatial proximity in genome organization. The oncogenic chromosomal translocations may provide a selective growth advantage or chance of secondary mutations in some stem or progenitor cells via different pathways, such as the formation of oncogenic fusion proteins and under the control of the new regulatory elements. Understanding the mechanisms of chromosomal translocations in cancer may help us to develop new approaches in early the diagnosis and target therapy of cancer.

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